RESEARCH ARTICLE

COVID-19 – exploring the implications of long-term condition type and extent of multimorbidity on years of life lost: a modelling study [version 1; peer review: 1 approved, 2 not approved]

Peter Hanlon1, Fergus Chadwick1, Anoop Shah2, Rachael Wood2, Jon Minton3, Gerry McCartney4, Colin Fischbacher3, Frances S. Mair1, Dirk Husmeier1, Jason Matthiopoulos1, David A. McAllister1,3

1University of Glasgow, Glasgow, UK
2University of Edinburgh, Edinburgh, UK
3Public Health Scotland, Edinburgh, UK
4Scottish Public Health Observatory, NHS Health Scotland, Glasgow, UK

Abstract

Background: The COVID-19 pandemic is responsible for increasing deaths globally. Most estimates have focused on numbers of deaths, with little direct quantification of years of life lost (YLL) through COVID-19. As most people dying with COVID-19 are older with underlying long-term conditions (LTCs), some have speculated that YLL are low. We aim to estimate YLL attributable to COVID-19, before and after adjustment for number/type of LTCs.

Methods: We first estimated YLL from COVID-19 using standard WHO life tables, based on published age/sex data from COVID-19 deaths in Italy. We then used aggregate data on number/type of LTCs to model likely combinations of LTCs among people dying with COVID-19. From these, we used routine UK healthcare data to estimate life expectancy based on age/sex/different combinations of LTCs. We then calculated YLL based on age, sex and type of LTCs and multimorbidity count.

Results: Using the standard WHO life tables, YLL per COVID-19 death was 14 for men and 12 for women. After adjustment for number and type of LTCs, the mean YLL was slightly lower, but remained high (13 and 11 years for men and women, respectively). The number and type of LTCs led to wide variability in the estimated YLL at a given age (e.g. at ≥80 years, YLL was >10 years for people with 0 LTCs, and <3 years for people with ≥6).

Conclusions: Deaths from COVID-19 represent a substantial burden in terms of per-person YLL, more than a decade, even after adjusting for the typical number and type of LTCs found in people dying of COVID-19. The extent of multimorbidity heavily influences the
estimated YLL at a given age. More comprehensive and standardised collection of data on LTCs is needed to better understand and quantify the global burden of COVID-19 and to guide policy-making and interventions.

**Keywords**
COVID-19, Coronavirus, Multimorbidity, Epidemiology, noncommunicable diseases

This article is included in the Coronavirus (COVID-19) collection.
Introduction

When severe, coronavirus disease 2019 (COVID-19) causes acute respiratory failure, often requiring mechanical ventilation\(^1\). Globally, as of 6\(^{th}\) April 2020, more than 1,200,000 confirmed cases have been reported including 67,000 deaths\(^2\). In response to this threat, governments have introduced non-pharmaceutical interventions such as physical distancing and the delivery of health services has radically changed, with resources diverted towards the management of COVID-19 and away from their usual activities\(^3\). These measures have aimed to limit a surge in cases that risks overwhelming healthcare services\(^4\).

Since few health care systems could have responded adequately to the increased need for acute care without these changes, these decisions were in some ways inevitable. However, in the absence of a vaccine, as societies seek to “return to normal”, decisions about the extent and nature of ongoing measures to limit spread of COVID-19 will be more difficult. These choices will require balancing the likely direct effects on mortality from COVID-19 against the likely indirect impacts on mortality for other conditions – due, for example, to inadequate access to necessary services for many people with long-term conditions (LTCs), potential reluctance of the public to attend for acute events such as myocardial infarction, or impacts from forced unemployment, loss of income and social isolation. The indirect effects are likely to be complex, most will be downstream, and will require extensive research to be better understood. However, we need to capture the direct effects of COVID-19 as accurately as possible now, via currently available data and methodologies.

Currently, most reports of COVID-19 deaths have used raw counts\(^5\). This may give a distorting picture of the mortality burden, however, as it does not consider how long someone who died from COVID-19 might otherwise have been expected to live. As people dying from COVID-19 are predominantly older and have pre-existing LTCs\(^6\), some have speculated that many of these people would have soon died of other causes and that life expectancy may therefore not being greatly impacted\(^6\). In national comparison, some have speculated that many of these people would have soon died of other causes and that life expectancy may therefore not being greatly impacted\(^6\). While multimorbidity, the presence of multiple LTCs, is known to be associated with increased mortality\(^7\), people with multimorbidity nonetheless can be expected to live for many years\(^8\). Raw counts of deaths may therefore mislead policy-makers and the public, causing them to either over- or under-estimate the total impact of COVID-19 related deaths.

Within epidemiology, there is a standard measure used to account for this difficulty, the years of potential life lost (YLL)\(^9\). YLL can be expressed per-capita as the average number of years an individual would have been expected to live had they not died of a given cause. The conventional approach to YLL uses data on the age at which deaths occurred combined with typical life expectancy at a given age, to estimate a weighted average of the number of years lost. YLL is used to allow fair comparisons of the health impact of different policies, such as different measures to address the pandemic. However, given the controversial role of multimorbidity in COVID-19 deaths it is also important to calculate YLL additionally considering the effects of the presence of a single LTC or multimorbidity.

Therefore, we propose to quantify the burden of mortality related to COVID-19, both using the conventional age-based YLL measure, and YLL additionally accounting for type and number of underlying LTCs.

Methods

WHO standard YLL approach

The standard approach for calculating years of life lost is to apply the distribution of ages among those who died from a specific cause to a standard life-table. For the purposes of international comparison, we opted to use the WHO 2010 Global Burden of Diseases table as the reference\(^10\), which presents YLL by age, but not by sex or extent of multimorbidity. This method involves summing the expected years of life remaining from the table according to the number (or for the mean YLL the proportion) of people dying within each age-band. We applied the age distribution of COVID-19 deaths in Italy from published data to estimate the YLL.

Overview of modelling to accommodate long-term conditions and multimorbidity

The remainder of the methods describes our approach to estimating YLL accounting for number and type of underlying LTC, along with age and sex. Our modelling comprised three main components: (i) estimating the prevalence of, and correlations between, LTCs among people dying with COVID-19; (ii) modelling UK life expectancy based on age, sex, and each combination of these LTCs separately; and (iii) combining these models to calculate the estimated YLL per death with COVID-19. These are summarised by age-group, sex, and multimorbidity counts (that take into account different combinations of LTCs).

The data sources used for each of these stages of modelling are summarised in Figure 1.

Rapid review

To inform our estimates of number and type of LTCs, we performed a rapid review to identify data on underlying conditions for people dying with COVID-19. We searched the WHO repository of COVID-19 studies on 24\(^{th}\) March 2020. To identify studies reporting data on LTCs among people who had died from Covid-19, we screened titles and abstracts of all epidemiological, clinical, case-series and review articles (n=1685). We identified and screened 77 potentially relevant full-text articles, of which four reported aggregate data on LTCs among people who had died of COVID-19. Three were small studies (32, 44, and 54 deaths, respectively) based in Wuhan, China\(^11\). However, the fourth was a comprehensive report from the Istituto Superiore di Sanità (ISS) (published each Tuesday and Wednesday) including data on 11 common LTCs (ischaemic heart disease, atrial fibrillation, heart failure, stroke, hypertension, diabetes, dementia, chronic obstructive pulmonary disease, active cancer in the past 5 years, chronic liver disease and chronic renal failure), as well as the number of patients who had 0, 1, 2 or ≥3 LTCs for 701 of the 6801 people who died with COVID-19 in Italy\(^12\). In view of the smaller sizes of the Chinese studies, and the greater dissimilarity of these populations with the UK relative to the Italian data, we opted not to include these in the analysis. These data were
used to construct a plausible scenario for the prevalence of combinations of LTCs among people who died from COVID-19 for the modelling presented here.

**Long-term condition prevalence and correlation models.** This first stage of our modelling aimed to estimate the prevalence and correlation between specific LTCs among people dying with COVID-19.

We utilised aggregate data on COVID-19 deaths from the Istituto Superiore di Sanità (ISS) in Italy. Since we were unable to obtain IPD for the Italian case-series of deaths from COVID-19, we had to infer the joint prevalence of LTCs from the summarised information available, i.e. the marginal distribution of multimorbidity counts (the row sums, or total number of diseases for each patient, wherein counts of ≥3 LTCs were collapsed into the single category of 3+) and the marginal distributions of LTC frequency (the columns sums, or the total number of patients with each LTC). To that end, we developed a Bayesian latent process model of disease prevalence and correlation and fitted it using Markov chain Monte Carlo (MCMC) to both elements in the published data. This analysis was applied jointly to the small number of deaths that had occurred in Scotland, primarily to aid convergence in Bayesian model fitting by providing some information about the correlation between LTCs. The Scottish subset of the data contained a partial record of known LTCs for individual patients, but the multimorbidity count per patient, as well as the marginal frequency of each LTC, were missing (hence, modelled as latent). Bayesian priors for the correlations between diseases were specified with a tendency to zero (shrinkage). Numerical investigations indicated little sensitivity of convergence to the strength of shrinkage, so we opted for weak shrinkage as a precautionary approach. This model gave us the full matrix of correlations between every combination of LTCs at the level of individuals, therefore providing us with a complete dependence structure of LTCs presented within the sample of COVID-19 mortalities. In order to propagate uncertainty through the analysis, from this fitted model (effective sample size of MCMC 410) we simulated 10,000 notionally “typical” patients, with plausible combinations of LTCs (under the combined Italian and Scottish data).

To test the sensitivity of our findings to the estimated correlations, we also estimated the YLL under two opposite extremes (i) that LTCs were independent and (ii) that LTCs were highly correlated. Unlike the Bayesian LTC mode, these sensitivity analyses did not use the information on the multimorbidity counts from the ISS report, but only the proportion of patients with each of the eleven comorbidities. For the “independent” scenario we created 11 vectors comprising 1s and 0s (respectively with and without the long term condition) corresponding in length to the number of patients. We then sampled from these vectors with replacement to obtain 10,000 simulated patients. For the “highly correlated” scenario we first sorted each vector, then combined them to form a 710x11 matrix, then sampled each row with replacement to obtain 10,000 simulated patients.
Age models. Next, we modelled the relationship between age and multimorbidity counts among people dying with COVID-19. We were unable to obtain direct estimates of the association between age and extent of multimorbidity among patients who had died from COVID-19. Therefore, we modelled two scenarios: independence between age and multimorbidity count (i.e., no correlation between age and multimorbidity count among people dying of COVID-19), and a positive association between age and multimorbidity count. To inform the latter, we examined data within SAIL for 145 patients who had influenza recorded as the cause of death in their death certificate in 2011. We found that for men, age increased by 4.7 years per unit increase in the number of LTCs until the count reached 6 after which there was no evidence of further increase. For women, the figure was 2.6. Therefore, we performed the modelling assuming that for COVID-19 the mean age increased by 5 years per unit increase in multimorbidity count across the range from 0 to 6 LTCs in men. To allow for some degree of uncertainty around this estimate by sampling from a normal distribution. We arbitrarily chose a standard deviation of 0.5. We estimated this similarly for women, but using a mean increase of age of 3 years per increase in multimorbidity count. We incorporated this information in a model fitted to the summary age data provided in the Italian case report. We obtained 10,000 samples from the posterior distribution for inclusion in the YLL calculations. SAIL analyses were approved by SAIL Information Governance Review Panel (Project 0830). Approval for the use of individual patient data in the analysis was given by the NHS Public Health Scotland Caldicott officer.

Survival models. For patients aged 50 years or older at death, we estimated mortality according to age, sex and combinations of each LTC using the Secure Anonymised Information Linkage (SAIL) databank. SAIL is a repository of routinely collected healthcare data (including primary care, hospital episodes, and mortality data) from a representative sample covering approximately 70% of the population of Wales. From these data, we identified all participants aged over 49 years who were registered with a participating practice for the duration of 2011 (approximately 0.85 million people). This period was selected as electronic coding of diagnoses was well established, and it allowed >6 years of follow-up. Age and sex were extracted from primary care records. We also identified all LTCs for which we had information of COVID-19 deaths from Italy. LTCs were identified using a combination of primary care data (using Read diagnostic codes) and hospital episodes (using ICD-10 codes). Individuals were considered to have a LTC if they had a relevant diagnostic code entered prior to 31st December 2011. Relevant codes were identified from the Charlson comorbidity index and the Elixhauser comorbidity index, which had established algorithms for identification from ICD-10 codes, and have been adapted for using Read codes in primary care. Code lists are available in the supplementary material.

All-cause mortality was assessed by linkage to national mortality registers from 1st January 2012 until August 2018 (last available data). Participants were censored if they de-registered from a participating SAIL practice. We used the flexsurv package in R (version 1.1.1) to fit a Gompertz model treating age as the timescale. We assessed the fit of this distribution graphically (supplementary material). In models stratified by sex we included all the LTCs as main effects as well as age-LTC interactions that improved the model fit in terms of the Akaike information criterion. In sensitivity analyses we also included two-way (comorbidity-comorbidity) and three-way (comorbidity-comorbidity-age) interaction terms for the four comorbidities with the largest effect measure estimates (COPD, heart failure, liver failure and dementia) requiring 12 additional parameters. To propagate uncertainty from the survival models we obtained 10,000 samples of the coefficient estimates by sampling from a multivariate normal distribution corresponding to the coefficients and variance-covariance matrix from the regression models.

Combination of comorbidity and mortality models. In the final analysis, we combined 10,000 samples from all three sources: LTC combination models, age models and survival models. We used the rate and shape parameters with the cumulative distribution function implemented in the flexsurv package to calculate the survival probabilities at 3-month intervals from aged 50 to 120 (to allow all curves to descend to zero). From these times and survival probabilities we estimated the mean survival, or life expectancy.

Bayesian models were written in the JAGS language and implemented using runjags for R (version 2.0.4), survival models were fit using the flexsurv package in R (version 1.1.1), and for the final analysis the model-outputs were also combined in R (version 3.6.1). The 95% uncertainty intervals were obtained using empirical bootstrapping, with the number of samples in the mean equal to the effective sample size from the LTC correlation model. All code, data (except individual-level data for Scotland), intermediate outputs and diagnostic plots are provided on GitHub (https://github.com/dmcalli2/covid19_yll_final).

Results

WHO life tables

The proportion of men and women in 10-year age-bands was reported for the 6801 deaths included in the ISS case report. On applying the proportion in each age-band to the WHO Global Burden of Disease 2010 life tables for men, we found that the YLL was 14.4 per person using the whole cohort and 14 after excluding those aged under 50. For women, comparable figures were 12.2 and 11.8 years, respectively.

Comorbidity models

For 710 patients who had died with COVID-19 for whom information on LTCs was presented in the ISS report, the proportion with each LTC was as follows: ischaemic heart disease 27.8%, atrial fibrillation 23.7%, heart failure 17.1%, stroke 11.3%, hypertension 73%, diabetes 31.3%, dementia 14.5%, chronic obstructive pulmonary disease 16.7%, active cancer in the past 5 years 17.3%, chronic liver disease 4.1%, chronic renal failure 22.2%. The ISS report also presented the proportion of patients who died with each of the following multimorbidity counts: 0 (2.1%), 1 (21.3%), 2 (25.9%) and ≥3 (50.7%). Using these data, alongside individual-level patient data for a small number of patients from Scotland to aid with model fitting,
we were able to simulate a set of realistic notional patients with specific combination of LTCs. The correlations between every pair of LTCs are shown in the appendix and the full posterior distributions from the modelling are available at GitHub (https://github.com/dmcalli2/covid19_yll_final)15.

**Age models**

Based on the proportions reported for each age-band, for men the mean age for the ISS deaths was 77.9 years when people aged less than 50 were excluded and 77.4 years overall. For women the figure was 81.1 for both. The models we fit to these data to smooth out the distribution and to make it easier to accommodate different scenarios for the association between age and multimorbidity counts comorbidity are shown in Figure 2; the distribution of age and multimorbidity counts for men and women are shown under the assumption that these are independent, and under the assumption that multimorbidity is associated with age.

**Survival models**

The coefficients for the survival models are shown in the supplementary appendix. Briefly, all LTCs other than hypertension were associated with increased mortality (in a model including 10 other LTCs), and for each LTC the association with mortality was attenuated as the baseline age increased. Figure 3 shows the survival curves applied to different age and combinations of LTCs, stratified by age-band and multimorbidity count. This figure shows how these associations and age relate to survival across the age range from 50 to 110 years old.

**Years of life lost**

For men the average YLL on adjusting for number and type of LTC as well as age was 13.1 (12.2–14.1). For women this value was 10.5 (9.7–11.3). The results were similar under the different assumptions for the age-multimorbidity association and in both sensitivity analyses, whether assuming strongly correlated or independent LTCs (Table 1). For comparison, the YLL based on age alone using the WHO tables was 14.0 and 11.8 for men and women, respectively.

Across the simulated patients there was substantial variation in YLL adjusted for multimorbidity count (Figure 4).

On stratifying the YLL estimates by sex, age and multimorbidity count (for the simulated patients) there were clear differences (Figure 5, Table 2) with the YLL ranging from around 2-years per person in men or women aged 80 with large numbers of LTCs, to around 35 years in younger people without any LTCs (Table 2). For most age-bands and most multimorbidity counts the YLL per person remained above 5. In sensitivity analyses including the survival models with additional comorbidity-comorbidity and comorbidity-comorbidity-age interaction terms, (despite these models having a better fit based on AIC) than the model presented here, the YLL only changed minimally from that seen in the main analysis. This was true overall YLL for each sex (13.1, 95% CI 12.2–14.0 and 10.5; 95% CI 9.7–11.3 for men and women respectively) and on additionally stratifying on age and multimorbidity count (as shown in Table 2). For the latter comparison,
Figure 3. Survival curves for all-cause mortality. Figures are paneled by age and sex. Individual lines represent survival curves for a single simulated patient with a given set of LTCs. From light to dark (yellow to blue) they show decreasing multimorbidity counts. There are 10,000 lines, one for each notional patient. Lines run from the age at which each simulated patient died (survival probability = 1) to when they would have died under the model (survival probability = 0). Patients with the same age and total multimorbidity count will have a different survival curve if they have a different set of 11 LTCs.

Table 1. Years of life lost (YLL) and 95% credible intervals under different modelling assumptions.

<table>
<thead>
<tr>
<th>LTC-LTC correlation</th>
<th>Age-multimorbidity correlation</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modelled</td>
<td>Associated</td>
<td>13.1 (12.2-14.1)</td>
<td>10.5 (9.7-11.3)</td>
</tr>
<tr>
<td>Modelled</td>
<td>Independent</td>
<td>11.2 (10.6-11.9)</td>
<td>9.1 (8.5-9.7)</td>
</tr>
<tr>
<td>Independent</td>
<td>Associated</td>
<td>12 (11.2-12.7)</td>
<td>9.9 (9.2-10.5)</td>
</tr>
<tr>
<td>Independent</td>
<td>Independent</td>
<td>11.5 (10.9-12.1)</td>
<td>9.5 (8.9-10.1)</td>
</tr>
<tr>
<td>Highly correlated</td>
<td>Associated</td>
<td>13.3 (12.4-14.3)</td>
<td>10.9 (10.1-11.8)</td>
</tr>
<tr>
<td>Highly correlated</td>
<td>Independent</td>
<td>12.9 (12.1-13.6)</td>
<td>10.5 (9.8-11.3)</td>
</tr>
</tbody>
</table>
Figure 4. YLL by sex. Coloured bars indicate the multimorbidity count from zero (dark/blue) to 11 (light/yellow).

Figure 5. YLL stratified by sex, age and multimorbidity count. Coloured bars indicate the multimorbidity count from zero (dark/blue) to 11 (light/yellow).
the largest difference – 0.7 YLL – was seen in women aged 50–59 with six comorbidities. For most age-comorbidity bands the YLL was the same, to one decimal place, under both survival models.

Discussion
Summary of main findings
Using published data on people who have died from COVID-19 and survival models based on age and multimorbidity count in a general population in the United Kingdom, we estimated the burden (years life lost) from COVID-19 related mortality. We make a number of important observations. First, using the WHO GBD 2010 life tables as the reference\(^1\), the estimated YLL was over a decade for COVID-19 deaths with 14 YLL in men and 12 in women. As such, mortality from COVID-19 represents a substantial burden to individuals and comparable to high burden LTCs such as ischaemic heart disease and chronic obstructive pulmonary disease. Second, YLL estimated from models using the prevalence of underlying LTCs based on patients dying from COVID-19 in Italy and age-, sex- and multimorbidity count-specific survival models in the UK did not drastically impact the YLL. Across both men and women, the number of YLL dropped to 13 and 11 years respectively. Third, across most age and multimorbidity count strata the estimated YLL per person remained substantial and generally above 5 years. This means that even after accounting for multimorbidity count, most individuals lost considerably more than the “1–2 years” suggested by some commentators\(^2\) perhaps reflecting the high prevalence of multimorbidity in this population, especially in those over the age of 50 years\(^2\)\(^3\). Finally, whilst the YLL remained high across most age- and multimorbidity count strata, the presence of multimorbidity did indeed influence the magnitude of the YLL. For example, in the elderly, over the age of 80, the estimated YLL in people with no LTCs was 11 years falling to less than two years with an increasing multimorbidity count.

YLL is a widely used metric to compare the relative impact of different causes of death and is used to guide policy-making and health service delivery and to prioritise interventions aimed at preventing deaths\(^2\). Using UK reports for approximate comparisons, the YLL for other conditions ranged, per capita from 8.2 for chronic obstructive pulmonary disease, 11.6 for coronary heart disease, 13.1 for pneumonia, and 21.6 for asthma\(^7\). Therefore, against these benchmarks, mortality from COVID-19 represents a substantial burden to individuals.

The estimated YLL can vary substantially depending on the reference population chosen and the age distribution among those who die. Moreover, where attempts are made to account for underlying conditions in those who died, the accuracy will depend on the quality and completeness of data both for those deaths, and in the reference population used to obtain estimates of survival according to those underlying conditions. Nonetheless, although imperfect, we would argue that public health agencies should present estimates of YLL for COVID-19, alongside the more usual counts of deaths. We have already seen that if agencies do not do so, commentators can and will fill this vacuum, sometimes making substantial errors such as using life expectancy at birth to make inferences about the years of life lost by someone who has already lived into later life and thereby considerably underestimating the impact of the disease on individuals\(^2\).

Strengths and limitations
Our analysis is novel in that it adjusts YLL for the number and type of underlying LTCs. This is important as people with underlying multimorbidity are recognised to be more vulnerable to COVID-19. However, although we had data for eleven common and important LTCs, we did not have markers of underlying disease severity among those who died. Severity of the underlying LTC has considerable impact on life expectancy\(^2\). Moreover,
we had no data for rarer severe LTCs, which may nonetheless be common among those who die from COVID-19 at younger ages. As such, the attenuation of YLL following adjustment for LTCs may be an underestimate. However, we think that this effect is unlikely to be substantial enough to reduce YLL to the orders of magnitude suggested by some commentators. Indeed, on stratifying by age and multimorbidity counts, we rarely found average YLLs of below three. Also, we were not able to adjust our estimates for other factors and exposures (such as socioeconomic status, occupation, smoking, health behaviours) which would have given a more accurate representation of life-expectancy in the absence of COVID-19.

We did not have access to large quantities of individual-level data with which to estimate the prevalence of different combinations of LTCs. Therefore, we fitted a complex model (which was methodologically innovative and will be the subject of a separate publication) to estimate the joint probabilities, using the overall (marginal) estimates of each LTC, and the overall multimorbidity counts alongside a small amount of individual-level data from Scotland to help with model fitting. This model did not fully converge and had wide posteriors (indicating substantial uncertainty) for the correlation between LTCs. We nonetheless included the results of this model in our analysis because (i) it represents the best estimate for the joint probabilities given the available data and importantly, (ii) the results for overall YLL remained substantially similar in widely different sensitivity analyses assuming either that LTCs are highly correlated among people dying from COVID-19 or that they are entirely independent.

Finally, given the emergent nature of the coronavirus pandemic, this study was conducted rapidly and under pressure of time. We chose the best data for age, sex and prevalence of LTCs that was available to us at the time of our modelling, but better-quality individual-level data specific to individual countries will yield substantially more reliable estimates. We would suggest that each public health agency should produce country-specific estimates, using the same LTC definitions in those who died as in the reference population and ideally to an agreed international protocol. Our study has used complex state-of-the-art statistical modelling and inference techniques, which rely on expensive computer simulations. Given the time constraints, we had to find an acceptable trade-off between estimation accuracy and time constraints. Therefore, we will continue to refine our work to improve the convergence of the numerical procedures, although we do not expect that our conclusions, either about the overall YLL per capita, or about the distribution of YLL within the population, will substantially change. We have also provided all our data (except individual-level data form the Scottish population, for which we provide a simulated substitute dataset) and code to allow others to check our modelling and correct any errors15.

Conclusion

Among patients dying of COVID-19, there appears to be a considerable burden in terms of years of life lost, commensurate with diseases such as coronary heart disease or pneumonia. While media coverage of the pandemic has focused heavily on COVID-19 affecting people with ‘underlying health conditions’, adjustment for number and type of LTCs only modestly reduces the estimated YLL due to COVID-19 compared to estimates based only on age and sex. Public health agencies and governments should report on YLL, ideally adjusting for the presence of underlying LTCs, to allow the public and policy-makers to better understand the burden of this disease.

Data availability

All code, data (except individual-level data for Scotland), intermediate outputs and diagnostic plots are provided on GitHub: https://github.com/dmcalli2/covid19_yll_final.

Source data


This project contains the source data used in performing this modelling study (except individual-level data for Scotland), which are also available via GitHub (https://github.com/dmcalli2/covid19_yll_final/tree/master/Data).

Individual-level data for Scotland are accessible via application to the electronic Data Research and Innovation Service (eDRIS) and the Public Benefit and Privacy Panel (PBPP) (https://www.isdscotland.org/Products-and-Services/EDRIS/). Individual-level data for Wales are available via application to the Secure Anonymised Information Linkage (SAIL) at https://saildatabank.com/. For both eDRIS and SAIL, individuals are required to complete information governance training, be affiliated with an appropriate organisation (e.g. a university, healthcare organisation, etc.) complete an application form, and the analysis must be performed to support research conducted in the public interest.

Extended data


This project contains the archived scripts used during this modelling study, which are also available via GitHub (https://github.com/dmcalli2/covid19_yll_final/tree/master/Scripts).

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Acknowledgements

We thank Professor Helen Colhoun, University of Edinburgh, for her feedback on a draft version of this manuscript.
References

   Publisher Full Text
   Reference Source
   Reference Source
   PubMed Abstract | Publisher Full Text | Free Full Text
   Published Abstract | Publisher Full Text | Free Full Text
   Published Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   Reference Source
   Publisher Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   Publisher Abstract | Publisher Full Text
   Reference Source
   Reference Source
15. McAlister D: Supplementary material.
   Reference Source
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   Reference Source
   Publisher Full Text
   Reference Source
   PubMed Abstract | Publisher Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   PubMed Abstract | Publisher Full Text | Free Full Text
   Reference Source
   PubMed Abstract | Publisher Full Text | Free Full Text
Open Peer Review

Current Peer Review Status: ✔️ ✗ ✗

Version 1

Reviewer Report 26 November 2020

https://doi.org/10.21956/wellcomeopenres.17385.r41111

© 2020 Chan M. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Mei Sum Chan
University of Oxford, Oxford, UK

Thank you for the opportunity to review this manuscript. This review relates to the version of the manuscript submitted for review (v1) and does not cover the addendum as the addendum was not mentioned in this version, nor does it refer to the authors’ responses to comments on the manuscript. The review also takes into account that this version was posted on 23 April 2020 and hence did not have access to the better quality data and results from similar studies that were published after this date.

Overall:
This is a highly topical investigation into the demographic impact of mortality from COVID-19 and the role of underlying conditions in these mortality patterns. The message that there is a large direct mortality burden from COVID-19, measured in terms of YLL, and that this the burden increases with number of underlying conditions, is clearly made by the study, particularly through results from the first approach (the standard WHO life table approach) and sensitivity analyses of the second approach. However, insufficient evidence was provided on the validity of the second and main approach, a novel complex simulation study of COVID-19 mortality in people with different LTC profiles, both in terms of the statistical rigour and the use of health data within the model. I recommend that substantial model development is carried out to resolve statistical issues and to assess model diagnostics, preferably in the separate methodological investigation that the authors mentioned, before being used in its final form in this empirical study to make policy recommendations.

The majority of the sections were clear, and compelling reasons were given for conducting this research and for using these results to inform policy and public dialogue. The use of a rapid review to acquire and assess data on underlying conditions is also commendable. The aims were not fully clear and did not match the rest of the manuscript: a target or reference population was not specified, no results by type of multimorbidity were reported even though they were accounted for in the model, and the manuscript focused on the design and application of the novel second approach when this was not a stated aim. The methods, while detailed, were also unclear for the second approach: multiple datasets, model descriptions and procedures were
interweaved in no particular order in each subsection, it was difficult to differentiate the role of data vs assumptions, and apart from scenario testing, no model diagnostic or checking procedures were mentioned for the Bayesian components. Some key results on the LTC model convergence and posterior distribution were reported in the Discussion rather than the Results section. One of the conclusions did not appear to match the results well.

The authors have provided the non-IPD data, annotated code and codelists for this analysis, and given details on the access request procedures for the IPD datasets. Display items for modelled distributions and YLLs were useful but were difficult to interpret for survival curves (Figure 3). A summarised version of Figure 3 would be more useful.

My key concerns were:

1. The authors reported in the Discussion section that the LTC model in the second approach ‘did not fully converge’. This is a key statistical issue should have been reported much earlier in the manuscript and steps taken to ensure model convergence at the analysis stage. No model diagnostics (for model selection, convergence or goodness of fit) were reported for the LTC model and age model components. Therefore I have major concerns over the validity of the model structure and its results. I also wonder how the authors managed to extract results from the LTC model and how these results should be interpreted since the model was not optimised. The authors’ expectation that the results will not change substantially with future modifications to achieve convergence is not sufficient. If the model lacked input data, why were influenza rather than COVID-19 deaths (specifically the influenza deaths in 2011; Methods section) used to supplement the age model but not the LTC model? What quantity of data or correlation structure in the data was required to enable the model to converge? Is there a way to jointly model the LTC joint prevalence and age distribution? The authors should consider placing more emphasis on the first approach or the simpler sensitivity analyses, or eliminating features of the model that exacerbated non-convergence or may have led to overspecification in this study. Hopefully this would also reduce the reliance of the model on distributional assumptions input by the authors.

2. The abstract described little of the data and methods used for the second approach. The source of data was stated as ‘UK healthcare data’, which was somewhat misleading when in fact only a combination of Scottish and Welsh health records were used and were mixed with aggregate level Italian death data. I could not detect the use of statistical models from reading the abstract, much less a simulation study using a combination of two Bayesian models and one parametric survival model.

3. It was not clear which population the authors intended to model or make recommendations for. This was not stated in the aims, results or discussion, but the choice of data appeared to have a UK focus. The authors have used Scottish, Welsh and Italian data mixed together – presumably these were the datasets that were available to the authors in that short window. However, which population(s) would the results relate to? If only Italian data on underlying conditions was identified in the rapid review, why not focus on Italian data for the rest of the analysis for consistency? The choice of country matters as patterns in multimorbidity and mortality with multimorbidity depend on care provision and demographic characteristics (Nunes et al 2016). The results would also be more informative if country-level differences in mortality profiles at ages 50+ in Italy, Scotland and Wales did not contribute to the reported YLLs.
4. Additionally, the populations used in each model component (Figure 1) were mismatched. The LTC and age models were based on deaths from COVID-19 and/or influenza and their LTC profile at the time of death in several datasets, while the survival model was based on the unselected SAIL population and their LTC profile at baseline. These choices were reasonable within each model component, but inconsistent when these components were combined. The choice of the complex LTC and age model design appeared to be a consequence of using sparse data (deaths from COVID-19 and/or influenza). It would be useful to assess whether the correlation structures of age and LTCs of those who died from these causes were substantially different from the structures of their respective wider populations.

5. Since the authors reported in the Discussion section that the LTC model ‘had wide posteriors (indicating substantial uncertainty)’, the rationale for using a complex LTC model component as part of the main model in addition to the two extreme scenarios of independent LTCs and highly correlated LTCs is unclear. Running the model using those two scenarios alone was sufficient to provide a range of YLLs that would still address the aims of this study and avoid many of the issues raised in this review. In fact, Table 1 shows that the ranges of YLLs described by these two scenarios were not large and the YLLs were substantially larger than zero when age and multimorbidity counts were treated as associated.

6. The authors’ second conclusion that ‘adjustment for number and type of LTCs only modestly reduces the estimated YLL due to COVID-19 compared to estimates based only on age and sex’ seems to gloss over the more policy-relevant finding that there were substantial differences in YLLs by multimorbidity count (Table 2).

Minor comments:
1. Please refer to the relevant citation for ‘age distribution of COVID-19 deaths in Italy from published data’ in the WHO standard YLL approach subsection.

2. Please spell out the first mentions of ‘IPD’ and ‘SAIL’, and move the description of SAIL to the first mention.

3. Please specify what the ‘high correlation’ scenario is rather than the procedure used to obtain it (I think this scenario is specified more clearly in the R code rather than the main text.) The ‘independent’ scenario probably does not require explanation, but if explained, the word ‘random’ should be added.

4. The authors’ comparisons with YLLs from a ‘UK report’ for pneumonia was useful, and vital in the absence of LTC model and age model diagnostics. However, this ‘UK report’ only contains YLLs for England and Wales and not the whole of UK. Published YLLs for other flu pandemics or outbreaks could also be more relevant comparisons.

5. It should be acknowledged that the analysis does not take into account COVID-19 deaths at ages under 50 years, which were rare but may have a non-negligible impact on the summary YLLs for the second approach.

6. The authors refer to the same Github repository for all supplementary material and
appendices, which contains a large number of files, mostly datasets, codelists, code and raw output, and no explanation of its contents. It would be helpful to report the interpretations of the outputs and to refer to specific files in the repository in each instance.

7. The estimation of YLLs by type of LTCs was alluded to in the aims but not reported. Some results on YLLs for particular combinations, perhaps the most prevalent combinations, would be more clinically informative than the YLLs by multimorbidity counts. Alternatively, a ranking of LTCs by their lethality or a combined measure of lethality and prevalence would be informative too.

8. The colour coding in Figure 3 was not explained (but is presumably the same as the other figures).

9. The resolutions of the figures could be improved so that the axis labels are more readable.

10. The caption for Table 2 should be revised to clarify that YLLs are tabulated by LTC count and not type.

11. The authors acknowledged that YLL for COVID-19 is an ‘imperfect’ measure, but did not explain why. It would be helpful to add limitations of either YLL approach (eg the YLL models used here do not allow for competing risks) or consider alternative health metrics (eg YLD or DALY) in the Discussion section.

12. The ‘orders of magnitude suggested by some commentators’ mentioned in the Strength and limitations section should cite the relevant reference. Evidence of suggestions or claims by multiple commentators rather than a single commentator would also be appreciated.

13. The Discussion section focused on YLLs by number of LTCs and did not consider the wider context of multiple interlinked risk factors for COVID-19 deaths, several of which are available in the SAIL data (socioeconomic and health behavioural factors). The relative importance of age, sex and number of LTCs (and types of LTCs) should be given some consideration too.

14. The YLL terminology is correct, but it may be worth clarifying (especially to readers who are unfamiliar with YLL or epidemiology) that these YLLs estimate the direct impact of COVID-19 deaths rather than the indirect impact of COVID-19-related outcomes.

15. The comparison of raw death counts with YLLs per person as reporting metrics should be refined as the authors and health organisations appear to stand at cross purposes. One key use of raw death counts is to track the evolution of the pandemic in real time, whereas these YLLs do not track time trends or describe the aggregate mortality burden.

I have limited experience with Bayesian models and would recommend that a reviewer with specific expertise in Bayesian modelling in JAGS is invited at the next round to add any further comments on the Bayesian components of the models if these remain in the analyses.

References
Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, medical statistics, gerontology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 09 November 2020
https://doi.org/10.21956/wellcomeopenres.17385.r41112

© 2020 Stokes J. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jonathan Stokes
Division of Population Health, Health Services Research & Primary Care, University of Manchester, Manchester, UK

Thank you for the opportunity to review a very interesting article exploring the impact of COVID-19 on years of life lost (YLL), adjusting for multimorbid patterns in the population. The topic is clearly highly relevant, and the authors do a good job of explaining how moving beyond the raw numbers of COVID deaths is increasingly important for policymakers, one way of doing so is through YLL. They use a variety of datasets from different countries/contexts to estimate a raw YLL and a multimorbidity-adjusted YLL. The headline figures the authors report are startling, 13
and 11 years for men and women respectively after adjusting for multimorbidity. I do, however, have some major concerns on these estimates, mostly to do with data sources, potential selection effects, and how the reported modelling figure relates to observed actual figures. I would like to see the authors justifying/addressing these prior to recommending indexing. Below I provide more details on the major concerns and then more specific comments on each section. I hope the authors find these useful for strengthening their paper and look forward to seeing the revised version.

Major comments:

- You draw on a variety of data sources. I'm not entirely convinced it makes sense to put all that you've chosen together, though, or that the datasets (especially now) are the best available. You draw on data primarily from Italy for the ‘LTC’ and ‘Age’ models. But Italy is quite a specific context in terms of COVID-19, one where the health system was overwhelmed and, like any other one context, where specific policies were implemented – both of which likely affect the death profile. Is the profile of deaths in this context actually going to be generalisable to any other? The ‘Survival’ model, on the other hand, is from Welsh data. Again, I'm not convinced the mortality profile will be comparable to Italy in ‘normal times’ let alone ‘COVID times’. For example, life expectancy in the UK is 2-3 years less than in Italy and the UK burden of premature death by LTCs is higher than the EU average. The use of WHO life tables is again a potential concern, particularly with no sex-specific details. Life expectancy differs significantly across sex, as does the negative effect of COVID-19. Particularly for the Italian data, the very small numbers are also concerning. You say in the article that at the time this was best available, which makes sense. Surely now there is a better source, though? It would be nice to see all data sources coming from the same country to avoid additional confounding introduced by policy/other context differences. Also, YLL will likely vary significantly by place and over time (e.g. with improvements to policy/treatments and as immunity begins to develop in populations). Making the data sources clearer and more unified would help justify the where/when of the YLL figure you actually present. At the moment it is not at all clear how to interpret the YLL to any context.

- Linked to the above, but probably a more fundamental concern, I wonder if some of the datasets come from a biased population (i.e. selection concerns)? My concern is that both the ‘LTC’ and ‘Age’ models use data from dead patients only, but the ‘Survival’ model then uses all patients with healthcare contacts in Wales. The data sets focusing only on patients who have died can't be taking into account differences in likelihood of exposure to the virus (for example, more deprived persons with more comorbidities are more likely to be exposed through types of employment and subsequently to die – there are likely going to be different LTC patterns/relationships in the dead versus general population) or severity (for example, a majority of deaths in the UK and other countries are from care home patients – a person with asthma in the general population is going to have a very different life expectancy to someone in a care home with asthma). Can you justify the use of LTC patterns only in patients who have died? On this, I do wonder if there is something you can do with data on those who test positive to at least slightly address this point, perhaps in a two-part model, i.e. first conditioning on exposure to the virus given a set of observables (ideally containing at least deprivation, preferably also setting, e.g. care home), then on subsequent probability of death?
The YLL figure just doesn't seem to sit with observed reality. I realise this is a modelling study, but it would be nice to compare your findings to what we have actually observed. For example, what is the average age of death expected from your model compared to observed COVID age of death? Something to contextualise the very high observed average age of death of COVID patients (by some accounts very similar or higher than the average life expectancy for the general population) with the YLL figure you give is needed in the discussion section and/or throughout the results.

Lastly, I have econometric modelling experience, but not Bayesian. I would recommend to the editorial team to have someone with Bayesian modelling expertise to additionally review the manuscript before a final decision is made.

Specific:

○ Introduction
  ○ I agree with the authors that YLL is an improvement over raw counts of deaths. But, there are also other methods that improve on raw counts, for example excess deaths. It would be good to contextualise/compare the YLL concept with excess deaths, and with concepts such as quality-adjusted life years (the latter might come up again in limitations section also).
  ○ As above, agree that LTCs and multimorbidity are clearly important considerations for COVID YLL. However, so are other confounders, such as deprivation, etc. Again, would just be nice for some discussion of these other important aspects that are not currently considered in your analysis, either briefly here and/or discussion section.

○ Methods
  ○ Already mentioned in my summary at the top, but the neglect of sex-stratification in the WHO tables seems a major one. Can you justify/look for alternatives?
  ○ Can you justify the data sources from multiple countries and what the YLL that comes from combining them means? And/or, can you update the datasets to reflect a more coherent, understandable context? The strongest data seems to be the SAIL data you have access to. So, maybe drawing on ONS/CQC data (and life tables too) and/or other publications from the UK context might be a way to do this now? And/or, the US CDC seems to have a lot of data reporting on co-morbidities now, with at least much larger numbers if you still want to try and estimate a 'global' YLL estimate.
  ○ “IPD” (p.4) – spell out
  ○ For the LTC models, it is not obvious to me how/why you incorporate the Scottish data here. Can you make more clear what this adds and why it is necessary (especially with n=33)?
  ○ For the age models, why are you using SAIL data on influenza deaths? This is a different disease, so not obvious this is relevant. As above, perhaps there is better data available now?
  ○ “We arbitrarily chose a standard deviation of 0.5” (p.5). How much influence does this have? Sensitivity analysis?
  ○ “SAIL is a...” (p.5) You have already introduced SAIL data. Might want to move this up to first introduction.

○ Results
  ○ Throughout, I wondered how the figures you present would compare to the observed. This information should be available now, it would be nice to see validation
of the model in this/another way.
○ Table 2: Can you add the absolute number you are expecting to be observed dying in each of these age/MM groups, and again perhaps compare to observed?

○ Discussion
○ Make clear what the YLL is exactly, where/when does it relate to? How generalisable?
○ You compare the estimated YLL to established infections/LTCs. Can you say something about likely changes as vaccines/treatments emerge (in light of the billions and billions being spent on them relative to other conditions), and as COVID-19 becomes endemic in populations?
○ The definition of a COVID death varies somewhat across different countries, but tends to be fairly loose (e.g. suspected, or a positive test within X-days but not necessarily the recorded primary cause on the death certificate). Can you discuss implications of using this data, especially in relation to impact of other LTCs? Is it reducing the YLL of other conditions?
○ “As such, the attenuation of YLL following adjustment for LTCs may be an underestimate.” As above, could also be an over-estimate without accounting for exposure to virus/severity of LTCs/different healthy system and time context.
○ “This model did not fully converge and had wide posteriors (indicating substantial uncertainty) for the correlation between LTCs. We nonetheless included the results of this model in our analysis”. This sounds like a pretty big issue. Why is it not converging exactly? What happens when you simplify the model to allow it to converge?
○ “Finally, given the emergent nature of the coronavirus pandemic...”. This paragraph fine for a pre-print, but I think highlights the need for an update now in light of emerging data/evidence.
○ “Among patients dying of COVID-19, there appears to be a considerable burden in terms of years of life lost”. Large proportion of the excess deaths are care home residents. Please discuss severity of disease impact.
○ Quality of life matters too. Need to discuss limitations of YLL and reference important quality of life considerations too.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Partly
Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Research Fellow in Health Economics, PhD, and Master’s of Public Health. Expertise in evaluating new models of care for multimorbid patients.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 08 June 2020

https://doi.org/10.21956/wellcomeopenres.17385.r38609

© 2020 Martinez-Piedra R. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Ramon Martinez-Piedra**
Department of Non-Communicable Diseases and Mental Health, Pan American Health Organization, Washington, DC, USA

This study aims to quantify the burden of premature mortality related to COVID-19 using years of life lost as a health-gap measure. It goes further by quantifying premature mortality from COVID-19 based on multi-morbidity or number of underlying long-term conditions.

This is a relevant topic as the study can provide useful information for planning and prioritizing public health and health care interventions and policies. The methodological approach from this study can serve to further research studies particularly quantifying the impact of multi-morbidity on premature mortality.

The manuscript is well written, clear, and straight forward.

I don't have any major criticisms of the study and manuscript.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes
If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology, public health, health metrics, data analysis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

---

**Comments on this article**

**Version 1**

Reader Comment 27 May 2020  
**Benno Falkner**, Private, Raeren, Belgium

Dear authors,

I think it's an interesting way of analyzing and predicting life expectancy. I have to say I'm not into the statistics of all this, but I realized at least one simulated (?) patient had a 50% chance to reach 110 years. One of 10,000; so roughly one of 20000 will be older than 110 once in his life? It seems to be a little too much.

Another Problem is from statistics. To keep it simple, let's assume a Normal or similar distribution. In Germany we have a average life expectancy of 81 years and Covid 19 has an average of 80. So if I choose randomly from the lifespan distribution, I'll get a new distribution with almost the same average value. I don't know the variance, but for now it's ignored. So the Covid-19 deaths could be such a set taken from the same distribution. A shift by 10 years would move the mean to approximately 91 for this group. Ok, in this group are people who are young and the average life would increase but not by 10 years. So my main question is, why is a group with comorbidities dying because of Covid-19 with an perhaps significantly higher life expectations than average. Of course this is true for some and all should have lived longer but not 10 years. At this point variances of those groups need to be compared.

Please show and compare age distributions of Covid-19 deaths, all population age at death and your calculated age patients could have reached.

Thanks and all the best  
Benno Falkner
**Competing Interests:** No competing interests were disclosed.

Reader Comment 21 May 2020

**Alex Robinson**, Self, USA

Figure 3 is misleading. Looks like an artifact of painting lots of lines in little space. The lines should be much smaller than 1 pixel in thickness, but are not.

Too, it might be interesting to see medians in addition to averages for some of these conclusion numbers.

Also, with respect to YLL’s, it might be worthwhile to assign some values to those years. As in, do you consider the year when you’re 80 years old to be equivalent in any way to the year you’re 30? Could be better. Could be worse. But I'll bet on worse. And, way, way shorter if they are the same.

**Competing Interests:** None.

Author Response 18 May 2020

**David McAllister**, University of Glasgow, Glasgow, UK

Thank you for your reply Alex Williams.

I think we have already addressed these questions in the commend headed "In response to Jason Bloomberg and David Bernstein".

**Competing Interests:** None

Reader Comment 15 May 2020

**Alex Williams**, Thinkingslow.org, Amsterdam, UK

It did not make sense for you to use GBD 2010 loss functions when you had access to ONS expected remaining years for UK - in your github files you even show that this overestimates compared to ONS by between min 20% up to 28% for male years remaining. In addition you don't mention how you treat years remaining for 85+ - do you stop at the GBD 2010 figure of 5.05 or do you use actual remaining years which falls off quite precipitously after 85 and around 30% of male deaths with COVID-19 on the death certificate are over 85 years old. Also the point made by another reader that although you don't have data on severity it stands to reason that those dying of COVID-19 with 2.7 comorbidities (March 2020) are likely to be severe comorbidities. The highest infection fatality ratio is around 9.3% for 80+ meaning that 90.7% will survive so it seems probable that only those with serious comorbidities (and hence low remaining years) are vulnerable.

Professor Ferguson mentions "I mean by the end of year what proportion of people who died from
COVID-19 would have died anyhow? It might be as much as half to two thirds of the deaths..". It appears that your YLL of 13.1 years was based on taking inappropriate data set (GBD 2010) and making unreasonable assumptions on severity. The average COVID related death is 79.2 years old with 2.7 comorbidities (March 2020) - a YLL of 13.1 appears very high - please restate using ONS numbers and more realistic assumptions about severity.

**Competing Interests:** I do not believe the authors conclusions as they appear counter-intuitive and flatly contradict statements made by Professor Ferguson of Imperial College and other research

---

Reader Comment 15 May 2020

Marius Rubo, University of Fribourg, Fribourg, Switzerland

Dear authors,

I personally welcome this study for starting an important discussion. However, I think the logic behind the analysis is more fundamentally flawed than previous commentators have noted.

Let me explain: The study starts with the correct assumption that, as people get older, their life expectancy increases since they can no longer die younger than what they already are at each point in time (so, their life expectancy is based on the average lifespan of other people who have lived at least as long as the person is now). However, comparing the age of a person who has just died with the distribution of lifespans of people who got to live at least the same time does not answer any relevant question here. Following this study's logic, you could get lifespan data from people who matched any arbitrary variable – say, people whose first name started with the letter “D” – compare their lifespan (which will not deviate from that of the general population) with their life expectancy on the day they died and find out that these people still had more than 10 years to live. Now does having a first name that starts with the letter “D” cost you 10 years of your life? Of course not.

I think a more meaningful comparison would be the lifespan of people with and without a certain feature, in this case the presence of COVID-19.

All the best,
Marius Rubo

**Competing Interests:** no competing interests

---

Reader Comment 12 May 2020

Karl Ulrich Gutschke, private, Hildesheim, Germany

The YLL estimate is based on the assumption that Covid 19 is the only cause of death. The study has no significance for deaths only with Covid 19. This important limitation is missing.
Competing Interests: none

Reader Comment 11 May 2020
Krist Vaesen, Eindhoven University of Technology, Eindhoven, The Netherlands

Dear authors,

thanks for this interesting study. I was genuinely surprised by your results.

A question: you report on mean YLL (13 years in men, 11 years in women). Do you obtain similar results when you calculate median (rather than mean) YLL values?

Many thanks in advance for your response.

Best,
Krist

Competing Interests: No competing interests.

Reader Comment 10 May 2020
Leslie Dalton, Dalton Pathology, Austin, TX, USA

Dear Doctors

It is stated,” The ISS report also presented the proportion of patients who died with each of the following multimorbidity counts: 0 (2.1%), 1 (21.3%), 2 (25.9%) and ≥3 (50.7%). “

Then it is stated,” the proportion with each LTC was as follows:- ischaemic heart disease 27.8%, atrial fibrillation 23.7%, heart failure 17.1%, stroke 11.3%, hypertension 73%, diabetes 31.3%, dementia 14.5%, chronic obstructive pulmonary disease 16.7%, active cancer in the past 5 years 17.3%, chronic liver disease 4.1%, chronic renal failure 22.2%. “

Then it is stated:
“As such, mortality from COVID-19 represents a substantial burden to individuals and comparable to high burden LTCs such as ischaemic heart disease and chronic obstructive pulmonary disease. “

Then it is stated, “Using UK reports for approximate comparisons, the YLL for other conditions ranged, per capita from 8.2 for chronic obstructive pulmonary disease, 11.6 for coronary heart disease, 13.1 for pneumonia, and 21.6 for asthma”
My comment: What we have is most with COVID have comorbidities in which the comorbidities have YLL comparable to COVID. You cannot divide one from the other. 75% have both COVID AND 2 or more comorbidities. There are simply not enough deaths from 0 comorbidity patients to say much about COVID YLL as a disease in and of itself.

Again we revisit 75% have two comorbidities and only 2% none.

What is the tie vote?. A common statistical practice is to use overall survival and the assault to the body which comes first is the culprit. Given only one thing to be labelled as reason for death, a patient riddled with metastatic breast cancer is first assumed to die of breast cancer and not the PE, or HAI, or COVID or other alphabet.

Also, we have to be very careful in how we provide editorial in conclusions of burden since we also know countries with poverty have a lower life expectancy than those more fortunate. The economic devastation, and job loss, is a great threat to YLL for our youthful of which most of these do not have secure academic positions

**Competing Interests:** Grandparent

Reader Comment 07 May 2020

**Wolfram Merzyn**, Private, Oberursel, Germany

Dear Prof. McAllister,

I have just looked through the WHO-Table for Years of Life Lost on which your study is based. It seems that this table does not fit actual data very well. For example, according to the WHO table an 81 year old can expect to live for 13.63 more years if we neglect any LTC issues. (Thus, she/he loses 13.63 years of life if dying at the age of 81 due to Covid 19.) The actual value for Germany, however, is not 13.63 years, but only about 8 years. (7.44 for men, 8.84 for women to be precise.) The numbers for Italy and Great Britain should be similar. Thus, it seems that taking the WHO table (instead of real world data on life expectancies) leads you to substantially overestimate the years of life lost due to Covid 19.

Yours truly,

Wolfram Merzyn

**Competing Interests:** No competing interests

Author Response 06 May 2020

**David McAllister**, University of Glasgow, Glasgow, UK

In response to Jason Bloomberg and David Bernstein.
Our work was a response to the assertion has been that “because those dying are older and have lots of comorbidity, they probably don't have to live”. I think JB and DB may be making a different statement that “notwithstanding the fact that the average life expectancy is still quite long among older people with comorbidity, those dying from COVID-19 are likely atypical compared to the average among older people with comorbidity”.

I think we are talking here about residual confounding, i.e., after you take into account the known/measured variables, are there remaining differences between patients on which we estimated life expectancy (the general community in Wales) and those dying of COVID-19 in the Italian data.

I think one has two options with residual confounding. Either to state this as an assumption/limitation and/or try and model it in some kind of sensitivity analysis.

Professor Andy Briggs effectively does the latter (https://avalonecon.com/estimating-qaly-losses-associated-with-deaths-in-hospital-covid-19/) looking at the effect of quite large multipliers on life expectancy, implemented via an excel tool. This would allow the commentators or others to explore the impact of different mortality rate ratios based on different assumptions as to the degree of residual confounding.

We have taken the former approach. As we are not aware of any empirical evidence to provide us with an estimate for the magnitude of the residual confounding due to unmeasured characteristics (e.g. frailty, functional limitation).

This is because, in order to make the assertion that those dying from COVID19 are atypical of their fellows who are similar in terms of age, sex and comorbidity we would argue that empirical evidence to support that claim is needed. Not least because, although we cannot know how strong they are, there may be selection pressures in the opposite direction. For example, someone with relatively mild COPD might go food shopping themselves, whereas someone with more severe disease might have someone else shop for them, thereby reducing their infection risk. Since the risk of death is the product of the risk of infection and the case fatality, this mechanism would tend to select for less severe COPD among those dying from COVID-19.

We argue that additional data, ideally on functional limitations (e.g. able to walk to shops, able to walk up stairs) and frailty measures (e.g. grip strength, lung capacity, six-minute walking distance) should be obtained to allow us to estimate the YLL more accurately using more empirical evidence.

Nonetheless, we think that this reasoning should not be applied to care home residents. Our results came out before the large numbers who were dying in care homes became apparent and this was not the focus of our work. Instead we agree that we should estimate mortality (and YLL) in care homes separately. Importantly, care home residents are a well-defined population so the task of estimating life expectancy in this group should be achievable in most settings.

**Competing Interests:** No competing interests were disclosed.
Reader Comment 03 May 2020

**Jason Blumberg**, Other, USA, USA

I'm perplexed by this study. How can it be assumed that the Covid victims would have lived the average life expectancy unless there's no or minimal standard deviation around that average? Wouldn't it be more compelling to compare to the minimum life expectancy of each cohort? Otherwise, you are implicitly assuming that the people who are dying are more or less representative of the average, which seems like a major assumption that, if untrue, would render your conclusions pretty useless. I hope I'm missing something here because it would seem far more intuitive to assume that people who are dying are the most vulnerable of their respective cohorts.

**Competing Interests:** None

---

Reader Comment 02 May 2020

**David Bernstein**, George Mason University, USA

I see you have partially addressed this already, but this was going to be my comment: Two people who are coded with the same disease could be in vastly different circumstances? We know the virus has taken a huge toll on nursing homes. An 82 year old with heart disease who lives in a nursing home is not similarly-situated, life expectancy-wise, to an 82 year old who is otherwise doing well and is self-sufficient. The former would assumedly be much more likely to succumb to Covid-19 than the latter. Similarly, "otherwise-healthy" people who succumb to Covid-19 can be expected to, on average, be more likely to have an undiagnosed health issue than those who don't. Is that taken into account? If neither of these are taken into account, the effect on life expectancy must be reduced.

Now, I see you've responded that this should NOT have a major effect on life expectancy. I don't see how you can be so confident. A *huge* percentage of deaths, wildly disproportionate, have been in nursing ("care") homes. This is an extremely unhealthy population. In the U.S., iirc, the average life expectancy for someone entering a nursing home is something like 18 months. You simply can't compare an otherwise healthy 82 year old with heart disease to someone whose heart disease so enfeebles him or her that they need to be in a nursing home.

**Competing Interests:** None.

---

Author Response 30 Apr 2020

**David McAllister**, University of Glasgow, Glasgow, UK

Thanks for your comment Martin Johnson. Please see this very rapid addendum we posted on our github repository which I think addresses your comments https://github.com/dmcalli2/covid19_yll_final/blob/master/Scripts/Addendum.md. We will rapidly incorporate these additions into an updated version of the official manuscript as soon as possible.
Competing Interests: No competing interests were disclosed.

Reader Comment 28 Apr 2020

Martin Johnson, , London, UK

Useful start to this important question, well done. Given the high correlation of morbidities with COVID-19 deaths (91% with an average of 2.7 pre-existing conditions UK ONS data to March) your conclusion only one-year reduction in YLL due to comorbidities does not feel correct and warrants further analysis. You list what I think is a critical factor to determine the impact of comorbidities, ‘did not have markers of underlying disease severity among those who died’ for example there is a huge difference in YLL for a patient with Stage 3 or 4 COPD vs Stage 1 or 2. Analysis of care home COVID-19 deaths may assist given that 50% of those coming into a care home die within 15 months BUPA homes only https://eprints.lse.ac.uk/33895/1/dp2769.pdf) both i) those coming to hospital with COVID-19 from a care home and COVID-19 deaths within a care home (although further complicated by ONS capturing both death directly from COVID_19 where COVID-19 or suspected COVID-19 was mentioned anywhere on the death certificate.

Your data set of 701 deaths in Italy is quite small with the rapid increase in UK deaths and the model established updating the model with a larger data set I believe has some urgency, although ONS together with Palantir should already have this analysis.

Competing Interests: None

Author Response 26 Apr 2020

David McAllister, University of Glasgow, Glasgow, UK

Davide please see reference 14. Their website is here https://www.epicentro.iss.it/. The authors of the report at listed at the foot of the link given in reference 14

Competing Interests: No competing interests were disclosed.

Reader Comment 25 Apr 2020

Davide DeiTos, Mine, Italy

Sorry, I am not able to find the source, site and organization of the data related death in Italy, Can you help me?

Many thanks
Davide

Competing Interests: No competing interests were disclosed.
Author Response 25 Apr 2020

David McAllister, University of Glasgow, Glasgow, UK

Thanks for these comments.
We agree with Chris Hope that among patients with long term conditions, those with more severe disease or greater frailty may be at higher risk of dying from COVID19. We have acknowledged this in the manuscript. However, we would be surprised if this had a large enough effect to result in a substantial decrement in life expectancy

Thank you to Per Stangeland for his question about the representativeness of the Italian data. According to the Istituto Superiore di Sanità (ISS) the report we based our analysis on defines deaths as "COVID-19 related deaths presented in this report are those occurring in patients who test positive for SARSCoV-2 RT by PCR, independently from pre-existing diseases" (see https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_26_marzo_eng.pdf).

Competing Interests: Author of paper.

Reader Comment 24 Apr 2020

Chris Hope, Doctor, Cambridge, UK

Am I right in thinking that the YLL for each condition, or combination, is taken from the average years of life that someone with that condition would have left? Have you considered that COVID-19 might be killing the weakest people with each condition, which would make your estimate too large, possibly greatly so.
Could you perform a check by asking a random sample of the doctors treating the patients to tell you how many YLL they think are appropriate for that individual patient?

Competing Interests: None

Reader Comment 23 Apr 2020

Per Stangeland, University of Malaga, Spain

I'm looking at the age distribution of your sample, from the attached Github file. I'm getting an average age of 81 for females, 77 for males. Is this correct?
Could you comment on how representative your sample is? There are reports of geriatric care patients who have not been included in the total death toll in Italy.

Competing Interests: No competing interests were disclosed.