PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Disparities of infant and neonatal mortality trends in Greece during the years of economic crisis by ethnicity, place of residence and human development index: a nationwide population study
AUTHORS	Siahanidou, Tania; Dessypris, Nick; Analitis, Antonis; Mihas, Constantinos; Evangelou, Evangelos; Chrousos, George; PETRIDOU, ELENI

VERSION 1 – REVIEW

REVIEWER	Maaya Kita Sugai Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Japan
REVIEW RETURNED	12-Sep-2018

GENERAL COMMENTS	The paper suffers from major flaws in the methodology due to lack of overcoming the limitations in the time-series analysis, lack of information and misinterpretation in conducting the time-series analysis and joinpoint trend analysis. It needs to be revised to either not do three separate TSA as they have done, or drop the TSA altogether, or drop the joinpoint analysis as I have suggested. Methods The authors mention until and since when the data was available for nationality and place of residence, however, it would be clearer if they had written from when to when, e.g. “available for years X-X.” There are many problems with the time series analysis (TSA). - The TSA has too few data points, and the authors have not explained whether they differenced the series to achieve stationarity. - The authors have not explained which forms of serial dependence they tested for. - Since the authors did not handle log-transformed rates, their models can include rates below 0. - The authors have not explained how they obtained the two different slopes. It looks like they have fit a TSA with a step term and a change in slope term, but they have not shown whether the change in slope is significant. The authors have reported the significance of the slope before and after the economic crisis, but this is not sufficient in assessing time trends. The authors have not explained what the added benefit of jointpoint plus TSA is. The authors should address these points below. - Are they meant to be using joinpoint to inform the choice of where to put the breakpoint for TSA? If so why do they choose

	three break points at 2008, 2010 and 2012 when the joinpoint clearly says that the breakpoint is 2012? - What does it mean that the joinpoint analysis says that the impact of the crisis was delayed by 4 years to 2012? What does it mean that Greek and non-Greek women see a breakpoint in 2011 or 2012, but when combined it is in 2008? - How reliable is a joinpoint analysis with only 12 data points? Did they log the data before doing the analysis? The authors should make a choice of years for when to set the breakpoint, and not do three separate TSA as they have done, or they should drop the TSA altogether, or drop the joinpoint analysis. All their results seem to disagree with each other – for example table 2 gives a 4.5% per year decrease in IMR in Greek mothers, but figure 2 suggests an 18% per year decrease (if we assume that the -0.18 refers to a percentage change and not an absolute annual change, in which case we do not know what the percentage change is). Results In the figures presented, if the authors drew a line for the year the economic crisis occurred, it would have been easier for readers to see the trends before and after the economic crisis. The figures contain too much information and are visually unfriendly. For example, in figure 2 and 3, coefficients and its 95% confidence intervals could perhaps be presented separately in a supplementary file, and terminology such as “coefficient” should be spelled out, if not terminologies abbreviated should be expressed elsewhere (i.e. footnote). The estimation of annual percentage change in table 1, for the Poisson regression, is conducted across all years? Conducting this instead for two time bands (years before and after the economic crisis separately) would have been better and more informative, as the trends will be approximated if it was estimated for all years. Discussion It would have been better if the authors interpreted further on how being Greek or not Greek could have implications policy-wise, e.g. migration policy. Are there maternal and child health related health benefits that non-Greek citizens are prohibited to receive which should be changed given the findings of this research? There should be more discussion on who non-Greek are, and more information on the size of the population at risk. The flow of people going outside Greece after the economic crises was not mentioned (although the flow of people coming to the country was mentioned). Could it be that affluent people left the country which decreased the average income of the population? Or is it that people with lower income moved out of the country to search for jobs? How did the birth rate or the average marriage age change over the years? The discussion would improve if the authors elaborated on these points. The authors should consider the possibility that there may have been more families who chose to abort their child rather than giving birth, during or after the economic crisis, and how the trend in stillbirth in Greece could have affected the infant mortality rate.

	In the discussion the authors mention increase in stillbirth rate in young Greek women, however, they do not touch upon how and in what way it affects the outcomes of interest in this research. “Perinatal” refers to livebirths that face death within 7 days or stillbirths. In the last sentence, the authors mention several possible interventions to reduce perinatal indicators, however, the focus of this study is infant mortality, and specific interventions for early neonatal mortality should be highlighted in particular if authors would want to argue the importance of decreasing ENMR. Otherwise, an argument in the end emphasizing improvement in ENMR that would lead to overall decrease in IMR, may be more relevant for the scope of this research. Given these comments, the authors should improve their statistical methodology, and should revise to make clear and expand on the points not discussed in their manuscript to provide comprehensive evidence relevant for policy. Acknowledgement I would like to thank Dr. Stuart Gilmour, Professor of Biostatistics at the Graduate School of Public Health, St. Luke’s International University, for his valuable advice in conducting this peer review.

REVIEWER	Jennifer Zeitlin INSERM, Paris
REVIEW RETURNED	16-Sep-2018

GENERAL COMMENTS	This study uses unlinked data from the Hellenic Statistical Authority on births and deaths to compute annual infant mortality rates and analyzes trends in these rates by nationality (Greek vs. foreign nationality), place of residence (urban/rural) as well as trends in the HDI index. Infant’s age of death was also available. The authors' aim is to assess how the economic crisis may have impacted on infant mortality for Greek nationals and migrant women. They show that after declines at the beginning of the period, there was a rise in the IMR among Greek women. For migrant women, I was concerned about the findings, as discussed below. One of the problems with this analysis, as the authors recognize in the limitations to the paper, is that they are not able to analyze the characteristics of the deaths or the individual socioeconomic or demographic characteristics of the mothers. The main statistical analysis involves using techniques to measure time trends, identify patterns and assess whether they are significant (I am not an expert in time series analyses). There also seems to have been a major shift in migration patterns which calls into question using migrants at the beginning of the study as a comparison group for migrants at the end. The IMR for migrants in the beginning of the study is very low for migrants which creates strange trends over the period. Without data on who the migrants are, it is difficult to interpret the meaning of these trends. There are additional analyses that the authors could undertake to improve this paper:

	If data are available on migrant groups, it would be important to present these data by place of origin of the migrants and give some information on their IMR risks. In the absence of these data, I would suggest focusing only on women of Greek origin. More descriptive data are needed on the total number of births and deaths over the years, as changes in fertility may also be related to changes in mortality. Some information on whether the characteristics of childbearing women have changed (even if unlinked to deaths) would also be of interest. It would also be helpful to visualize the trends in the HDI juxtaposed with those of IMR (and also presented in a descriptive table by year). Similarly, the trends for rural/urban could be presented. The major restriction of this analysis is that the data are limited to rates over 13 years. If the authors were able to have data by region and could have measures of the differential impact of the crisis by region, this would also allow for more in-depth investigation of their hypotheses. Finally, comment and further analysis is needed on the recording of infant deaths and the potential for changes in these practices over the period. The IMR (in particular the ENMR) is highly sensitive to the recording of deaths at the limits of viability. While the authors do not have information on gestational age, they could look at trends in the proportion of deaths in the first hour of life using age of death, as these are likely to capture the most immature newborns. Perhaps the authors could provide some information on the prevalence of live births by gestational age (even if they cannot link to deaths) as most of the births at 22 and 23 weeks of gestation will result in a neonatal deaths, and preferably the live and stillbirths by gestation to capture any changes in practices (see, for instance: Smith L, Draper ES, Manktelow BN, Pritchard C, Field DJ. Comparing regional infant death rates: the influence of preterm births <24 weeks of gestation. Arch Dis Child Fetal Neonatal Ed. 2013 Mar;98(2):F103-7)

REVIEWER	Dr Rafdzah Ahmad Zaki University Malaya
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	In general, this is a good research area. However, this article need improvement before can be considered for publication. 1. Study objective: Author need to rephrase the objective. Focus more on trend rather than exploring the role of sociodemographic factor. Suggestion: To study the trend of infant (IMR) and neonatal mortality rate trends in Greece during the period 2004-2016. 2. I think it is good to show the trend of livebirth over the year. This might be affected by the economy crisis too. 3. Although data on livebirth and death were not linked, author could present the demographic info comparing these two variables. Can be either in a table or chart. At least this will give some idea on possible factor could affect the trend. Eg percentage of rural/urban among livebirth vs death 4. “Starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers” – any issue with quality of data or underreporting?

	5. Overall, this study found that Greek show decreasing trend while non-Greek have increasing trend: author should discuss more on this. Any changes in term of health policy/services before/after economic crisis? 6. Conclusion: Abstract Line 21: “HDI and rural residence were significant predictors of infant health”. Predictor is not suitable word to use, especially when author did not test any significant association. 7. Table 1: “Any” can replace to “All” 8. Table 2: “Any” can replace to “All”. Why have different break time period for all the group? 9. Figure 2: Not clear. 10. This article need English editing

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Reviewer Name: Maaya Kita Sugai
Institution and Country: Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Japan

The paper suffers from major flaws in the methodology due to lack of overcoming the limitations in the time-series analysis, lack of information and misinterpretation in conducting the time-series analysis and joinpoint trend analysis. It needs to be revised to either not do three separate TSA as they have done, or drop the TSA altogether, or drop the joinpoint analysis as I have suggested.

Thank you for reviewing our ms. In the revised version we have clarified the different methods (Poisson regression, joinpoint and *interrupted* time-series) used in the analysis, as well as the value of applying each alternative methodological approach in addressing the study questions (page 8).

Methods
The authors mention until and since when the data was available for nationality and place of residence, however, it would be clearer if they had written from when to when, e.g. “available for years X-X.”

Revised according to your suggestion (page 8, lines 3-4)

There are many problems with the time series analysis (TSA).
- The TSA has too few data points, and the authors have not explained whether they differenced the series to achieve stationarity.
- The authors have not explained which forms of serial dependence they tested for.
- Since the authors did not handle log-transformed rates, their models can include rates below 0.
- The authors have not explained how they obtained the two different slopes. It looks like they have fit a TSA with a step term and a change in slope term, but they have not shown whether the change in slope is significant. The authors have reported the significance of the slope before and after the economic crisis, but this is not sufficient in assessing time trends.

Following the Reviewer’s comment, we have added the inherently rather short study period in the limitations of the study (page 13). To serve the purpose of our approach, i.e., to evaluate the effect of the crisis, we used additionally the Interrupted Time Series (ITS) Analysis, which allows exploring the effect of crisis in time scenarios proposed by the investigator as to take into account possible time lags in observing the effect of the crisis. ITS analysis can be used even for few observations, but the results must be presented with caution. Autoregressive integrated moving-average models have been used to control for autocorrelation and to estimate treatment effects over multiple periods. No log-

transformation is needed. We have added a reference regarding these methodological concerns of the Reviewer (page 13).

In the revised version of our manuscript, changes in slopes of the ITS analyses have been added in Figure 2 (now figure 2 and figure 3). As clarified in the Methods (page 8), we aimed at examining the impact of crisis on IMR and its components using three prespecified years, notably 2008 as the year of crisis initiation, and in two successive periods two years apart (2010 and 2012), to control for possible time lags in observing the impact of the crisis. In our ITS analysis a slope "<year of interest" is fitted until the introduction of the crisis, ">year of interest" represents the change in the level of the mortality immediately following the initiation of the crisis and "change of slope" represents the differences between pre and post crisis intervention slopes. Thus we look for p values to indicate an immediate change in mortality or "change of slope" to indicate a change in mortality over time.

The authors have not explained what the added benefit of jointpoint plus TSA is. The authors should address these points below.

- Are they meant to be using joinpoint to inform the choice of where to put the breakpoint for TSA? If so why do they choose three break points at 2008, 2010 and 2012 when the joinpoint clearly says that the breakpoint is 2012?

Following the Reviewer's comment, we have further clarified in the revised manuscript the value of using three alternative methodological approaches. Indeed, Poisson regression provides an overall IMR trend for the study period, whereas joinpoint regression, following an automated algorithm, generates any break(s) in the slope i.e., 2012 in our study; lastly, ITS allows to explore the effect of crisis in predefined by the researchers time points; we opted to use firstly 2008, which is considered the initiation of crisis in financial terms and two subsequent time points 2010 and 2012 to allow for any time lags needed for the crisis to exert its impact on IMR overall as well as by maternal ethnicity and specified covariates (page 8)

- What does it mean that the joinpoint analysis says that the impact of the crisis was delayed by 4 years to 2012?

The joinpoint regression analysis derived-break of the decreasing to a sizable increasing, albeit non-statistically significant, IMR trend among Greek infants, was in 2012 (Results, page 11); we assumed this break is more likely to reflect a delay in the impact of the 2008 crisis by 4 years and further tested this assumption by the ITS analyses. Of note, there have been no wars or other massive adverse changes among Greek families of reproductive age or radical health care reforms in Greece during the respective time periods that could impact negatively on the IMR.

What does it mean that Greek and non-Greek women see a breakpoint in 2011 or 2012, but when combined it is in 2008?

The study population is heterogeneous comprising mostly infants born to Greek mothers, but also to mothers of non-Greek nationality, mostly migrants during the recent decade and people in need. To correct for the possibly distorted results of the combined (all maternal nationalities together) analyses we considered it essential to perform separate analyses by maternal nationality. Indeed, for infants born to Greek mothers, the joinpoint regression analysis showed decreasing IMR and ENMR trends till 2012 and 2011, respectively; on the contrary, IMR trends were increasing during the same period for infants born to non-Greek mothers. Possibly due to the opposite direction in IMR trends up to 2011-2012 between Greek infants and those born to non-Greek mothers, the year 2008 was identified, by joinpoint regression analysis, as a break in IMR and ENMR trends in the entire study population (Table 3).

We added a relevant comment in the Discussion section as follows: "The importance of two sub-analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized; when trends in the entire study population were assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of previous relevant studies in Greece which did not take into consideration the maternal nationality".[20] (Discussion, page 15)

- How reliable is a joinpoint analysis with only 12 data points? Did they log the data before doing the analysis?

Based on the guidance for joinpoint analysis (Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335-51. PMID:10649300, https://surveillance.cancer.gov/joinpoint/), this analysis can be applied with a small number of breaks e.g. 0 to 1 in our study. The program itself controls for the number of breaks.

The authors should make a choice of years for when to set the breakpoint, and not do three separate TSA as they have done, or they should drop the TSA altogether, or drop the joinpoint analysis. All their results seem to disagree with each other – for example table 2 gives a 4.5% per year decrease in IMR in Greek mothers, but figure 2 suggests an 18% per year decrease (if we assume that the -0.18 refers to a percentage change and not an absolute annual change, in which case we do not know what the percentage change is).

Please see above for our replies regarding the methodology we used. Figure 2 and Figure 3 present coefficients of the ITS analyses and not percentages; we beg to disagree that the results are conflicting in this case.

Results
In the figures presented, if the authors drew a line for the year the economic crisis occurred, it would have been easier for readers to see the trends before and after the economic crisis.

In Figure 1, as well as in Table 1, we present the results for the overall period. In Figure 2 (now Figure 2 and Figure 3), the line referring to the year that supposingly had an impact on IMR trends is integrated into the graphs.

The figures contain too much information and are visually unfriendly. For example, in figure 2 and 3, coefficients and its 95% confidence intervals could perhaps be presented separately in a supplementary file, and terminology such as “coefficient” should be spelled out, if not terminologies abbreviated should be expressed elsewhere (i.e. footnote).

We opted to present the relative information of each graph along with the graph itself and to not introduce one more table. It is up to the Editor to decide what is more reader friendly.

The estimation of annual percentage change in table 1, for the Poisson regression, is conducted across all years? Conducting this instead for two time bands (years before and after the economic crisis separately) would have been better and more informative, as the trends will be approximated if it was estimated for all years.

Indeed, the estimation of annual percentage change in Table 1 (now Table 2), for the Poisson regression, was conducted across the whole study period aiming to provide comparable trends with European countries irrespective of the crisis. Thereafter, joinpoint regression and ITS analyses and subanalyses were applied in periods before and after the crisis as described above.

Discussion

It would have been better if the authors interpreted further on how being Greek or not Greek could have implication policy-wise, e.g. migration policy. Are there maternal and child health related health benefits that non-Greek citizens are prohibited to receive which should be changed given the findings of this research?

We thank the Reviewer for the suggestion. We have revised the Discussion accordingly (page 17-18).

“Barriers in the access of refugees to the Greek health care system have been mostly related to language, culture, and inadequate information about the healthcare system, but also include difficulties in the coordination of Health Services, transportation problems, issues in obtaining

expertise medical assessment in the camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for health and social care services, and administrative barriers, among others.[54] In response, the Greek government and several Non-Governmental Organizations initiated commendable actions into improving these situations i.e. provision of National Health System services free of charge for uninsured and vulnerable social groups including asylum seekers , translation services in public hospitals, access to specialist care/treatment with Gynecologists (mostly women), midwives, dentists, psychologists, and psychiatrists being lately included in the camp clinics;[54] these actions may have prevented deterioration of IMR which are being kept at steady levels after 2011 in infants of non-Greek mothers; efforts should be continued and intensified, however, as to ensure equity with local populations".

There should be more discussion on who non-Greek are, and more information on the size of the population at risk.

We thank the Reviewer for the comment. The majority of non-Greek mothers are from Balkan countries. After 2008, however, refugees flew more from Asian countries; the numbers are small, to allow sub-analyses and reliable results by country of origin as we mention in the Discussion (page 14) "In non-Greek mothers….the numbers by individual maternal nationality were, however, small to explore the tentative influence of the changing maternal nationality case mix during the study period". … "Actually, in the pre-crisis era, non-Greek mothers of newborn comprised mainly economic migrants, most of them of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece experienced an influx of refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.[16,17]"

The size of the population at risk: "The annual average proportion of non-Greek mothers was 16.3%" (Results, page 9).

The flow of people going outside Greece after the economic crises was not mentioned (although the flow of people coming to the country was mentioned). Could it be that affluent people left the country which decreased the average income of the population? Or is it that people with lower income moved out of the country to search for jobs? How did the birth rate or the average marriage age change over the years? The discussion would improve if the authors elaborated on these points.

The Reviewer is right. We have enriched the Discussion (page 14) on the emigration of Greeks, birth rate and fertility rate changes over the years, as follows:

"Simultaneously with immigration to/through Greece, the country experienced the third wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left Greece since the onset of the economic crisis, in 2008, seeking new opportunities and employment in other countries, mainly Germany, the United Kingdom and the Netherlands.[39,40] The current emigration wave of Greeks involved mostly highly-educated people (the so called "brain-drain") of young age, leading to a decrease in the number of Greek women of childbearing age.[41] This fact, along with the decrease in the fertility rate by almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual number of livebirths in Greece by almost 23% during the period of the economic crisis.[41,42] Furthermore, the flow of mostly affluent and well educated people going outside Greece might have also contributed, to a certain extent, to the observed increases in IMR among Greek children following the crisis.

The authors should consider the possibility that there may have been more families who chose to abort their child rather than giving birth, during or after the economic crisis, and how the trend in stillbirth in Greece could have affected the infant mortality rate. In the discussion the authors mention increase in stillbirth rate in young Greek women, however, they do not touch upon how and in what way it affects the outcomes of interest in this research.

We agree that possibly there may have been families who chose abortion rather than giving birth to a child during the economic crisis; there are no sound official data on the freely performed abortions, however. Nevertheless, neither abortions nor stillbirths, seem to influence the infant mortality rate which is estimated by the number of deaths per 1,000 livebirths. In the Discussion (page 16) we now mention that "Increased incidence of impaired perinatal parameters including low birth weight, prematurity and increased maternal age and rate of caesarian section, have been reported during the years of the economic decline in Greece.[18,19] " In one of these citations, the authors also mention

increase in stillbirth rate, but only in young Greek women younger than 25 years of age, whereas no significant change in stillbirth rates overall was observed.

"Perinatal" refers to livebirths that face death within 7 days or stillbirths. In the last sentence, the authors mention several possible interventions to reduce perinatal indicators, however, the focus of this study is infant mortality, and specific interventions for early neonatal mortality should be highlighted in particular if authors would want to argue the importance of decreasing ENMR. Otherwise, an argument in the end emphasizing improvement in ENMR that would lead to overall decrease in IMR, may be more relevant for the scope of this research.

Following the Reviewer's comment, the last sentence has been revised accordingly. "Irrespective of the crisis, improvements in the quality of perinatal and neonatal care, including centralization of very preterm deliveries, establishment of regional perinatal centers, monitoring of the implementation of evidence-based practices in maternity and neonatal units, as well as increase in health expenditures, health care workforce, number of doctors and midwifes/nurses, could decrease ENMR, eventually leading to overall decrease in IMR in Greece.[50] "

Given these comments, the authors should improve their statistical methodology, and should revise to make clear and expand on the points not discussed in their manuscript to provide comprehensive evidence relevant for policy.

We thank you for the summarizing point. We have revised our manuscript to accommodate all meaningful suggestions.

Acknowledgement
I would like to thank Dr. Stuart Gilmour, Professor of Biostatistics at the Graduate School of Public Health, St. Luke's International University, for his valuable advice in conducting this peer review.

We also thank Professor Gilmour for the time spent reviewing our study.

Reviewer #2
Reviewer Name: Jennifer Zeitlin
Institution and Country: INSERM, Paris

This study uses unlinked data from the Hellenic Statistical Authority on births and deaths to compute annual infant mortality rates and analyzes trends in these rates by nationality (Greek vs. foreign nationality), place of residence (urban/rural) as well as trends in the HDI index. Infant's age of death was also available.
The authors' aim is to assess how the economic crisis may have impacted on infant mortality for Greek nationals and migrant women. They show that after declines at the beginning of the period, there was a rise in the IMR among Greek women. For migrant women, I was concerned about the findings, as discussed below.

One of the problems with this analysis, as the authors recognize in the limitations to the paper, is that they are not able to analyze the characteristics of the deaths or the individual socioeconomic or demographic characteristics of the mothers. The main statistical analysis involves using techniques to measure time trends, identify patterns and assess whether they are significant (I am not an expert in time series analyses).

There also seems to have been a major shift in migration patterns which calls into question using migrants at the beginning of the study as a comparison group for migrants at the end. The IMR for migrants in the beginning of the study is very low for migrants which creates strange trends over the period. Without data on who the migrants are, it is difficult to interpret the meaning of these trends.

Thank you for your thorough review and comments. We added in the revised version of the manuscript information regarding who the migrants are: "among the remaining 615 deaths of infants born to non-Greek mothers, 298 (48.5%) were of infants born to Albanian mothers, 146 (23.7%) of infants born to mothers from Balkan countries and countries of the former Soviet Union, 77 (12.5%)

from Asia, 47 (7.6%) from countries of the European Union or other developed countries, and 47 (7.6%) from Africa (Results, page 10).

Thus, the majority of non-Greek mothers were from Balkan countries. Analyzing groups according to the place of origin would be ideal, but as the figures are very small, the results could not be reliable. In addition, the time period with available information on maternal nationality and place of residence was rather short, as mentioned in the limitations section of the Discussion (page 13).

There are additional analyses that the authors could undertake to improve this paper:If data are available on migrant groups, it would be important to present these data by place of origin of the migrants and give some information on their IMR risks. In the absence of these data, I would suggest focusing only on women of Greek origin.

Please see our previous reply. Data are available, but sub-analyses by specific country of origin of the mothers, might have led to unreliable results. We have emphasized, however, in the Discussion that “this issue needs to be further followed-up by other types of research methodology” (page 14).

More descriptive data are needed on the total number of births and deaths over the years, as changes in fertility may also be related to changes in mortality. Some information on whether the characteristics of childbearing women have changed (even if unlinked to deaths) would also be of interest. It would also be helpful to visualize the trends in the HDI juxtaposed with those of IMR (and also presented in a descriptive table by year). Similarly, the trends for rural/urban could be presented.

We thank the Reviewer of the comment. A descriptive table showing the number of livebirths and infant deaths over the years, as well as infant mortality rates per 1000 livebirths in infants born to Greek and non-Greek mothers, has been added in the revised version of the manuscript (Table 1, page 27) . The analysis was based on mortality rates, so the number of births per year was taken into account.

Unfortunately, individual data regarding maternal characteristics, other than nationality and place of residence, were not available to be presented in the Results section. However, we have added in the Discussion freely available information from Eurostat and citations on emigration of Greeks leading to a decrease in the number of women of childbearing age, and we also present fertility rate changes over the years of the economic crisis (page 14-15).

The major restriction of this analysis is that the data are limited to rates over 13 years. If the authors were able to have data by region and could have measures of the differential impact of the crisis by region, this would also allow for more in-depth investigation of their hypotheses.

Data by region would indeed improve our manuscript. Unfortunately, they are missing.

Finally, comment and further analysis is needed on the recording of infant deaths and the potential for changes in these practices over the period. The IMR (in particular the ENMR) is highly sensitive to the recording of deaths at the limits of viability. While the authors do not have information on gestational age, they could look at trends in the proportion of deaths in the first hour of life using age of death, as these are likely to capture the most immature newborns. Perhaps the authors could provide some information on the prevalence of live births by gestational age (even if they cannot link to deaths) as most of the births at 22 and 23 weeks of gestation will result in a neonatal deaths, and preferably the live and stillbirths by gestation to capture any changes in practices (see, for instance: Smith L, Draper ES, Manktelow BN, Pritchard C, Field DJ. Comparing regional infant death rates: the influence of preterm births <24 weeks of gestation. Arch Dis Child Fetal Neonatal Ed. 2013 Mar; 98(2):F103-7)

We thank the Reviewer for the comment. Infant death rates are indeed influenced by variation in the registration of births in case of uncertain viability (Smith L, Arch Dis Child Fetal Neonat Ed. 2013). In Greece, like in other countries (Smith L, Arch Dis Child Fetal Neonat Ed. 2017), misclassification in reporting of extremely preterm births of <24 weeks of gestation, as live or stillborn, may exist. Further analysis of IMR trends after excluding extremely preterm births would be useful to minimize any registration variation; however, as mentioned in the limitations of this study, gestational age data of the study population are missing. We have added this comment in the Discussion section (page 17).

Following the Reviewer's comment we analyzed separately the infant deaths in the first day of life; trends of mortality in this age group over the study period were non-significant (average annual percent change; -1.22%; 95% CI -3.79% to 1.42%; p=0.36). We have inserted a comment in the Results and the Discussion sections (page 11 and 17, respectively).

Reviewer #3
Reviewer Name: Dr Rafdzah Ahmad Zaki
Institution and Country: University Malaya

In general, this is a good research area. However, this article need improvement before can be considered for publication.
1. Study objective:
Author need to rephrase the objective. Focus more on trend rather than exploring the role of sociodemographic factor.
Suggestion: To study the trend of infant (IMR) and neonatal mortality rate trends in Greece during the period 2004-2016.

We thank the Reviewer for the suggestion and have accordingly revised the study objective so that the aim is in line with the conclusions (page 3).

2. I think it is good to show the trend of livebirth over the year. This might be affected by the economy crisis too.

A descriptive table showing the number of livebirths over the years has been added in the revised version of the manuscript (Table 1, page 27). The analysis was based on mortality rates, so the number of births per year was taken into account.

3. Although data on livebirth and death were not linked, author could present the demographic info comparing these two variables. Can be either in a table or chart. At least this will give some idea on possible factor could affect the trend. Egpercentage of rural/urban among livebirth vs death

The descriptive Table 1 in the revised manuscript shows the number of livebirths and infant deaths over the years, as well as infant mortality rates per 1000 livebirths separately in infants born to Greek and non-Greek mothers (page 27).

4. "Starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers" – any issue with quality of data or underreporting?

Data included in the analyses were all provided by the National Statistical Authority of Greece, with no evidence of essential changes in the data reporting methods that may have differentially impacted on data completeness and quality during the study period. We comment in the Discussion that "It could be suggested that changes in the homogeneity of foreign mothers during the study period, in association with the country's economic difficulties, might have led from the "healthy migrant effect", observed before 2008, to the deterioration of IM indicators and IMR trends, afterwards, in infants born to non-Greek mothers." (page 14)

5. Overall, this study found that Greek show decreasing trend while non-Greek have increasing trend: author should discuss more on this. Any changes in term of health policy/services before/after economic crisis?

Relevant comments have been added in the Discussion (pages 17-18)

6. Conclusion: Abstract Line 21: "HDI and rural residence were significant predictors of infant health". Predictor is not suitable word to use, especially when author did not test any significant association.

The phrase has been revised: "HDI and rural residence were significantly associated with IMR".

7. Table 1: “Any” can replace to “All”

It has been revised; “Any” has been replaced by “All” in Table 1 (now Table 2).

8. Table 2: “Any” can replace to “All”. Why have different break time period for all the group?

The suggested correction has been made.

As regards the different break time period in the entire study population in comparison with infants born to Greek or non-Greek mothers, it should be clarified that the study population is heterogeneous comprising mostly infants born to Greek mothers, but also to mothers of non-Greek nationality, mostly migrants during the recent decade and people in need. To control for the possibly distorted results of the combined (all maternal nationalities together) analyses we considered it essential to perform separate analyses by maternal nationality. Indeed, for infants born to Greek mothers the joinpoint regression analysis showed decreasing IMR and ENMR trends till 2012 and 2011, respectively; on the contrary, IMR trends were increasing during the same period for infants born to non-Greek mothers. Possibly due to the opposite direction in IMR trends up to 2011-2012 between Greek infants and those born to non-Greek mothers, year 2008 was identified in the joinpoint regression analysis, as a break in IMR and ENMR trends in the entire study population (Table 3).

We added a relevant comment in the Discussion section as follows: “The importance of two sub-analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized; when trends in the entire study population were assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of previous relevant studies in Greece which did not take into consideration the maternal nationality”.[20] (Discussion, page 15)

9. Figure 2: Not clear.

Figure 2 has been revised, as suggested.

10. This article need English editing

We tried to improve English in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Jennifer Zeitlin Inserm, Paris
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	The authors have made many changes to their manuscript based on the reviewers' comments. They were very responsive to a number of my comments, as well. However, I still feel strongly that the data on non-Greek women cannot be interpreted without a better understanding of where the migrants come from and how their characteristics have changed over time. I cannot see the usefulness of providing this trend data without being able to interpret it. The authors have now provided a breakdown of the main nationalities, however, what is important is not this breakdown over the whole period, but how this changed. In particular, changes between the period when mortality was about 1.5 per 1000 from 2004 to 2008 (this, by the way, is lower than rates reported from countries with the lowest mortality worldwide) and when it was more in the 3-4 range (from 2009-2016).

	My suggestion would be to include the analysis on non-Greeks in supplementary material and to describe the results in the text. The authors could explain that they did not do their main analysis on this group because they were not able to account for changes in the composition of the migrant population. The authors could then include in Table 1 some more detail on the urban/rural differences which are interesting, but not easy to interpret without data on births and deaths, as shown in this table. I was also disappointed that the HDI trends over time were not given as it is also difficult to appreciate this relationship reported in the paper without this information. At the very least, it would be helpful to have them in the supplementary material.

REVIEWER	Nicholas Moloci Dow Division of Health Services Research, Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America
REVIEW RETURNED	24-Feb-2019

GENERAL COMMENTS	This study uses two separate data sources from the Hellenic Statistical Authority that records the birth and death of infants in Greece, but the two data sources are not able to be linked. The authors are examining the impact of the Greek economic crisis on the infant mortality rate and subsequent time periods. In order to assess trends in the infant mortality rate the authors use Poisson regression, joinpoint regression and an interrupted time series. The study examines changes over the study period which is from 2004-2016. This paper answers an interesting and important question, however, the methods used to answer this question need improvement. This paper uses three types of statistical analysis to assess changes in the IMR and its not entirely clear why all three methods are needed. This adds complexity to the analysis that is not required and can be answered by simplifying the analysis. In particular the joinpoint analysis seems to confuse the overall message. The authors state that an algorithm picked the particular analysis points, however, it's not clear how that algorithm worked in picking the date and it's not discussed. Please include this information. The authors have an interest in assessing the impact of the Greek economic crisis which occurred in 2008, however, in the joinpoint and ITS the authors have different inflection dates. While the authors discuss there may be a lagged effect, there is no justification as to why the years they examine are picked. Authors should provide clear justification for the dates picked. Further, the dates that are picked in the ITS do not match with the dates that result from the joinpoint regression, adding complexity to understanding the results. To simplify, authors could remove the joinpoint regression and preform the Poisson regression examining the same time points as in the ITS. For the joinpoint regression results, different time points are picked for the Greek vs. Non-Greek mothers and for all mothers. This makes it difficult for readers to compare changes in IMR since the time points are not the same. Further, why are the results only

	presented for IMR and ENMR? Please provide the additional mortality measures. It is not clear what, if any, variables are in the Poisson regression. Please better specify what is in the models in order to help with reproducibility. For the table 2 Poisson regression, it is not clear what years are used for each type of analysis. In the methods section the authors state that the residence information is only available for 2004-2014; is this reflected in the Urban vs Rural results presented? It appears the time frames are different for the results being presented in table 2; this may confuse readers as the overall time frame of the study is from 2004-2016. Having multiple time frames across different analyses makes it difficult to interpret the results in a meaningful way. If possible, please restrict analyses to time periods that are consistent across all data sources. For the ITS, having three different inflection points adds complexity that is unnecessary and gives different results for each analysis. If the authors wish to evaluate multiple time periods, they can assess using multiple linear splines. Authors state several times that results are “erroneously” not significant. Please remove this wording; just because a result does not match a prespecified theory, does not make the results erroneous. Authors in the result section highlight results that are “borderline significant”, however, once a threshold for statistical significance is set, the results are either significant or not statistically significant. Please remove borderline language. Please provide confidence intervals for point estimates on figures. Please address how stillborn infants are recorded in the data. The discussion section seems to overreach from the what the analysis show. It was quite lengthy, please reduce to most salient points and limitations.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer #2

Reviewer Name: Jennifer Zeitlin

Institution and Country: Inserm, Paris

The authors have made many changes to their manuscript based on the reviewers' comments. They were very responsive to a number of my comments, as well. However, I still feel strongly that the data on non-Greek women cannot be interpreted without a better understanding of where the migrants come from and how their characteristics have changed over time. I cannot see the usefulness of providing this trend data without being able to interpret it. The authors have now provided a

breakdown of the main nationalities, however, what is important is not this breakdown over the whole period, but how this changed. In particular, changes between the period when mortality was about 1.5 per 1000 from 2004 to 2008 (this, by the way, is lower than rates reported from countries with the lowest mortality worldwide) and when it was more in the 3-4 range (from 2009-2016).

My suggestion would be to include the analysis on non-Greeks in supplementary material and to describe the results in the text. The authors could explain that they did not do their main analysis on this group because they were not able to account for changes in the composition of the migrant population. The authors could then include in Table 1 some more detail on the urban/rural differences which are interesting, but not easy to interpret without data on births and deaths, as shown in this table.

In the revised manuscript, we further calculated the average annual percent change (APC) of infant mortality rates (IMR) by nationality of non-Greek mothers. We found significant increases of IMR trends during the study period in all ethnic groups, especially in infants born to mothers from Africa. More specifically, APC (95% CI) was 7.6% (4.2% to 11.1%) in infants born to Albanian mothers, 8.6% (3.7% to 13.8%) in infants born to mothers from Balkan countries and countries of the former Soviet Union, 9.4% (2.8% to 16.3%) in infants born to mothers from Asia, 9.4% (1.1% to 18.3%) in infants born to mothers from countries of the European Union or other developed countries, and 21.1% (11.0% to 32.3%) in infants born to mothers from Africa (page 11). These findings reflect changes in the composition of the migrant population over time. Thus, we opted not to include the analysis on non-Greeks in supplementary material; however, it is upon the Editor's decision.

Following your suggestion to present urban/rural differences, we have added in the revised manuscript one more Table (Suppl Table 1) showing infant deaths and total infant mortality rates (IMR) by place of residence (urban/semiurban vs. rural areas). This Table has been included as Supplemental in order not to exceed significantly the limit on the total number of Tables and Figures according to the journal's instructions to authors.

I was also disappointed that the HDI trends over time were not given as it is also difficult to appreciate this relationship reported in the paper without this information. At the very least, it would be helpful to have them in the supplementary material.

Human Development Index (HDI) values by year in Greece during the study period are now presented in Table 1.

Moreover, HDI trends over time were calculated and found to be increased significantly during the study period; APC (95% CI): 0.1% (0.06% to 0.13%) (page 11).

Response to Reviewer #4

Reviewer Name: Nicholas Moloci

Institution and Country: Dow Division of Health Services Research, Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America

This study uses two separate data sources from the Hellenic Statistical Authority that records the birth and death of infants in Greece, but the two data sources are not able to be linked. The authors are examining the impact of the Greek economic crisis on the infant mortality rate and subsequent time periods. In order to assess trends in the infant mortality rate the authors use Poisson regression,

joinpoint regression and an interrupted time series. The study examines changes over the study period which is from 2004-2016.

This paper answers an interesting and important question, however, the methods used to answer this question need improvement.

This paper uses three types of statistical analysis to assess changes in the IMR and its not entirely clear why all three methods are needed. This adds complexity to the analysis that is not required and can be answered by simplifying the analysis. In particular the joinpoint analysis seems to confuse the overall message. The authors state that an algorithm picked the particular analysis points, however, it's not clear how that algorithm worked in picking the date and it's not discussed. Please include this information.

Indeed, we applied three different approaches in statistical analysis, each one of them providing information on different aspects and based on various assumptions. We agree that this may add on the complexity of the analysis, however due to transparency issues and adequate reporting we have chosen to report results from all three approaches. For example, a Poisson regression approach might be an appropriate method to adequately assess the time trends of mortality rates; however our data are clearly stratified by maternal nationality and residency, and mortality rates have been severely affected from the fiscal crisis of 2008 onwards. Therefore, we opted to include additional methods (i.e joinpoint regression and ITS analyses as sensitivity analysis) that take into account the aforementioned parameters and allow us to make robust inferences regarding our data.

In particular the Joinpoint regression analysis is usually applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. Time points are identified automatically by a software program. As it is mentioned in the Materials and Methods section (page 9), we used the Joinpoint Regression Program, Version 4.5.0.1. We have provided additional justification on the use of joinpoint regression analysis in the text (page 8), but further explanation of the methodology possibly goes beyond the purposes of this study.

We leave at the editor's discretion the choice to omit one of the three methods of statistical analysis, even though we strongly believe that all methods are complimentary and should be presented in order to avoid poor reporting of the results.

The authors have an interest in assessing the impact of the Greek economic crisis which occurred in 2008, however, in the joinpoint and ITS the authors have different inflection dates. While the authors discuss there may be a lagged effect, there is no justification as to why the years they examine are picked. Authors should provide clear justification for the dates picked. Further, the dates that are picked in the ITS do not match with the dates that result from the joinpoint regression, adding complexity to understanding the results. To simplify, authors could remove the joinpoint regression and preform the Poisson regression examining the same time points as in the ITS.

As mentioned above, in joinpoint regression analysis, time points are picked automatically by a software program. On the contrary, by ITS analyses, the impact of prespecified years on IM time trends was explored.

We mention in Materials and Methods (page 8) that "Joinpoint regression analysis22 was thereafter applied to automatically derive, by a software program, different segments in the mortality evolution curves overall, as well as those by maternal nationality and place of residence; the Joinpoint regression analysis is usually applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. Interrupted Time Series (ITS) analyses were also undertaken as a sensitivity analysis to further explore the effect of crisis on IMR and its components in alternative prespecified years, notably 2008, considered to indicate the initiation of the crisis in

Greece as the value of the Gross Domestic Product of the country was maximum at that year but dropped afterwards (Source: Aggregate National Accounts), and in two successive periods two years apart (2010 and 2012), to control for possible time lags in observing the impact of the crisis."

For the joinpoint regression results, different time points are picked for the Greek vs. Non-Greek mothers and for all mothers. This makes it difficult for readers to compare changes in IMR since the time points are not the same. Further, why are the results only presented for IMR and ENMR? Please provide the additional mortality measures.

Please see our previous comments as regards the time points picked automatically by joinpoint regression analysis. To our opinion, the different time points in infants born to Greek vs. non-Greek mothers reflect the different impact of crisis on IMR trends in these populations. We also discuss (page 15, Discussion section) that "The importance of two sub-analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized; when trends in the entire study population were assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of previous relevant studies in Greece which did not take into consideration the maternal nationality.20 "

In Table 3 the results are only presented for IMR and ENMR, because no break was identified by jointpoint regression analysis in the additional mortality measures. It is reported in the legend of Table 3 that Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant mortality rates by maternal nationality are presented only for indices showing breaks in the time period examined.

It is not clear what, if any, variables are in the Poisson regression. Please better specify what is in the models in order to help with reproducibility.

In the revised manuscript we specified that "Annual percent of change (APC) during the study period was initially estimated through univariate Poisson regression analysis using the underlying population of each set as an offset variable. Subsequently, data were stratified and analyzed by maternal nationality (Greek vs. non-Greek) and place of residence (Urban/Semi-urban vs. Rural)." (page 8)

For the table 2 Poisson regression, it is not clear what years are used for each type of analysis. In the methods section the authors state that the residence information is only available for 2004-2014; is this reflected in the Urban vs Rural results presented? It appears the time frames are different for the results being presented in table 2; this may confuse readers as the overall time frame of the study is from 2004-2016. Having multiple time frames across different analyses makes it difficult to interpret the results in a meaningful way. If possible, please restrict analyses to time periods that are consistent across all data sources.

Thank you for your comment. Indeed, individual data for all livebirths and infant deaths were provided by the Hellenic Statistical Authority (ELSTAT) for a 13-year period (2004-2016). However, information on residency was only available for years 2004-2014; this is the only parameter with a different time frame in our analysis. We opted not to restrict all analyses to the time period 2004-2014, so as to include in the study the most current data.

For the ITS, having three different inflection points adds complexity that is unnecessary and gives different results for each analysis. If the authors wish to evaluate multiple time periods, they can assess using multiple linear splines.

We explained above why we examined by ITS three prespecified years (2008, 2010 and 2012). We leave at editor's discretion the choice to omit ITS analyses.

Authors state several times that results are “erroneously” not significant. Please remove this wording; just because a result does not match a prespecified theory, does not make the results erroneous.

These phrases have been revised (in pages 3 and 11).

Authors in the result section highlight results that are “borderline significant”, however, once a threshold for statistical significance is set, the results are either significant or not statistically significant. Please remove borderline language.

It has been revised (in pages 4 and 12).

Please provide confidence intervals for point estimates on figures.

Confidence intervals have been provided.

Please address how stillborn infants are recorded in the data.

Only livebirths and deaths of infants born alive were analyzed. We mention in the Materials and Methods section (page 8) that “Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of deaths over the number of livebirths per year”.

The discussion section seems to overreach from the what the analysis show. It was quite lengthy, please reduce to most salient points and limitations.

The discussion section is indeed lengthier than the one submitted initially as in the previous version of manuscript (R1) we had to reply satisfactorily to the reviewers’ comments. In the current version of our manuscript (R2), we tried to shorten the Discussion as much as possible, however without omitting replies to the previous reviewers’ comments.

VERSION 3 – REVIEW

REVIEWER	Nicholas Moloci Dow Division of Health Services Research, Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America

REVIEW RETURNED	31-Mar-2019

GENERAL COMMENTS	I still have several concerns with the methods and analysis of this manuscript. Further only specific results are being highlighted in results and discussion, while there are many possible results that could be discussed, that are not. If authors wish to keep all three regression types included there are discrepancies that need to be addressed. Further, if the ITS is to be used a sensitivity analysis to the Joinpoint Regression, it makes it difficult to compare results with two different time periods. As other reviewers have noted, I have concerns about the Non-Greek population. As the authors have stated, there has been an increase in migrants to Greece and with them has come their infant children. How are infants born to non-Greek mothers whom are being born in another country but who come to Greece and then die being recorded in the data? For the Joinpoint Regression (JPR) do the authors prespecify the number of possible joinpoints or does the software determine the number of joinpoints? If it is automatic, what are the criteria that the software uses to determine where the joinpoint is? If it is not automatic, did the authors test other possible joinpoints? Were there multiple permutations of this? Please describe. If the JPR is going to be an important part of your results, please put in table 3 all possible mortality results. Page 3 Line 59 Please change wording to reflect that due to the increase in non-Greek mother IMR, there is no significant change in overall IMR for all of Greece over the time frame of the study. Page 4 Line 7 Please remove all wording of “at the limit of statistical significance”. Also, since this result is not statistically significant it does not make sense to report that there were increases in IMR. Page 10 Line 59 While the Poisson results show a decrease in IMR and PNMR they do not show a change in ENMR LNMR. Please note. Page 11 Line 2 Please clarify “albeit differentially by place of residence” since the overall mortality rates you’re comparing to are from the whole time period, whereas, the residence mortality rates are not over the same time period. Page 12 Line 8 Do you mean to state infants born to Greek mothers? When stating Greek infants, this can be confusing as it could be to either Greek or Non-Greek mothers. Page 12 Line 10 The results state that the JPR shows a significant decrease in IMR for infants born to Greek mothers for 2004-2012 and then no significant change from 2012-2016. However, this result is

	contradicted by the ITS analysis showing no significant change in slope but showing an increase in mortality after 2012 (p=0.0001) in the IMR during the same time period. Please report this in your results highlighting the discordant significance between the two methods. Page 12 Line 12 Please remove language that the decrease in IMR is due to ENMR. The two measures in table 3 are looking at different time points and each contribution of the other mortality components are not presented in table 3, making it difficult to interpret that ENMR is the driving force. Page 12 Line 17 First, either the result is significant or not. The pre-specified alpha is 0.05, however, the result is 0.07, thus not significant. Please remove language of “at the limit of statistical significance”. Page 12 Line 17 For the ENMR results post 2011, please also state that the ITS showed no significant increase in trend for the post 2012 time period p=.07, however, that it does show a significant increase in the post 2010 time period. Page 12 Line 22 Please state in results that while the JPR finds a significant increase in IMR for non-Greek mothers, the ITS depending on when the year of interest is being defined (2010 or 2012) the increase is either not significant (2010 p=0.11) or significant (2012 p=0.001). Page 12 Line 27 Please clarify language no statistically significant change may be clearer than no fluctuation in the IMR rate of non-Greek mothers from 2011-2016. Please also state that the ITS results also show no change in IMR over the 2010/2012 time periods. Page 12 Line 30 The authors state that the ITS results confirm that of the JPR. However, there are several discrepancies between the two methods. Some are highlighted above. Also, the JPR results presented in this paper do not show the ENMR of non-greek mothers, LNMR or PNMR of all mothers. There is no way to interpret that the two regression types concur on all of these possible mortality outcomes. Further, there are no presented results showing the ITS for the all mothers IMR/ENMR/LNMR/PNMR. Please remove this wording. Please correct in the abstract and discussion the results listed above. Please highlight in the discussion how sensitive the results are depending on the method used.

VERSION 3 – AUTHOR RESPONSE

Response to Reviewer #4

Reviewer Name: Nicholas Moloci

Institution and Country: Dow Division of Health Services Research, Department ofUrology, University of Michigan Medical School, Ann Arbor, Michigan, United Statesof America

I still have several concerns with the methods and analysis of this manuscript.Further only specific results are beinghighlighted in results and discussion, whilethere are many possible results that could be discussed, that are not. If authorswish to keep all three regression types included there are discrepancies that needto be addressed. Further, if the ITS is to be used a sensitivity analysis to the Joinpoint Regression, it makes it difficult to compare results with two differenttime periods.

Although the three regression methods used may add on the complexity of the analysis and the interpretation of the results, our decision to present all of them is driven by our group's commission to excellence and a matter of transparency and adequate reporting of the data according to proper practices that improve scientific research. We strongly believe that the reporting of all three models provides significant information and highlights the results from various perspectives.

According to reviewer's suggestions, additional results and discrepancies among them have been further presented and discussed. For example, we now include in the joinpoint regression results (Table 3) data relevant to late neonatal (LNMR) and post neonatal (PNMR) mortality time trends. We also present in more details the results of joinpoint regression and ITS analyses (page 12-13).

As other reviewers have noted, I have concerns about the Non-Greek population. Asthe authors have stated, there has been an increase in migrants to Greece and withthem has come their infant children. How are infants born to non-Greek mothers whomare being born in another country but who come to Greece and then die being recordedin the data?

We report in the Materials and Methods section that this study uses two separate data sources provided by the Hellenic Statistical Authority (ELSTAT); one that records live births and a second one recording infant deaths in Greece. Linkage of the two files was not possible as the personal identification number was not available in ELSTAT. Calculation of IMR and its components was based on the number of livebirths; we mention the absence of a linkage system between birth and death data as a limitationof the study (page 4-Strengths and Limitations, page 14-Discussion section).

For the Joinpoint Regression (JPR) do the authors prespecify the number of possible joinpoints or does the software determine the number of joinpoints? If it isautomatic, what are the criteria that the software uses to determine where the joinpoint is? If it is not automatic, did the authors test other possible joinpoints? Were there multiple permutations of this? Please describe.

We have now clarified in the methods section (page 8). "In details, the Joinpoint regression analysis is applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. The location of the joinpoint is not known a priori and is to be estimated from the data. Therefore, the software takes trend data (e.g. IM rates) and fits the simplest joinpoint model based on the data. The user supplies the minimum and maximum number of joinpoints. The algorithm starts with the minimum number of joinpoint (e.g. 0 joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model (up to that maximum number). Significance is tested using a Monte Carlo Permutation method. In all models examined in this study, a minimum number of 0 joinpoints and a maximum one of 2 joinpoints were tested. "

If the JPR is going to be an important part of your results, please put in table 3all possible mortality results.

Joinpoint regression was mainly used to identify different segments in the mortality evolution curves either overall or by maternal nationality; that's why only indices showing breaks in the time period examined were presented in Table 3 in the previous version of our manuscript. Following reviewer's suggestion, all mortality results have now been included in Table 3. We have clarified in the footnote of the Table that no break was identified for ENMR in non-Greeks, as well as for LNMR and PNMR measures in Greeks, non-Greeks or the total study population.

Page 3 Line 59

Please change wording to reflect that due to the increase in non-Greek mother IMR,there is no significant change in overall IMRfor all of Greece over the time frameof the study.

It has been revised accordingly. “By contrast, among infants of non-Greek mothers, the low starting IMR/ENMR/LNMR/PNMR increased significantly (max ENMR: +12.5%; 8.6% to 16.5%) leading to a non-significant time-trend pattern overall in Greece”.

Page 4 Line 7

Please remove all wording of “at the limit of statistical significance”. Also, sincethis result is not statistically significant it does not make sense to report thatthere were increases in IMR.

The phrase has been revised and the wording “at the limit of statistical significance” has been removed. Instead it has been written that “joinpoint regression analyses among Greek mothers’ infants indicated non-significant increasing trends of IMR and ENMR following the crisis (+9.3%, 2012-2016, p=0.07 and +10.2%, 2011-2016, p=0.06, respectively)”. The increasing trends in these indices, though statistically non-significant, were in concordance with the results of ITS analyses.

Page 10 Line 59

While the Poisson results show a decrease in IMR and PNMR they do not show a change in ENMR LNMR. Please note.

It has been revised accordingly (page 11). “Overall, during the study-period (2004-2016), among infants born to Greek mothers, Poisson regression analyses showed decreasing trends in IMR and PNMR (-0.9%; 95% CI -1.7% to -0.1% and -1.6%; -3.0% to -0.2% annually, respectively, p=0.02 for each), whereas no significant change in ENMR and LNMR was observed (Table 2)”.

Page 11 Line 2

Please clarify “albeit differentially by place of residence” since the overallmortality rates you’re comparing to are from the whole time period, whereas, theresidence mortality rates are not over the same time period.

In the revised manuscript, the residence mortality rates have been updated in order to include the missing years. Thus, all the data refer to the period 2004-2016. Table 2, as well as the relevant figures in the text (page 11), have been revised accordingly.

Page 12 Line 8

Do you mean to state infants born to Greek mothers? When stating Greek infants, thiscan be confusing as it could be to either Greek or Non-Greek mothers.

It has been changed to “infants born to Greek mothers”.

Page 12 Line 10

The results state that the JPR shows a significant decrease in IMR for infants bornto Greek mothers for 2004-2012 and then no significant change from 2012-2016.However, this result is contradicted by the ITS analysis showing no significantchange in slope but showing an increase in mortality after 2012 (p=0.0001) in theIMR during the same time period. Please report this in your results highlighting thediscordant significance between the two methods.

We highlighted in the Results section the discordant significance between joinpoint regression and ITS analyses. We report in the first paragraph of page 13 that “Compared to the joinpoint regression showing non-significant increases in IMR from 2012 to 2016 for infants born to Greek mothers, ITS analysis showed a significant increase in IMR (p=0.0001) in this population during the same time period; it further identified significant increases in LNMR (p=0.0004) and PNMR trends (p=0.03).”

Page 12 Line 12

Please remove language that the decrease in IMR is due to ENMR. The two measures intable 3 are looking at different time points and each contribution of the othermortality components are not presented in table 3, making it difficult to interpretthat ENMR is the driving force.

It has been revised accordingly. “By joinpoint regression analyses, a break was identified in the IMR curve among infants born to Greek mothers restricting the decreasing IMR trend to the period 2004-2012 (-4.5%; 95% CI -7.6% to -1.3% annually, p=0.01); a significant decline in ENMR trend till 2011 (-6.5%; 95% CI -11.4% to -1.4% annually, p=0.02) was also found (Table 3).”

Page 12 Line 17

First, either the result is significant or not. The pre-specified alpha is 0.05, however, the result is 0.07, thus not significant. Please remove language of “at thelimit of statistical significance”.

It has been removed.

Page 12 Line 17

For the ENMR results post 2011, please also state that the ITS showed no significant increase in trend for the post 2012 time period p=.07, however, that it does show asignificant increase in the post 2010 time period.

It has been revised accordingly (page 13). “As regards the non-significant increases of ENMR trends after the year 2011 by joinpoint regression in infants born to Greek mothers (p=0.06), ITS analysis showed a non-significant increase during the post 2012 time period (p=0.07); however, a significant increase during the post 2010 time period in these infants was observed (p=0.01) (Figure 2)”.

Page 12 Line 22

Please state in results that while the JPR finds a significant increase in IMR fornon-Greek mothers, the ITS depending on when the year of interest is being defined2010 or 2012) the increase is either not significant (2010 p=0.11) or significant(2012 p=0.001).

We have added this statement in the last paragraph of the Results section (page 13). “In infants born to non-Greek mothers, while a significant increase in IMR trends was found by joinpoint regression analyses during the period 2004-2011, by ITS analyses –depending on when the year of interest was being defined (2010 or 2012)- the increase was either not significant (2004-2010, p=0.11) or significant (2004-2012, p=0.001) (Figure 3).

Page 12 Line 27

Please clarify language no statistically significant change may be clearer than nofluctuation in the IMR rate of non-Greek mothers from 2011-2016. Please also statethat the ITS results also show no change in IMR over the 2010/2012 time periods.

Both issues have been revised accordingly (pages 12-13).

Page 12 Line 30

The authors state that the ITS results confirm that of the JPR. However, there areseveral discrepancies between the two methods. Some are highlighted above. Also, theJPR results presented in this paper do not show the ENMR of non-greek mothers, LNMRor PNMR of all mothers. There is no way to interpret that the two regression typesconcur on all of these possible mortality outcomes. Further, there are no presentedresults showing the ITS for the all mothers IMR/ENMR/LNMR/PNMR. Please remove thiswording.

The wording has been removed and the paragraph has been revised in order to describe, as clearly as possible, discrepancies among the results of the two statistical methods (Results section, last paragraph, page 13).

Please correct in the abstract and discussion the results listed above.

Please highlight in the discussion how sensitive the results are depending on themethod used.

The abstract and the Discussion have been revised. Moreover, it has been highlighted in the Discussion (1st paragraph) how sensitive the results are depending on the method used.

VERSION 4 – REVIEW

REVIEWER	Nicholas Moloci Dow Division of Health Services Research, Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America
REVIEW RETURNED	28-Jun-2019

GENERAL COMMENTS	This paper is much improved.