PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Salt reduction in England from 2003 to 2011 – Its relationship to blood pressure, stroke and ischemic heart disease mortality
AUTHORS	He, Feng; Pombo-Rodrigues, Sonia; MacGregor, Graham

VERSION 1 - REVIEW

REVIEWER	Simon Capewell University of Liverpool, UK
REVIEW RETURNED	29-Dec-2013

GENERAL COMMENTS	Blood pressure and cardiovascular mortality in England from 2003 to 2011 − The impact of salt reduction. He et al. BMJ Open 2013-004549 This is an interesting paper. Basically very good. However, it would be even better after a few minor amendments. In a very constructive spirit, I a few suggestions are offered below. ABSTRACT Basically fine “Non-institutionalised population surveys” is too brief. Need to add some further details about the HSE & NDNS surveys in a couple of brief sentences Last sentence of the Abstract Results needs to be more explicit: “Although salt intake was not measured in these participants, the fact that the average salt intake in a random sample of the UK population fell by 15% during the same period, suggests that these falls in BP would be largely attributable to the reduction in salt intake, RATHER THAN ANTI-HYPERTENSIVE MEDICATIONS.” Last sentence of Abstract Conclusions needs to be stronger: “ The reduction in salt intake is likely to be a major contributor to the fall in BP from 2003 to 2011 in England. As a result, it would also have SUBSTANTIALLY contributed to the decreases in stroke and IHD mortality.” Strengths and Limitations (page 3) Need to add another one, please: The observed BP fall was approximately twice as large as might have been predicted purely from the decline in dietary salt intake; this merits further research. INTRODUCTION Basically fine.

	First paragraph, third sentence (“The recent analysis of global disease burden….”) is a bit strong, it would benefit from adding the word “approximately” here and there. Second paragraph is weak, having overlooked a highly relevant paper Bajekal et al. PLoS Medicine 2012 9(6): e1001237. It needs to reference this analysis and devote a sentence or two to the key messages. Crucially, the authors need to state somewhere in the intro, the population systolic BP salt reduction relationship from their own Cochrane review: (BMJ 2013;346:f1325 doi: 10.1136/bmj.f1325): a reduction of 4.4 g/day salt reduces systolic blood pressure by an average of 4.18 mmHg. METHODS Basically fine. RESULTS Basically fine DISCUSSION Basically fine. Discussion needs to acknowledge that the observed BP fall was approximately twice as large as might have been predicted purely from the observed decline in dietary salt intake; (BMJ 2013;346:f1325 doi: 10.1136/bmj.f1325): this is interesting merits some further brief comment. Page 11, line 21 “However, the small proportion of the population in Scotland, Wales and Northern Ireland (altogether accounting for 16% of the total UK population) would indicate that the bias, if any, would be small. “ This sentence needs to be re-written to incorporate the main messages from Chen Ji, et al; BMJ Open 2013;3:e002246 . Spatial variation of salt intake in Britain and association with socioeconomic status. The Discussion also needs to acknowledge, deWilde et al. Trends in Blood Pressure in England: Good Treatment or Good Luck? . J Epidemiol Community Health 2012;66:A41 doi:10.1136/jech-2012-201753.106 Particularly their conclusion that “less than 25% of the decline in male SBP is attributable to treatment. " The Conclusions look a bit weak, and are currently vulnerable to the “So What?” comment. They need to be strengthened. It would be nice to see some sort of public health message, perhaps along the lines of " no room for complacency", and "the pressing need for effective UK policies to achieve further reductions in salt intake, aiming for a specific target, and mentioning either the WHO <5g or the NICE <3g/day target? "

REVIEWER	Caryl Nowson School of Exercise and Nutrition Sciences Deakin University 221, Burwood Highway Burwood Victoria 3125
REVIEW RETURNED	02-Jan-2014

GENERAL COMMENTS	The conclusion in the abstract seems to overstate the contribution of salt intake to reduction in blood pressure, when clearly there are a number of factors that contributed to this fall, which probably include sodium. This paper documents the estimated fall in mean population blood pressure and cardiovascular mortality in England from 2003 to 2011 as derived from health survey data conducted in a representative population sample and relates this data to the mean fall in dietary salt intake that occurred in a separate survey conducted in 2000/2001, 2005/06, 2008 and 2011 utilising 24hr urine collections. The authors we assumed that the changes in BP, after adjusting for the above variables which included almost all other factors known to be related to BP, were largely attributable to the changes in population salt intake which occurred during the same period. There are a number of issues that require clarification. 1. A separate analysis was performed on those not taking anti-hypertensive therapy to assess the predictors of systolic and diastolic blood pressure. Although a number of factors were including in the model to predict blood pressure including year of measurement, age, gender, ethnic group, income, alcohol, fruit and vegetable intake and bmi which explained 28% of the variance of SBP and 16% of DBP. However smoking status does not seem to have been included and I would have thought that this would have a major impact. 2. As BMI increased, presumably this was associated with a significant increase in BP? It would be useful to include data on the beta coefficients, 95%CI and p values for the variables entered into the regression model. 3. Is it possible to identify the types of stroke where the reduction was seen eg haemorrhagic/ischaemic and how this might be relevant to reduction in salt intake. 4. It seems rather an overstatement the reduction is salt intake is likely to be a major contributor to the fall in BP when the analysis presented only indirectly supports this conclusion as it was not possible to test the effect of salt reduction in the sample populations analysed as there were different populations. Perhaps a conclusion that a reduction in salt intake in during this period is a likely contributor to this reduction. 5. Is it possible for the authors to comment on the robustness/limitations of comparing data across different sample populations across different years, particularly for variables such as fruit and vegetable intake as the mean number of serves per day does vary with possibly reduction in intake from 2006 to 2011; 3.8 to 3.6 serves per day. Minor points 1. Abstract suggest re-wording ‘It is likely that all of these factors, along with improvements in the treatments of BP,

	cholesterol…..contributed to falls in stroke as one of the variables listed was an increase in BMI which would be likely to increase not decrease stroke risk (unless that was not the case in the analysis).

REVIEWER	Nancy J Aburto UN World Food Programme Italy
REVIEW RETURNED	13-Jan-2014

GENERAL COMMENTS	The manuscript entitled “Blood pressure and cardiovascular mortality in England from 2003 to 2011 − The impact of salt reduction” presents a very interesting correlation between population salt intake as measured by 24-hour urinary sodium excretion and population based mortality from IHD and stroke. Nonetheless, there are a number of issues with the way in which the manuscript is presented that require addressing. These issues are cross-cutting and affect terminology and presentation throughout the manuscript. 1) The title states “…impact of salt reduction”, which implies a casual relationship that cannot be determined through the analysis presented in this manuscript and should be tempered. 2) The objective is stated as “… determine the extent to which the reduction in salt intake [that] occurred during this period contributed to those changes [in stoke and IHD mortality and BP].” (page 2, lins9-10). The wording in this objective implies that the manuscript will be able to address the causal relationship between salt reduction and the outcomes of interest. The causality between salt and the health outcomes cannot be addressed through the analysis conducted and the manuscript should be adjusted to redress that implication: a) Page 4, line 33 – “to determine the extent to which the reduction in salt….”. Suggest more tempered wording such as “to determine the relationship between reduction in salt intake and BP and mortality from stroke and IHD…” b) Page 8, line 27-28 – “…that these falls in BP were likely to be attributable to the reduction in population salt intake that occurred during this period.” Appears to overstate what the results suggest. Suggest more tempered wording. c) Page 10, line 22 – “… salt intake led to a fall in population BP…”. Statement suggests causality and should be revised based on the fact that this analysis cannot address causality. 3) In a similar tone to the previous comment, the wording throughout the manuscript implies that the analyses definitively show a causal and strong relationship between salt consumption and BP and mortality from IHD and stroke, and this reviewer feels that doing so detracts from the important results that the manuscript does actually demonstrate. a) Page 2, line 52 – “major” should be removed b) Page 3, line 38 – “.. BP were largely attributable to the reduction…” should be tempered c) Page 8, lines 45 – 47 - the words “stongly” and “major” should be edited to be more guarded d) Page 11, line 28 – the word “major” should be removed 4) Though stated multiple times that the analysis include “almost all other factors known to be related to BP”, it does seem that some important variables were not included. Based on the description of the regression model on page 6, lines18 – 28, cholesterol intake, family history of high BP, previous history of high BP or heart disease or stroke, physical activity level, and (perhaps most

	importantly) smoking were not included in the model. These are examples of variables not taken into account that have an effect on BP, and there are surely others. Given this limitation in the model, this reviewer suggests the following: a) Remove the wording of “almost all other factors” throughout the manuscript. b) Address how variables that were measured might be proxies for other variables (e.g. F&V intake for dietary fiber(?)) c) Address the limitations to the model based on the variables that could not be included in the model d) Explain why smoking (of all variables) was not included in the model 5) Abstract: a) There is an inconsistency in lines 32 and 34 where BMI increased and then it is said “it is likely that all of these factors… contributed to the falls in stroke and IHD”. This inconsistency should be fixed b) Based on adjustments in the manuscript, the abstract should be adjusted accordingly especially with regards to the use of more tempered terminology to express the results and conclusions. 6) Article summary: a) See previous comments on overstating the results and implications thereof b) under key messages, the way in which salt intake was measured should be noted c) the second limitation should be clarified to more clearly explain that salt intake was not measured in those who BP and mortality were measured d) there should be a limitation regarding from which populations these samples were taken (i.e. UK v England v England/Wales). This statement should be adjusted based on adjustments in the manuscript (see below). 7) Introduction: a) See previous comments on overstating a realistic objective for this analysis b) Page 4, line 6 – requires a reference c) The introduction should provide more detail on what sample comprised the surveys d) Page 4, line 36 – refers to CVD mortality whereas the manuscript refers to IHD and stroke mortality. The wording should be consistent throughout the manuscript. 8) Methods: a) Upper age limit of sample should be noted b) Page 5, lines 40-45 – There needs to be more detail on the death data. The authors should be explicit on how the each type of death was defined. The lack of explanation of how death by each type of morbidity is defined is a weakness in the paper because any limitations or biases that the definition may produce cannot be assessed because of lack of clarity. c) Page 6, line 13 – How were BP treatment and other treatments defined? Did this include only pharmacological treatments? Would medically supervised weight loss treatments? Exercise regimens? Others? Be included? Again limitations (or strengths) based on these definitions cannot be assessed because of lack of detail here. 9) Results: a) See previous comments on overstating the results and implications thereof 10) Discussion: a) See previous comments on overstating the results and implications thereof b) Page 9, lines 2-18 – This paragraph seems to be entirely

	misplaced in the manuscript. If there is a question regarding the 'pay for performance programme', then it should be introduced in the introduction. If that is not a research question (which this reviewer assumes it is not), then the discussion regarding this programme should be reintroduced in a different, more coherent form. c) The strengths and limitations should be greatly expanded especially with regards to how the varying background populations from which the survey samples were drawn may bias the results (i.e. surveys from UK vs. England vs. England/Wales etc.) There are perhaps urban/rural differentiations in those populations or socio-economic differences that should be more clearly discussed. Another limitation (or potential strength) that should be discussed is how variables were measured in all surveys. d) A statistician should discuss how 16% of the population (page 11, line 23) might bias results. 11) The manuscript would be improved by another round of copy editing to correct grammatical and typographical errors.

VERSION 1 – AUTHOR RESPONSE

1) The title states "…impact of salt reduction", which implies a casual relationship that cannot be determined through the analysis presented in this manuscript and should be tempered.

Answers: We have changed the title. Please see the answers to Point 1 raised by the Editors for details.

2) The objective is stated as "… determine the extent to which the reduction in salt intake [that] occurred during this period contributed to those changes [in stoke and IHD mortality and BP]." (page 2, lins9-10). The wording in this objective implies that the manuscript will be able to address the causal relationship between salt reduction and the outcomes of interest. The causality between salt and the health outcomes cannot be addressed through the analysis conducted and the manuscript should be adjusted to redress that implication:
a) Page 4, line 33 – "to determine the extent to which the reduction in salt….". Suggest more tempered wording such as "to determine the relationship between reduction in salt intake and BP and mortality from stroke and IHD…"

Answers: We have modified the Abstract and Introduction as suggested.

b) Page 8, line 27-28 – "…that these falls in BP were likely to be attributable to the reduction in population salt intake that occurred during this period." Appears to overstate what the results suggest. Suggest more tempered wording.

Answers: We have modified this sentence to "…that the falls in BP were likely to be largely attributable to the reduction in population salt intake that occurred during this period."

c) Page 10, line 22 – "… salt intake led to a fall in population BP…". Statement suggests causality and should be revised based on the fact that this analysis cannot address causality.

Answers: We have modified this sentence to "… a reduction in salt intake was related to a fall in population BP…".

3) In a similar tone to the previous comment, the wording throughout the manuscript implies that the analyses definitively show a causal and strong relationship between salt consumption and BP and mortality from IHD and stroke, and this reviewer feels that doing so detracts from the important results that the manuscript does actually demonstrate.

Answers: We have re-worded a number of phrases using a more modest term in several places throughout the paper.

a) Page 2, line 52 – “major” should be removed

Answers: We have changed “a major” to “an important”.

b) Page 3, line 38 – “.. BP were largely attributable to the reduction…” should be tempered

Answers: This phrase has not been changed as we have used the word “largely”.

c) Page 8, lines 45 – 47 - the words “strongly” and “major” should be edited to be more guarded

Answers: We have deleted “strongly” and changed “the major” to “an important”.

d) Page 11, line 28 – the word “major” should be removed

Answers: We have changed “a major” to “an important”.

4) Though stated multiple times that the analysis include “almost all other factors known to be related to BP”, it does seem that some important variables were not included. Based on the description of the regression model on page 6, lines18 – 28, cholesterol intake, family history of high BP, previous history of high BP or heart disease or stroke, physical activity level, and (perhaps most importantly) smoking were not included in the model. These are examples of variables not taken into account that have an effect on BP, and there are surely others. Given this limitation in the model, this reviewer suggests the following:
a) Remove the wording of “almost all other factors” throughout the manuscript.

Answers: We have modified the phrase “almost all other factors” to “almost all other major factors”. The major factors that determine population BP include salt intake, fruit and vegetable consumption, overweight and obesity, alcohol consumption and physical activity. In our analysis, we have considered all of these major factors with the exception of physical activity level which was recorded in 2003, but not in the 2011 survey. We have added this limitation to the Discussion.
Professor Caryl Nowson has raised a similar point on smoking. We have re-analysed the data by including smoking as an additional independent variable in the regression model. The results were unchanged and smoking was not significantly associated with either systolic (P=0.327) or diastolic BP (P=0.957).

b) Address how variables that were measured might be proxies for other variables (e.g. F&V intake for dietary fiber(?))

Answers: We agree that fruit and vegetable intake might be proxies for dietary fiber and potassium intake. Indeed, it is well established that a higher potassium intake lowers blood pressure, and one of the mechanisms by which a higher consumption of fruit and vegetable lowers blood pressure is through its high potassium content. We did not add such discussions to our manuscript as we feel that this is not very relevant to our key messages.

c) Address the limitations to the model based on the variables that could not be included in the model

Answers: Amended as suggested.

d) Explain why smoking (of all variables) was not included in the model

Answers: A similar point was also raised by Professor Caryl Nowson. Please see answers to that point for details.

5) Abstract:
a) There is an inconsistency in lines 32 and 34 where BMI increased and then it is said “it is likely that all of these factors… contributed to the falls in stroke and IHD”. This inconsistency should be fixed

Answers: This has been corrected.

b) Based on adjustments in the manuscript, the abstract should be adjusted accordingly especially with regards to the use of more tempered terminology to express the results and conclusions.

Answers: The abstract has been modified to reflect other changes made to the manuscript in relation to “more tempered terminology” as suggested.

6) Article summary:
a) See previous comments on overstating the results and implications thereof

Answers: Modified as suggested.

b) under key messages, the way in which salt intake was measured should be noted

Answers: We have already reported that salt intake was measured by 24-hour urinary sodium. This has been highlighted in yellow in the revised manuscript.

c) the second limitation should be clarified to more clearly explain that salt intake was not measured in those who BP and mortality were measured

Answers: In the “Key messages”, we have already reported that “Salt intake, a major determinant of population BP, was not included in this analysis because it was not measured in these participants.” This has been highlighted in yellow in the revised manuscript.

d) there should be a limitation regarding from which populations these samples were taken (i.e. UK v England v England/Wales). This statement should be adjusted based on adjustments in the manuscript (see below).

Answers: We have added a detailed discussion on this point to the Discussion Section.

7) Introduction:
a) See previous comments on overstating a realistic objective for this analysis

Answers: We have re-written the Introduction.

b) Page 4, line 6 – requires a reference

Answers: A reference has been added.

c) The introduction should provide more detail on what sample comprised the surveys

Answers: We have modified the last sentence of the Introduction to briefly describe the sample surveyed “…we analysed the data from a series of health surveys carried out in a nationally representative sample of the population in England.” Because we used the data from several surveys, it is difficult to provide details for the samples of all surveys. In the method section, we have referred to the original report of each survey. Additionally, we have reported our inclusion criteria and the number of participants included in our analysis from each survey in the Methods, Table 1 and the Abstract

d) Page 4, line 36 – refers to CVD mortality whereas the manuscript refers to IHD and stroke mortality. The wording should be consistent throughout the manuscript.

Answers: We have made this change throughout the manuscript.

8) Methods:
a) Upper age limit of sample should be noted

Answers: There is no upper age limit for the Health Survey for England. The age range was 19 to 64 years for individuals who completed 24-hour urine collections in the National Diet and Nutrition Survey. We have added this to the Methods. Additionally, we have added a paragraph reporting the results from a separate analysis that included only individuals aged 19-64 years. We have also added a brief discussion to the Discussion section.

b) Page 5, lines 40-45 – There needs to be more detail on the death data. The authors should be explicit on how the each type of death was defined. The lack of explanation of how death by each type of morbidity is defined is a weakness in the paper because any limitations or biases that the definition may produce cannot be assessed because of lack of clarity.

Answers: We have added the following sentence to the Methods – "Deaths were certified by medical practitioners, using the Medical Certificate of Cause of Death.[21]"

c) Page 6, line 13 – How were BP treatment and other treatments defined? Did this include only pharmacological treatments? Would medically supervised weight loss treatments? Exercise regimens? Others? Be included? Again limitations (or strengths) based on these definitions cannot be assessed because of lack of detail here.

Answers: We have clarified that BP treatment refers to anti-hypertensive medication only and have changed this term throughout the manuscript.

9) Results:
a) See previous comments on overstating the results and implications thereof

Answers: Modified.

10) Discussion:
a) See previous comments on overstating the results and implications thereof

Answers: Modified.

b) Page 9, lines 2-18 – This paragraph seems to be entirely misplaced in the manuscript. If there is a question regarding the 'pay for performance programme', then it should be introduced in the introduction. If that is not a research question (which this reviewer assumes it is not), then the discussion regarding this programme should be reintroduced in a different, more coherent form.

Answers: This paragraph has been deleted.

c) The strengths and limitations should be greatly expanded especially with regards to how the varying background populations from which the survey samples were drawn may bias the results (i.e. surveys from UK vs. England vs. England/Wales etc.) There are perhaps urban/rural differentiations in those populations or socio-economic differences that should be more clearly discussed. Another limitation (or potential strength) that should be discussed is how variables were measured in all surveys.
d) A statistician should discuss how 16% of the population (page 11, line 23) might bias results.

Answers: We have expanded the limitations and discussed the varying background populations in more detail.

11) The manuscript would be improved by another round of copy editing to correct grammatical and typographical errors.

Answers: We have now carefully checked the manuscript to avoid grammatical and typographical error.

I believe this manuscript presents a very interesting ecological comparison of salt intake and BP and mortality from IHD and stroke in the UK. However, given the number of limitations regarding the varying data sets used to conduct the analyses, the manuscript is presented in much too definitive

terms. Presenting the article in this way actually detracts from the interesting findings. The reader is left feeling a bit skeptical because there are too many limitations not mentioned, and thus the results are put into question. If the authors rework the manuscript to clearly discuss those limitations and frame the manuscript in terms of what the data can at least point towards, the reader is more interested in the outcomes. This reviewer would suggest that for greater readership and impact from this manuscript that the authors rework the presentation to 1) be more guarded in the presentation and 2) be more clear regarding limitations.

Answers: We are very grateful for your comments. We have modified the paper as suggested. The changes are highlighted in yellow in the revised manuscript.