

Dr. Elizabeth Loder, MD
Editorial Team
BMJ

Dear Dr. Loder,

On behalf of myself and all of the co-authors, I wanted to thank you for giving me the opportunity to re-submit our manuscript. The reviewers' comments are greatly appreciated and by responding to their critical assessment, we believe that our manuscript is significantly improved.

We have addressed all comments in the following pages; the comments are repeated verbatim, and our responses to those comments are displayed in **bold print**. Where applicable, we have indicated the location within the manuscript that the revision can be found. In addition, changes made to the manuscript are marked clearly in yellow highlighting.

We hope you find this revision suitable for publication in *BMJ*.

Lea Borgi, MD, MMSc

Comments from committee meeting:

- 1) We wondered if some of the findings might be driven by sodium content rather than potatoes themselves. Could you discuss this more thoroughly?

We agree with you about sodium being an important potential confounder. We did discuss this in the Discussion section, but will elaborate further.

We have therefore revised our manuscript and added the following in the Discussion, paragraph 6:

Fourth, as with any observational study, our findings could be explained by residual confounding; for example, potatoes are often consumed with salt and added fat (such as butter or margarine). The increased sodium content could explain the association of boiled/baked potatoes with hypertension. However, our results did not materially change after we adjusted for sodium intake or trans and saturated fat.

- 2) Please include a full statement on patient involvement. Typically we ask that the statement be worded as follows (if this accurately reflects the extent of patient involvement):

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community. **This has been done under Patient Involvement in the Methods section (1st paragraph).**

- 3) Our statistician had a number of comments. She will be reviewing the revised version of the paper and will be looking for responses to the following:

*For all analyses the pooled HR are presented using fixed effects models whereas random effect models would be better to generalise from (Wang mentions this too). The random effects models should be presented.

As a secondary analysis, we reanalyzed our pooled estimates using random rather than fixed effects meta-analysis. The results were not materially changed. As an example, the random effects pooled HR for the intake of 1 or more servings/day of total potatoes (baked, boiled or mashed potatoes and French fries) was 1.13 (95% IC: 0.91-1.40, p-trend 0.02). The individual pooled HRs using random effects for boiled/baked potatoes, French fries, and potato chips were similar or identical to the pooled HRs using fixed effect meta-analysis; however, confidence intervals were slightly wider.

We have revised the manuscript and added the following:

- **In the Statistical analysis of the Methods section, paragraph 4:**

Finally, we reanalyzed the pooled HRs using random effect models.

- **In the Results section, paragraph 5:**

Pooled HRs did not materially change when using random effect models as compared with fixed effect models.

*It does seem that sex may be a major factor and this is alluded to in the discussion. The HPFS (male) cohort appear to have a different relationship than the other 2 (female) cohorts. We think there should be more discussion of this, although since sex and cohort are confounded there is no way to separate the potential effects.

We agree with these comments and revised our manuscript accordingly in the Discussion section, paragraph 5:

We found a few differences between the women and the men cohorts. There was an increased risk of hypertension with increasing consumption of boiled, baked or mashed potatoes in both female cohorts, but not in the male cohort. These findings, as well as the lack of association of potato chips with the incidence of hypertension in HPFS were unexpected.

* Information for 3 potato groups was collected in 9 categories. These categories were collapsed for the analysis into 4 for each potato group and 5 categories for all 3 groups combined. It is not clear how cumulative averages over time were calculated for the analyses. Does this mean the modal category recorded at that time?

In order to represent long term dietary intake for each individual in the cohort, we calculated the cumulative weighted average intake of each type of potato (boiled/baked potatoes, French fries, and potato chips) using information from all dietary questionnaires preceding a hypertension event or censoring event. This cumulative average was recalculated for each individual in the cohort at each questionnaire cycle. Thus, exposure status was permitted to change over the course of follow-up. Total potato consumption was calculated by summing the frequency of eating boiled/baked potatoes and French fries (potato chips were excluded, being analyzed separately). Although we did not include this explanation in the manuscript, we could do so at the discretion of the editor.

* The substitution analyses use the HRs for the alternatives to represent the 'effect' of replacing one portion of potatoes. Whilst these HR will give the difference associated with a unit increase, why is a unit decrease in potatoes (and the associated fall in HR) also incorporated into the calculation?

For the substitution analyses, we used a serving-based replacement. We created continuous variables for all vegetables (starchy and non-starchy vegetables), non-starchy vegetables, starchy vegetables minus boiled/baked potatoes. Then, in one model, we simultaneously put the above mentioned variables and boiled/baked potatoes. The point estimate for non-starchy vegetables was obtained and was interpreted as the effect of replacing one serving of boiled/baked potato with a non-starchy vegetable.

We did not include this explanation in the manuscript but would do so at the discretion of the editor.

*Only one HR from table 6 (substitution analyses) is discussed in the text and this is highlighted as significant. The other values should also be discussed to reach a conclusion from the findings here. Why is the NHS II value only given in the results section? (The more appropriate combined value is given in the abstract.)

We agree with you and have revised the manuscript and added the following in the Results section, last paragraph:

Replacing one serving/day of baked, boiled or mashed potatoes with one serving/day of a non-starchy vegetable was associated with a lower adjusted pooled HR of 0.93([0.89-0.96]; p-value<0.001).

* The results in table 5 require more discussion. A significant association becomes non-significant after adjustment for a variety of factors. What is the adjustment that is making a difference?

We agree with the reviewer and have added the following to the manuscript in the Results section, paragraph 4:

Also, increased consumption of potato chips was associated with an increased risk of hypertension in NHS II (HR=1.24 [1.16-1.32]; p-trend<0.001) when age-adjusted, but not when a multivariate model was used (HR=1.02 [0.96-1.09]; p-trend=0.61). This loss of significance was primarily due to confounding by BMI (Table 5).

* Hypertension was self-reported and presumably the participants gave a date of onset which was used in the cox models. We should clarify this and that it would not be better to have used interval censored models (ie. if it was only recorded as present/absent at each of the 4 year assessments).

We apologize that this was not clear in our original submission. Indeed, we did you interval censoring, and have added the following in the Statistical analysis section, first paragraph:

As the month and year of the hypertension diagnosis by a health professional was provided by participants, we used an interval-censoring model by calculating each participant's person-time (in months) from the date of the baseline questionnaire to the date of hypertension diagnosis, date of death, or end of follow-up (2010 for NHS and HPFS, and 2011 for NHS II), whichever came first.

*It should also be clarified that the cox models incorporated the updated BMI, smoking etc. information as time-varying covariate.

Again, we apologize that this was not clear in our original submission. Indeed, covariates that could change over time were included as time-varying covariates. We have therefore revised our manuscript to add the following in the statistical analysis section, paragraph 2:

We adjusted for the following potential confounders, updating them as time-varying covariates using information from successive questionnaires:

- 4) We wonder whether it is appropriate to use the phrase "long term" in the title. Do we know that participants continued these dietary patterns long term?

We agree with this comment and have changed the title to:

Potato Intake and the Incidence of Hypertension in Three Prospective Cohort Studies

Reviewer 1:

*The introduction is too US centric for an international audience. It would be useful to refer to international recommendations (eg WHO recommendations about portions of fruit and vegetables state "Potatoes, sweet potatoes, cassava and other starchy roots are not classified as fruits or vegetables" <http://www.who.int/mediacentre/factsheets/fs394/en/> although FAO guidelines do not.

We agree with the reviewer's comment and have added the following in the Introduction, paragraph 2:

On the international front, the World Health Organization (WHO) does not include potatoes as vegetables.

*The major limitation of the study is that the determination of hypertension based on self-report. While validation studies have confirmed the positive predictive value of this against samples of measured blood pressure in the cohorts, they have not confirmed the negative predictive value of this. Other studies have suggested an 89% NPV (Okura Y 2004). It should be discussed that false negative individuals may have had lower educational background or income and this may have been correlated diet.

We agree with the reviewer's comment and updated our manuscript the following:

- **In the Assessment of Hypertension (Methods section), first paragraph:**

In NHS, 77% of 51 cases of self-reported hypertension had a BP >160/95 mmHg and a 100% had a BP >140/90 mmHg; none of the women who did not report a diagnosis of hypertension were found to be hypertensive by medical record review. In HPFS, out of 114 participants without a self-report of hypertension, only two were found to have hypertension.

- **In the Discussion section, paragraph 6:**

Yet our method of hypertension ascertainment (self-report by trained health professionals of similar educational backgrounds) has been extensively validated in all three cohorts.

*The findings that participants who consumed 4 or more servings of potato chips per week had a lower risk of developing hypertension in men in the HPFS and no association in the other two cohorts is puzzling. This is discussed. However the most likely explanation is residual

confounding. It is possible that sodium intake was poorly assessed in the food frequency questionnaire (high variances from urinary sodium and potassium have been reported from FFQ especially in men who may have been less familiar with food preparation in the last century – eg Day N, McKeown N et al Int J Epidemiology 2001).

We agree with the reviewer and have revised our manuscript, in the Discussion section, paragraph 5:

Residual confounding could explain these discrepancies, in particular from sodium content.

Reviewer: 2

I only have one minor suggestion:

The associations in table 2, 3, and 5 seem heterogeneous among 3 cohort studies, with non-significant or inverse associations observed in HPFS. Please provide a P value for heterogeneity for these associations. If P for heterogeneity is statistically significant, a random effect model should be used for the pooled analyses. If not, please mention the results in the text.

We agree with the reviewer and have addressed this issue that was previously mentioned by the statistician (see above).

Reviewer: 3

Overall, few remarks on the scope, the methods, the results and the discussion as presented in the paper. A couple of thoughts though:

- the most embarrassing part of the paper is the absence of effect of potato chips on blood pressure, including a depressing effect in one of the cohorts under study (participants consuming ≥ 4 servings/week of potato chips have a lower risk of developing hypertension). If the association between boiled potatoes and French fries is taken as granted, thus the association with chips is expected to be stronger. Could it be that the consumption of chips is associated with healthier meals (e.g., more crude vegetables and fruits?) Or, conversely, the consumption of French fries could be associated to high meat consumption? I understand from the paper that the statistical methods that the effect of potatoes have been isolated, but only up to a certain point. And I do not believe that the recent changes in oil composition (less transfat) is a good explanation.

We agree with the reviewer; the lack of association of potato chips with an increased incidence of hypertension was unexpected. This could be due to residual confounding, especially from sodium intake. Also, men who consumed more potato chips (≥ 4 servings/week) did have slightly higher fruit consumption when compared with those who consumed potato chips less than once a month (mean consumption of 1.7 servings of fruit per day compared to 1.4). Although we did our best to control for potential confounding in a prospective fashion, it is possible that some negative confounding accounts for the nonsignificant findings in young women and the inverse association in men. Although we did

not include this more extensive discussion in the manuscript, we would do so upon the discretion of the editor.

- there is nothing on the cost of including or excluding potato vs. vegetables. This should be briefly addressed within the context of the current US debate.

We agree with the reviewer that this is an important aspect of potato consumption and that a cost-effective analysis should be done; however, we believe this was outside the scope of our paper. Subsequent studies looking at this issue are needed.