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CORRESPONDENCE

# REVISED Years of life lost estimates cannot always be taken at face value: Response to "COVID-19 – exploring the implications of long-term condition type and extent of multimorbidity on years of life lost: a modelling study" [version 2; peer review: 2 approved, 1 approved with reservations]

Marius Rubo [iD][1], Peter Czuppon[2-4]

[1]Department of Psychology, University of Fribourg, Fribourg, 1700, Switzerland
[2]Institute of Ecology and Environmental Sciences, Sorbonne Université, Paris, 75252, France
[3]Centre Interdisciplinaire de Recherche en Biologie, Collège de France, Paris, 75005, France
[4]Institute for Evolution & Biodiversity, University Münster, 48149 Münster, Germany

## Abstract

In their recent analysis, Hanlon *et al*. estimated the years of life lost (YLL) in people who have died with COVID-19 by following and expanding on the WHO standard approach. We welcome this research as an attempt to draw a more accurate picture of the mortality burden of this disease which has been involved in the deaths of more than 300,000 people worldwide as of May 2020. However, we argue that obtained YLL estimates (13 years for men and 11 years for women) are interpreted in a misleading way. Even with the presented efforts to control for the role of multimorbidity in COVID-19 deaths, these estimates cannot be interpreted to imply "how long someone who died from COVID-19 might otherwise have been expected to live". By example we analyze the underlying problem which renders such an interpretation of YLL estimates impossible, and outline potential approaches to control for the problem.

## Keywords

COVID-19, Mortality Burden, Years of Life Lost, Data Selection Bias

**Open Peer Review**

**Approval Status** ✓ ? ✓

| | 1 | 2 | 3 |
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| **version 2** (revision) 13 Jan 2022 | ✓ view | | ✓ view |
| **version 1** 11 Jun 2020 | ✗ view | ? view | ? view |

1. **David A. Leon** [iD], London School of Hygiene and Tropical Medicine, London, UK

2. **Mohsen Mirzaei** [iD], Shahid Sadoughi University of Medical Sciences, Yazd, Iran

3. **Yijun Lou** [iD], Hong Kong Polytechnic University, Hong Kong, China

Any reports and responses or comments on the article can be found at the end of the article.
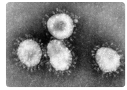
This article is included in the Coronavirus (COVID-19) collection.

**Corresponding author:** Marius Rubo (marius.rubo@unifr.ch)

**Author roles: Rubo M**: Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Czuppon P**: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Writing – Review & Editing

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## Introduction: The debate around COVID-19's mortality burden

Hanlon *et al.* (2020) motivate their modelling study with the observation that raw death counts can exaggerate the mortality burden of COVID-19 (by weighing equally the death of elderly people, whose life expectancy may only be several years, with those of younger people who might otherwise expect to continue to live for decades), while, on the other hand, some statements in the public media have likely underestimated the mortality burden (by simply emphasizing the proximity of age of death in people dying with COVID-19 to that of people dying in the general population, neglecting the fact that even people who have surpassed the average age of death can usually expect to continue to live for years). The authors then propose to calculate years of life lost (YLL) using WHO life tables as a means to express the "average number of years an individual would have been expected to live had they not died of a given cause".

## Years of life lost estimates elucidate in some situations, mislead in others

The attribution of YLL estimates to a person's cause of death is complicated by the fact that YLL estimates are always positive and were found to amount to 9–10 years in the general population (Marshall, 2010). This observation led Marshall (2010) to conclude that "if years of life lost per death is calculated to be about 9–10 years, it is not out of the ordinary and means that the age at death is congruent to the MLTW [Model Life Table West] age structure". For this reason, YLL estimates are often merely compared between diseases (e.g. Murray *et al.*, 2012) rather than interpreted directly (i.e., to imply how long someone who died might have been expected to live). Since Hanlon *et al.* (2020) aimed for an interpretation of YLL estimates at face value, we illustrate here using hypothetical examples how YLL estimates can be interpreted.

As an example where YLL estimates can be interpreted directly, consider a man who dies from a brain tumor at the age of 40. When we know that, in the specific country, men who have lived to the age of 40 will, on average, continue to live until 85, it seems fair to infer that the brain tumor has cost this person about 45 years of his life. More detailed analyses may additionally incorporate other variables from the deceased. If we know that he suffered from a long-term condition (LTC) such as Diabetes, we may specifically look for a reference group of other men from the same country matched on this variable and see how long they, on average, continued to live after they had reached the age of 40. This more accurate

estimate will typically not differ strongly from the original estimate as there are no common preconditions which very drastically reduce life expectancy of a 40-year-old to, say, as little as 10 years.

For an example where the calculation of YLL would be clearly misleading, consider a hypothetical town where a previously little-known exotic fruit named jackfruit gains popularity. If a scientist were to investigate the hypothesis that eating jackfruits is bad for people's health and results in premature deaths, she could collect data from all people who died in this town and were known to regularly eat this fruit, and compute YLL for each of them. For instance, when a person died aged 82, she reads from a life table that other people who lived to be 82 would then, on average, continue to live for another 8 years, and notes this value as YLL for the specific person. She obtains an average YLL estimate of 10 years for people who ate jackfruits and concludes that the fruit shortens people's lives.

The interpretation of YLL estimates should be reasonable in the case of the man who died of a brain cancer since we can assume that his death can be attributed to a specific cause. There should not be much uncertainty around this attribution, since 1) there is a clear and observable causal model of how brain tumors can end the life of a person regardless of other health parameters and 2) other natural and possibly unobserved or unknown causes of death at the age of 40 are so rare that they may reasonably be ruled out. By contrast, the scientist investigating the effect of jackfruits starts out with a (as we would argue) wrong assumption (that eating jackfruits leads to premature deaths), but this assumption is never corrected in the process of calculating YLL values. Note that defining the reference group ever more precisely will reduce, but never eliminate the problem. Even if people are matched on multiple variables (say, a hundred variables known to predict longevity), they would still be the youngest to die in their reference group.

While the cause of death assumed in the jackfruit example was not associated at all with the true cause of death (and serves here only to exemplify that even a wrongly assumed cause of death may be associated with substantial YLLs), there is wide agreement that COVID-19 does in fact play an important role in the deaths of people who die with COVID-19. At the same time, COVID-19 does not lead to a person's death in a virtually monocausal manner as it can be observed with brain tumors. Instead, as indicated in the older age and presence of pre-existing LTCs in people dying with COVID-19, the disease interacts with poor prior health in causing an individual's death. A somewhat similar relationship is seen in the often lethal effect of *Pneumocystis jirovecii* specifically in people with AIDS (Tellez *et al.*, 2008). To account for the role of interacting factors in causing the death of COVID-19 patients, Hanlon *et al.* (2020) therefore adjust their analysis for the number of LTCs, consequently observing a reduction in YLLs. Note that if reference groups were defined more narrowly (perhaps incorporating the type or severity of LTCs), YLL estimates can be expected to further decrease, but not increase: when people are grouped more precisely along risk factors,

the variance in their remaining lifetime shrinks (as its predictability increases), resulting in a smaller average difference in remaining lifetime for each dying person and other people who got to live at least as long.

## Interpreting YLL estimates

To avoid partially misattributing YLL estimates to an individual factor, when in fact a combination of factors led up to people's deaths, one could compare YLL estimates in a group of interest (people who died with COVID-19) with those in the general population. Applying the approach of Marshall (2010) to the life table of the WHO for Italy from 2016[1] results in 9.5 and 8 YLL for men and women, respectively. Subtracting these baseline YLL values from the uncorrected cause-specific YLL estimates found by Hanlon *et al.* (2020) we obtain 4.5 and 4 YLL for men and women, respectively (see GitHub and *Extended data* for scripts and data source (Czuppon & Rubo, 2020)). However, we would argue that subtracting such a YLL "baseline" from obtained YLL values could also be misleading in the case of COVID-19 where especially elderly people are seriously affected. Consider another hypothetical example here: if a serial killer were to specifically murder elderly people (say, above the mean age of death) and one subtracted such a YLL baseline from the victims' YLL values, one would obtain negative YLL estimates (which would, if interpreted at face value, indicate that being murdered by that serial killer prolongs one's life). We would argue that in this case, no correction to the obtained YLL values is needed as there is virtually no uncertainty around the cause of death (the murder mono-causally killed the victims, signifying that if it were not for the murder, the victims could be assumed to be representative for their reference groups). On the other hand, we would suggest subtracting 100% of the baseline from YLL values obtained in the jackfruit example as we would not attribute any causal effect here.

More generally, when YLL estimates are to be interpreted directly, we suggest to subtract a fraction of such a YLL baseline depending on the amount of uncertainty surrounding the cause of death (see also the literature about exposed YLL estimations, e.g. Hammitt *et al.* (2020)). The rationale behind causal attributions have been described in general by Cheng & Novick (1992) and Pearl (2009) and were investigated in the domain of epidemiology by Suzuki *et al.* (2012). Problematically, however, the data available to Hanlon *et al.* (2020) do not allow for a thorough analysis of causal links between COVID-19, other health factors and people's deaths. We therefore suggest to use obtained YLL estimates only for the purpose of comparing them with those in other studies and to avoid a direct interpretation, which would be misleading.

An alternative approach to investigate the burden of mortality due to COVID-19 is to compare monthly mortality curves normalized over the age classes from years prior to the pandemic to the excess in corresponding mortality curves as obtained since the beginning of the pandemic. Computing the average age at death for both curves can give a reasonable estimate in case we are sure that the difference is exclusively attributable to the ongoing pandemic (but not necessarily to COVID-19 in a direct manner). A similar approach has been proposed to estimate the excess in overall mortality due to COVID-19 (Leon *et al.*, 2020).

## Data availability
### Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

### Extended data
**Python scripts alongside all necessary data tables available at:** https://github.com/pczuppon/YLL_computation.

**Archived scripts at time of publication:** http://doi.org/10.5281/zenodo.3874662 (Czuppon & Rubo, 2020).

**License:** Creative Commons Attribution 4.0 International.

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[1] https://apps.who.int/gho/data/view.main.60800?lang=en (accessed 25/05/2020)

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**PubMed Abstract** | **Publisher Full Text**

# Open Peer Review

## Current Peer Review Status: ✓ ? ✓

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**Version 2**

Reviewer Report 24 February 2022

https://doi.org/10.21956/wellcomeopenres.19450.r48029

✓ **David A. Leon** [ID]

Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

The authors have revised their critique of Hanlon *et al.,* in response to reviewers' comments. Their piece is now shorter and somewhat clearer. The final paragraph of the revised critique is helpful as it more explicitly lays out than before an alternative to using YLL to estimate the mortality burden of COVID using instead excess some form of excess death.

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Epidemiology, excess deaths, demographic trends

**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.**

Reviewer Report 14 February 2022

https://doi.org/10.21956/wellcomeopenres.19450.r48030

✓ **Yijun Lou** [ID]

Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong, China

No further comments.

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Theoretical epidemiology and mathematical biology.

**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.**

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Version 1

Reviewer Report 11 June 2021

https://doi.org/10.21956/wellcomeopenres.17565.r44032

? **Yijun Lou** iD

Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong, China

Due to the complexity and multi-causality nature involved, it is challenging to measure YLL for a given disease in a heterogeneous population. The authors highlighted some wonderful constraints in measuring/interpreting this index.

Two examples in the section "Years of life lost estimates elucidate in some situations, mislead in others" would not be appropriate in the context of COVID-19. The first example is related to a specific individual (or a homogeneous population), while YLL is an index for the population of individuals with different characteristics and different age/death/disease distributions were used in the study by Hanlon *et al.*. The second jackfruits example is not applicable to the case for COVID-19 (which was also mentioned in page 4.)

The authors emphasied that "The interpretation of YLL estimates should be reasonable in the case of the man who died of a brain cancer since we can assume that his death can be mono-causally attributed to a specific cause." Although YLL estimates in Hanlon *et al*. measure the direct impact of COVID-19 deaths rather than the indirect impact of COVID-19-related outcomes., the terminology YLL itself would make sense in the multi-causality case, through direct and indirect effects (as discussed in Hanlon et al.).

In fact, the age distribution of COVID-19 deaths of COVID-19 and age model were employed in Hanlon *et al.* The hypothetical example of a serial killer may not give rise to a negative YLL value, as claimed in Page 5.

**Is the rationale for commenting on the previous publication clearly described?**
Yes

**Are any opinions stated well-argued, clear and cogent?**
Yes

**Are arguments sufficiently supported by evidence from the published literature or by new data and results?**

Yes

**Is the conclusion balanced and justified on the basis of the presented arguments?**

Partly

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Theoretical epidemiology and mathematical biology.

**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, however I have significant reservations, as outlined above.**

Reviewer Report 19 February 2021

https://doi.org/10.21956/wellcomeopenres.17565.r42434

**?**   **Mohsen Mirzaei** (ID)

Yazd Cardiovascular Research Center, Health monitoring research center, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

There are limitations mentioned by the authors for the index. This type of critique of the YLL index is correct. But it should be noted that this is not a new problem. The purpose of this index is to compare different diseases and societies. Therefore, with the same calculation method, comparison will not be a problem.

So the jackfruits example is not appropriate. For this critique, it would be better to cite an example - a disease that is more deadly in the elderly.

Another point mentioned in the text but not explained is that the elderly have underlying disease. This can cause comorbidity. Calculating the YLL according to the underlying disease can help to understand the authors' critique, because the estimates in YLL are based on the lack of underlying disease and this can distort the result. Overall; the indexing of this manuscript could draw the attention of others to future YLL corona calculations, and recommend that the authors write suggestions in manuscript editing so that future researchers can take the authors' advice more carefully in calculating the "Years of Life Lost" for diseases such as COVID-19. Suggest calculating a method that helps solve the problem in the calculation, not just express the problem.

**Is the rationale for commenting on the previous publication clearly described?**

Yes

**Are any opinions stated well-argued, clear and cogent?**
Partly

**Are arguments sufficiently supported by evidence from the published literature or by new data and results?**
Partly

**Is the conclusion balanced and justified on the basis of the presented arguments?**
Yes

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Public Health, Burden of disease, Non-Communicable disease epidemiology.

**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, however I have significant reservations, as outlined above.**

Reviewer Report 17 July 2020

https://doi.org/10.21956/wellcomeopenres.17565.r39187

✗

**David A. Leon** iD

Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

This commentary raises several questions about the use and interpretation of Years of Life Lost (YLL) that go beyond the specific paper by Hanlon *et al.* that the authors have focussed upon. The key issue is one that has already been discussed in several publications by RJ Marshall one of which is cited by Rubo & Czuppon. A more accessible paper by Marshall that makes the key relevant point was published in 2004.[1] Marshall points out the counter-intuitive result that YLL is substantial and positive even when calculated for the chosen reference or standard population used such as the Standard WHO lifetables used by Hanlon *et al.* in one part of their analysis. To calculate YLL in this situation you simply multiply the number of deaths from a cause of interest (or indeed all causes together) occurring in a defined age group by the conditional expectation of life at that age. This of necessity yields a number that is much higher than zero. Marshall does this for the Model Life Table West (MLTW) and shows that there is a crude YLL per death of around 9 years. For logical reasons, it cannot be zero. Importantly this means that the figure of 9 years cannot, therefore, be interpreted as showing that a population with a mortality structure of MLTW has an average age at death (per death) 9 years higher than itself! This is an unsatisfactory but

inescapable property of YLLs.

It is this paradox and limitation of YLL that must lead Rubo & Czuppon to take issue with the few places in Hanlon where they refer to a metric of "how long someone who died from COVID-19 might otherwise have been expected to live". Clearly YLL does not provide this metric when interpreted in absolute terms. However, comparing YLLs by age and according to number of long-term conditions as Hanlon *et al.* do is meaningful – showing that YLLs decline with the extent of comorbidity and age.

Rubo & Czuppon could have made this point in a simpler and more direct fashion. It is worth making given the original motivation of Hanlon *et al.* which was to counter claims that most people who die of COVID-19 in countries such as the UK are at an age and level of frailty that means their deaths would have been brought forward by only a small amount.

The commentary by Rubo & Czuppon however is difficult to follow. They return repeatedly to the notion of "uncertainty around the precise cause of death". While this cannot be disputed, I could not follow why this was an issue with respect to YLLs or their interpretation. This would need substantial clarification if it was to be retained in the commentary.

Overall the commentary would benefit from some light touch language editing and careful proofreading (there are a number of typos). It could also be substantially shortened.

**References**

1. Marshall RJ: Standard expected years of life lost as a measure of mortality: norms and reference to New Zealand data.*Aust N Z J Public Health*. 2004; **28** (5): 452-7 PubMed Abstract | Publisher Full Text

**Is the rationale for commenting on the previous publication clearly described?**

Partly

**Are any opinions stated well-argued, clear and cogent?**

Partly

**Are arguments sufficiently supported by evidence from the published literature or by new data and results?**

Partly

**Is the conclusion balanced and justified on the basis of the presented arguments?**

Partly

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Epidemiology, excess deaths, demographic trends

**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.**

Author Response 05 Aug 2020

**Marius Rubo**, University of Fribourg, Fribourg, Switzerland

We thank the reviewer for reading and reviewing our work.

We are pleased to read that the reviewer agrees with us that the YLL estimates obtained in the study by Hanlon et al. cannot be interpreted to imply "how long someone who died from COVID-19 might otherwise have been expected to live". The presence of this direct interpretation in the work by Hanlon et al. is the object of our criticism.

As the reviewer seems to agree with our main argumentation and conclusion, we are confused as to why he rated our work as not being "of an acceptable scientific standard". We would like to note that we do not consider our manuscript as a scientific research article but as a comment (or response) to the article published by Hanlon et al. (2020). As such, we do not emphasize adding new scientific insight into the methodology of YLL estimates, but focus on describing how caveats in the interpretation of YLLs refer to the study by Hanlon et al. which has been prominently cited in the public media.

Regarding our explanations of problems with YLL estimates, the most tangible objection to our commentary seems to be that the reviewer "could not follow why [the uncertainty around the precise cause of death] was an issue with respect to YLLs or their interpretation". In our commentary we argue that YLL estimates can be interpreted directly (or, in the reviewer's words, "in absolute terms") when the cause of death is fully known. In this sense, our objection to the direct interpretation of YLLs does not merely rest on an intrinsic property of YLLs (that they can never be zero), but rather on the missing causal modelling of factors that led to people's deaths and which would allow for an interpretation in absolute terms.

The reviewer mentions that the misleading direct interpretation of YLL estimates is present in "few places in Hanlon". In fact, we only counted one instance where this direct interpretation is explicitly present. However, note that this misleading interpretation is already being cited in several academic works (e.g. Pearce, Lawlor & Brickley, 2020), and, following Hanlon et al.'s press release (which also contains the direct interpretation) has become the dominant theme in many of the more than 100 news reports citing the study. This is why we suggested to correct this (and only this) point in the manuscript by Hanlon et al. (2020) and to transparently discuss the interpretability of the results.

Pearce, N., Lawlor, D. A., & Brickley, E. B. (2020). Comparisons between countries are essential for the control of COVID-19. *International Journal of Epidemiology.*

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

# Comments on this article

**Version 1**

Author Response 29 Jun 2020

**Marius Rubo**, University of Fribourg, Fribourg, Switzerland

Reply to Karl Ulrich Gutschke:

We thank Mr. Gutschke for his comment. We agree that the interactions between different preconditions and COVID-19 in causing an infected person's death need to be better understood before we can estimate how long the deceased might have otherwise lived. However, we would argue that a comparative use of YLL estimates (where obtained values are compared between diseases, not interpreted at face value) are quite informative even at the present stage.
We furthermore agree that autopsies may help to better understand the cause of death in people who died with COVID-19. We would, however, argue that even autopsies do not allow to construct a complete causal model of death (which would be needed to allocate fractions of the YLL estimate to individual factors). For example, Elezkurtaj et al. (2020) describe autopsy findings from 26 people who died with COVID-19 and conclude that "causes of death were directly related to COVID-19 in the majority of decedents". This study shows that COVID-19 is unequivocally involved in the deaths of the majority of these 26 people. At the same time, knowing that COVID-19 is usually harmless in people at good health and unfolds its deadly potential mostly in people in a comparatively bad state of health, the state of health must be seen as part of the causation in these people's death. This also gives us another way of describing why a direct interpretation of YLL estimates is misleading here: If there is a robust correlation between the state of health and the risk of dying with COVID-19 *between* different reference groups, it is difficult to justify the assumption that no such correlation exists *within* these reference groups (thus, the information value of comparing a deceased with other people from the reference group who lived at least as long is partly unclear).

Kind regards,
Marius Rubo and Peter Czuppon


Elezkurtaj, S., Greuel, S., Ihlow, J., Michaelis, E., Bischoff, P., Kunze, C. A., ... & Miller, F. (2020). Causes of Death and Comorbidities in Patients with COVID-19. medRxiv.

***Competing Interests:*** none




Author Response 26 Jun 2020

**Marius Rubo**, University of Fribourg, Fribourg, Switzerland

Reply to Hanlon et al.:

We thank Hanlon et al. for their reply to our commentary to their study. We agree with most of their remarks, but do not think that they rebutted our criticism. Since we feel that their response bypasses the core of our commentary, we attempt here to clarify possible misunderstandings.

The central object of our criticism is not the use of YLL calculations per se, but the interpretation of

resulting estimates at face value. We reiterate here that, as we argue, the interpretation of YLL estimates as "how long someone who died from COVID-19 might otherwise have been expected to live" is misleading. Such a direct interpretation is not hindered by the uncertainty around these estimates, but by the presence of a selection bias which unidirectionally inflates these values relative to values that could be interpreted in a direct sense. This selection bias is not just another possible confound which may or may not be affirmed with additional data. Instead, if one accepts the fact that COVID-19 does not kill people in a monocausal manner (as Hanlon et al. do), we argue that the existence of this selection bias can be inferred logically. We do not claim the discovery of this problem to ourselves, but referenced the work of other authors who have touched upon it before (e.g. Marshall, 2010). The problem is not specific to COVID-19 but exists with other diseases as well (especially when people die at an older age) and likely explains why many authors avoid such a direct interpretation of YLL estimates (e.g. Nichols et al., 2019).

Before we go into more detail about the interpretation of YLL estimates, we would like to emphasize that we agree with Hanlon et al. about the utility of YLL estimates and their newer derivates like QALY and DALY. We also agree that "age-conditional life expectancies are higher than unconditional life expectancies" (a conceptual basis of YLL calculation to which we made a passing reference in our introduction ourselves), and also noticed the presence of what Hanlon et al. describe as an "unconditional life expectancy fallacy" in several public statements. Moreover, we agree that "multiple causes are the norm rather than the exception in human mortality", an idea which is also expressed in Rothman's sufficient-cause model (Rothman, Greenland & Lash, 2008). Lastly, we readily admit that excess rates have their own methodological problems and should not entirely replace YLL estimates.

### Direct versus comparative interpretation of YLL estimates

We disagree with Hanlon et al. about the interpretation of the results of these YLL calculations in situations where the cause of death is not fully known. We do not assert that YLL estimates should not be used when an assumed cause of death may not be the sole cause of death. In our view, YLL estimates can be used in these situations, but to quantify the *comparative* burden of disease. To clarify what we mean by "direct" (or "at face value") and "comparative", we give a brief example. Assuming that a risk factor A is associated with YLL estimates of 12 years, then a direct interpretation of this value would be to say "people who died while having risk factor A would, on average, have been expected to live for another 12 years had they not had the risk factor". We used the hypothetical jackfruit example to show that this interpretation is only sensible if one can be sure that risk factor A really is *the* cause of death. This is because there is a baseline of YLL estimates (which is obtained when assuming a random or completely wrong cause of death) which is not 0 years, but, as we compute, 8 years for women and 9.5 years for men (applying the 2016 WHO table for Italy). We argued in our commentary that when a wrong assumption about a cause of death results in the statistical mirage we observe here, then a *partly* wrong assumption about a cause of death will be *partly* inflated. By contrast, if another risk factor B was associated with YLL estimates of 14 years, a comparative use of YLL estimates would be to say "Risk factor B is associated with a larger burden of mortality compared to risk factor A". In our view, this interpretation is usually justified and useful even when there is some uncertainty around the true cause of death.

### Uncertainty around the cause of death means selecting partly on the mere grounds of

**having died**
A direct interpretation of YLL values obtained in Hanlon et al.'s study would therefore be correct if we could be sure that deaths in patients suffering from COVID-19 were caused only by COVID-19. However, reading Hanlon et al.'s reply, we assume that they – like us – do not assume a monocausal relationship in this context. We reiterate here that, when the cause of death is partly unknown, people selected for a YLL analysis are selected partly on the mere grounds of having died rather than on the grounds of having died from the assumed cause (this problem is what we described as a *data selection bias*), and resulting YLL estimates are partly composed of what we call the YLL baseline (which cannot be interpreted in a meaningful way).

The reason why we argue this problem to be mitigated in the context of people who died at a younger age while carrying a risk factor is that in younger age, each death stands at a starker contrast against the relative absence of deaths in the reference group, allowing for a stronger causal attribution of a death to the risk factor. It is true that a wrong cause of death attribution may occur at younger age as well and would even more strongly add to inflated YLL estimates (we read from the 2016 WHO table for Italy that, averaged between men and women, people dying between 40 and 44 add almost 5 times as many YLLs to the statistics as people dying between 80 and 84). At the same time, death at younger age is so rare (reading from the same table, we find the risk of dying within the next 5 years to increase 56-fold between these age categories) that wrong or partly wrong cause of death attributions in people dying with a specific risk factor will, in sum, play a smaller role in younger people compared to older people. We think that our commentary should be more explicit about this context and will likely revise this part in the next version depending on the reviewers' comments.

The existence of a bias in selecting deceased people for a specific YLL analysis is not to say that mechanisms leading to an infection with COVID-19 cannot, in principle, point in the opposite direction (i.e. disproportionately affect the healthiest, rather than the least healthy, within specific reference groups). Hanlon et al. offer a plausible speculation in this regard ("It is possible, for example, that people with severe chronic obstructive pulmonary disease are more likely to choose to self-isolate than people with mild chronic obstructive pulmonary disease."). We agree, but would like to note that 1. this speculation requires empirical backup (a note which does not contradict Hanlon et al.'s comment) and 2. such effects are independent from the selection bias we deduced logically and which does not require any additional empirical data (see also the discussion in Section 3 in Marshall, 2010). We would argue that it is not valid to interpret estimates in a way which is known to be analytically biased in a specific direction and then justify this decision with speculations on possible empirical biases pointing in a different direction.

To sum up, we welcome the study conducted by Hanlon et al., which contributes to better describe the mortality burden of COVID-19 in comparison to other diseases and risk factors. However, we stress again that resulting estimates should not be taken to imply how long someone who died with COVID-19 might otherwise have been expected to live. At the same time, note that the presence of such a direct interpretation is our only objection to the work of Hanlon et al., and we do not object the comparisons of YLL estimates with those of other diseases (like ischemic heart disease and chronic obstructive pulmonary disease) or the general procedure of obtaining YLL estimates.

Kind regards,
Marius Rubo and Peter Czuppon

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***Competing Interests:*** none

Reader Comment 17 Jun 2020

**Karl Ulrich Gutschke**, private, Hildesheim, Germany

With the nice jackfruit example, Rubo and Czuppon vividly show which fatal mistakes can be made if the condition of monocausality in the case of deaths from the coronavirus is waived. Except in cases where Covid-19 disease is the sole cause of death, the years of life lost cannot be calculated in the same way as Hanlon et al. did it here.
As Hanlon admits, in most cases there are multiple causes of death, one of which is Covid-19. The possibly very complicated interaction of the factors leading to death would *first have to be researched*, as the German professor Püschel did with his autopsies in Hamburg, *before calculating the YLL.*
This means that the results of the study are not applicable to most corona deaths. In addition, as Hanlon suspects, the study results cannot be applied to deaths in care home residents. The latter roughly make up about half of all corona deaths.
Because these two limitations are not explicitly mentioned in the study, it leads to considerable misunderstandings in the public discussion about the dangerousness of Covid-19.

***Competing Interests:*** none

Reader Comment 11 Jun 2020

**Peter Hanlon**, University of Glasgow, Institute for Health and Wellbeing, Glasgow, UK

We thank Drs Rubo and Zuppon for their detailed commentary on our recent paper, and for courteously providing us with a copy of their manuscript prior to publication which allowed us time

to read and respond.

We hope that we have faithfully characterised their statements in these responses, which we have enumerated below.

**Years of life lost is "neither simple to compute nor to comprehend"**
We read the Gardner and Sandborn paper (1990) from which the authors obtained the criticism of years of life lost that it is "neither simple to compute nor to comprehend". Fortunately, however, the criticisms of YLL in the 1990 paper – of inconsistencies in the method for calculating YLL, differences in ages for cut-offs and in weights to different ages – have been rendered obsolete by advances in the field. In the two major fields where YLL (and related but more abstracted measures such as DALYs and QALYS) in which YLL is most commonly used – disease burden estimation and health economics - are now highly mature. Consequently, methods for calculating YLL, and the interpretation of the outputs of such calculations are now well established ( https://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf).

An important question to address after stating that YLL is 'neither simple to compute nor to comprehend' is 'compared to what?' A common error of comprehension we have seen has been to look at the average age of death (period life expectancy) in a population, and the average age of death among suspected/confirmed COVID-19 cases, and to assume that this difference represents the years (or months) of life lost due to COVID-19. This simple interpretation has led to back-of-the-envelope estimates that the YLL from each of these deaths could be 'just a few months' and thus that the Lockdown measures implemented across much of the world are grossly disproportionate. This interpretation is a fallacy because period life expectancies (at birth) are *unconditional*, including the forces of mortality at all ages in a given year. Instead, understanding the mortality impact of COVID-19 requires careful reasoning about *conditional* life expectancies, reasoning about distribution of additional years subpopulations can be expected to live conditional on having already reached a given age ('x') but not having been exposed to COVID-19. The reason for this is simple: a person who has reached the age of (say) 60 is no longer at risk of dying at age 59 or younger; these mortality hurdles have already been cleared. It is for this reason that age-conditional life expectancies are higher than unconditional life expectancies, often by margins that may surprise casual analysts and observers.

Note in the above the concept of YLL was implicitly accepted, and indeed used as a core plank in the argument that the Lockdown responses have been disproportionate. This gives weight to the argument that YLLs are fairly intuitive and easy to comprehend, even if not quite as simple to compute, largely given the unconditional life expectancy fallacy outlined above. However, even this issue is fairly easy to address through the use of conditional rather than unconditional lifetables. These lifetables can be conditioned not just on age, but other demographic attributes, as well as lifestyle risk factors, and as well as comorbidities. Given we know that persons who contracted COVID-19 and then died in hospitals in Italy had a known range of existing comorbidies and ages, this could be presented as it was calculated, as a series of individual distributions from conditional lifetables. However we hope you agree that presenting each lifetable separately would be uninformative, and so a reasonable and intuitive summary measure should be used instead. This summary measure is the YLL, which we present with credible intervals rather than a simple point estimate.

**YLL cannot be used in COVID-19 because COVID-19 may not have been the sole, or in the commentator's term "mono" cause of death**
We of course agree that where a person dies from a different cause of death, even where they died having tested positive for SARS-CoV2, the YLL should not be attributed to COVID-19.
Indeed, we have already argued that mortality rates taken from (multimorbid) general population samples should not be used to estimate YLL deaths in care home residents on the grounds that this group are known to have a much shorter life expectancy than the general population ( https://github.com/dmcalli2/covid19_yll_final/blob/master/Scripts/Addendum.md). These comments highlight an additional reason not to use this method to estimate YLL in care home residents. Deaths in care homes with COVID-19 are likely to be misclassified and many deaths may not be due to COVID-19. Of course, equally, and especially early during the pandemic, deaths due to COVID-19 may have been incorrectly attributed to other causes of death such as influenza, unspecified pneumonia and cardiovascular disease.

On the other hand, in patients admitted to hospital, where testing and imaging are widely available, there is much more confidence that deaths occurring within 28 days of a positive test (a commonly used definition) are caused by COVID-19.

In a broader criticism of the use of YLL, the commentators also seem to argue, and we apologise if we misunderstood, that YLL is only valid where a single cause of death can be identified. The disease, to use their term, should be mono-causal. However, multiple causes are the norm rather than the exception in human mortality, as reflected in the WHO "International Form of Medical Certificate of Cause of Death" (https://apps.who.int/iris/handle/10665/40557). Consequently, the best established models of causation in epidemiology are multi-causal, such as Rothman's sufficient-cause model (Modern Epidemiology, Third Edition pp 8-9). Indeed, few causes of death could meet the requirement for mono-causality, and YLL could certainly never be calculated for long-term conditions, let alone for infectious diseases if this argument was accepted.

**YLL is only salient for causes of death which occur at younger ages**
We do not follow the reasoning that YLL is "much less salient when the average age of death in a particular group is clearly smaller compared to the age of death in the general population". Firstly, we are not clear what the commentators mean when they refer to *the* age of death. Secondly, this argument undermines itself because it relies on a calculation (albeit an informal one) of YLL. If someone who is expected to die many years after their age at death (i.e. if they have a substantial YLL) it is useful to calculate YLL, otherwise not. Finally, this advice against calculating YLL for diseases which cause death in older people is inconsistent with established practice in both health technology assessments and global burden of disease estimation. In both disciplines YLL (and the related QALY measure) are frequently calculated for conditions which mostly cause death in older people. For a stark example please see the GBD study of dementia and recent NICE assessment of dementia drugs ( https://www.nice.org.uk/guidance/ta217/chapter/4-Evidence-and-interpretation and https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30403-4/fulltext).

**Excess deaths produce better estimates of the number of COVID-19 deaths than do reported deaths**
We agree that calculating the excess deaths (i.e. comparing the deaths historically to current

deaths) is a useful way of estimating deaths due to infectious diseases. Unlike seasonal influenza, however, COVID-19 has been accompanied by radical changes across society which themselves are likely to impact on mortality. Measures of excess deaths will conflate the direct effect and indirect effects of COVID-19 and can therefore be of little help to policy-makers seeking to make policy choices. We outlined the need to make such choices in the second paragraph of our introduction "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"

**Residual confounding causes biased estimates of YLL**
In the presence of any residual confounding – due to imperfect information, model misspecification etc., the authors argue that measures of YLL are intrinsically biased towards larger effects. In principle we do not think that this is true. If a cause of death is associated with factors which reduce the risk of competing causes of mortality, failure to account for these will under-estimate life expectancy. Even for COVID-19 it is not difficult to think of an example where this may be the case. It is possible, for example, that people with severe chronic obstructive pulmonary disease are more likely to choose to self-isolate than people with mild chronic obstructive pulmonary disease. Estimating life expectancy, as we did, for unselected people with COPD would, to the extent that this phenomenon occurs, under-estimate years of life lost.

Nevertheless, we are willing to concede – as we did in the original manuscript - that residual confounding may on average cause an overestimation of YLL. We stated:

*"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[28]. 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**" [emphasis new for this response].*

Nonetheless, residual confounding, or at least uncertainty around residual confounding, is inevitable outside of a very narrow range of study designs (i.e. those that contain an element of randomisation) and it is not clear how such residual confounding should be addressed. It is of course possible to apply a rate ratio for the magnitude of some hypothetical confounders (or from residual confounding due to measurement error) which will attenuate the YLL. Indeed, anyone is free to do so using the publicly available data and code (https://github.com/dmcalli2/covid19_yll_final/). However, we are not aware of any source of information to inform either the magnitude or uncertainty around such a multiplier. Without such information, an analyst can obtain any YLL they wish by choosing a rate ratio of sufficient magnitude.

Rather, we would argue, as we did in the manuscript, that each public health agency should use the best available data for estimating YLL in COVID-19 in order to support policy making. *"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".*

Finally, on the point of residual confounding, the crucial policy decision around COVID-19 concerns the direct and indirect effects of the pandemic. To support such decision-making the YLL arising from directly attributable causes (e.g. pneumonia death) can therefore be compared with those arising from indirect causes (e.g. delayed cancer therapy). The commentator's concerns about the tendency of residual confounding to increase YLL would surely apply similarly to both the direct and indirect effects. This is especially likely to be true for this policy comparison since older people with comorbid diseases are most susceptible to both the direct and indirect effects of COVID-19.

**The conclusions were rushed**
The commentators quoted our manuscript in order to offer an excuse on our behalf for what in their view was "rushed conclusions" and "misleading information". We were quoted as stating that the study was "conducted rapidly and under pressure of time".

These words did appear in the manuscript, but in the following, rather different, context:

*"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."*

As we hope is clear from the above, the effect of the time pressures was to limit our access to data, not to limit our efforts to draw measured conclusions.

Peter Hanlon (on behalf of the co-authors)

***Competing Interests:*** Author of the article to which this commentary refers.