Dear editor:

I am grateful for the opportunity to revise our manuscript (Manuscript No.: BMJ-2019-052342). I would like to thank you for critical reading of this paper and for reviewers' valuable suggestions.

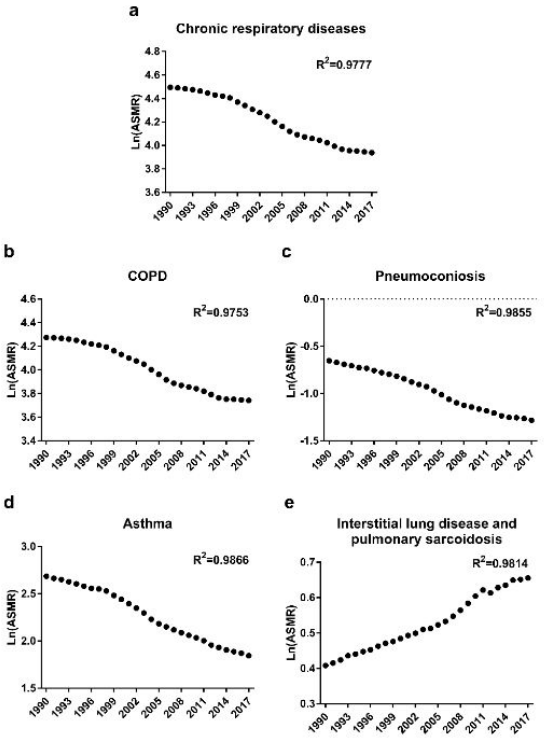
All the authors have seriously discussed about all these comments. According to the reviewers' comments, we have done our best to revise the manuscript. Our response to the major points that you listed are as follows:

1. The results section is a bit number heavy, where the authors focus on countries with the highest and lowest rates. Perhaps more informative is that we would like to see the numeric values for all 195 countries in Supp material as Tables. We need tables of the disease rates for each country as well as the maps. The main results section could then be condensed somewhat.

Response: Thank you for your suggestion. The estimates of age-standardized mortality rates from COPD, pneumoconiosis, asthma, and interstitial lung disease and pulmonary sarcoidosis for all 195 countries in 2017 are listed in newly added Supplemental Table 3. The global maps for age-standardized mortality rates from the four types of chronic respiratory diseases in 2017 are shown in original Figure 1a, Supplemental Figure 1a, Supplemental Figure 2a and Supplemental Figure 3a. The results in the manuscript were summarized for easier understanding and highlighting key points in the revised version.

2. Please explain the assumptions one reviewer mentioned, i.e. regarding linearity - sometimes these are overlooked (more serious) or done, verified but not specifically mentioned (less serious). Perhaps a sentence or two on this would suffice.

Response: According to the previous study[1-4], Generalized linear model (GLM) is widely used in calculating EAPC for the age-standardized rate. The characteristics of the variables in our study are consistent with that in previous study. Furthermore, the relationship between ln(ASMR) and the calendar year can be perfectly explained by a linear model (R^2 is close to 1), as shown in the figure below. Thus, GLM is suitable for investigating the temporal trend of ASMR.



3. The authors describe the SDI ranging from (0-1) - more details on what this represents would be useful. E.g. is 0 or 1 good or bad? And how does this lead to the classifications, e.g. high and low regions.

Response: The SDI is a composite indicator of the incomes per capita, average educational attainment, and total fertility rates. The SDI values ranged from 0 (lowest income, fewest years of schooling, and highest fertility) to 1 (highest income, most years of schooling, and lowest fertility). As a composite, a location with an SDI of 0 would have a theoretical minimum level of development relevant to these health outcomes, while a location with an SDI of 1 would have a theoretical maximum level of development relevant to these health outcomes. The methods used to calculate the SDI are in Supplement material 2. Countries and territories were classified as high, high-middle, middle, low-middle and low SDI regions. The cutoff values used to determine quintiles for analysis were then computed using country-level estimates of SDI for the year 2017, excluding countries with populations less than 1 million.

4. highlight the results and report the large numbers as 3.32 million rather than the confusing 3,317.2 thousand. In general, 3 significant figures would be about right.

Response: Thank you for your suggestion on numerical expressions. The confusing numerical expressions are converted to a concise form in the revised version (lines 2-6 in the second paragraph of the results; lines 1 in the fourth paragraph of the results).

5. Caution with use of the word 'significantly increased' when it is unclear this phrase does not come from the use of a statistical test to be compared. I would revise this.

Response: Thank you for the suggestion. We would use the word ‘significantly’ with caution. Some modifications were made in the revised version.

6. They should provide more information on what how the SDI is calculated and interpreted as it features so prominently throughout the paper but general readers won't be familiar with it.

Response: Developed by GBD researchers and used to help produce these estimates, the Socio-demographic Index (SDI) is a composite indicator of development status strongly correlated with health outcomes. SDI captures three different but important aspects of development: income, education, and fertility. Compared with the Human Development Index (HDI), SDI makes it easier to predict health outcomes.

SDI is the geometric mean of 0 to 1 indices of total fertility rate under the age of 25 (TFU25), mean education for those ages 15 and older (EDU15+), and lag distributed income (LDI) per capita. As a composite, a location with an SDI of 0 would have a theoretical minimum level of development relevant to health, while a location with an SDI of 1 would have a theoretical maximum level. The methods used to calculate the SDI are in Supplement material 2.

7. When reporting % change over time it is important to be clear when this is "per annum" and when it is "before and after". eg

   a) "Unlike other CRDs, the global ASMR due to interstitial lung disease and pulmonary sarcoidosis increased at an average of 0.97% (95% UI 0.92-1.03%) from 1990 to 2017". They mean per year, I think.

   b) "The number of deaths due to COPD in 2017 corresponded to a 23% increase compared with that in 1990". They mean overall before and after I think.

Response: Thank you for your suggestion. The problem you put forward is extremely important. We had made some modification for easier understanding in the revised version. When we reported an annual percentage change, “per annum” or “annually” was used.

8. One editor commented: “I kept forgetting what ASMR, SDI, CRDs and EAPC were. Maybe keep these spelled out each time? COPD and DALY are more familiar.”

Response: Thanks for the comments. Normally, the abbreviations were used to avoid cumbersome repetition and enhance understanding. The terms, such as ASMR, SDI, CRDs and EAPC, might be difficult to follow. Thus, the full names of ASMR, SDI, CRDs and EAPC were spelled out each time in the revised version.

9. This paper contains no PPI declaration or the mandatory dissemination plan. Please have the authors read and apply our instructions to authors and supply a declaration in their own words.

Response: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. Dissemination the results to study participants or patient organizations is not applicable. The PPI declaration and dissemination declaration were inserted before references in the revised version.

Point-by-point responses to the reviewer are listed as following:
Replies to reviewer #1:

1. Abstract: please specify “DisMod-MR 2.1” as Bayesian meta-regression tool.

Response: Thank you for your suggestion. DisMod-MR 2.1, as a Bayesian meta-regression modeling tool was developed for GBD analyses. Abstract has been modified about the model in the revised version.

2. Abstract: suggest to cut the “Findings” part by 50% and include some estimates for CRD risk factors, and to pronounce socio-demographics (income, education) as the single most important chronic respiratory disease risk factor to be addressed in order to further decrease mortality in developing countries.

Response: Thank you for the valuable suggestion. The findings focused on the impact of risk factors on chronic respiratory diseases. The relationship between SDI and mortality rates were specified. We have made some modifications in the part of findings accordingly in the revised version.

3. Methods: Based on open data from the GBD 2017, the present manuscript is based on secondary data analysis. However, in order to provide reliable and transparent findings, I would like to ask the authors to provide their statistical analysis syntax and data set in an open science repository (e.g. Open Science Framework) to be assessable for independent re-analysis.

Response: Thank you for the suggestion. We will provide the original raw data and statistical analysis syntax as one supplemental file. If the manuscript was published in an open access journal, we will provide URLs to openly accessible websites where these materials can be found.

4. Results: suggest to use "confidence interval" instead of "uncertainty interval" throughout the manuscript.

Response: Thank you for your suggestion. Some statisticians believe that "uncertainty interval" is better than "confidence interval" in describing weakness in statistics.[5] However, "confidence interval" is more familiar to the readers. So far, "confidence interval" largely outnumbers "uncertainty interval" in an online search. Therefore, to help with accessing the manuscript, "uncertainty interval" has been changed to "confidence interval" in the revised version.

5. Discussion: suggest to strengthen discussion regarding the global under-recognition, misdiagnosis and inequity (in prevalence) of COPD.

Response: Thank you for the thoughtful suggestion. Spirometry-defined COPD is highly prevalent. COPD misdiagnosis and underdiagnosis are major problems, which may lead to an underestimation of the disease burden. We discussed the problem as part of the limitations of our study.

Replies to reviewer #2:

1. The authors obtained DALY and mortality data for CRDs in 195 countries and territories from GBD 2017 data available online. However, the diagnosis of CRDs in different data or study of each country may be different. Could you give a detailed description for the specific methods used to deal with the inconsistency, which can have a direct impact on the results?

Response: Sources used to estimate chronic respiratory disease mortality included vital registration, verbal autopsy, and surveillance data from China. The standard CODEm modelling approach was applied to estimate deaths due to chronic respiratory diseases. Chronic respiratory diseases served as the parent cause to chronic obstructive pulmonary disease, pneumoconiosis (including silicosis, asbestosis, coal worker's pneumoconiosis, other pneumoconiosis), asthma, interstitial lung disease and pulmonary sarcoidosis, and other chronic respiratory diseases. Functionally, this means the death estimates for chronic respiratory diseases serve as a "parent" envelope into which the "child" causes are squeezed by the CodCorrect algorithm. This approach helps to use a broader range of data, specifically verbal autopsy data, which cannot be accurately mapped to specific respiratory diseases.

Misclassification and varying case definitions are commonly encountered in population health measurement. A key component of the GBD analyses is to identify and correct for such sources of measurement bias. To account for systematic differences in different methods of case ascertainment between different studies, GBD used study-level covariates on whether or not studies used a doctor-given diagnosis, whether or not they used clinical records to ascertain a diagnosis.

2. Data source: As this is GBD study, incorporating data from 195 countries must be a great challenge for author, not only for outcome but also for risk factors. The definition for risk factors including secondhand smoking, particulate matter pollution, high body mass index should also be clarified. This is very important for interpretation of results.

Response: The risk factor hierarchy and accompanying exposure definitions are clarified in the previous study.[6]

Second-hand smoke is defined as average daily exposure to air particulate matter from second-hand smoke with an aerodynamic diameter smaller than 2.5 μg， measured in $\mu g/m^3$, among non-smokers.

Particulate matter pollution is one type of air pollution, including ambient particulate matter pollution and household air pollution from solid fuels. Ambient particulate matter pollution is defined as annual average daily exposure to outdoor air concentrations of particulate matter with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$), measured in $\mu g/m^3$. Household air pollution from solid fuels is defined as individual exposure to $PM_{2.5}$ due to use of solid cooking fuel.

The other type of air pollution is ambient ozone pollution, which is defined as seasonal (6-month period with highest ozone) 8-h daily maximum ozone concentrations, measured in parts per billion.

High body-mass index represents one of metabolic risks, measured in kg/m^2. Theoretical minimum risk exposure level of high BMI is 20–25 kg/m^2.

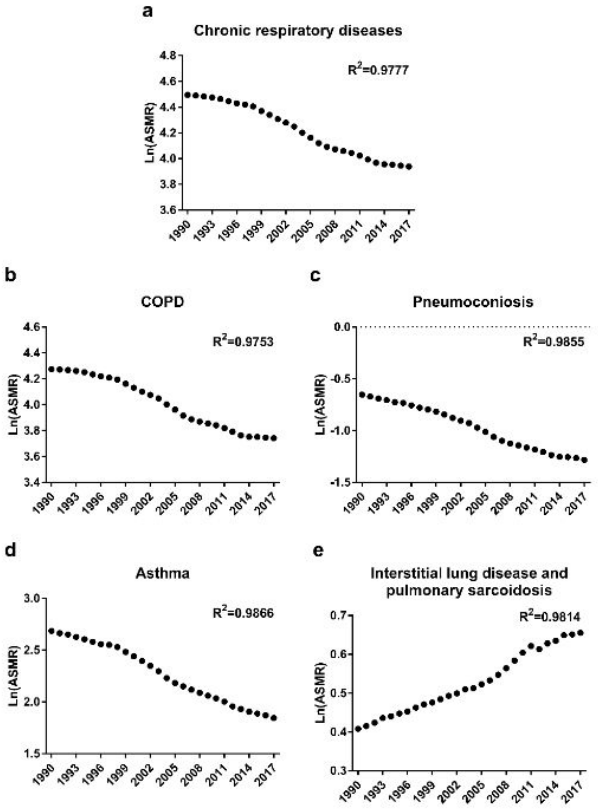
3. Data source: Please give definition for “high, high-middle, middle, low-middle and low SDI regions”

Response: Socio-demographic Index (SDI) is the geometric mean of 0 to 1 indices of total fertility rate under the age of 25 (TFU25), mean education for those ages 15 and older (EDU15+), and lag distributed income (LDI) per capita. The SDI values ranged from 0 (lowest income, fewest years of schooling, and highest fertility) to 1 (highest income, most years of schooling, and lowest fertility). The methods used to calculate the SDI are in Supplement material 2. Countries and territories were classified as high, high-middle, middle, low-middle and low SDI regions. The cutoff values used to determine quintiles for analysis were computed using country-level estimates of SDI for the year 2017, excluding countries with populations less than 1 million.

4. Statistical analyses: The author employed generalized linear model with a Gaussian

distribution to calculate estimated annual percentage change (EAPC) of the ASMR. The generalized linear model method here requires an assumption that expected value of the response is related to the time by a logarithm expression, that is, a linear relationship should exist between the ln(ASMR) and the calendar year, which is equivalent to a constant change assumption. Such assumption is important and a significant deviation from linearity assumption (e.g., increase at first and decrease later which have trend of quadratic function) might greatly undermine the validity of the results, which makes an assessment of the linearity based on scatter plots necessary here, to check whether the linearity assumption holds.

Response: Thank you very much for your thoughtful comment. According to the previous study[1-4], EAPC is a summary and widely used measure of the age-standardized rate trend over a specified interval. Generalized linear model (GLM) is widely used in calculating EAPC. The characteristics of the variables in our study are consistent with that in previous study. Furthermore, if data lies approximately along a straight line, a linear model may be the best. The relationship between ln(ASMR) and the calendar year can be perfectly explained by a linear model (R^2 is close to 1), as shown in the figure below. Thus, GLM is suitable for investigating the temporal trend of ASMR.



5. Statistical analyses: Pearson correlation coefficient was used to measure the strength of the association between the SDI and ASMR. However, Pearson correlation assume a linear relationship exists, which refers to a "straight line" relationship between the variables. Moreover, the homoscedasticity assumption, which means the size of the error is the same for all values of the independent variable, should also be considered. While, according to supplement figure 5, I am struggling to be convinced that the homoscedasticity assumption could hold. Besides, the influence of outliers, which could pull the line of best fit formed by the correlation too far in one direction or another, should also be assessed here.

Response: Thank you very much for your great suggestion. The interest is the strength and direction of the monotonic relationship between SDI and ASMR, instead of linear or nonlinear. It is difficult and unnecessary to model a perfect relation with a function. The normality of the variables was assessed, and the results showed that the distributions are non-normal. The Spearman's rank-order correlation is less sensitive than the Pearson correlation to outliers. Thus, we re-select Spearman correlation which

is hardly affected by outliers. The relationship between SDI and ASMR, as well as the change in the SDI and EAPC of ASMR were analyzed using Spearman's rank-order correlation in the revised version (Fig. 5, Fig. 7, Suppl. Fig. 5, Suppl. Fig. 7 and Suppl. Fig. 10).

6. "Approximately 2.87 billion DALYs were attributed to CRDs from 1990 to 2017 worldwide." This number cannot be found in Tables or Figures. The authors should give an explanation for how this number was calculated.

Response: Thank you for your great comment. The number of "approximately 2.87 billion" was not sufficiently accurate in describing the DALY due to CRDs from 1990 to 2017. According to the GBD 2017, DALYs due to CRDs ranged 97.2 to 112.3 million per year from 1990 to 2017. We have made some modifications accordingly in the revised version (lines 1 and 2 in the first paragraph in the results).

7. "Nevertheless, the ASMR declined by an average of 2.41% (95% UI 2.27-2.56%) during the same period" This number cannot be found in Tables or Figures. The authors should give an explanation for how this number was calculated.

Response: The average rate of decline in ASMR, which was represented by the EAPC, was calculated using a generalized linear model, as mentioned in the part of statistical analyses.

8. Risk factors: "Tobacco-attributable deaths decreased as the SDI declined". The description is contrary to results shown in Figure 8a.

Response: In Figure 8a, tobacco was the most important risk factor for death from COPD in high and middle SDI regions. Particulate matter pollution explained most of the deaths in low-SDI regions. Thus, the proportion of tobacco-attributable ASMR in mortality attributed to all risks decreased as the SDI declined. The meaning of the word "tobacco-attributable deaths" is not clear enough and we have revised it accordingly in the revised version.

9. The results shown in Figure 6b is very confusing. What is the difference between tobacco and smoking as the results for these two items was different? The authors used the term “tobacco” when introducing risk exposures in Data sources without mentioning “smoking”. Please give your definition if these two words refer to different things in this manuscript.

Response: Tobacco represents one of the behavioral risks, including smoking, chewing tobacco and second-hand smoke. Smoking is defined as prevalence of current use of any smoked tobacco product and prevalence of former use of any smoked tobacco product; among current smokers, cigarette equivalents smoked per smoker per day and cumulative pack-years of exposure; among former smokers, number of years since quitting. Chewing tobacco is defined as current use of any chewing tobacco product. Second-hand smoke is defined as average daily exposure to air particulate matter from second-hand smoke with an aerodynamic diameter smaller than 2.5 μg， measured in μg/m^3, among non-smokers. The risk factors for COPD are smoking and secondhand smoke rather than chewing tobacco. In Figure 6b, the contributions of the two risk factors are investigated separately.

10. SDI was a key point among risk factors. However, discussion section about SDI was mainly repetition for the contents in results section. The discussion should be more specific, with mentioning which countries have high, high-middle, …, low SDI and the explanation for opposite direction for the association of SDI with COPD/pneumoconiosis/asthma and interstitial lung disease/pulmonary sarcoidosis.

Response: Thank you for the suggestion. The SDI was identified as a key factor that affected the death rate and lose of health, possibly explaining regional variations. We specified the countries with highest and lowest mortality rates as SDI quintiles in order to find out the commonness among different countries with a similar level of mortality. As we mentioned in the manuscript, the negative correlation between the SDI and mortality rates due to COPD and asthma reflects better health services in high SDI countries could reduce mortality. The key to reducing mortality of penumoconiosis is reductions in exposures and incidence. ILD are expected to impose increasing burdens

on individuals and societies due to the growing trend of the global SDI.

11. In "Statistical analyses", the 95% UIs should be determined using the 2.5th and 97.5th percentiles of the ordered 1000 values.

Response: Thank you for suggestion regarding the definition of 95% UI. Some modifications are proposed here to make it easier to understand in the paragraph of the statistical analyses in the revised version.

12. The numbers of decimal places in Supplementary Table 2 should be consistent.

Response: Thank you for your suggestion. The numbers in revised Supplementary Table 2 have been expressed to 2 decimal places consistently.

13. Add correlation coefficients and p values to Supplementary Figure 5.

Response: Thank you for the suggestion. In order to clearly illustrate the relationship between EAPC in the ASMR due to chronic respiratory diseases and the change in the SDI, correlation coefficients and p values have been added to Supplementary Figure 5.

In addition, this project was supported by grants from the National Key R&D Program of China (2016YFC1304500) and the National Natural Science Foundation of China (81700052). During the initial submission, we did not find the corresponding name of the program of National Key R&D Program of China on the online submission site and it was therefore not added to the original version. We wonder whether the fund can be added to the revised version.

Reference

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3 Dhillon PK, Yeole BB, Dikshit R, et al. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976-2005: an age-period-cohort analysis. Br J Cancer 2011; 105:723-730

4 Esteve J BE, Raymond L. Statistical methods in cancer research. Volume IV. Descriptive epidemiology. IARC Sci Publ 1994; 4:1-302

5 Gelman A, Greenland S. Are confidence intervals better termed "uncertainty intervals"? BMJ 2019; 366:l5381

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