PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake and Prostate Cancer Risk: a Meta-Analysis
AUTHORS	Carleton, Amanda; Sievenpiper, John; Jenkins, David; de Souza, Russell; McKeown-Eyssen, Gail

VERSION 1 - REVIEW

REVIEWER	Le Kang, PhD Research Fellow US Food and Drug Administration USA
REVIEW RETURNED	21-Nov-2012

GENERAL COMMENTS	Review of BMJ Open (bmjopen-2012-002280) "Case-Control and Prospective Studies of Dietary Alpha-Linolenic Acid Intake and Prostate Cancer Risk: a Meta-Analysis" The manuscript studies the association between ALA intake and prostate cancer risk from a meta-analysis perspective. The article is well written, even there is no clear confirmation reached afterwards. interpretation of I2 is confusing in your article. Why 85% is interpreted as "considerable" (line 166) but 90% is interpreted as "substantial"? Minor: Page 2, line 50 Remove "which"

REVIEWER	Carayol Marion, PhD candidate, University of Montpellier, France I do not declare any conflict of interest.
REVIEW RETURNED	03-Dec-2012

THE STUDY	Key messages 2 and 3 are very close. One of these two points should concern prospective studies. Results in the abstract are contradictory and introduce confusion for readers. Some sentences are not very clear or very well written and should be rephrased in the discussion part.
RESULTS & CONCLUSIONS	Because of heterogeneity, authors have done subgroup analyses. The main result in a non significant and heterogenous association but subgroup analyses resulted in protective non significant or in protective significant leading to some potential confusion for readers.

GENERAL COMMENTS	This manuscript is a meta-analysis investigating the effect of dietary alpha-linolenic acid (ALA) on prostate cancer risk in prospective and case-control studies. This manuscript presents a good methodology but results and discussion are confused. In addition, objective justification and contribution to the research field remain unclear. I have two major concerns and several minor concerns. Major concerns: 1/ As stated in the introduction of the manuscript, although a protective effect of ALA has been established to prevent cardio-vascular diseases, the impact of ALA consumption on prostate cancer remains unclear so new research on this topic is of interest. However, my major concern about this manuscript is the lack of new contribution to this research area. Several recent meta-analyses have already pooled prospective and retrospective studies on ALA and prostate cancer: the same prospective studies were included by Carayol et al. in 2010 who reported a pooled RR of 0.97 (95% CI:0.86–1.10) very closed to the one reported here 0.95 (95% CI:0.84–1.09). Simon et al. in 2009 pooled prospective and retrospective studies together - pooled RR=1.20 (95%CI:1.01-1.43) - and separately – for retrospective studies, pooled OR=1.51 (95%CI: 0.95-2.39). In the introduction of the manuscript, the authors do not justify the need of conducting this meta-analysis while they know that others have been recently published. They included one more study published in 2011 (William et al.) than previous meta-analyses and they reported less significant pooled RR for analyses including retrospective and all studies. However, they described the same results as Carayol et al. for prospective studies in terms of effect estimates and heterogeneity sources. The objective and methodology of this manuscript lack of originality and then do not contribute much to the research field. I suppose that the authors could find a more original approach. Moreover, justifications of conducting this review are not explicitly stated in the introduction part. 2/ Reading between the lines, I have the impression that authors would prefer to conclude to a protective effect of ALA on prostate cancer rather than an absence of effect. To my opinion, in a systematic review and meta-analysis, authors should interpret findings with an objective point of view, except if they state that they want to confirm one particular hypothesis which it is not the case here. Thus, as findings in studies are contradictory, a neutral point of view is more appropriate than a confirmatory point of view. Here are some examples: - Lines 185-188: the first stated result is that they demonstrated “heterogeneous effects”, I would recommend to change to “non significant heterogeneous effects” - Lines 261-264: “The overall effect of ALA on prostate cancer was found to be non-significant and may be attributed to…”. I would recommend to change to “but could result from” - Line 321: “causation is difficult to establish”. Being aware of

non significant findings, why would the authors like to establish causation?

- Lines 322-323 and 366: “to elucidate whether ALA has a promotional or inhibitory effect on prostate cancer risk and development”. Again authors do not consider the possibility of an absence of association.
- Line 350-352: “However, upon removal of the studies, which reported large odds ratios, the association became weakly protective with decreased heterogeneity » is written in the key messages of the article, leading to the conclusion of a protective effect while the main results indicated non significant effects.

Minor concerns:

Statistical methods part:

- The analyses achieved and presented have to be planned and stated in the methods part. Results presented in figures 4 and 6 are not planned in methods part
- Can authors justify the consideration of ORs as approximations of RRs?
- Line 135: the authors declare that they performed meta-regression. Clarifications on the objective of meta-regressions and about the moderators tested are needed. I cannot find results of meta-regressions in the result part.

Result part:

- Funnel plots are mentioned in statistical part but are not reported in the result part. The 2 already mentioned meta-analyses have reported a publication bias exploring funnel plots.
- Results from Figure 4 are not mentioned in the text
- Line 163, it is mentioned that “Seven studies reported a protective effect of ALA intake on prostate cancer, 2 of which were significant”. However, I can find only one significant in table 1.
- Line 166: “However, there was evidence of considerable inter-study heterogeneity (I2=85%, P<0.00001). Systematic removal of each study during sensitivity analyses did not suggest any single study was an influential outlier” + same remark line 174. It appears on figure 2 that risk estimates of Ramon 2000 and De Stefani 2000 (and maybe Bidoli as well) are heterogeneous with others. Authors should probably try to explore I^2 without Ramon and De Stefani.

Discussion part:

The discussion content is of interest but this part can be improved. It is not very well written and not well structured. Some results are not presented in results part but in the discussion part (line 190).

The authors highlight heterogeneity in their manuscript, identifying

	the heterogeneous studies but do not discuss which particular characteristics of these studies could lead to these heterogeneous results, e.g. line 200-201: “the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain.” The discussion part could be better organized. The authors have made a part untitled “limitations and possible sources of heterogeneity”. However, they did not state all the sources that they have pointed out in the previous parts of the discussion section. For example, some factors identified in the part “variation on the effect of ALA between studies” are potential sources of heterogeneity for sure. About the sources of heterogeneity, the authors did not collect nor mention the adjustment variables taken into account in the RRs or ORs collected from the included studies. Differences in adjustment could probably result in differences in risk estimates. The remark of authors about the sources of ALA which could differ across countries is a very relevant and interesting point and especially if ALA could be an indicator of a healthy pattern in some countries and an indicator of an unhealthy pattern in others (lines 214-218). Could the authors add some references line 218 that show that an unhealthy/healthy lifestyle may contribute to an increased/decreased risk of prostate cancer? Some sentences are not very clear or very well written and should be rephrased: - Lines 229-231: “The Uruguayan study…” - Lines 265-269: “The mean dietary ALA…” - Lines 277-279: ”Finally, our analysis…” - Lines 330-333: “However, the relation…”

VERSION 1 – AUTHOR RESPONSE

Reviewer: Le Kang, PhD, Research Fellow, US Food and Drug Administration, USA

The manuscript studies the association between ALA intake and prostate cancer risk from a meta-analysis perspective. The article is well written, even there is no clear confirmation reached afterwards.

Thank you for your support of our article.

1) Interpretation of I2 is confusing in your article. Why 85% is interpreted as “considerable” (line 166) but 90% is interpreted as “substantial”?

Thank you for pointing out this source of confusion. We have made the terminology more consistent, so that all readers reach the correct understanding. (P7, L189 and L204)

2) Minor: Page 2, line 50. Remove “which”

As requested, we have removed the word “which.” (P2, L50)

Reviewer: Carayol Marion, PhD candidate, University of Montpellier, France

Key messages 2 and 3 are very close. One of these two points should concern prospective studies. Results in the abstract are contradictory and introduce confusion for readers.
Some sentences are not very clear or very well written and should be rephrased in the discussion part.

Because of heterogeneity, authors have done subgroup analyses. The main result in a non significant and heterogenous association but subgroup analyses resulted in protective non significant or in protective significant leading to some potential confusion for readers.

This manuscript is a meta-analysis investigating the effect of dietary alpha-linolenic acid (ALA) on prostate cancer risk in prospective and case-control studies. This manuscript presents a good methodology but results and discussion are confused. In addition, objective justification and contribution to the research field remain unclear. I have two major concerns and several minor concerns.

Major concerns:

1) As stated in the introduction of the manuscript, although a protective effect of ALA has been established to prevent cardio-vascular diseases, the impact of ALA consumption on prostate cancer remains unclear so new research on this topic is of interest. However, my major concern about this manuscript is the lack of new contribution to this research area. Several recent meta-analyses have already pooled prospective and retrospective studies on ALA and prostate cancer: the same prospective studies were included by Carayol et al. in 2010 who reported a pooled RR of 0.97 (95% CI:0.86–1.10) very closed to the one reported here 0.95 (95% CI:0.84–1.09). Simon et al. in 2009 pooled prospective and retrospective studies together - pooled RR=1.20 (95%CI:1.01-1.43) - and separately – for retrospective studies, pooled OR=1.51 (95%CI: 0.95-2.39). In the introduction of the manuscript, the authors do not justify the need of conducting this meta-analysis while they know that others have been recently published. They included one more study published in 2011 (William et al.) than previous meta-analyses and they reported less significant pooled RR for analyses including retrospective and all studies. However, they described the same results as Carayol et al. for prospective studies in terms of effect estimates and heterogeneity sources. The objective and methodology of this manuscript lack of originality and then do not contribute much to the research field. I suppose that the authors could find a more original approach.

Thank you for your excellent and detailed review that we found most constructive. We agree that due to the continued concern of the impact of dietary ALA on prostate cancer and the need to use ALA on cardiovascular health, additional research is required to help clarify the relationship and is therefore of sustained importance. Our goal with this meta-analysis was to update the current knowledge in the field by integrating new studies and thereby expand the totality of the evidence. As the reviewer mentioned, there is one new study published by Williams et al. in 2011 that contains data that have not been included an any ALA-prostate cancer meta-analysis to date. Since the last major meta-analysis was published in 2010, we therefore felt that conducting an updated meta-analysis was

reasonable. Although Simon et al. in 2009 did include a sub-group analysis of studies with ALA from dietary sources, these results have not been updated in 3 years and the data from the Health Professionals Follow-Up Study by Giovannucci et al. was updated and the data by Williams et al. published in 2011 is not included. Further, since dietary ALA analysis was not the main analysis of the paper, sources of heterogeneity and publication bias for this association were not investigated in the study. We agree that our results from the analysis of prospective studies alone are similar to those published by Carayol et al. in 2010. Despite a difference in protocol and using our own search and analysis techniques, we arrived at the same conclusions, which we feel is important in that it reinforces their overall conclusions and validates previous work. Further, we think that the addition of the analysis of case-control studies involving only dietary ALA is a complement to these previous results and aids in furthering understanding of the body of evidence as a whole. Since we feel that our study is well-conducted and follows best practice protocols, we thought that BMJ Open would be a suitable journal to publish in as its mandate is "to ensure that any well-conducted study has a home where it can be fully reported" and "will welcome both high and lower impact studies." (BMJ Open: Frequently Asked Questions. BMJ Open. Published 2012. Retrieved December 24, 2012, from http://bmjopen.bmj.com/site/about/faqs.xhtml#1.)

2) Moreover, justifications of conducting this review are not explicitly stated in the introduction part.

We agree that the justification of this meta-analysis can be more clearly expressed in the Introduction. The introduction has been revised accordingly. (P3-4, L88-99)

3) Reading between the lines, I have the impression that authors would prefer to conclude to a protective effect of ALA on prostate cancer rather than an absence of effect. To my opinion, in a systematic review and meta-analysis, authors should interpret findings with an objective point of view, except if they state that they want to confirm one particular hypothesis which it is not the case here. Thus, as findings in studies are contradictory, a neutral point of view is more appropriate than a confirmatory point of view. Here are some examples:

We agree that objectivity is important when interpreting results and our apologies if any other impression was had. Revisions have been made throughout the paper to reflect a more neutral and objective tone.

4) - Lines 185-188: the first stated result is that they demonstrated "heterogeneous effects", I would recommend to change to "non significant heterogeneous effects"

Thank you for your suggestion. We have clarified the statement with your suggested change. (P8, L217-218)

5) - Lines 261-264: "The overall effect of ALA on prostate cancer was found to be non-significant and may be attributed to…". I would recommend to change to "but could result from"

As requested, we have made the suggested language change. (P11, L331-332)

6) - Line 321: "causation is difficult to establish". Being aware of non significant findings, why would the authors like to establish causation?

Our apologies for this confusion. The statement was meant to reflect that causation is difficult to establish through the use of observational studies and since our meta-analysis is comprised of observational studies, causation cannot be established. We have rewritten this portion for clarification. (P13, L384-386)

7) - Lines 322-323 and 366: “to elucidate whether ALA has a promotional or inhibitory effect on prostate cancer risk and development”. Again authors do not consider the possibility of an absence of association.

We agree that an absence of an association between ALA and prostate cancer risk should be considered. We have added a mention of the possibility of an absence of association. (P13, L387-388 and P15, L430)

8) - Line 350-352: “However, upon removal of the studies, which reported large odds ratios, the association became weakly protective with decreased heterogeneity » is written in the key messages of the article, leading to the conclusion of a protective effect while the main results indicated non significant effects.

Thank you for this point. We have clarified the language to reflect a non significant protective association with decreased heterogeneity in the subgroup analysis. (P14, L415-416)

Minor concerns:

Statistical methods part:
9) - The analyses achieved and presented have to be planned and stated in the methods part. Results presented in figures 4 and 6 are not planned in methods part

We agree that these analyses need to be mentioned in the Methods section. To this point, we did state in the original version that “the influence of individual studies was investigated by systematically removing each study and recalculating the pooled effect.” We have revised the Statistical Analysis portion to explicitly state the a priori and post hoc analyses. (P5-6, L145-153)

10) - Can authors justify the consideration of ORs as approximations of RRs?

As stated in the original manuscript, previous meta-analyses investigating prostate cancer have used ORs to approximate RRs, including meta-analyses investigating the association between ALA and prostate cancer. As further justification, the article by Davies et al. published in BMJ in 1998 (Davies et al. When can odds ratios mislead? BMJ. 1998 March 28; 316(7136): 989–991.) indicates that “…there is no point at which the degree of overstatement is likely to lead to qualitatively different judgments about the study. Substantial discrepancies between the odds ratio and the relative risk are seen only when the effect sizes are large and the initial risk is high” and since the initial risk of prostate cancer is low, with a lifetime risk estimated at 16% by Surveillance Epidemiology and End Results (SEER) for the National Cancer Institute, it is unlikely that there will be a substantial discrepancy in approximating ORs to RRs. This justification will be added to the Methods section. (P5, 139-142)

11) - Line 135: the authors declare that they performed meta-regression. Clarifications on the objective of meta-regressions and about the moderators tested are needed. I cannot find results of meta-regressions in the result part.

We agree that a little more clarification of the meta-regression may benefit the reader. As stated in the Statistical Analysis section of the original manuscript, “Meta-regressions were performed to assess the significance of study design on effect modification” and in the Results section within the Subgroup Analyses portion, we indicated “no evidence of effect measure modification according to study design (P for heterogeneity = 0.331). The result from the meta-regression has now been more explicitly stated. (P7, L186-187)

Result part:
12) - Funnel plots are mentioned in statistical part but are not reported in the result part. The 2 already mentioned meta-analyses have reported a publication bias exploring funnel plots.

Thank you for this point. As stated in the original version, we investigated publication bias by visually inspected funnel plots, but only reported the formal testing of publication bias using Begg's and Egger's tests. We have revised this section to clarify our analysis of publication bias. (P6, L153)

13) - Results from Figure 4 are not mentioned in the text

Thank you for bringing our attention to this omission. The results from Figure 4 are now included in the Results section. (P7, L191-195)

14) - Line 163, it is mentioned that "Seven studies reported a protective effect of ALA intake on prostate cancer, 2 of which were significant". However, I can find only one significant in table 1.

Many thanks for your close reading of the manuscript. There is only one study demonstrating a significantly protective effect of ALA intake on prostate cancer. We have revised this in the manuscript text. (P6, L178)

15) - Line 166: "However, there was evidence of considerable inter-study heterogeneity (I2=85%, P<0.00001). Systematic removal of each study during sensitivity analyses did not suggest any single study was an influential outlier" + same remark line 174. It appears on figure 2 that risk estimates of Ramon 2000 and De Stefani 2000 (and maybe Bidoli as well) are heterogeneous with others. Authors should probably try to explore I^2 without Ramon and De Stefani.

We agree that the studies by Ramon et al. and De Stefani et al. appear to be heterogeneous from the other studies and towards this end, in the original version, we explored I2 without these 2 studies and found that I2=68%, P=0.01 (Figure 4). We will take your lead and now also explore I2 without the study by Bidoli et al. in addition to the previous removal of the Ramon et al. and De Stefani et al. studies. (P7, L191-199)

Discussion part:
16) The discussion content is of interest but this part can be improved. It is not very well written and not well structured. Some results are not presented in results part but in the discussion part (line 190).

We agree that all results should first be presented in the Results section. We have moved any results first presented in the Discussion to the Results section. (P7, L191-195)

17) The authors highlight heterogeneity in their manuscript, identifying the heterogeneous studies but do not discuss which particular characteristics of these studies could lead to these heterogeneous results, e.g. line 200-201: "the case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain."

Our apologies for the lack of clarity – our exploration of the characteristics of these studies leading to heterogeneous results can be found in the Discussion section of the original manuscript. The main characteristic discussed that differentiated these 2 studies from the rest is that the source of dietary ALA was predominately from meat rather than vegetable sources. We explored the importance of identifying dietary sources of ALA and what the nature of the foods may indicate in terms of diet and lifestyle with respect to prostate cancer risk. (P9, L253-270)

18) The discussion part could be better organized. The authors have made a part untitled “limitations and possible sources of heterogeneity”. However, they did not state all the sources that they have pointed out in the previous parts of the discussion section. For example, some factors identified in the part “variation on the effect of ALA between studies” are potential sources of heterogeneity for sure.

We agree that the Discussion section can be better organized. We have altered the headings within the Discussion and have included all stated potential sources of heterogeneity in the appropriate section. (P8-13, L234-379)

19) About the sources of heterogeneity, the authors did not collect nor mention the adjustment variables taken into account in the RRs or ORs collected from the included studies. Differences in adjustment could probably result in differences in risk estimates.

We agree that this is a point of discussion. We have now included a mention of the adjustment variables taken into account in the RRs and ORs from the included studies. (P11-12, L300-317)

20) The remark of authors about the sources of ALA which could differ across countries is a very relevant and interesting point and especially if ALA could be an indicator of a healthy pattern in some countries and an indicator of an unhealthy pattern in others (lines 214-218). Could the authors add some references line 218 that show that an unhealthy/healthy lifestyle may contribute to an increased/decreased risk of prostate cancer?

Thank you for your support of our argument that the sources of ALA that can differ between countries may be indicative of a certain lifestyle pattern that in itself may contribute to prostate cancer risk. We have included evidence that suggests this argument from the dietary pattern analysis studies of Walker et al. 2005, Wu et al. 2006, and Tseng et al. 2004. (P9, L252)

Some sentences are not very clear or very well written and should be rephrased:
21) - Lines 229-231: “The Uruguayan study…” (P9, L263-266)
- Lines 265-269: “The mean dietary ALA…” (P12, L335-339)
- Lines 277-279: ”Finally, our analysis…” (P12, L347-349)
- Lines 330-333: “However, the relation…” (P13-14, L394-397)

We agree that these sentences can be written more clearly to enhance the reader’s understanding. These sentences have been revised accordingly.

VERSION 2 – REVIEW

REVIEWER	Marion Carayol, MS, PhD candidate INSERM UMR 1027, Paul Sabatier University, Toulouse, France I have no conflict of interest to declare.
REVIEW RETURNED	15-Feb-2013

THE STUDY	Methods and results from a priori and post hoc subgroup analyses have to be made clearer. Key messages: Point 3 should be focused on prospective studies.
GENERAL COMMENTS	I thank the authors for their concern in taking into account suggestions from the first review. Their manuscript has been improved and is clearer for readers. Especially, they have made the discussion part very clear now. I still have some little concerns.

The authors justify their meta-analysis by the need of updating findings from previous meta-analyses. However, dates of literature search are confused: “We conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009)”. It should be updated until end of 2012.

I have some trouble understanding methods and results from a priori and post hoc subgroup analyses.
P7 : « In an a priori meta-regression, we found no evidence of effect measure modification according to study design (P for heterogeneity= 0.331). »
To my knowledge, meta-regression analyses do not lead to obtain « P for heterogeneity », but a beta coefficient and its associated p-value. Did the authors really achieved meta-regression and can they clarify method and result?
P8&11 : « Duration of follow-up in prospective studies was found to be positively but not significantly associated with the magnitude of relative risk (r=0.47). »
The reported association looks like a correlation here. Moderation effect in meta-analyses cannot be determined from simple correlation analyses; it has to take into account weights from included studies. Here again method and results remain unclear. If authors did perform a simple correlation analysis, it is not a suitable method so it should be removed.

Regarding heterogeneity and shift observed with Giovannucci study, the authors wrote: P11 : « So, the heterogeneity induced by this study may indicate that follow-up duration is positively related to the strength of the association between ALA and prostate cancer risk ». This statement only rely on one observation so relation of follow up and positive association should only be proposed as a hypothesis. How could this relation be explained according to the authors? I suggest that it could reflect a cohort effect, i.e. an effect of the period. For example, prostate cancer detection may have evolved across years with the increase use of prostate cancer screening in recent years affecting cancer stage at detection.

P13: « The association between ALA intake and prostate cancer risk was stronger overall in the case-control studies than in the prospective studies » As both study design led to non significant findings, this statement should be deleted.

A word is missing p14 l394

The adjective « weakly » is used by the authors several times across the manuscript. However, this term is imprecise and I would prefer « unsignificantly » when appropriate. For example, P8 l223 : « the association became weakly protective » should be changed to « the association became unsignificantly protective »

At 3 times, regarding results from case-control studies the authors mentioned something like: “The case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. »
This statement lacks of information. I would suggest changing to something like “The case control studies suggested unsignificant increased risk with high heterogeneity, particularly due to the inclusion of two studies with very high odds ratios. As

	heterogeneous results cannot be explained by population or dietary particular characteristics, it highlights poor reliability of the case-control study design involving recall bias, as dietary intake information is collected after disease development in case-control studies. » Key messages: Point 3 should be focused on prospective studies. Statistical analysis that included case-control studies removing Bidoli should not be reported in the article as removing this study is not very well justified and as it did not change results. Figures: Figures 4 and 5 are not necessary and should be removed; results in the text are sufficient and too many forest plots could be confusing for readers. Moreover, in a matter of making the forest plots clearer, I suggest that the authors remove names and references of the removed studies.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Marion Carayol, MS, PhD candidate, INSERM UMR 1027, Paul Sabatier University, Toulouse, France

Methods and results from a priori and post hoc subgroup analyses have to be made clearer.

Key messages: Point 3 should be focused on prospective studies.

I thank the authors for their concern in taking into account suggestions from the first review. Their manuscript has been improved and is clearer for readers. Especially, they have made the discussion part very clear now.

I still have some little concerns.

The authors justify their meta-analysis by the need of updating findings from previous meta-analyses. However, dates of literature search are confused: “We conducted a search of MEDLINE (1948-April 17, 2009) and EMBASE (1974-April 17, 2009)”. It should be updated until end of 2012.

As stated in the original manuscript, the literature search was last updated on August 28, 2012. We have clarified the language to make this point more clear. (P4, L106-110)

I have some trouble understanding methods and results from a priori and post hoc subgroup analyses.

P7 : « In an a priori meta-regression, we found no evidence of effect measure modification according to study design (P for heterogeneity= 0.331). »
To my knowledge, meta-regression analyses do not lead to obtain « P for heterogeneity », but a beta coefficient and its associated p-value. Did the authors really achieved meta-regression and can they clarify method and result?

Thank you for bringing this issue to our attention. Yes, the authors achieved meta-regression and this

has been updated in the Methods section of the manuscript. The result has been corrected as the P-value of the associated beta coefficient for study design = 0.331. (P5-6, L151-153; P7, L187-188)

P8&11 : « Duration of follow-up in prospective studies was found to be positively but not significantly associated with the magnitude of relative risk (r=0.47). »
The reported association looks like a correlation here. Moderation effect in meta-analyses cannot be determined from simple correlation analyses; it has to take into account weights from included studies. Here again method and results remain unclear. If authors did perform a simple correlation analysis, it is not a suitable method so it should be removed.

We agree that a simple correlation analysis is not a suitable method and we have removed the Pearson's correlation from the manuscript. (P6, L151-152; P7, L201; P11, L326)

Regarding heterogeneity and shift observed with Giovannucci study, the authors wrote: P11 : « So, the heterogeneity induced by this study may indicate that follow-up duration is positively related to the strength of the association between ALA and prostate cancer risk ». This statement only rely on one observation so relation of follow up and positive association should only be proposed as a hypothesis. How could this relation be explained according to the authors? I suggest that it could reflect a cohort effect, i.e. an effect of the period. For example, prostate cancer detection may have evolved across years with the increase use of prostate cancer screening in recent years affecting cancer stage at detection.

We agree with your point and have changed the statement to a hypothesis. We also agree with your suggestion that the relationship may be explained by the effect of time within prospective cohort studies and we have included this idea in the discussion. (P11, L324-329)

P13: « The association between ALA intake and prostate cancer risk was stronger overall in the case-control studies than in the prospective studies » As both study design led to non significant findings, this statement should be deleted.
Thank you for this suggestion. As indicated, we have deleted this statement and revised the point. (P13, L374-376)

A word is missing p14 l394

Thank you for pointing out this omission. The sentence has been corrected. (P13, L390)

The adjective « weakly » is used by the authors several times across the manuscript. However, this term is imprecise and I would prefer « unsignificantly » when appropriate. For example, P8 l223 : « the association became weakly protective » should be changed to « the association became unsignificantly protective »

We agree that results can be described more precisely with the use of the term "non-significantly." Revisions have been made throughout the manuscript using this term. (P7, L195; P8, L216 and L219; P9, L255 and 256; P14, L414)

At 3 times, regarding results from case-control studies the authors mentioned something like: "The

case control studies suggested an element of increased risk, which was dependent on the inclusion of two studies with very high odds ratios, the reasons for which are difficult to explain. » This statement lacks of information. I would suggest changing to something like “The case control studies suggested unsignificant increased risk with high heterogeneity, particularly due to the inclusion of two studies with very high odds ratios. As heterogeneous results cannot be explained by population or dietary particular characteristics, it highlights poor reliability of the case-control study design involving recall bias, as dietary intake information is collected after disease development in case-control studies. »

Thank you for suggested revision. A version of this edit has been incorporated into the manuscript. (P8, L223-231)

Key messages: Point 3 should be focused on prospective studies.

Thank you for this point. We have now refocused the third Key Message on our results with respect to the prospective studies. (P14, L417-420)

Statistical analysis that included case-control studies removing Bidoli should not be reported in the article as removing this study is not very well justified and as it did not change results.

We agree that the removal of the study by Bidoli et al. did not change the results and is therefore not well justified for inclusion in this manuscript. We have removed this analysis. (P7, L196)

Figures:
Figures 4 and 5 are not necessary and should be removed; results in the text are sufficient and too many forest plots could be confusing for readers.

We agree that Figures 4 and 5 are not a necessity for the manuscript and they have been removed. (P17)

Moreover, in a matter of making the forest plots clearer, I suggest that the authors remove names and references of the removed studies.

Thank you for your suggestion for making the forest plots more clear. We have removed the names and references of the studies not included in the analyses. (P17, Figure 5)