

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of economic austerity and prosperity events on suicide in Greece: a 30-year interrupted time-series analysis
AUTHORS	Branas, Charles; Kastanaki, Anastasia; Michalodimitrakis, Manolis; Tzougas, John; Kranioti, Elena; Theodorakis, Pavlos; Carr, Brendan; Wiebe, Douglas

VERSION 1 - REVIEW

REVIEWER	Alexis Benos Lab of Public Health, Aristotle University Medical School, Thessaloniki, Greece
REVIEW RETURNED	10-Jun-2014

GENERAL COMMENTS	<p>1. in Methods</p> <p>1. first paragraph: the phrase in red is not necessary We included all suicide deaths, regardless of age, since younger individuals who committed suicide, in having the capacity to act to take their own life, also likely had the capacity to perceive how they, individuals they knew, or Greeks generally were impacted by the country's economic situation.</p> <p>2. In the next paragraph the source of the data (E>LSTAS>T) is only necessary, not the goals of the authority...</p> <p>3. in 3rd oaragraph 4th line: n stead of Greek certificates it would be better Death certificates in Greece</p> <p>4. in Conclusions (page 12): Our analysis points to a significant increase in suicides following austerity-related events in Greece. Given these findings, we concur with others that a more robust mental healthcare system that offers more screening, follow-up, and treatment of people with suicidal ideation and accompanying mental health conditions is clearly in order for Greece.^{1,6,36} Less expensive telephone and web-based psychotherapies that build long-term relationships between clients and providers also appear to hold promise in reducing suicidal ideation and might be considered.³⁸ In addition to these potential strategies, enhanced access to everyday activities, goods, and services that are not available in some areas, as well as reduced access to the means of suicide among high-risk populations, are also important strategies to consider.^{18,23,33} While potentially useful, these suicide reduction strategies nevertheless do not directly</p>
-------------------------	---

	<p>address the overarching and persistent issue of the austerity-related events themselves. As future austerity measures are considered, greater weight should be given to the unintended mental health consequences of these measures. Greater attention should also be paid to the public reporting of austerity measures and any subsequent suicide-related events that may follow (including the framing of analyses such as this one), while still maintaining open journalism and accurate reporting.^{39,40} It has been argued that the policies of austerity implemented in Greece have been largely unscientific.¹ Future economic policies, and the public messaging of these policies and related events, may benefit from the findings documented here.</p> <p>All the red highlighted part is not necessary. Propositions and phrases regarding the treatment of mental health conditions that were not mentioned or discussed in the body of the paper. The main aim of the paper is the time-series analysis of the suicide mortality and not the possible preventive and caring activities.</p>
--	---

REVIEWER	A. E. Kentikelenis Research Associate, Department of Sociology, University of Cambridge
REVIEW RETURNED	27-Jun-2014

GENERAL COMMENTS	<p>The Greek economic crisis and the associated policy response has attracted much academic and media attention over the past years. Much debate has centered on the purported health effects of the crisis, and there are ongoing disagreements about whether the crisis has indeed affected the health of the Greek population. The authors of this timely study take on one of the contentious issues – suicides – using data from the past 30 years. Using quantitative techniques, the authors find support for some arguments in the literature that austerity measures of recent years have ‘marked the beginning of significant, abrupt and sustained increases in total suicides’. This study represents an important step in the right direction in examining the purported relationship between economic change and suicides. I believe that this study merits publication in BMJ Open following a number of major revisions. My suggestions have the objective of generating a more nuanced understanding of the situation in the country. The authors may want to consider how to build on these suggestions, and also how to make the paper more appealing to international audiences. Advice on the latter is only cursorily offered below, but the main suggestion is to strengthen the theoretical component of the paper by clearly specifying mechanisms linking crises and suicides on the basis of the available literature (and using those to inform research design).</p> <p>Methodology: I am not convinced about the appropriateness of the methods and variables used. The authors conducted an interrupted time series analysis using ARIMA models. Why have they not used an appropriate time-series regression model controlling for a number of independent variables? Data on growth, unemployment, etc, are</p>
-------------------------	--

available on a monthly basis and could be examined further. There is an established literature on these issues and the authors could draw on this.

This brings me to my concerns about the interruptions the authors examined 'that may have impacted suicide over the study period' (Table 1). The rationale by which these interruptions were selected is not transparent and is defensible only with difficulty. A couple of examples illustrate the point: First, the authors identify Greece's acceptance in the EMU as a key prosperity-related interruption: why use June 2000 and not January 2002, when the Euro was introduced in Greece (arguably a more concrete manifestation of economic change than EMU accession)? Second, on the basis of what data do the authors identify the December 2008 riots following the police shooting a teenager with 'concerns over the economy'? More generally, the rationale for the interruptions selected should – in my view – be informed by plausible mechanisms and theoretical expectations. In the experience of Greece, a so-called Memorandum of Economic and Financial Policies (and associated Memorandum of Understanding) agreed upon with the creditors (IMF, Eur. Commission, ECB) may be passed by the Parliament at time 't', but the actual policies – say, cuts to pensions or unemployment benefits, or labor market reforms – may actually be implemented at time 't+5months'. The authors' approach suggests that it is the former and not the latter that may mark an interruption, and I do not find this convincing. The authors could invest some time in building such a database on when major cuts and reforms were implemented and investigate this further. Spikes in growth and unemployment could also be examined as interruptions. At minimum, the authors should spell out in greater detail which austerity measures or reforms were introduced and why they are expected to matter as an interruption.

The authors examine four time series: (1) all suicides, (2) male suicides, (3) female suicides, and (4) all suicides plus potentially misclassified suicides. With little effort, they could expand this to 6 time series: (1) all suicides, (2) male suicides, (3) female suicides, and (4) all suicides plus potentially misclassified suicides, (5) male suicides plus potentially misclassified suicides, (6) female suicides plus potentially misclassified suicides. Such results could be reported in a Web Appendix if they add nothing new to the analysis. The authors could also stratify by age, at minimum by people of working age and those over the age of 65. I would anticipate that there are different channels via which economic conditions may contribute to suicides among – say – 50-year old men and 80-year old women, and this should somehow be captured in the analysis. On p. 5, the authors state they included all suicide deaths regardless of age. This may be warranted, but I would suggest that they examine the models by excluding underage persons (this could serve as a robustness check).

Theoretical framing

The authors seem to suggest that the periods of prosperity would be associated with declines in suicides (p. 7, 9). This is not what much of the literature suggests. Starting with Durkheim, much research has argued that periods of rapid economic change – whether growth or deep recessions – are associated with increases in suicides. This literature should be cited (and the arguments advanced in the paper correspondingly amended).

Returning to my point above, the authors could explicitly and in detail address which plausible channels link the economic conditions to suicides. Unemployment, household over-indebtedness, the

	<p>flexibilization of the labor market, and cuts to benefits, entitlements, and pensions may be such channels. The Lopez Bernal et al (2013) study that the authors cite is an important step to that direction. The authors only note the potential relevance of unemployment in the Discussion on p. 11: there is a very large literature available documenting such links and it could be cited.</p> <p>Introduction The introduction can be strengthened. First, contra the first sentence, the 'global economic crisis' is not really global, it is concentrated in the developed world, and Europe in particular. In the first paragraph, sentence 3, the authors link austerity measures to 'inaccuracies in national finances'. The 'Greek statistics' debacle is part of the story, but surely it is epiphenomenal to a range of other factors plaguing the Greek economy then (high debt, low competitiveness, overspending on bad projects, waste, etc)? The second paragraph leaves the reader with questions. The authors fall short of arguing that media are overstating the situation. This contradicts their point above that the Greek crisis is the 'foundational economic crisis in Europe'. The crisis is very much real – see unemployment, poverty, and economic contraction rates. The reason that media 'discuss little else' is not presumably because they have nothing better to talk about, but because the situation that Greeks encounter is bleak. That is not to say that media have provided a sophisticated coverage of events (much to the contrary). In any case, the point the authors are trying to make here should be clarified.</p> <p>The authors refer to academic literature 'speculating' about the impact of austerity on health. The authors cite 4 papers, but I invite them to consult the recent systematic review by Simou and Koutsogeorgou for further references.</p> <p>Table 2 The authors could improve the presentation of the table as it is currently hard to read</p>
--	---

REVIEWER	Dr Elias Kondilis Queen Mary, University of London UK
REVIEW RETURNED	05-Aug-2014

GENERAL COMMENTS	<p>This is an interesting and timely study on the impact of the current economic crisis on suicide mortality. It is the first time-trend analysis that uses monthly suicide data from Greece. The paper confirms and builds on previous observations regarding the negative mental health effects of austerity and recession in Europe.</p> <p>The authors might want to consider the following suggestions:</p> <ul style="list-style-type: none"> • The authors classified the highly publicized events that might be associated with the fluctuations of suicide mortality, to prosperity- and austerity-related. It would be useful if the authors could further explain what they mean with these terms. For
-------------------------	--

	<p>example the study defines the period from September 1997 to August 2004 as a “prosperity period”. This assumption is relatively accurate depending on how they define prosperity (Greek economy during that period expanded at a 3% of GDP annual rate while austerity measures were rapidly implemented as the country was struggling to meet the strict criteria for adopting the euro). Similarly, it is unclear how the beginning of the recession in Greece in 2008 (table 1) could be considered as an austerity-related event; one would argue that the contractionary effects of austerity in Greece became evident only by late 2010.</p> <ul style="list-style-type: none"> • It would also be useful if the authors could further explain why they decided to define these periods using media and government archives rather than indicators such as GDP growth rate, unemployment rate, public expenditure or social expenditure growth rates. For example the beginning of the 2008 recession in Greece was heavily underestimated by the Greek government and underrepresented in the media at that time; the official data revealing the true impact of the “Great recession” on Greece’s economic growth in late 2008 were several times revised and publicized with great delay. Therefore, it would be useful if the authors could further explain and develop their hypothesis and distinguish the actual economic facts (eg. recession, unemployment, public expenditure cutbacks) from the way these were presented by the media or the government. • The authors correctly state that one of the limitations of their study is that the significant shifts that they identified may have been related to other unmeasured by the study events. This limitation is more than evident in the way they interpret the abrupt increase of male suicide mortality in April 2012. The authors suggest that this increase is probably related to a highly publicised suicide of a Greek pensioner in Syntagma square in Athens. Nevertheless, many other factors might have contributed to this sharp increase, such as the announcement of the Greek elections (11th April 2012) which triggered the discussions on the possible withdrawal of Greece from the Eurozone (“Grexit”), creating a situation of economic uncertainty; the approval by the Greek parliament (March 2012) of the second Economic Adjustment Programme which almost tripled the amount of fiscal consolidation measures that the country agreed to implement as part of its loan arrangement with the Troika. • Page 5, §2, “the toxic economic conditions accompanying the austerity measures – high unemployment, inflation, etc –”: Based on the fact that inflation has been constantly decreasing since 2010 and Greece is now actually facing deflation, the authors might want to revise their previous statement. • Page 5, §3: The authors should double-check the numbering of their references.
--	---

REVIEWER	Dr Melina Dritsaki Clinical Trials Unit Warwick Medical School University of Warwick Coventry UK
REVIEW RETURNED	08-Aug-2014

GENERAL COMMENTS

Comments

Overall, this paper is a considerable contribution to research in suicide trends in Greece and particular in relation to austerity measures. I would like to raise some points which I hope make some constructive criticism to the current work

1. What is missing from the paper is a definition of “prosperity” and “austerity”, in order to understand more deeply why and how the authors chose the 12 events/statements. It’s not very clear how the 12 events were identified?
2. Also, one would have expected to see a mixture of both “prosperity” and “austerity”-related interruptions during the whole period of the study starting from 1983-2012. Instead the authors limit the analysis to 2 sub-periods with pre-specified cut-off points. They cluster the sample period in a way that it does not meet the objectives of the paper with respect to its time series nature. This is very critical and affects the whole interpretation of the results hence after.
3. There is no description of the population under examination in the paper. There is brief description of the statistical tests being performed in the first paragraph of the section “statistical analyses”, but tables or narratives are missing.
4. Results are presented in terms of means. The mean as a value is merely meaningful if we don’t know what is the total population under consideration (which is the denominator?).
5. The authors have split the analysis by sex. Is there an underlying theory or hypothesis testing to support this split? What about other socioeconomic factors ie ethnicity, income group, education attainment, marital status ?
6. On page 8 under “Statistical analyses” authors refer to the plots of autocorrelation function and partial autocorrelation function, from which apart from seasonality tests we could check time series stationarity , as well as estimating the values for p,d,q in order to identify with precision the ARIMA (p,d,q) (P,D,Q)s model. Figures referring to identification that authors have used are missing from the paper.
7. Page 14, Figure 1, authors present the monthly trends in suicide across Greece: (a) All suicides (b) male suicides, (c) female suicides and (d) all suicides & potentially misclassified suicides. This figure clearly suggests that all variables have a seasonality. It is not clear how seasonality has been eliminated from the time series. To be more specific I will highlight the methods of eliminating seasonality which are:
 - Multiplicative
 - Additive
 - Pseudo additive and
 - Log-additiveHave the authors used any of the aforementioned methods and which one? If so this should be referred to in the text.

8. Time series seasonality can be tested with the F statistic (F-tests for seasonality) or with moving seasonality test as long as ANOVA tables have been constructed or with parametric tests with Kruskal-Wallis statistics.
9. Moreover, authors could also specify if the data used apart from seasonality there is evidence of trend either linear, or polynomial or cycle or even irregular component by applying relevant tests
10. It is not also clear in the text which methods have been used to estimate the models (least squares or exact maximum likelihood)
11. Estimations as presented on page 15 and figure 2 do not present with clarity the estimated models with all statistical and diagnostic tests for example adjusted R-square for goodness of fit or the Ljung and Box-Q statistic for autocorrelation.

How the paper could be further developed:

1. I strongly believe that a potential link of the ELSTAT database with demographics, socioeconomic characteristics, ethnicity, age, location, employment status, education level, marital status, etc as well as health outcome measures will give a more comprehensive picture of the suicide trends.
2. The way austerity and prosperity- related events have been chosen it seems that they are all media-driven. So, there is a lot of discussion around how media effect people's short and long-term mental wellbeing and to what extent they magnify or not the reality in Greek economy and society. Obviously suicide coverage on the media is more attractive during recession and austerity periods rather than prosperous times, as expected
3. For policy making reformations it is equally important not only to know the trends of suicide and its relation of major economic events (prosperity/austerity measures) but also to understand the population who committed suicide. Social interactions and environment is undoubtedly co-related with mental health well-being, but need to separate those in order to understand the problem to its holistic context.
4. There is no inference about the healthcare system in Greece throughout the paper nor any description of the current mental health services or description of the mental health status of the population under consideration. The conclusion makes a considerable logic loop, proposing "a more robust mental healthcare system...". This statement does not link with the previous sections of the paper and cannot be drawn as

	<p>a natural conclusion and recommendation for policy makers. Hence, I believe it is invalid as a concluding remark.</p> <p>5. Also, the results from the application of ARIMA models are understated in terms of their predictive power. ARIMA models, whose first researchers to used them where Box and Jenkins (1970) [who are not mentioned anywhere in the text], have managed to answer if time series could be represented in an ARIMA model (p,d,q) or <input type="text"/> and then make predictions about their future trends. There are no predictions made in the current analysis, or any recommendations.</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name Alexis Benos

Institution and Country Lab of Public Health,

Aristotle University Medical School,

Thessaloniki, Greece

Please state any competing interests or state 'None declared': None declared

If you have any further comments for the authors please enter them below.

1. *in Methods*

1. *first paragraph: the phrase in red is not necessary*

We included all suicide deaths, regardless of age, since younger individuals who committed suicide, in having the capacity to act to take their own life, also likely had the capacity to perceive how they, individuals they knew, or Greeks generally were impacted by the country's economic situation.

Thank you for pointing this out. We have now removed the portion of this paragraph as suggested by the reviewer.

2. *In the next paragraph the source of the data (E>LSTAS>T) is only necessary, not the goals of the authority...*

We have greatly reduced the wording and description of the ELSTAT in this paragraph.

3. in 3rd paragraph 4th line: instead of Greek certificates it would be better Death certificates in Greece

This change has also now been made.

4. in Conclusions

(page 12):

Our analysis points to a significant increase in suicides following austerity-related events in Greece. Given these findings, we concur with others that a more robust mental healthcare system that offers more screening, follow-up, and treatment of people with suicidal ideation and accompanying mental health conditions is clearly in order for Greece.^{1,6,36} Less expensive telephone and web-based psychotherapies that build long-term relationships between clients and providers also appear to hold promise in reducing suicidal ideation and might be considered.³⁸ In addition to these potential strategies, enhanced access to everyday activities, goods, and services that are not available in some areas, as well as reduced access to the means of suicide among high-risk populations, are also important strategies to consider.^{18,23,33}

While potentially useful, these suicide reduction strategies nevertheless do not directly address the overarching and persistent issue of the austerity-related events themselves. As future austerity measures are considered, greater weight should be given to the unintended mental health consequences of these measures. Greater attention should also be paid to the public reporting of austerity measures and any subsequent suicide-related events that may follow (including the framing of analyses such as this one), while still maintaining open journalism and accurate reporting.^{39,40} It has been argued that the policies of austerity implemented in Greece have been largely unscientific.¹ Future economic policies, and the public messaging of these policies and related events, may benefit from the findings documented here.

All the red highlighted part is not necessary. Propositions and phrases regarding the treatment of mental health conditions that were not mentioned or discussed in the body of the paper. The main aim of the paper is the time-series analysis of the suicide mortality and not the possible preventive and caring activities.

Thank you and we agree. We have now removed these paragraphs in our Conclusion section.

Reviewer: 2

Reviewer Name A. E. Kentikelenis

Institution and Country Research Associate, Department of Sociology, University of Cambridge

Please state any competing interests or state 'None declared': None declared

The Greek economic crisis and the associated policy response has attracted much academic and media attention over the past years. Much debate has centered on the purported health effects of the crisis, and there are ongoing disagreements about whether the crisis has indeed affected the health of the Greek population. The authors of this timely study take on one of the contentious issues – suicides – using data from the past 30 years. Using quantitative techniques, the authors find support for some arguments in the literature that austerity measures of recent years have 'marked the beginning of significant, abrupt and sustained increases in total suicides'. This study represents an important step in the right direction in examining the purported relationship between economic change and suicides. I believe that this study merits publication in BMJ Open following a number of major revisions. My suggestions have the objective of generating a more nuanced understanding of the situation in the country. The authors may want to consider how to build on these suggestions, and also how to make the paper more appealing to international audiences. Advice on the latter is only cursorily offered below, but the main suggestion is to strengthen the theoretical component of the paper by clearly specifying mechanisms linking crises and suicides on the basis of the available literature (and using those to inform research design).

Very worthwhile suggestions and we have endeavored to address all of these.

Methodology:

I am not convinced about the appropriateness of the methods and variables used. The authors conducted an interrupted time series analysis using ARIMA models. Why have they not used an appropriate time-series regression model controlling for a number of independent variables? Data on growth, unemployment, etc., are available on a monthly basis and could be examined further. There is an established literature on these issues and the authors could draw on this.

The methods we used for our analysis are highly appropriate to answer the research questions and study aims we have specifically posed in terms of the acute impact of events as abrupt interruptions-

in-time. The reviewer is correct that there are other regression modeling approaches that could have been used, but these other models are typically applied to the study of measures of long-term trends, such as growth and unemployment, not specific and abrupt interruptions-in-time, such as the austerity events that we chose for study in our paper. Growth and unemployment are longer term processes-through-time and can be distinguished from acute onset events that are abrupt interruptions-in-time. To be clear, our paper's intent was to study these abrupt interruptions-in-time using ARIMA models to control for other independent variables, including long-term trends, through standard, well-accepted detrending and model fitting techniques. The paper's intent was not to overtly study these other long-term trends nor was it necessary to include these trends as covariates because of how the ARIMA approach fits a model to the observed outcome time series (in support of this, see the references below – Box and Jenkins, McCleary and Hay, McCain and McCleary, Cook and Campbell).

Moreover, a very recent paper by Antonakakis and Collins in *Social Science and Medicine* reported on an analysis of long-term sociodemographic and economic conditions and suicide in Greece (see reference below - Antonakakis and Collins). We are not inclined to repeat this analysis but now reference this recent paper and discuss its important findings and their relevance to our current manuscript. Our study nevertheless remains of distinct value, different from the recent Antonakakis paper in its analysis and testing of the impact of specific, abrupt economic austerity and prosperity events on monthly suicides in Greece. Based on this recently published paper and the reviewer's excellent comments, we have made several major changes throughout our paper, including very important changes to the title of the paper and its stated aims, in distinguishing it from prior work on long-term trends and suicide and clearly demonstrating that its methods are firmly established, long-standing, appropriate, and valid.

In addition, and to quote McCleary and Hay, page 20: "whereas regression models can be built on the basis of prior research and/or theory, ARIMA models must be built empirically from the data. Because ARIMA models must be identified from the data to be modeled, relatively long time series are required. No time series that we analyze ... is shorter than 50 observations long...use this as a rule of thumb when deciding to analyze time series data from an ARIMA or regression approach." The prior work by Antonakakis and Collins, and other prior works, while being highly important contributions, analyzed time series of yearly/annual dataset of less than $n=50$ observations. Our dataset is a monthly time series consisting of $n=360$ monthly observations and, as such, is again most appropriately analyzed using ARIMA models.

The ARIMA technique enables us to fit a model to the data that accurately predicts the number of suicides that occurred each month in Greece over the time series. It does this by predicting each monthly observation of suicides as a function of the number of suicides that occurred in one *or more* past months, rather than from a regression modeling approach that only predicts suicides from covariates and fixed lags of covariates (e.g., only from *one* prior, fixed time period as a lag, as in only the past month). Again, in this way, ARIMA modeling thus permits us to empirically determine the appropriate lag from the data themselves, as opposed to making potentially incorrect assumptions about the fixed magnitudes of the lags. (McCleary and Hay, Chapter 2).

Supporting references that have now been added to the paper:

Box G, Jenkins G. (1976). *Time series analysis: Forecasting and control*, San Francisco: Holden-Day.

McCleary R, Hay R, Jr. Applied time series analysis for the social sciences. Beverly Hills: Sage; 1980.

McCain LJ, McCleary R. The statistical analysis of the simple interrupted time-series quasi-experiment. In: Cook TD, Campbell DT, eds. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Boston: Houghton Mifflin; 1979.

Cook DT, Campbell DT. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Boston: Houghton Mifflin; 1979.

Antonakakis N, Collins A. The impact of fiscal austerity on suicide: on the empirics of a modern Greek tragedy. *Social Science & Medicine* 2014;112: 39-50

This brings me to my concerns about the interruptions the authors examined 'that may have impacted suicide over the study period' (Table 1). The rationale by which these interruptions were selected is not transparent and is defensible only with difficulty. A couple of examples illustrate the point: First, the authors identify Greece's acceptance in the EMU as a key prosperity-related interruption: why use June 2000 and not January 2002, when the Euro was introduced in Greece (arguably a more concrete manifestation of economic change than EMU accession)?

We agree and have now added January 2002 as a new interruption-in-time that may have impacted suicide over the study period. In fact, after adding this interruption to our analyses, we found that it was significantly associated with an abrupt, but temporary decrease in male suicide. This was the only prosperity-related event that corresponded with a significant change in suicide and we have now added this new, important finding to our paper and abstract. Thank you for the excellent suggestion.

Second, on the basis of what data do the authors identify the December 2008 riots following the police shooting a teenager with 'concerns over the economy'?

We agree and have now removed December 2008 as an interruption-in-time in our analysis.

More generally, the rationale for the interruptions selected should – in my view – be informed by plausible mechanisms and theoretical expectations. In the experience of Greece, a so-called Memorandum of Economic and Financial Policies (and associated Memorandum of Understanding) agreed upon with the creditors (IMF, Eur. Commission, ECB) may be passed by the Parliament at time 't', but the actual policies – say, cuts to pensions or unemployment benefits, or labor market reforms – may actually be implemented at time 't+5months'.

This is a reasonable point but because actual "implementation" can be interpreted and defined as beginning in many different ways, it was not possible to accurately identify the exact number of months that passed before the "implementation" onset of each interruption that we studied, i.e., the "+5" described by the reviewer was not a constant interval and could have been +1, +6, or +12, etc. What was known with greater certainty, for instance, was the month of passage by Parliament and this was the type of interruption that we theorized had an effect on suicide because it was the also the

type of interruption that was recognizable to the news media and was widely disseminated to the Greek public who were at risk for suicide.

The authors' approach suggests that it is the former and not the latter that may mark an interruption, and I do not find this convincing. The authors could invest some time in building such a database on when major cuts and reforms were implemented and investigate this further. Spikes in growth and unemployment could also be examined as interruptions. At minimum, the authors should spell out in greater detail which austerity measures or reforms were introduced and why they are expected to matter as an interruption.

This is a useful comment and we have now provided greater detail in terms of which austerity measures or reforms were introduced and why they were expected to matter as a interruptions-in-time that could affect suicide.

The authors examine four time series: (1) all suicides, (2) male suicides, (3) female suicides, and (4) all suicides plus potentially misclassified suicides. With little effort, they could expand this to 6 time series: (1) all suicides, (2) male suicides, (3) female suicides, and (4) all suicides plus potentially misclassified suicides, (5) male suicides plus potentially misclassified suicides, (6) female suicides plus potentially misclassified suicides. Such results could be reported in a Web Appendix if they add nothing new to the analysis. The authors could also stratify by age, at minimum by people of working age and those over the age of 65. I would anticipate that there are different channels via which economic conditions may contribute to suicides among – say – 50-year old men and 80-year old women, and this should somehow be captured in the analysis. On p. 5, the authors state they included all suicide deaths regardless of age. This may be warranted, but I would suggest that they examine the models by excluding underage persons (this could serve as a robustness check).

This is another useful and important comment, and we conducted an analysis of potentially misclassified suicides to broadly investigate whether this bias was a threat to the validity of our study. We found that it was not, and in fact our use of this misclassification test is, to the best of our knowledge, the first time this sort of robustness test has been done in the longitudinal analysis of suicides. While possible, we have little reason to think that the misclassification of suicide in Greece would occur differently by gender, and this is beyond the scope of our paper's aims to determine. Similarly, additional analyses stratified or restricted by age are very interesting, although beyond the scope of our analyses. However, we are in agreement with the reviewer's thoughtful comment, and have now added text in the paper that these important analyses be pursued in future studies. Thank you.

Theoretical framing

The authors seem to suggest that the periods of prosperity would be associated with declines in suicides (p. 7, 9). This is not what much of the literature suggests. Starting with Durkheim, much research has argued that periods of rapid economic change – whether growth or deep recessions – are associated with increases in suicides. This literature should be cited (and the arguments advanced in the paper correspondingly amended).

We now see this as a possibility and thank the reviewer for pointing it out. We now discuss this two-sided possibility in our paper (i.e. that periods of rapid economic change – whether growth or deep recessions – are associated with increases in suicides) and have cited additional, relevant literature, including the work of Durkheim.

Returning to my point above, the authors could explicitly and in detail address which plausible channels link the economic conditions to suicides. Unemployment, household over-indebtedness, the flexibilization of the labor market, and cuts to benefits, entitlements, and pensions may be such channels. The Lopez Bernal et al (2013) study that the authors cite is an important step to that direction. The authors only note the potential relevance of unemployment in the Discussion on p. 11: there is a very large literature available documenting such links and it could be cited.

We have now added text to our paper more explicitly discussing plausible channels that link economic conditions, including those mentioned by the reviewer, to suicides. As suggested, we draw further from the Lopez Bernal reference and have also now added the very recent 2014 paper by Antonakakis and Collins in Social Science and Medicine that reported on an analysis of long-term sociodemographic and economic conditions and suicide in Greece.

Introduction

The introduction can be strengthened. First, contra the first sentence, the 'global economic crisis' is not really global, it is concentrated in the developed world, and Europe in particular.

We have now changed the first sentence of the Introduction to be more specific.

In the first paragraph, sentence 3, the authors link austerity measures to 'inaccuracies in national finances'. The 'Greek statistics' debacle is part of the story, but surely it is epiphenomenal to a range of other factors plaguing the Greek economy then (high debt, low competitiveness, overspending on bad projects, waste, etc.)? The second paragraph leaves the reader with questions. The authors fall short of arguing that media are overstating the situation. This contradicts their point above that the Greek crisis is the 'foundational economic crisis in Europe'. The crisis is very much real – see unemployment, poverty, and economic contraction rates. The reason that media 'discuss little else' is not presumably because they have nothing better to talk about, but because the situation that Greeks encounter is bleak. That is not to say that media have provided a sophisticated coverage of events (much to the contrary). In any case, the point the authors are trying to make here should be clarified.

We have now changed text in our Introduction to better clarify and frame our study as per the reviewer's suggestion.

The authors refer to academic literature 'speculating' about the impact of austerity on health. The authors cite 4 papers, but I invite them to consult the recent systematic review by Simou and Koutsogeorgou for further references.

Excellent recommendation. We have now consulted this systematic review and have added it to our paper. (Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: A systematic review. Health Policy 2014; 115: 111-119)

Table 2

The authors could improve the presentation of the table as it is currently hard to read.

We have now added some section breaks to make this Table easier to read.

Reviewer: 3

Reviewer Name Dr Elias Kondilis

Institution and Country Queen Mary, University of London

UK

Please state any competing interests or state 'None declared': None declared

REVIEWER'S REPORT

This is an interesting and timely study on the impact of the current economic crisis on suicide mortality. It is the first time-trend analysis that uses monthly suicide data from Greece. The paper confirms and builds on previous observations regarding the negative mental health effects of austerity and recession in Europe.

The authors might want to consider the following suggestions:

· *The authors classified the highly publicized events that might be associated with the fluctuations of suicide mortality, to prosperity- and austerity-related. It would be useful if the authors could further explain what they mean with these terms. For example the study defines the period from September 1997 to August 2004 as a "prosperity period". This assumption is relatively accurate depending on how they define prosperity (Greek economy during that period expanded at a 3% of GDP annual rate while austerity measures were rapidly implemented as the country was struggling to meet the strict criteria for adopting the euro). Similarly, it is unclear how the beginning of the recession*

in Greece in 2008 (table 1) could be considered as an austerity-related event; one would argue that the contractionary effects of austerity in Greece became evident only by late 2010.

Thank you for this useful comment. We have now removed the “prosperity” and “austerity” periods and their cut-off points to avoid any confusion. These sub-period analyses were merely added to provide secondary information, over and above the interruptions themselves, but can be omitted in response to the reviewers’ comments, with no change in the paper’s primary aims.

· It would also be useful if the authors could further explain why they decided to define these periods using media and government archives rather than indicators such as GDP growth rate, unemployment rate, public expenditure or social expenditure growth rates. For example the beginning of the 2008 recession in Greece was heavily underestimated by the Greek government and underrepresented in the media at that time; the official data revealing the true impact of the “Great recession” on Greece’s economic growth in late 2008 were several times revised and publicized with great delay. Therefore, it would be useful if the authors could further explain and develop their hypothesis and distinguish the actual economic facts (e.g. recession, unemployment, public expenditure cutbacks) from the way these were presented by the media or the government.

We searched news media archives and other publications to identify austerity-related and prosperity-related events that occurred in Greece during the study period and that were highly publicized and thus likely detected by the Greek public. In being highly publicized and widely known to the general public, these events were hypothesized as potentially having had an impact on the mental health and well-being of individual Greeks thereby potentially leading to increases or decreases in suicide. Owing to the reviewers’ comments, this has now been changed and more clearly described in the paper and its references, including references to media reports from October 2008.

· The authors correctly state that one of the limitations of their study is that the significant shifts that they identified may have been related to other unmeasured by the study events. This limitation is more than evident in the way they interpret the abrupt increase of male suicide mortality in April 2012. The authors suggest that this increase is probably related to a highly publicised suicide of a Greek pensioner in Syntagma square in Athens. Nevertheless, many other factors might have contributed to this sharp increase, such as the announcement of the Greek elections (11th April 2012) which triggered the discussions on the possible withdrawal of Greece from the Eurozone (“Grexit”), creating a situation of economic uncertainty; the approval by the Greek parliament (March 2012) of the second Economic Adjustment Programme which almost tripled the amount of fiscal consolidation measures that the country agreed to implement as part of its loan arrangement with the Troika.

We agree and have now added this important point to our Limitations section.

· Page 5, §2, “the toxic economic conditions accompanying the austerity measures – high unemployment, inflation, etc. –”: Based on the fact that inflation has been constantly decreasing since 2010 and Greece is now actually facing deflation, the authors might want to revise their previous statement.

Yes, thank you. We have now revised the text in our Introduction section based on this overlooked point.

· *Page 5, §3: The authors should double-check the numbering of their references.*

Thank you – we have now checked these references.

Declaration of competing interests

I declare that I have no competing interests

Reviewer: 4

Reviewer Name Dr Melina Dritsaki

Institution and Country Clinical Trials Unit

Warwick Medical School

University of Warwick

Coventry

UK

Please state any competing interests or state 'None declared': None declared

Please see attached file

Comments

Overall, this paper is a considerable contribution to research in suicide trends in Greece and particular in relation to austerity measures. I would like to raise some points which I hope make some constructive criticism to the current work.

Thank you very much for your compliment and for your thoughtful and constructive suggestions. We respond to each of your comments below.

1. What is missing from the paper is a definition of “prosperity” and “austerity”, in order to understand more deeply why and how the authors chose the 12 events/statements. It’s not very clear how the 12 events were identified?

We searched news media archives and other publications to identify austerity-related and prosperity-related events that occurred in Greece during the study period and that were highly publicized and thus likely detected by the Greek public. In being highly publicized and widely known to the general public, these events were hypothesized as potentially having had an impact on the mental health and well-being of individual Greeks thereby potentially leading to increases or decreases in suicide. Owing to the reviewers’ comments, this has now been changed and more clearly described in the paper and its references

2. Also, one would have expected to see a mixture of both “prosperity” and “austerity”-related interruptions during the whole period of the study starting from 1983-2012. Instead the authors limit the analysis to 2 sub-periods with pre-specified cut-off points. They cluster the sample period in a way that it does not meet the objectives of the paper with respect to its time series nature. This is very critical and affects the whole interpretation of the results hence after.

We have now removed the “prosperity” and “austerity” periods and their cut-off points. These sub-period analyses were merely added to provide secondary information, over and above the interruptions themselves, but can be omitted in response to the reviewers’ comments with no change in the paper’s primary aims.

3. There is no description of the population under examination in the paper. There is brief description of the statistical tests being performed in the first paragraph of the section “statistical analyses”, but tables or narratives are missing.

We have added text to describe the basic demographic and economic characteristics of the population of Greece during the study period.

4. Results are presented in terms of means. The mean as a value is merely meaningful if we don’t know what is the total population under consideration (which is the denominator?).

The mean values referred to by the reviewer are the mean number of additional suicides that occurred per month after a specific interruption-in-time compared to the mean number of suicides that occurred per month before the interruption-in-time. We were unclear about how these were calculated. For example, for total suicide (male and female combined), we report that there was an increase starting in June 2011 and that after that time, the mean number of suicides was 34.7% greater than before that time (which translated to mean that an additional 11.2 suicides started occurring per month). So, in this example, the “denominator” was the mean number of suicides that had been occurring per month before June 2011. We have now added text to the Methods section of the paper explaining these calculations in response to the reviewer’s concern.

5. The authors have split the analysis by sex. Is there an underlying theory or hypothesis testing to support this split? What about other socioeconomic factors i.e. ethnicity, income group, education attainment, marital status ?

We split the analysis by sex given that, in much of the world and in Greece, suicide deaths are more common among men than women. Moreover, gender-specific differences have been demonstrated among suicide rates and general economic trends in Greece (Antonakakis and Collins, Social Science and Medicine, 2014). Given this evidence, we wanted to conduct the study in a way that would let us identify whether there was evidence that the impact of austerity measures on suicide was different between men and women. We have now added text and references to the paper describing this underlying theory. We did not have any hypotheses about other socioeconomic factors, as stratification variables, and thus have left these for consideration in future analyses and manuscripts.

6. On page 8 under “Statistical analyses” authors refer to the plots of autocorrelation function and partial autocorrelation function, from which apart from seasonality tests we could check time series stationarity , as well as estimating the values for p,d,q in order to identify with precision the ARIMA (p,d,q) (P,D,Q)s model. Figures referring to identification that authors have used are missing from the paper.

We should have made it clear that we used plots of the autocorrelation function (ACF) that partial autocorrelation function (PACF) to test the residuals to make sure that they were white noise (to make sure they did not contain autocorrelation in generally and not contain seasonal autocorrelation), but that we did not present these in the paper. This paper is written for the audience of BMJ Open which is a general audience, as opposed to the type of audience of a methods or statistics or epidemiology journal. We think it is not warranted to publish plots of the ACF and PACF of the residuals as those are too technical. However, to be responsive to the reviewer’s important interest in these diagnostics, below we present the ACF of the residuals for total suicide, as an example. As you can see, none of the correlations within 24 lags were statistically significant (we would see a spike at lag 12 and lag 24 if there was seasonal autocorrelation in the residuals) and the Q statistic was 13.6, which is not statically significant and provides evidence that the residuals overall were white noise.

ACF res3.

NAME OF THE SERIES RES3
TIME PERIOD ANALYZED 13 TO 360
MEAN OF THE (DIFFERENCED) SERIES 0.1396
STANDARD DEVIATION OF THE SERIES 6.8108
T-VALUE OF MEAN (AGAINST ZERO) 0.3823

AUTOCORRELATIONS

1- 12	.08	.06	-.03	-.01	.07	-.01	.04	-.01	.03	.01	.07	-.05
ST.E.	.05	.05	.05	.05	.05	.05	.05	.05	.05	.05	.05	.05
Q	2.2	3.5	3.8	3.8	5.6	5.6	6.2	6.3	6.6	6.6	8.4	9.4
13- 24	.02	.04	-.03	-.03	.05	.05	-.02	-.04	-.00	.01	.02	.02
ST.E.	.06	.06	.06	.06	.06	.06	.06	.06	.06	.06	.06	.06
Q	9.6	10.1	10.4	10.7	11.6	12.5	12.6	13.3	13.3	13.3	13.4	13.6

-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4 0.6 0.8 1.0

+-----+-----+-----+-----+-----+-----+-----+-----+-----+

|

1	0.08	+ IXX+
2	0.06	+ IXX+
3	-0.03	+ XI +
4	-0.01	+ I +
5	0.07	+ IXX+

6	-0.01	+ I +
7	0.04	+ IX +
8	-0.01	+ I +
9	0.03	+ IX +
10	0.01	+ I +
11	0.07	+ IXX+
12	-0.05	+ XI +
13	0.02	+ IX +
14	0.04	+ IX +
15	-0.03	+ XI +
16	-0.03	+ XI +
17	0.05	+ IX +
18	0.05	+ IX +
19	-0.02	+ I +
20	-0.04	+ XI +
21	0.00	+ I +
22	0.01	+ I +
23	0.02	+ I +
24	0.02	+ IX +
--		

7. Page 14, Figure 1, authors present the monthly trends in suicide across Greece: (a)

All suicides (b) male suicides, (c) female suicides and (d) all suicides & potentially misclassified suicides. This figure clearly suggests that all variables have a

seasonality. It is not clear how seasonality has been eliminated from the time series.

To be more specific I will highlight the methods of eliminating seasonality which are:

- Multiplicative
- Additive
- Pseudo additive and
- Log-additive

Have the authors used any of the aforementioned methods and which one? If so this should be referred to in the text.

No, we did not use any of these methods. We used methods that fit various types of ARIMA models to multiple time series; this process involved identifying whether seasonality existed (i.e., seasonal autocorrelation) and removing seasonality from the time series. Removing seasonality was accomplished by differencing the time series at each lag as was indicated. In Table 1, in the footnote, we report the type of ARIMA model that was fit to each of our time series. For example, the total suicide time series was fit with an ARIMA(0,0,0)(0,1,1)₁₂ model. By convention, the value “1” that we have presented in bold in the second set of parentheses mean that we differenced the time series seasonally. That is, from each value, we subtracted the number of suicides that occurred 12 months earlier to remove seasonality. In presenting our ARIMA model specifications in Table 1, we also report the method that was used to eliminate seasonality. Box and Jenkins (1976) or McCleary and Hay (1980) that we have now referenced in response to the reviewer’s concern, can be consulted for further information and details of the role that differencing plays in time series analysis.

8. Time series seasonality can be tested with the F statistic (F-tests for seasonality) or with moving seasonality test as long as ANOVA tables have been constructs or with parametric tests with Kruskal-Wallis statistics.

Thank you for this further comment. As noted above, we used conventional ARIMA modeling techniques to identify and account for seasonality in our time series data. The procedure we follow is the procedure recommended by McCleary and Hay (1980). The fact that seasonality existed and needed to be controlled for was clear from the plots of the ACF and PACF of the suicide time series.

9. Moreover, authors could also specify if the data used apart from seasonality there is evidence of trend either linear, or polynomial or cycle or even irregular component by applying relevant tests

Another excellent question. In the beginning of the Results section, we did also report that we examined in general whether a “linear trend” was present in any of our time series. We also found no evidence of any other type of cycle and have now added text to the paper reporting this.

If a time series exhibits a trend, it means that there is a systematic increase or decrease in the level of the time series. McCain and McCleary (1979, p. 236-237) write that most time series in the social sciences do exhibit trend. They go on to say that, fortunately, trend can almost always be removed from a time series by differencing it (i.e., from each value, subtracting the value one observation earlier; or if the trend is seasonal, then subtracting from each value the value one season earlier, e.g., 12 observations earlier for monthly data).

If we detrend a time series by differencing it, doing so does not change any of the deterministic qualities of the time series, especially those representing intervention effects that we want to test for significance. Also, it does not mean that trend is not incorporated into the statistical ARIMA model.

Here is how differencing is described by McCain and McCleary (1979, p, 236-237. Consider the sequence:

1, 2, 3, 4, 5, ..., N

If this sequence is treated as a time series, it will have a secular trend and needs to be differenced before fitting the time series with an ARIMA model. If we difference the series, that is, subtract the first observation from the second, the second from the third, and so on:

$$2 - 1 = 1$$

$$3 - 2 = 1$$

$$4 - 3 = 1$$

$$5 - 4 = 1$$

and so on, we get a new time series:

1, 1, 1, 1,,, 1

which has no trend and thus is ready for ARIMA modeling. The reason that detrending a time series does not prevent us from still testing for the impact of austerity measures is because we simply add another parameter to the time series model to represent the trend: a constant. If the above sequence were the time series of interest, the value of 1 would be added to the statistical ARIMA model to represent the slope of the data, and it would be tested to determine whether it is significantly different than 0.

After we detrended each time series, we did include a constant in each model to represent the trend. However, the coefficient was not significant for total suicide, and not for male suicide, and not for female suicide. This means that there was no evidence that the level of suicide trended statistically upward or downward in Greece over the study period, despite the fact that, to the eye, the graphs of the time series may suggest that a gradual trend was present. We have now added text to make it clear that there was not a remarkable trend in suicide over the study period and reference this detrending process in the paper.

10. It is not also clear in the text which methods have been used to estimate the models

(least squares or exact maximum likelihood)

The models were fit initially with conditional maximum likelihood and then retested with exact

maximum likelihood. We have added this sentence to the manuscript.

11. Estimations as presented on page 15 and figure 2 do not present with clarity the estimated models with all statistical and diagnostic tests for example adjusted Rsquare for goodness of fit or the Ljung and Box-Q statistic for autocorrelation.

The R-square value is not the best measure of goodness of fit for a time series and we have not included it here (see: McCleary R, Hay R, Jr. Applied time series analysis for the social sciences. Beverly Hills: Sage; 1980; P. 127). This is because, over long periods of time, values hover around the mean level of the time series and so most of the variance will be accounted for by the mean and relatively little will be accounted for by the coefficients of the ARIMA model (either autoregressive parameters or moving average parameters). However, in line with the reviewer's useful comment, in our original manuscript we stated that the Q-statistics we calculated indicated a good fit, but we did not state the Q-statistic values. In response, we have now added these values to the revised manuscript.

How the paper could be further developed:

1. I strongly believe that a potential link of the ELSTAT database with demographics, socioeconomic characteristics, ethnicity, age, location, employment status, education level, marital status, etc. as well as health outcome measures will give a more comprehensive picture of the suicide trends.

While we agree and thank the reviewer for suggesting this, we want to maintain our paper's original intent of testing the impact of specific, abrupt economic austerity and prosperity events on suicide in Greece. This original intent was not as clear as it could have been in our original submission and we have now changed much of the text in our paper, as well as the title of the paper itself, to better reflect this. We have also now added some information about demographics and the economy over the period under study. The many other sociodemographic factors suggested by the reviewer are excellent, and we intend to more closely consider these in future analyses and manuscripts. Moreover, a very recent paper by Antonakakis and Collins in Social Science and Medicine reported on an analysis of sociodemographic and economic conditions much like those suggested by the reviewer (Antonakakis N, Collins A. The impact of fiscal austerity on suicide: on the empirics of a modern Greek tragedy. Social Science & Medicine 2014;112: 39-50). We now reference this recent paper. Our study remains of value, different and distinct from the recent Antonakakis paper however in its analysis and testing of the impact of specific, abrupt economic austerity and prosperity events on suicide in Greece.

2. The way austerity and prosperity- related events have been chosen it seems that they are all media-driven. So , there is a lot of discussion around how media

effect people's short and long-term mental wellbeing and to what extent the magnify or not the reality in Greek economy and society. Obviously suicide coverage on the media is more attractive during recession and austerity periods rather than prosperous times, as expected

We have now added language to the paper to make our choice of austerity and prosperity-related events for analysis clearer.

3. For policy making reformations it is equally important not only to know the trends of suicide and it's relation of major economic events (prosperity/austerity measures) but also to understand the population who committed suicide. Social interactions and environment is undoubtedly co-related with mental health wellbeing, but need to separate those in order to understand the problem to its holistic context.

Our paper's aim was not to study long-term trends in suicide. We are studying whether specific, acute events had an abrupt impact on the number of suicides that occurred thereafter. Regarding social interactions and the environment, an investigator would need data individual-level data to make valid inferences about mechanisms that are leading people to commit suicide. We used aggregate-level data in form of a time series that was appropriate to test our hypotheses about austerity measures. Future studies of individual-level data may give further insight and we have now added language calling for such studies.

4. There is no inference about the healthcare system in Greece throughout the paper nor any description of the current mental health services or description of the mental health status of the population under consideration. The conclusion makes a considerable logic loop, proposing "a more robust mental healthcare system....". This statements does not link with the previous sections of the paper and cannot be drawn as a natural conclusion and recommendation for policy makers. Hence, I believe it is invalid as a concluding remark.

We agree and have now deleted this and several other sentences in our Conclusion section.

5. Also, the results from the application of ARIMA models are understated in terms of their predictive power. ARIMA models, whose first researchers to used them where Box and Jenkins (1970) [who are not mentioned anywhere in the text], have managed to answer if time series could be represented in an ARIMA model (p,d,q) or $t t$ $d \phi (L)_ Y = \delta + \theta (L)\epsilon$ and then make predictions about their future trends. There are no predictions made in the current analysis, or any recommendations.

Investigators who want to conduct a time series analysis to make forecasts about how the time series will continue beyond the period of observation would be best served by building a more complex multivariate ARIMA model, which is better at making forecasts than are univariate ARIMA models, like the ones we are using in our study. Univariate time series models typically give reliable forecasts for only the first two or three observations in the future (McCleary and Hay, p, 205). However, because forecasting was not an aim of our study, we have retained our original univariate ARIMA model structure, which functions equally well for the analysis of interruptions-in-time. Thanks to the reviewer for their excellent comment.

We now also cite Box and Jenkins (1976) in response to the reviewer's additional concern.

REFERENCES

- Box GEP, Jenkins GM. Time-Series Analysis: Forecasting and Control. San Francisco: Holden-Day; 1976.
- McCleary R, Hay R, Jr. Applied time series analysis for the social sciences. Beverly Hills: Sage; 1980.
- McCain LJ, McCleary R. The statistical analysis of the simple interrupted time-series quasi-experiment. In: Cook TD, Campbell DT, eds. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Boston: Houghton Mifflin; 1979.

VERSION 2 – REVIEW

REVIEWER	A. E. Kentikelenis University of Cambridge
REVIEW RETURNED	19-Sep-2014
GENERAL COMMENTS	I welcome the opportunity to read the updated version of the paper by Branias and colleagues. The authors provide an original and

	important contribution to knowledge, and I have no doubts that the paper will be well-received and cited. I recommend its publication and applaud the authors for taking on this significant and timely question.
--	---

REVIEWER	Dr Melina Dritsaki Clinical Trials Unit Warwick Medical School University of Warwick Coventry, CV4 7AL UK
REVIEW RETURNED	02-Oct-2014

GENERAL COMMENTS	The authors managed to successfully address most of the points previously suggested for improving the paper. Also, they have provided adequate reasoning to why they have considered, but not implemented other comments. Therefore, I am happy to accept the manuscript for publication.
-------------------------	---