PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Seasonal variation in mortality secondary to acute myocardial infarction in England and Wales: a secondary data analysis
AUTHORS	Ogbebor, Osakpolor; Odugbemi, Babatunde; Maheswaran, Ravi; Patel, Kavya

VERSION 1 – REVIEW

REVIEWER	William B. Grant Sunlight, Nutrition and Health Research Center, USA
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	This paper should be cited and discussed as it analyzed seasonal variations in mortality rates in the U.S. It noted a minor increased mortality rate from January 25 to March 21, which was attributed to low vitamin D status. Grant WB, Bhottoa HP, Boucher BJ. Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene expression, and infections. J Steroid Biochem Mol Biol. 2017 Oct;173:5-12 The possible role of vitamin D must be discussed. Additional papers on vitamin D and AMI: Milazzo V, De Metrio M, Cosentino N, Marenzi G, Tremoli E. Vitamin D and acute myocardial infarction. World J Cardiol. 2017 Jan 26;9(1):14-20. Gondim F, Caribé A, Vasconcelos KF, Segundo AD, Bandeira F. Vitamin D Deficiency Is Associated with Severity of Acute Coronary Syndrome in Patients with Type 2 Diabetes and High Rates of Sun Exposure. Clin Med Insights Endocrinol Diabetes. 2016 Sep 1;9:37-41. Tokarz A, Kusnierz-Cabala B, Kuźniewski M, Gacoń J, Mazur-Laskowska M, Stępień EŁ. Seasonal effect of vitamin D deficiency in patients with acute myocardial infarction. Kardiol Pol. 2016;74(8):786-792. Roy A, Lakshmy R, Tarik M, Tandon N, Reddy KS, Prabhakaran D. Independent association of severe vitamin D deficiency as a risk of acute myocardial infarction in Indians. Indian Heart J. 2015 Jan-Feb;67(1):27-32. Ng LL, Sandhu JK, Squire IB, Davies JE, Jones DJ. Vitamin D and prognosis in acute myocardial infarction. Int J Cardiol. 2013 Oct 3;168(3):2341-6.

REVIEWER	Ville Kytö

	Turku University Hospital, Finland
REVIEW RETURNED	02-Nov-2017

GENERAL COMMENTS	This is interesting paper using a large data-base. Results are interesting and potentially important. Major shortcoming is however the currently inadequate statistical testing of presented results. Paper is generally well written. Below are my comments: Abstract: - Please calculate the significance of seasonal mortality variation (see below). - Please calculate the significance of a)overall AMI mortality trend and b)EWM trend (see below) - Statement ”Seasonal variation in mortality secondary to AMI does occur in England and Wales.” in conclusion appears to be wrong. Seasonal variation is very likely to be true (although authors need to test it), but there may not be a declining trend for it (although this needs to be tested as well). Methdology: - Formula MA (y, d) = MO (y, d). R. is given, but it remains unclear what is .R in this. Should it be X? - In neg bin modelling age is included in the model. Was there any gender related differences? - All statistical methods used should be given in methods (e.g. correlation analysis for temperature vs. mortality). - What statistical program was used? How did you define significant p-value? Results: - Percentages for excess winter mortality are given. Significance of these is however not statistically tested. This should be done (and details given in methods). - Significance of a) overall AMI mortality and b) EWM mortality in relation to time (trend) must be tested if statements about their significance are given. There are multiple tests available for this (e.g. Negative binomial regression). - Table 2: Please give % of EWM also in totals - Table 3: o Results of neg bin regression are given as OR. In methods the regression link is however stated to be log. Please review this. Using log link should result in RR and using logit link as OR. o OR/RR is calculable for regression coefficient and SE –thus these are not necessary. It would improve the table to give EWM % results instead. Discussion: - What is known about AMI occurrence in winter vs. other seasons? - What is known about seasonal variation of other ischemic cardiovascular diseases? E.g. in-hospital mortality of ischemic stroke has seasonal variation (reference Ann Med. 2017 Jun;49(4):310-318.).

VERSION 1 – AUTHOR RESPONSE

There are several factors which could be possibly associated with excess winter mortality include seasonal variations in solar ultraviolet-B (UVB) doses and serum 25-hydroxyvitamin D [25(OH)D] concentrations, gene expression, ambient temperature and humidity, UVB effects on environmental pathogen load, environmental pollutants and allergens, and photoperiod (or length of day)1. Amongst these factors, possibly 25(OH)D concentration (<20 ng/ml) would be modifiable risk factor and its supplementation might reduce death rates significantly in winter months. Several RCTs are ongoing and these will provide results to clarify whether vitamin D deficiency as a causal and reversible factor to prevent cardiovascular disease.

1. Grant WB, Bhottoa HP, Boucher BJ. Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene expression, and infections. J Steroid Biochem Mol Biol. 2017 Oct;173:5-12

- Please calculate the significance of seasonal mortality variation (see below). Seasonal mortality was statistically significantly higher in winter months compared to non-winter months for all individual years under observation and overall (p<0.001).
- Please calculate the significance of a)overall AMI mortality trend – significant trend for reduction in AMI associated mortality was observed over the period (p<0.001) and b)EWM trend - significant trend remains relatively the same in excess winter mortality was observed over the period (p<0.001).

- Statement "Seasonal variation in mortality secondary to AMI does occur in England and Wales." in conclusion appears to be wrong. Seasonal variation is very likely to be true (although authors need to test it). The statement holds true for winter mortality. The paper shows there is excess winter mortality compared than other months. The methodology used to establish a odds ratio is emphasized in excess with mortality which shows a odds of dying during winter over the study period to be 1.17 (CI - 1.17, 1.18).

- Formula MA (y, d) = MO (y, d). R. is given, but it remains unclear what is .R in this. Should it be X?
R is the comparability ratio: the ICD-10/ICD-9 comparability ratio for acute myocardial infarction 0.9889 was used to adjust ICD-9 coded death counts to ICD 10. The analysis was then carried out as though the entire data was coded using ICD 10.
Anderson RN, M. Miniño AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD–9 and ICD–10: preliminary estimates. Natl Vital Stat. 2001; 49 (2): 1-32.

- In neg bin modelling age is included in the model. Was there any gender related differences?

Sex distribution was not available in the data provided. That was one of the limitations of the study.

- All statistical methods used should be given in methods (e.g. correlation analysis for temperature vs. mortality).
* Direct correlation between mean monthly temperature and monthly mortality rate was carried out with a significant level set at <0.05

* Addition trend analysis with ARiMA and forecasting was carried out with SPSS at a significant level < 0.05

- What statistical program was used? How did you define significant p-value?

All analysis was carried out using the Statistical package for social sciences (SPSS) version 19. Significant p – value was define as less then 0.05.

- Percentages for excess winter mortality are given. Significance of these is however not statistically tested. This should be done (and details given in methods).

These percentages are a measure of excess winter mortality which is the excess winter mortality index and represents the addition percentage during winter. IT is more described as a odds ratio (the excess winter mortality ratio). Find attached a table which reflects this and the confidence intervals.

Year Period Excess winter mortality ratio (CI)

Age:	0 to 64 years	65 to 74 years	75 years +	Total
97/98	1.09 (1.07, 1.11)	1.16 (1.15, 1.18)	1.16 (1.15, 1.17)	1.15 (1.14, 1.16)
98/99	1.12 (1.09, 1.14)	1.18 (1.17, 1.20)	1.23 (1.22, 1.24)	1.20 (1.19, 1.21)
99/00	1.15 (1.13, 1.17)	1.17 (1.16, 1.19)	1.29 (1.28, 1.31)	1.24 (1.24, 1.25)
00/01	1.07 (1.05, 1.09)	1.11 (1.09, 1.13)	1.15 (1.14, 1.16)	1.13 (1.12, 1.14)
01/02	1.14 (1.11, 1.16)	1.15 (1.13, 1.17)	1.16 (1.15, 1.17)	1.16 (1.15, 1.17)
02/03	1.11 (1.08, 1.13)	1.15 (1.13, 1.17)	1.17 (1.16, 1.18)	1.16 (1.15, 1.17)
03/04	1.15 (1.13, 1.18)	1.10 (1.08, 1.12)	1.17 (1.16, 1.18)	1.15 (1.14, 1.16)
04/05	1.09 (1.06, 1.11)	1.21 (1.19, 1.23)	1.21 (1.19, 1.22)	1.19 (1.18, 1.20)
Total	1.11 (1.10, 1.13)	1.16 (1.14, 1.17)	1.19 (1.18, 1.20)	1.17 (1.17, 1.18)

o Results of neg bin regression are given as OR. In methods the regression link is however stated to be log. Please review this. Using log link should result in RR and using logit link as OR.

The table is supposed to read relative risk. The paragraph describing the results in the table clearly states relative risk.

“A regression analysis was carried using a negative binomial regression to estimate the excess winter mortality ratio and age (Table 3). The relative risk of excess mortality in age groups 65 to 74 years and 75 years and above was 1.36 and 2.45 respectively compared to the younger age group”. Find table in additional file

OR/RR is calculable for regression coefficient and SE –thus these are not necessary. It would improve the table to give EWM % results instead.
- See amended table

VERSION 2 – REVIEW

REVIEWER	Ville Kytö Turku University Hospital, Heart Center, Finland
REVIEW RETURNED	02-Jan-2018

GENERAL COMMENTS	Manuscript has improved with revision. I have two further minor comments: 1. Term "mortality" is repeated in abstract conclusion.

	2. In Methods it is stated "This was done using this formula: MA (y, d) = MO (y, d). R. ". It is still unclear what ". R." means.

REVIEWER	William B. Grant Sunlight, Nutrition and Health Research Center, United States
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	Abstract Conclusion: Excess winter mortality secondary to AMI does occur in England and Wales. Excess winter deaths due to AMI have remained high despite decline in overall mortality. More research is needed to identify the relationship of sex, temperature, acclimatization and excess winter deaths due to AMI. Comment: the role of UVB exposure and vitamin D should also be included in such a study. Studies over time have observed an increase in mortality rate during winter months1-3. This appears to be a global phenomenon with evidence of excess winter mortality occurring in a number of European countries, including the United Kingdom4,5, Japan6 , Brazil7 , Canada2, the United States3 New Zealand 8 and likely any country where a winter season occurs. Comment: Might be worthwhile to mention results from two countries at temperature extremes: Douglas AS, al-Sayer H, Rawles JM, Allan TM. Seasonality of disease in Kuwait. Lancet. 1991 Jun 8;337(8754):1393-7. Grjibovski AM, Nurgaliyeva N, Kosbayeva A, Menne B. No association between temperature and deaths from cardiovascular and cerebrovasculardiseases during the cold season in Astana, Kazakhstan--the second coldest capital in the world. Int J Circumpolar Health. 2012;71. Factors that are considered to play a role include socioeconomic status17, influenza18,19 and age16. Comment: Also, UVB/vitamin D. R values should be given to two decimal places. Besides the demonstrable winter excess, the monthly mortality rate plot showed a double peak. A peak in mortality, which was clearly above the mean mortality rate, was observed around the month of March. This second peak in mortality was less than that seen in the months of December and January. Comment: Possible explanation: Holiday effect near year end: Knight J, Schilling C, Barnett A, Jackson R, Clarke P. Revisiting the "Christmas Holiday Effect" in the Southern Hemisphere. J Am Heart Assoc. 2016 Dec 22;5(12). pii: e005098 Phillips D, Barker GE, Brewer KM. Christmas and New Year as risk factors for death. Soc Sci Med. 2010 Oct;71(8):1463-71. Shah M, Bhalla V, Patnaik S, Maludum O, Lu M, Figueredo VM. Heart failure and the holidays. Clin Res Cardiol. 2016 Oct;105(10):865-72. Vitamin D effect in March, when 25-hydroxyvitamin D concentrations are lowest Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45

	y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007 Mar;85(3):860-8. There are several factors which could be possibly associated with excess winter mortality and this may include seasonal variations in solar ultraviolet-B (UVB) doses and serum 25-hydroxyvitamin D [25(OH)D] concentrations, gene expression, ambient temperature and humidity, UVB effects on environmental pathogen load, environmental pollutants and allergens, and photoperiod (or length of day)25. Amongst these factors, possibly 25(OH)D concentration (<20 ng/ml) would be modifiable risk factor and its supplementation might reduce death rates significantly in winter months. Several RCTs are ongoing and these will provide results to clarify whether vitamin D deficiency as a causal and reversible factor to prevent cardiovascular disease. Comment: A combination of ecological, observational studies and clinical trials and studies of mechanisms provide the best evidence regarding the role of UVB and vitamin D on diseases with large seasonality such as cardiovascular disease and respiratory tract infections. See, e.g., Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study Group. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010 Oct 1;106(7):963-8. Grübler MR, März W, Pilz S, Grammer TB, Trummer C, Müllner C, Schwetz V, Pandis M, Verheyen N, Tomaschitz A, Fiordelisi A, Laudisio D, Cipolletta E, Iaccarino G. Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence. Rev Endocr Metab Disord. 2017 Jun;18(2):259-272. Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C, Olsson H. Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. J Intern Med. 2016 Oct;280(4):375-87. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583. Mirhosseini N, Vatanparast H, Kimball SM. The Association between Serum 25(OH)D Status and Blood Pressure in Participants of a Community-Based Program Taking Vitamin D Supplements. Nutrients. 2017 Nov 14;9(11). pii: E1244. Sluyter JD, Camargo CA Jr, Stewart AW, Waayer D, Lawes CMM, Toop L, Khaw KT, Thom SAM, Hametner B, Wassertheurer S, Parker KH, Hughes AD, Scragg R. Effect of Monthly, High-Dose, Long-Term Vitamin D Supplementation on Central Blood Pressure Parameters: A Randomized Controlled Trial Substudy. J Am Heart Assoc. 2017 Oct 24;6(10). pii: e006802 Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes. 2012 Nov 1;5(6):819-29. Unfortunately, most vitamin D clinical trials reported or in progress to date were not properly designed or conducted, so it may be awhile

	before clinical trials complete the story re vitamin D. Grant WB, Boucher BJ, Bhattoa HJ, Lahore. Why vitamin D clinical trials should be based on 25-hydroxyvitamin D concentrations. JSBMB. J Steroid Biochem Mol Biol. 2017 Aug 22. pii: S0960-0760(17)30223-6. doi: 10.1016/j.jsbmb.2017.08.009. [Epub ahead of print] Grant WB, Boucher BJ. Randomized controlled trials of vitamin D and cancer incidence: A modeling study. PLos One. 2017 May 1;12(5):e0176448. Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev. 2014 Jan;72(1):48-54. Since the authors have cited the recent paper on the seasonality of death rates in the U.S. as an afterthought, it would be very useful if they would include an analysis of the role of UVB and vitamin D in the study from the beginning and evaluate their possible contributions in parallel to those of temperature. It should not require any additional data processing but would involve reviewing more of the literature on the health benefits of vitamin D.

VERSION 2 – AUTHOR RESPONSE

Many thanks for the suggestions from the 2 reviewers. Changes have been made to the main manuscript.

Reviewer: 1

- Changes in the manuscript have been made to reflect the possible impact of vitamin D. This was done both in the background and discussion session.

- R values have been rounded up to two decimal places

- The results from the paper from Kazakhstan was already alluded to in the discussion of the winter paradox. This discussion was expanded further to included behavioral factors. This particular paper was not referenced.

Reviewer 2

- R is ICD-10/ICD-9 comparability ratio. For example 10, 000 deaths coded with ICD-9 becomes 9889 deaths when compared to data coded with ICD-10.

VERSION 3 – REVIEW

REVIEWER	William B. Grant Sunlight, Nutrition and Health Research Center, USA
REVIEW RETURNED	02-Feb-2018

GENERAL COMMENTS	Thanks for making the changes. Vitamin D levels Should be 25-hydroxyvitamin D levels

	There is the suggestion that correction of vitamin deficiency may reduce the cardiovascular risk. Should be There is the suggestion that correction of vitamin D deficiency may reduce the cardiovascular risk.

VERSION 3 – AUTHOR RESPONSE

Dear editor

Thank you very much for your helpful comments and the reviewers' feedback.

We thank Reviewer 1 for his kind feedback and have made the changes to document.

We also agree with the editor and have refined the strengths and limitations as can be seen in the updated manuscript. We also incorporated the limitations of the study and generalisability in the last paragraph of the discussion. Also attached, as an additional file, is the strobe checklist. We used a combined checklist as the there is no checklist that clearly fits with our study design.

Also the abstract has been edited as required and the patient and public involvement statement was introduced in the methods.

We hope this amply addresses the issues identified with our paper. If you require any clarification or further amendments, please do not hesitate to contact us.