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 1; peer review: awaiting peer review]

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Abstract
In their recent analysis, Hanlon et al. set out to estimate 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 of data selection bias which, in the context of COVID-19, 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

This article is included in the Coronavirus (COVID-19) collection.
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Author roles: Rubo M: Conceptualization, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; Czuppon P: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: As a Correspondence to an article published on Wellcome Open Research, The Wellcome Trust covered the article processing charge for this article; however, the Wellcome Trust was not involved in funding this work. This work has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement PolyPath 844369 (PC).

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How to cite this article: Rubo M and Czuppon P. 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 1; peer review: awaiting peer review] Wellcome Open Research 2020, 5:137
https://doi.org/10.12688/wellcomeopenres.16015.1

First published: 11 Jun 2020, 5:137 https://doi.org/10.12688/wellcomeopenres.16015.1
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 to more accurately describe the burden of mortality. In introducing this approach, the authors start with the correct assumption that “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”. While this idea may seem immediately intuitive, “it is neither simple to compute nor to comprehend” (Gardner & Sanborn, 1990, p. 328). Reckoning that, outside of idealized models, the cause of death is only ever given within degrees of uncertainty, we will argue here that YLL estimates can be taken at face value only if a) there exists a causal model which allows to precisely describe the interaction of factors which led to a person’s death (and not only the fact that a factor of interest is unequivocally involved) or b) the age of death in the population of interest is much smaller than the age of death in the general population. Neither of these enabling conditions are given in the context of COVID-19.

Years of life lost estimates elucidate in some situations, mislead in others
The goal of this comment is to develop a qualitative, conceptual understanding of why the interpretation of YLL estimates rests on specific preconditions and why they are not met in the case of COVID-19. For this purpose, we will first introduce two hypothetical examples, one where the interpretation of YLL estimates is clearly correct and one where it is clearly misleading.

An example where the interpretation of YLL estimates would be correct could be that of 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 exercised regularly, did not smoke but suffered from some long-term conditions (LTCs) such as Diabetes, we may specifically look for a reference group of other men from the same country matched on these variables and see how long they, on average, continued to live after they had reached the age of 40. This more accurate comparison will give us an even better estimate of the YLL in the specific case, but no matter how many variables we include when defining a reference group, it 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 also refines the model by restricting the reference group along a variety of health-related variables, but still obtains positive YLL values (she necessarily does, because she still compares each person with other people who lived at least as long (Bonneux, 2002; Marshall, 2010)) and considers the hypothesis proven.

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. 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. The lesson here is that you have to get the cause of death right prior to performing a YLL calculation. Note that defining the reference group ever more precisely will reduce, but never eliminate the problem that cases are selected based on the mere fact that they have died rather than on the fact that they have died of a specific given cause. Even if people who died after regularly eating jackfruits are compared against others who are matched on an abundance of variables (say, a hundred variables known to predict longevity), they would still be the youngest to die in their reference group. It is because of this selection bias that the individuals in a YLL analysis, where the assumed cause of death is incorrect or not entirely correct, can never be representative of their reference group.

Any uncertainty around the cause of death inflates years of life lost estimates
We have seen that YLL estimates can provide a reasonable and intuitive measure for how many years a person has lost due to a specific cause of death, but that these estimates can also be wildly misleading when applied regardless of their constraints. Next, we intend to outline how well the situation surrounding COVID-19 may fit the constraints needed to obtain meaningfully interpretable YLL estimates.
While the cause of death assumed for the YLL analysis in the jackfruit example was not associated at all with the true cause of death, there is wide agreement that COVID-19 does in fact play an important role in the deaths of people who die while suffering from COVID-19. Crucially, however, this observation is not identical with the assumption that COVID-19 was the cause of death. Hanlon et al. (2020) themselves acknowledged that “people dying from COVID-19 are predominantly older and have pre-existing LTCs” (citing, among others, Zhou et al. (2020)), but did not acknowledge that this observation must be integrated not only in how reference groups in a YLL analysis are defined, but also in how the cause of death itself is defined. In the presence of such moderating or additive effects with other variables, the cause of death must be viewed as a combination of COVID-19 with other preconditions. Crucially, as the assumed cause of death in this YLL analysis (people were mono-causally killed by COVID-19) partly misses the true cause of death (COVID-19, together with other known and unknown preconditions, led to people’s death), people in this analysis are also selected partly on the mere grounds of having died rather than on the grounds of having died from COVID-19. As we have seen, selecting cases on the mere grounds of having died rather than of having died from a given cause has one specific effect: it unidirectionally inflates resulting YLL values. This observation may seem counter-intuitive considering that in many applications of statistics, adding uncertainty to an underlying variable will increase the uncertainty around resulting estimates, but will often not bias estimates in a specific direction. The situation is different here. Knowing that we cannot precisely predict the death of people suffering from COVID-19 even when employing all available data on sex, age and LTCs (a remark which would seem trivial in most other contexts), we must infer that there exists residual and/or unmeasured confounding (Fewell et al., 2007) which has additionally contributed to the fact that these individuals were the first to die within their reference group (in other words, the effect of these unknown confounds must have had a life-shortening rather than a life-extending effect on these individuals, relative to their reference group).

Since it is quite common that the cause of death of a person is not perfectly known, one may ask why YLLs are used in epidemiology at all. Firstly, the problem of a selection bias resulting from uncertain causes of death is existent, but 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. If a disease frequently kills 40-year-old individuals, the underlying mechanism that leads to the death may of course also incorporate an interaction of the disease with other (partly unknown) preconditions. However, since a combination of any such preconditions with any other diseases (be they known or unknown) only very rarely leads to a death among this age group, the cause of death can be more strongly attributed to the disease even in the absence of a precise causal model. The rationale behind such 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). We assume that Gardner & Sanborn (1990) – whom Hanlon et al. (2020) cite – do not themselves elaborate on this topic since they noted that YLL “has been promoted to emphasize specific causes of death affecting younger age groups”. Secondly, several publications have employed YLL estimates not with the goal of interpreting them directly, but rather to compare them between different diseases (e.g. Murray et al., 2012). This application (which we would deem valid given the amount of uncertainty around each disease’s role in people’s death is comparable) is present in the Hanlon et al. (2020) study, too. Here, however, the authors furthermore interpret YLL estimates directly, which is the object of our criticism.

Considering that the uncertainty surrounding the exact cause of death in patients who died with COVID-19 is well-documented (simply by our inability to precisely predict who will die while suffering from COVID-19 and who will not), and further considering that any deviation of the assumed cause of death from the true cause of death leads to a selection bias in the context of a YLL analysis (especially when people of interest died at an older age), we were perplexed to read that the authors treated those dying from COVID-19 as representative of their reference group. While the authors acknowledged that they “did not have markers of underlying disease severity among those who died” and that they “had no data for rarer severe LTCs”, they nonetheless asserted that “this effect is unlikely to be substantial enough to reduce YLL to the orders of magnitude suggested by some commentators.” The authors furthermore stated during the open review process that “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”. As we have seen above, those who died with COVID-19 are a priori atypical of their fellows to the extent that their cause of death is uncertain. The authors’ efforts in defining reference groups as narrowly as possible by including LTCs may reduce, but can never eliminate this fundamental problem.

Other ways to deal with this irresolvable problem

In our view, a more meaningful approach to investigating the burden of mortality due to COVID-19 is to compare monthly mortality curves normalized over the age classes from the last decade to the excess in corresponding mortality curves as obtained since the beginning of the pandemic. Computing the average age of death for both curves will 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 mono-causal manner). A similar approach has been proposed to estimate the excess in overall mortality due to COVID-19 (Leon et al., 2020). Admittedly though, data of this type are rarely accessible.

If one wishes to continue using YLL estimates in the context of COVID-19 and interpret them directly (which we think appears tempting when the boundary conditions for a direct interpretability are met), we suggest correcting for the uncertainty surrounding the exact cause of death. Marshall (2010) estimated YLL values for the general population (when no cause of death is specifically assumed – an assumption which is functionally equivalent to assuming a random cause of death) to be around 9–10 years and proposed for YLL estimates concerning...
specified causes of death 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 age structure” (p. 407). Applying this approach to the life table of the WHO for Italy from 2016 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 would not yield fair estimates in the case of COVID-19 either since it seems that with this disease, 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 cannot reasonably attribute any causal effect here. More generally, we would suggest correcting for a possible data collection bias by subtracting 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)). Note that using such an approach, the correctness of YLL estimates would now hinge on the correctness of uncertainty estimates regarding the cause of death – a precondition which we consider irresolvable. However, since such an estimation of uncertainty could both under- and overestimate the true value, this approach would at least eliminate a unidirectional bias which can only ever inflate YLL estimates.

It has been shown in a variety of cases that standard measures in epidemiology can be, and are, frequently used in misleading ways, even by medical experts (Gigerenzer et al., 2007). We argue that this is also true for the study by Hanlon et al. (2020). By not properly accounting for the uncertainty around the precise cause of death, the study is unprotected against a bias in data selection, leading to YLL estimates which must be considered inflated if one interprets them directly, as the authors do. The authors themselves noted that their study was “conducted rapidly and under pressure of time”. In our personal view, these circumstances may explain rushed conclusions, and we express respect to the huge effort that was taken under these circumstances. Nonetheless, we suggest to revise the interpretation of the data at hand and to prevent misleading information from further spreading into the public.

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.


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References


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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](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](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](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](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 – 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”. 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.