PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The COVID-19 mortality effects of underlying health conditions in India: a modelling study
AUTHORS	Novosad, Paul; Jain, Radhika; Campion, Alison; Asher, Sam

VERSION 1 – REVIEW

REVIEWER	Paddy Ssentongo, MD, MPH Penn State University
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	Summary The manuscript by Novosad et al. " The COVID-19 mortality effects of underlying health conditions in India: a modeling study" explores multimorbidity impact on the mortality from COVID-19 among age-specific populations in India, a lower-middle-income country (LMIC), contrasting them with England, a high-income country (HIC) General comment: Strength The study's major strength is the use of the recent District Level Household Survey-4 and Annual Health Survey data for India, which are nationally representative surveys. Second, the topic is of enormous interest during the COVID-19 pandemic as India, like many other low -and -middle-income economies, transitions from the burden of infectious diseases that of chronic diseases such as hypertension and diabetes. Weakness The ecology study design is subject to ecological fallacy, making the interpretation of the findings limited. Nevertheless, the study adds to the growing body of literature, the contributing factors to the COVID-19 mortalities in low- and middle- income economies. Finally, authors should avoid derogatory phrases such as "poor" and use global health and culturally appropriate phrases such as "low- and middle-income countries" and "high-income countries" throughout the manuscript. Specific comments: Abstract: Line 19-21: Authors should explicitly indicate that data was aggregated. Although the participants used for the exposure of interest (country-specific prevalence of comorbidities) are given, the

	data source for the outcome (India mortality rates due to COVID-19) is missing. Authors should provide the source of COVID-19 deaths, or should clarify the outcome of interest. Line 24-27: The authors should change the primary outcome from 'the proportional increased to age-specific mortality" to "age-specific mortality" Line 30-36: Authors should avoid using causal words such as "increased" or "reduced" but rather substitute with "higher" or "lower" respectively. In addition, comorbidity cannot "reduce" mortality. Suggested phrase: "Comorbidities were associated with a lower risk of mortality in India compared to England". Strengths and limitations of this study Line 6-8: Please replace "lower-income" with "lower-middle-income country" Line 13-14" Please replace "overstate" with "overestimates" Line 13-15: The authors should clarify what they mean by the "largest analysis "to date. The authors should provide the sample size used to make this claim. Line 20-24: This point is rather confusing because data on HIV/AIDS, malnutrition, and other comorbidities specific to low- and middle- income countries exist. Why didn't the authors explore their effects on the association between COVID-19 and mortality? Does the limitation point imply that the author did not report these associations are the data is not available? Introduction: Line 16-17: It is not clear what the author means by "underlying population health". Please rephrase. Methods: The authors state that OpenSAFELY was the source of RR for the COVID-19 mortality for England. However, it's not clear the source of COVID-19 mortality data for India. Please clarify this. The authors should clarify whether or not they had access to the individual-level data from District Level Household Survey-4 and Annual Health Survey, and had to aggregate the comorbidities by age groups. Results: Figure 2: Y-axis typo in population health. In addition, the current title for the Y-axis is confusing. Consider changing to "RR of COVID-19 mortality". Unless you are implying the risk of having comorbidity as opposed to the risk of death. Figure 2 caption and legend: change health conditions to "comorbidities" Figure 3 caption and legend: "conditions" to comorbidities"

	The age categorization used here provided by the District Level Household Survey-4 and Annual Health Survey data? If not, the authors should state how they recategorized age. As suggested above, avoid using causal language through the manuscript. Replace “increase” by associated with “higher” etc.

REVIEWER	Manas Pratim Roy Ministry of Health and Family Welfare, New Delhi, India
REVIEW RETURNED	11-Sep-2020

GENERAL COMMENTS	Well written article. Please mention the source of DLHS data for obesity in males. The reports available indicate BMI only in females. From Table 2, hypertension seems to be a protective factor. Explanation might be added. Relative risk for uncontrolled hypertension is 1.94 in Table and 1.95 in Text. Discussion may be elaborated further, with findings from other countries.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. “The ecology study design is subject to ecological fallacy, making the interpretation of the ndings limited.

We agree that there are limitations to the interpretation of our ndings. Because we do not have access to complete patient-level data from India and England, we perform an exercise with the population data available to determine if di erent distributions of comorbidities in England and India can explain the discrepancy in the age distribution of COVID-19 fatalities between the two countries. One major assumption we are forced to make without patient-level data is that the relative risk of each comorbidity is independent of other comorbidities. In reality, it is possible that there are signi cant interactions between comorbidities such that a patient with high blood pressure and diabetes is at much greater risk than the simple combination of each of those independent risk factors. However even with the limitations, we can say that we nd no evidence that comorbidities alone can explain why a larger share of India’s COVID-19 deaths are people under 60 relative to England.

2. Clarify that the DLHS and AHS data was aggregated from the individual level.

In the methods section, we have clari ed that we accessed DLHS and AHS data at the individual level and then aggregated to the national level. We include a detailed accounting of this aggregation along with an explanation of how we de ned each health condition from the biomarker data reported in the Indian surveys in the Appendix.

3. “Line 30-36: Authors should avoid using causal words such as "increased" or “reduced” but rather substitute with “higher” or “lower” respectively. Also, comorbidity cannot "reduce" mortality. Suggested phrase: “Comorbidities were associated with a lower risk of mortality in India compared to England”.

We understand the concern about asserting a causal relationship between comorbidities and mortality, though in this case we are talking about how estimates of mortality are impacted by the estimated risk of each comorbidity and the incidence rate of that comorbidity in a population. We want to stress that in the mathematical model we have used, the relative risk of each comorbidity, when combined with the population age and sex distribution and incidence of that comorbidity, really does cause increase or decrease in the estimate of total population mortality.

4. "Why didn't the authors explore [the e ects of HIV/AIDS, malnutrition, and other comorbidities speci c to low- and middle- income countries exist] on the association between COVID-19 and mortality?"

This study relies on age-speci c estimates of the mortality risk of each particular condition that has been

identi ed as a signi cant comorbidity for COVID-19 patients (as of summer 2020). While there is data on the incidence of HIV/AIDS, malnutrition, and other comorbidities speci c to LMICs, we are not aware of studies comparable to Williamson et al. (2020) to quantify the increased mortality risk a COVID-19 patient will face if they have one such comorbidity. This is largely due to the fact that the rst outbreaks of COVID-19 and large studies of the virus occurred in high income countries- speci cally why conditions with higher incidence rates in LMICs would not be captured by such studies. These studies require large populations and patient-level medical data. We used the best age- and gender-speci c hazard ratios on comorbidities available to us, those reported for each condition from the OpenSAFELY study, which meant we were limited to the comorbidities reported in that study. We encourage future research to investigate the association of other potential comorbidities such as HIV/AIDS and malnutrition on increased mortality risk from COVID-19.

5. "The authors state that OpenSAFELY was the source of RR for the COVID-19 mortality for England. However, it's not clear the source of COVID-19 mortality data for India. Please clarify this."

The RR estimates for each comorbidity from OpenSAFELY are independent evaluations of the increased mortality risk an individual will face if they have that particular comorbidity at the time of COVID-19 infection. The RR estimate for each comorbidity is independent of the age, gender, or nationality of an individual, as well as the other comorbidities that individual may have. We applied the OpenSAFELY RR estimates to the populations of both India and England to estimate mortality rates for each country. The population of each country is de ned by the age-speci c incidence of each comorbidity as well as the age and sex distributions, but we assume that the age-speci c RR estimates are contant between the two countries. Therefore we do not have a separate source for Indian mortality data. We clari ed in the text that we make this assumption that RRs are the same in England and in India.

6. "The age categorization used here provided by the District Level Household Survey-4 and Annual Health Survey data? If not, the authors should state how they recategorized age."

We used individual-level data from DLHS-4 and AHS, which report respondent ages, so no recategorization was required. When the underlying aggregate data sources had age

boundaries that did not match Williamson et al. (2020) (the source for mortality hazard ratios), we performed non-linear interpolations of age-speci c prevalence and re-aggregated to the targeted age categories. We have added a sentence to the methods section explaining this.

7. Terminology and wording suggestions.

We have changed all "poor" and "wealthy" terms to "low and middle income" and "high income" to describe di erent countries. We removed causal language following the reviewer's suggestion. All other wording suggestions made by the reviewer have been addressed.

Reviewer 2

1. Please mention the source of DLHS data for obesity in males. The reports available indicate BMI only in females.

We used individual-level height and weight data from DLHS and AHS to calculate the BMI of every individual in the survey. We then classi ed BMI into standard obesity categories. Because height and weight data was available for both males and females, we were able to estimate obesity measures for both. The calculation is described in the data appendix.

2. From Table 2, hypertension seems to be a protective factor. Explanation might be added. Relative risk for uncontrolled diabetes is 1.94 in Table and 1.95 in Text.

The 0.89 RR estimate from OpenSAFELY is indeed surprising for hypertension. It is possible that the strong correlation with age means that much of the hypertension risk is attributed to age in the British data, though without patient-level data it is di cult to explore further. Note that we estimated hypertension to have a RR between 1.04 and 1.064 in New York state data, which is not protective. Using the New York RR estimate did not change our major ndings. We have corrected the uncontrolled diabetes estimate in the text.

3. Discussion may be elaborated further, with ndings from other countries.

VERSION 2 – REVIEW

REVIEWER	Paddy Ssentongo Penn State University, United States
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	The authors have addressed my concerned. The paper can be published.

REVIEWER	Manas Pratim Roy Ministry of Health & Family Welfare New Delhi, India
REVIEW RETURNED	09-Nov-2020

GENERAL COMMENTS	Changes are satisfactory.