PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	THE EFFECTS OF ECONOMIC CRISES ON POPULATION HEALTH OUTCOMES IN LATIN AMERICA, 1981-2010: AN ECOLOGICAL STUDY
AUTHORS	Williams, Callum; Gilbert, Barnabas; Zeltner, Thomas; Watkins, Johnathan; Atun, Rifat; Maruthappu, Mahiben

VERSION 1 - REVIEW

REVIEWER	Miryam de Souza Minayo Oswaldo Cruz Foundation, Brazil.
REVIEW RETURNED	09-Mar-2015

GENERAL COMMENTS	Page 7 (25-30). The allusion to Venezuela and Argentina does not add any value to the article and explains nothing, since the article does not return to this subject and not deepens the comment. I suggest deleting the reference. Pages 14 and 15. DISCUSSION would be enriched by the "Policy implications for Latin America's current crisis", without pausing the ideas. It is possible to merge the two texts excluding the subtitle.

REVIEWER	George Rachiotis Department of Hygiene and Epidemiology, Medical Faculty, School of Health Sciences, University of Thessaly, Greece
REVIEW RETURNED	17-Apr-2015

GENERAL COMMENTS	The authors presented the results of an ecological study on the impact of economic crises on health endpoints in Latin America during the period 1981-2010. Statistical analysis revealed that unemployment and inflation were associated with a significant negative impact on several mortality indicators. Notably, the health impact of unemployment was larger than inflation.This is a very interesting paper with important policy implications which deserves publication in BMJ Open. I have some comments for authors. 1. Are there data on the impact of unemployment, inflation, and GDP per capita on suicide rates, or rates of infectious diseases (e.g. TBC)? Suicides and infectious diseases are sensitive markers/ indicators of the health impact of economic crisis. 2.The paper needs a comment about the quality of data and information about the procedure for the registration of death and issuance of death certificate in Latin America. Given that this ecological study is based on data from 19 countries in Latin America I would like to ask authors about possible inter-countrydifferences in the procedures of death registration and issuance of death

	certificate. 3. This is an ecological study and this should be mentioned in abstract and methods section of the manuscript. In addition, the limitations of this study design could be mentioned in the discusson. 4. In the discussion the authors are dealing with the causal pathways of risk factors and outcome. However they emphasized too mich on the role of inflation. I feel that more emphasis should be applied on the role of the unemployment which proved to be the most significant predictor of adult mortality. 5. More elaboration is needed regarding the abscense of a significant correlation between GDP per capita and health. 6. In the discussion the authors should use the criteria of Brandford Hill and discuss further the possible causative nature of their findings.

REVIEWER	Farah Farahati University of Maryland Baltimore County, USA
REVIEW RETURNED	17-Jul-2015

GENERAL COMMENTS	The study has an important policy implication in targeting the unemployment rate rather than GDP per capita and inflation rates to improve public health. Although the method is clear and adequately described, there is no mean descriptive statistics of independent variables such as out-of-pocket expenses and average age or percentage of elderly of population. The results/findings contain new results and they are clearly communicated. However, there is lack of sufficient information and in-depth discussions on the similar studies/reviews using similar method in different countries/datasets. Comparing the results of this study with previous existed studies is very important since the results of re-running the analysis using the mortality data from the world bank database do not confirm the robustness of the main analyses. Conclusion is clearly written. This paper contains significant result that could contribute greatly to the field. Hence, I would like to see the revised version of this paper by comparing the results of previous studies using this method but different datasets in different countries, if there is any. Second, presenting the descriptive statistics of the independent variables such as out-of-pocket expenses and average age or percentage of elderly of population.

REVIEWER	Aaron Reeves University of Oxford, UK
REVIEW RETURNED	07-Sep-2015

GENERAL COMMENTS	This paper examines the association between the association between three economic indicators (unemployment, inflation, and

	GDP growth) on five measures of mortality in 19 Latin American countries. The authors argue that unemployment is a primary determinant of increased mortality across a range of age groups and suggest that this should shape economic policy in the region. Below are some further theoretical and methodological comments on the paper. 1. The authors acknowledge that the relationship between inflation and health is uncertain and under theorized. They offer a few sentences at the end of the paper articulating why there may be a link. This, however, appears to be post-hoc rationalization of a statistical association observed in these data. If the authors believe they have found something of interest then I think this should be a paper in its own right. This would allow the authors to think through the carefully both the determinants of inflation and the possible pathways through which inflation might harm health. In short, I remain unconvinced by the findings linking inflation and health - not because they are implausible but because they remain under theorized and uncertain. 2. The authors recognise that their three main economic indicators are closely associated. They test whether these variables are collinear and find they are not. Although this is somewhat surprising, there is another issue which I think the authors should address. Can these three variables theoretically be separated in the model? In other words, what would it mean for a country to see an increase in unemployment but holding inflation and GDP constant? For example, changes in unemployment will likely have important consequences for both inflation and GDP and so for these to be held constant other factors must be counter-acting the pressure of changes to unemployment. The authors appear aware of this in theory but do not seem to think about how this plays out in their models. This is problematic in general because it is difficult to interpret causally more than one predictor variable in an observational study. The problems deepen because this bidirectionality among these variables means that the authors appear to be conditioning on post-treatment variables. 3. This leads me to another point. The authors seem to place a causal interpretation on their analysis but I do not think they do enough to justify the claim that - conditional on the other covariates in the model - that the distribution of country-years to higher or lower unemployment is 'as-if' random. Given the problems the authors mention with collinearity between these variables, I wonder whether they are convinced that a causal interpretation is justified? If so, they need to do more to justify that their predictor variables are 'as-if' random conditional on these covariates. 4. The authors appear to use a country-specific time trend in the model. However, because of spatial correlation between these countries I think it would be helpful to re-estimate these models with year-dummies. 5. The equation has a gamma i time-trend that is not explained in the text. My guess was that this was the country-time trend but there is already a time trend for each country in the model. Could this term be explained in more detail? 6. Do the authors intend to examine the Change in health in year t subtracted from the average change in health for a specific country? This is a slightly unusual specification of the fixed effects model which seems to combine both the first-difference approach and the mean-centered approach. I have seen this used elsewhere but would like the authors to justify their decision. 7. Similarly, the authors use a measure of the annual change in

	GDP and so the fixed-effects model measures acceleration or deceleration in the change. Is this what they intend to estimate because the interpretation is slightly different than some of the previous models in this area which measure a mean-centered model of the level of GDP. 8. At the moment it seems the lags have been modeled separately but combining them in a Sims causality tests or a Granger Causality test would give more confidence in the findings and help resolve the direction of causality problem mentioning in the limitations. 9. The authors should be commended for the sensitivity tests they have carried out. However, it seems that they have not sufficiently engaged with the implications of these results. For example, the inflation results do seem particularly sensitive to these different model specification, raising important questions about whether this is an important driver of health. In short, the association between inflation and health is highly sensitive to control variables and extreme cases. 10. Why the differences between WB and IHME data? The authors should try to address why these differences exist. It raises some questions in my mind about the validity of the results. There are some strengths of this paper. While I am not convinced that the assumption behind the fixed-effects model necessarily holds in terms of some of the political or cultural drivers of health, I do think the authors have tried to address these potential problems. The paper is clearly written and I think the authors have tried - although perhaps not entirely successfully - to offer a causal framework for distal variables (such as inflation) which are very difficult to tie to individual health. The authors are also correct to identify important questions which do require further study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Page 7 (25-30). The allusion to Venezuela and Argentina does not add any value to the article and explains nothing, since the article does not return to this subject and not deepens the comment. I suggest deleting the reference.

We have removed former reference 27 and deleted the following text: “In October 2013, the mean inflation rate across Latin America stood at 8.0% [27]; clearly, the effect of this economic metric on population health deserves further investigation.”

2. Pages 14 and 15. DISCUSSION would be enriched by the "Policy implications for Latin America's current crisis", without pausing the ideas. It is possible to merge the two texts excluding the subtitle.

We have shifted the section on “Policy implications for Latin America’s current crisis” to its logical place in the discussion, introducing the study limitations after this.

Reviewer: 2

1. Are there data on the impact of unemployment, inflation, and GDP per capita on suicide rates, or rates of infectious diseases (e.g. TBC)? Suicides and infectious diseases are sensitive markers/ indicators of the health impact of economic crisis.

We have commented on Chang et al’s 2013 time trend analysis of the impact of the global economic crisis on suicide on the Americas. The following sentence has been added: “One time trend analysis found that suicide rates were 6.4% higher in 18 American countries than expected trends had predicted in the year following the global economic crash and rises in male suicide rates correlated with the magnitude of unemployment increases [37].” We also refer to a similar ecological study “on the impact of the economic crisis in Greece used a join-point analysis on data from the Hellenic Statistical Authority to show a clear increase in suicides in working-age persons that coincided with austerity measures [40].”

We have chosen not to comment specifically on the relationship between economic crises and rates of infectious disease, a very broad outcome measure, as this relationship is less clearly understood and has not been widely studied in Latin America.

2. The paper needs a comment about the quality of data and information about the procedure for the registration of death and issuance of death certificate in Latin America. Given that this ecological study is based on data from 19 countries in Latin America I would like to ask authors about possible inter-country differences in the procedures of death registration and issuance of death certificate.

We have now added an extra column in Table 2 that shows the civil registration coverage of death with the period selected on the basis of availability, overlap with the 1981-2010 study period and proximity to 2010.

3. This is an ecological study and this should be mentioned in abstract and methods section of the manuscript. In addition, the limitations of this study design could be mentioned in the discussion.

We now mention explicitly in both the abstract and methods sections, as well as the title, that this is an ecological study. Additionally, we have added the following paragraph to the limitations section: “Given its nature as an ecological study, we have been careful to avoid making inferences from the population data at the individual level. Numerous confounders have not been controlled for in our multivariate regression analysis and alternative time trend associations may yet be found. As such, we can only hypothesise about associations highlighted by our data and have strayed from making claims of causality.”

4. In the discussion the authors are dealing with the causal pathways of risk factors and outcome. However they emphasized too much on the role of inflation. I feel that more emphasis should be applied on the role of the unemployment which proved to be the most significant predictor of adult mortality.

By reorienting our discussion, we now describe the association between employment status and health as our primary policy implication for this paper and hypothesise that the inability of the unemployment to make out-of-pocket payments may play a dominant role in this association. In discussing the role of inflation, we continue to “advocate targeting unemployment at the expense of changes in inflation”, as “reinforced by our finding that in some robustness checks inflation did not demonstrate significant associations with mortality measures, whereas unemployment did”. We also add that our findings for inflation appear to be sensitive to differing specifications of our model; this raises important questions as to whether inflation is in fact an important driver of mortality outcomes in the present study.

5. More elaboration is needed regarding the absence of a significant correlation between GDP per capita and health.

We have added a paragraph detailing the results of a study examining economic expansion on age-adjusted mortality in the US, proposed reasons for these changes, and calling for further study to elucidate the current conflict in the literature.

“This supports the findings of studies showing, for example, that economic expansions over the course of the twentieth century were associated with raised mortality when regressing age-adjusted total mortality rates for specific population groups on GDP [21]. Proposed explanations for such changes have referred to rises in alcohol and tobacco consumption, reduced immune resilience with increased stress and less sleep, less social interaction, and increases in transport-related mortality. In the aftermath of the global financial crash, a significant proportion of the debate among policy makers has centred around the association between GDP and health outcomes [43, 44]. Our findings suggest that this discussion must be expanded to incorporate other economic metrics and that this should be a focus for future study.”

6. In the discussion the authors should use the criteria of Bradford Hill and discuss further the possible causative nature of their findings.

We have incorporated the Bradford Hill criteria in the limitations section in the following way: “Of the nine Bradford Hill criteria for causation, our findings for the relationship between unemployment and inflation on mortality outcomes meet criteria for strength, consistency, temporality, plausibility, biological gradient, and analogy. The strength and consistency criteria are not held for our findings on GDP per capita.”

We have also added to the limitations section that, given its nature as an ecological study, we are wary of “making claims of causality” and “can only hypothesise about associations highlighted by our data”. This is because “numerous confounders have not been controlled for in our multivariate regression analysis and alternative time trend associations may yet be found”.

Reviewer: 3

The study has an important policy implication in targeting the unemployment rate rather than GDP per capita and inflation rates to improve public health.
Although the method is clear and adequately described, there is no mean descriptive statistics of independent variables such as out-of-pocket expenses and average age or percentage of elderly of population.
The results/findings contain new results and they are clearly communicated. However, there is lack of sufficient information and in-depth discussions on the similar studies/reviews using similar method in different countries/datasets.
Comparing the results of this study with previous existed studies is very important since the results of re-running the analysis using the mortality data from the world bank database do not confirm the robustness of the main analyses.
Conclusion is clearly written. This paper contains significant result that could contribute greatly to the field. Hence, I would like to see the revised version of this paper by comparing the results of previous studies using this method but different datasets in different countries, if there is any. Second, presenting the descriptive statistics of the independent variables such as out-of-pocket expenses and average age or percentage of elderly of population.

We agree that out-of-pocket expenses and average age would be useful independent variables; regrettably, these data sets were not available. We would encourage these variables to be incorporated in a further study.

We refer to a prior ecological study using similar methods over a similar time frame on World Bank and WHO data to analyse the effects of changes in unemployment and public healthcare expenditure on cerebrovascular mortality. “A prior study by members of the present group used data from the

World Bank and World Health Organization to analyse the effects of changes in unemployment and public healthcare expenditure on cerebrovascular mortality across 99 countries between 1981and 2009 [41]. Using similar methods, controlling for country-specific differences in infrastructure and demographics and performing one- to five-year lag analyses and robustness checks, the investigators found that increases in unemployment and reductions in public healthcare expenditure are associated with significant increases in cerebrovascular mortality. Of note, these changes were independent of changes in inflation and GDP per capita."

We have also added detail to the relationship between our chosen economic variables and suicide (references 37 and 40) and have further elucidated the potential effect of GDP per capita (reference 21), as detailed above.

Reviewer: 4

1. The authors acknowledge that the relationship between inflation and health is uncertain and under theorized. They offer a few sentences at the end of the paper articulating why there may be a link. This, however, appears to be post-hoc rationalization of a statistical association observed in these data. If the authors believe they have found something of interest then I think this should be a paper in its own right. This would allow the authors to think through the carefully both the determinants of inflation and the possible pathways through which inflation might harm health. In short, I remain unconvinced by the findings linking inflation and health - not because they are implausible but because they remain under theorized and uncertain.
Although we have prioritised our findings on unemployment, which were significant across all five population health outcomes, we continue to acknowledge the relationship between inflation and health and to hypothesise what might be cause of deteriorating health outcomes with rising inflation rates. As recommended, we intend to expound these fully in a subsequent paper.

2. The authors recognise that their three main economic indicators are closely associated. They test whether these variables are collinear and find they are not. Although this is somewhat surprising, there is another issue which I think the authors should address. Can these three variables theoretically be separated in the model? In other words, what would it mean for a country to see an increase in unemployment but holding inflation and GDP constant? For example, changes in unemployment will likely have important consequences for both inflation and GDP and so for these to be held constant other factors must be counter-acting the pressure of changes to unemployment. The authors appear aware of this in theory but do not seem to think about how this plays out in their models. This is problematic in general because it is difficult to interpret causally more than one predictor variable in an observational study. The problems deepen because this bidirectionality among these variables means that the authors appear to be conditioning on post-treatment variables.

We agree with the reviewer that holding the other two independent variables of interest invariant to observe how changes in the third affect the dependent variable is a key point. However, this analysis was already incorporated into our approach, and we regret not clarifying this. Below, we have provided the sentence that describes this multiple regression. Therefore, the regression results presented in Tables 3-6 are the coefficients extracted from regressing mortality on all three main economic indicators along with the other controls where stated. We have also amended the subsequent sentence in which we had made an error in respect of the number of regression analyses performed. We hope this clarifies our analysis and adequately addresses the reviewer's concern.

"All of the three independent variables under investigation (namely unemployment level, inflation rate, and the growth rate of GDP per capita) were included in all the regression models, permitting, for example, unemployment and inflation to be controlled for when evaluating the effects of the growth rate of GDP per capita. We therefore ran five multiple regression models, with five different variables and extracted the coefficients of the three independent variables."

3. This leads me to another point. The authors seem to place a causal interpretation on their analysis but I do not think they do enough to justify the claim that - conditional on the other covariates in the model - that the distribution of country-years to higher or lower unemployment is 'as-if' random. Given the problems the authors mention with collinearity between these variables, I wonder whether they are convinced that a causal interpretation is justified?

In the limitations section, we have clarified our position on potential causality, stating that, given its nature as an ecological study, we are wary of "making claims of causality" and "can only hypothesise about associations highlighted by our data". This is because "numerous confounders have not been controlled for in our multivariate regression analysis and alternative time trend associations may yet be found". We also place our findings in the context of the Bradford Hill criteria for causation to show that, while there are some grounds on which to support causal claims, our evidence is only moderate in this regard.

4. The authors appear to use a country-specific time trend in the model. However, because of spatial correlation between these countries I think it would be helpful to re-estimate these models with year-dummies.
5. The equation has a gamma i time-trend that is not explained in the text. My guess was that this was the country-time trend but there is already a time trend for each country in the model. Could this term be explained in more detail?
6. Do the authors intend to examine the Change in health in year t subtracted from the average change in health for a specific country? This is a slightly unusual specification of the fixed effects model which seems to combine both the first-difference approach and the mean-centered approach. I have seen this used elsewhere but would like the authors to justify their decision.

We have now added a passage to the Methods section that describes the fixed-effects models we have used. We hope these address some of the points above, expressed throughout comments 4, 5 and 6:
"We thus used the following model:
$Hit = \beta 0 + \beta 1X1it +\ldots+ \beta kXkit + Uit + \eta t$

where Hit is the mortality-based response variable for which i is country and t is time in years; Xkit represents the independent variables, which include the three economic indicators of interest as well as the standard or expanded set of control variables; βk is the coefficient for the independent variables; and Uit is the error term; and η is a dummy variable for the countries included in the regression model."

7. Similarly, the authors use a measure of the annual change in GDP and so the fixed-effects model measures acceleration or deceleration in the change. Is this what they intend to estimate because the interpretation is slightly different than some of the previous models in this area which measure a mean-centered model of the level of GDP.

We wanted to measure annual changes in GDP to observe acceleration or deceleration effects, rather than use a mean-centered model, as this is in line with previous modelling in similar studies, e.g. reference 41.

8. At the moment it seems the lags have been modeled separately but combining them in a Sims causality tests or a Granger Causality test would give more confidence in the findings and help resolve the direction of causality problem mentioning in the limitations.

As suggested by Reviewer 2, we have applied the Bradford-Hill criteria for causality to show that, while there are some grounds on which to support causal claims, our evidence is only moderate in this regard. We feel that we can reliably make this claim in the context of the separate lag modelling currently performed.

9. The authors should be commended for the sensitivity tests they have carried out. However, it seems that they have not sufficiently engaged with the implications of these results. For example, the inflation results do seem particularly sensitive to these different model specification, raising important questions about whether this is an important driver of health. In short, the association between inflation and health is highly sensitive to control variables and extreme cases.

In our discussion section, we add that our findings for inflation appear to be sensitive to differing specifications of our model; this raises important questions as to whether inflation is in fact an important driver of mortality outcomes in the present study.

10. Why the differences between WB and IHME data? The authors should try to address why these differences exist. It raises some questions in my mind about the validity of the results.

We imagine that this comment pertains to the comparison against Table G in the Supplementary Appendix. The differences between WB mortality data and IHME mortality data are most likely due to differences in collection methods, as elucidated in the civil registration column in Table 2. We intend to explore this area more fully in a subsequent study.

VERSION 2 – REVIEW

REVIEWER	George Rachiotis University of Thessaly, Greece
REVIEW RETURNED	26-Nov-2015

GENERAL COMMENTS	The authors have adequately responded to my comments. However, they could to add a paragraph on data quality.