Cancer Causes and Control

Meat intake and non Hodgkin's lymphoma: a meta-analysis of observational studies

--Manuscript Draft--

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Response to Reviewers:	Reviewer 2 General: The MS was check by a professional editorial service 1.Changed as requested 2.Changed as requested 3.Following the reviewer advice, we have changed the sentence as follows “Following similar meta-analyses ([47, 48]), midpoint of each intake category was used when median intake per category was not reported.” 4.Following the reviewer advice, we have changed the sentence as follows “After a first examination of titles and abstracts to remove irrelevant articles and duplicates, we obtained 28 articles potentially relevant for the present meta-analysis. Additionally, 2 more articles were identified from reference lists. In total 30 full texts were assessed for eligibility (Figure 1).” 5.We agree with the reviewer and we have introduced a full paragraph in the discussion dealing with the NHL subtype issue (see also answer to rev 5 point 4b) 6.Following the reviewer advice, we have included a very recent reference (Domingo, Nadal 2016) that is specific on mentioned chemical compounds 7.We have partially followed reviewer advice. In table 2, P value specification (“P-value Q test”) was added in table heading. We have removed the P value referring to the meta-analytic model, as statistical significance can be inferred from the reported 95%CI. We did not add the number of cases for each row, as this information is already reported in table 1. We did add the number of cases and controls / cohort size to a new table with specifically data retrieved in primary articles for NHL subgroups,

	Supplemental table S9 (see also answer to rev 5, point 4b, 4d) 8.Because Daniel et al do not report the proportion of cases per each consumption category of processed meat (specifically the number of people exposed in each quintile is not reported). Those data are needed for dose-response analysis and are available only for red meat in Daniel et al. table 1. We have added a sentence in methods This method could only be applied to studies reporting association estimates with 95%CI and the proportion of cases in each consumption category for at least 3 categories [48].” 9. Following the reviewer advice, we have removed the separate reference list for supplemental tables. Reviewer 4 1.The MS was check by a professional editorial service 2.Following also rev 5 point 4c (see below), we have changed the sentence as follows “Compared to no meat consumption, the overall NHL relative risk increased not linearly with increased daily intake of red meat.” 3.Following the reviewer advice, we have changed the sentence as follows: “The type of diet and connected nutritional factors may be linked to NHL development [14, 24–26]” 4.Yes, at least from what we could understand from the published papers 5. To increase clarity, we have changed the sentence as follows “and 6 more studies because they reported NHL associations with specific types of meat (e.g. hamburger, bacon etc.) or with dietary intakes of no interests for the present meta-analysis [5, 56–60].” 6.Changed as requested 7.We carried out an in depth revision on how result and discussion of the dose –response analysis are reported. We now report also RR predicted by the model over intervals of 0.5 serving/day (see answer to rev 5, point 3a). 8.Following the reviewer advice, we tried to increase clarity of the first paragraph of results on subgroup analysis. 9.Following the reviewer advice, we have added a sentence in methods: “Sensitivity analysis was carried out by excluding one study at a time and examining each study impact on the summary result” 10.Following the reviewer advice, we have added in the first paragraph of results (Red and processed meat intake) a quantification of the relative influence of case control and cohort studies on the overall estimates. This issue is also now discussed in more detail (discussion, 3rd and 5th paragraphs) 11. Following the reviewer advice, we have modified the conclusion (see also answer to rev5 point 5c) 12.We added supplemental figure captions in supplemental material Reviewer 5 1a. Following the reviewer advice, we have included the latest statistics we could find (reference 2-4). If she/he is aware of different and more recent update we will be happy to include them. 1b. Following the reviewer advice, we have made a stronger point about NHL etiological heterogeneity either in the introduction (par 2) and discussion (par 4) 1c. Changed as requested

	2a. Changed through the MS as requested 2b. Changed as requested 3a. We agree with the reviewer that the dose-response analysis as several caveats and we modified the analysis trying to overcome at least some of them. We realized that instead of transforming doses into grams per day assuming a fixed portion size (120g of red meat and 50g of processed meat) as done in the previous draft we could use directly serving per time unit (day) that is reported in most articles (6 articles out of 8). This should reduce the variability among studies due to different measurements. Additionally, we used a second approach to estimate open-ended categories by using the amplitude of the nearest closed categories and avoiding the zero consumption assumption of the lowest category (that was criticized by reviewer 5). We are aware that also this approach is an approximation but we have reviewed recent meta-analysis in nutritional epidemiology and this seems to be the standard method that is applied when median intake per class is not reported. Compared to the one used in the previous draft of the MS (gram per day and zero consumption assumption in the lowest category), the qualitative shape of the relationship did not change when the alternative approach (serving per day and no zero consumption assumption in the lowest category) was used. We do agree that different methods of assessment of meat consumption possibly introduce heterogeneity in the analysis and we have reinforced this point in the discussion (par 6). 3b. Following the reviewer advice, we have removed the sentence mentioning to rare disease assumption. Regarding comparability between results from the 2 study designs, this is a common and often not-resolved situation in meta-analyses. We have now introduced the relative weight of cohort and case-control studies in each analysis as supplemental tables and detailed the subgroup analysis to population based and hospital based case-control studies. As reported in discussion par 5, our opinion is that positive association of NHL with meat consumptions is reported only in population based case-control studies, maybe because of biased exposure assessment. 4a. Changed as suggested. Now sentences read: “.. other 6 were excluded because reported NHL associations with specific types of meat (e.g. hamburger, bacon etc.) or with dietary intakes of no interests for the present meta-analysis. In 2 studies the 95%CI of the measured association was not deducible.” 4b. We agree with the reviewer on the heterogeneity argument and on the need of caution in interpreting the results. We reorganised the discussion to clarify what we think are the main causes of it. First, we added the following paragraph to introduce the discussion of limitations of present meta-analysis. “The low number of studies conducted so far hinders a proper statistical screening of the multiple sources of heterogeneity that affect the present analysis. Those include the lack of information on the number of cases by NHL subtype, study design (cohort, hospital and population based case-control studies), method of meat consumption assessment, categories of meat intake and covariates used to adjust the risk estimates.” Second, each of the above mentioned sources of uncertainty in study conclusion are thoroughly discussed in the following paragraphs of the discussion section (par 4-7). Third, the conclusion is modified accordingly (see point 5c). 4c. We followed reviewer advice and discuss only the qualitative pattern of modelled overall RR with increasing meat consumption (see point 5b). We have added in the results section the RR predicted from the model at different levels of consumption. The new result paragraph reads: “In dose-response meta-analysis NHL risk was associated with red meat consumption non linearly (P=0.04), with moderate not significant heterogeneity (I2= 29.8%, P=0.12). Compared with no red meat consumption, the predicted NHL relative risk was 1.01 (95% CI: 0.91, 1.12) for 0.5 serving/day, 1.11 (95% CI: 0.96, 1.33) for 1 serving/day and 1.46 (95% CI: 1.07, 2.00) for 1.5 serving/day. The NHL risk increased with processed meat consumption too, but the non-linear term was not significant (P=0.088) and the model showed moderate not significant heterogeneity (I2= 39.4%, P=0.06). Compared with no consumption, the predicted NHL relative risk for processed meat was 1.48 (95% CI: 1.18, 1.84) for 0.5 serving/day and 1.60 (95% CI: 1.08, 2.38) for 1 serving/day.”

	4d. We agree with reviewer comments on the very limited power of NHL subtype analysis. We have reported in supplemental table S7 the studies reporting association with each NHL subtype specifying the design and the number of cases of each study. We have added a new paragraph in the discussion and indicated the absence of enough data on effect of increased meat consumption by NHL subgroup as a major knowledge gap in the current literature. We have also restated this point in the conclusion. The new discussion paragraph reads: “First, red and processed meat intake may have different impacts on the development of lymphoma depending on NHL histological subtype [5]. NHL subtypes develop from different stages of lymphocyte differentiation and current understanding of the etiology of lymphomas points to different role of the various known risk factors [7]. Therefore, the result of associations reported in primary studies could be influenced by the relative frequencies of NHL subtypes among cases in the studied populations, making the use of all NHL as outcome questionable. Unfortunately, very few studies reported separate risk estimates by histological subtype and we did not find any significant association between DLBCL, FL and SLLCLL and red and processed meat intake, possibly because of the low statistical power. “ 4e. Following reviewer advice, we have removed the sentence with interpretation of results. 5a. Following reviewer advice we have restructured and redrafted parts of the discussion. We have down stated findings and avoided reporting results not already mentioned in the appropriate MS section. We hope that we were now more effective in discussing the limitations of the current literature on the NHL-meat consumption hypothesis. 5b. Following reviewer advice we have changed the sentence as follows “Qualitative analysis of the shape of the relationship between NHL risk and red meat intake suggests an increase of relative risk at high doses while the NHL-processed meat curve seems to level off (figure 4 and 5).” 5c. We do agree with the reviewer and changed the conclusions avoiding unsupported generalizations. Now it reads: “In conclusion, the results of this meta-analysis provided mixed and inconclusive evidences on the relationship between red and processed meat consumption and NHL. The observed positive association between red meat consumption and NHL was mainly supported by the effect estimates coming from case-control studies and several additional caveats were present in our analysis. Given the multiple sources of heterogeneity noticed in the current published literature, future prospective studies should focus on NHL major subtypes and perform a more precise quantitative assessment of diet.” 6.a Changed as suggested 6b. Changed as suggested 6c. Captions added 6d. Changed as suggested 6e. Formatted as suggested but not reversed (articles are more in number than score components and the resulting table was unreadable) 6f. Following reviewer advice we have tabulated all supplemental tables by study design 6g. Changed as suggested 6h. Captions added 7. Changed as suggested. 8. All grammatical problems listed were corrected as suggested (thank you)

	9.Corrected 10.Corrected 11.The sentence was removed 12.The sentence was removed and the terms changed through the MS as suggested.

Title: **Meat intake and Non-Hodgkin lymphoma: a meta-analysis of observational studies**

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Keywords: non-Hodgkin lymphoma, red meat, processed meat, dose-response meta-analysis

Abstract

Purpose: High intake of meat has been inconsistently associated with increased risk of Non-Hodgkin Lymphoma (NHL). We carried out a meta-analysis to summarise the evidence of published observational studies reporting association between red meat and processed meat intake and NHL risk.

Methods: Analytical studies reporting relative risks with 95% confidence intervals (95% CI) for the association between intake of red and/or processed meat and NHL or major histological subtypes were eligible. We conducted random-effects meta-analysis comparing lowest and highest intake categories and dose-response meta-analysis when risk estimates and intake levels were available for more than three exposure classes.

Results: Fourteen studies (4 cohort and 10 case-control) were included in the meta-analysis, involving a total of 10121 NHL cases. The overall relative risks of NHL for the highest versus the lowest category of consumption were 1.14 (95%CI: 1.03, 1.26) for red meat and 1.06 (95%CI: 0.98, 1.15) for processed meat. Significant associations were present when the analysis was restricted to case-control studies but not when restricted to cohort studies. No significant associations were found for major NHL etiological subtypes. Dose response meta-analysis could be based only on 8 studies that provided sufficient data and, compared to no meat consumption, the overall NHL relative risk increased not linearly with increased daily intake of red meat.

Conclusion: The observed positive association between red meat consumption and NHL is mainly supported by the effect estimates coming from case-control studies and is affected by multiple sources of heterogeneity. This meta-analysis provided mixed and inconclusive evidences on the supposed relationship between red and processed meat consumption and NHL.

Introduction

The non-Hodgkin lymphoma (NHL) is a cancer that originates from lymph glands or from cells contained in the lymphoid tissue of the immune system and forms a heterogeneous group of diseases, classified in over 40 types by the World Health Organization on the basis of histological and pathological characteristics [1]. The number of NHL cases worldwide corresponds to 2.7% of all cancer cases (excluding non melanoma skin cancer) [2] and recent estimates of incidence for United States and Europe are 19.2 and 11.9 per 100,000 respectively [3, 4].

The importance of different etiological factors for lymphomagenesis seems to be linked to the specific histological subtype [5, 6], as shown in detail by a recent large-scale collaborative study (e.g. the InterLymph Non-Hodgkin Lymphoma Subtypes Project, [6]). Although not consistent for each NHL subtype [7], known risk factors are immunosuppressive states [8, 9], infections [8, 10], type 2 diabetes [11, 12], blood transfusions [13, 14] and other medical conditions [8, 15]. Additionally, several environmental and life style risk factors have been associated with NHL including smoking [16], alcohol assumption [17], sun and UV radiation exposures [18, 19], chemicals and hair dyes [8] and obesity [20–23].

The type of diet and connected nutritional factors may be linked to NHL development [14, 24–26]. While higher intakes of dietary fibres, whole grain foods and several fruits and vegetables are reported to reduce the NHL risk [27–29], animal derived proteins and fat introduced through high meat consumption and dairy products are suggested to increase it [25, 30, 31].

Red and processed meats are sources of saturated fat and iron, and both have been related to cancer development through alteration of the energy balance and through induction of oxidative stress via generation of free radicals [32]. High intake of animal proteins has been linked to chronic antigenic stimulation through the absorption of proteins via the gastrointestinal epithelium, that may act with other factors such as viruses or genetic susceptibility in inducing NHL [33]. Alternatively, depending on the cooking technique, meats may be a source of heterocyclic amines, polycyclic aromatic hydrocarbons and N-nitroso compounds that were linked with the onset of several cancers [34].

Epidemiological evidence on the role of high intake of red and processed meat in relation to NHL is inconsistent. While some prospective studies suggested that higher consumption of meat, especially red meat, was associated with increased risk of NHL [30, 31], others did not [32, 35–37]. Additionally, several case-control studies also reported mixed results [38–41]. We carried out a

meta-analysis of published observational studies to clarify the potential association between red meat and processed meat intake and NHL.

Methods

Search strategy

A computerized literature search was independently conducted in Pubmed and Scopus from their inception to May 27, 2014, by 3 authors, using “lymphoma”, “meat”, “diet” as search terms. No language restrictions were imposed. In PubMed the term “lymphoma” was entered as MeSH term and the output limited to “humans”. In Scopus, we also used the term “NHL” and limited the output to the “medicine” subject area. Titles (and abstracts when needed) of all articles retrieved by the searches were assessed independently by the 3 authors and duplicates discarded. After title and abstract evaluation, papers that fulfilled the inclusion criteria were selected for full text appraisal. Disagreements were resolved by consensus. Additionally, reference lists of retrieved articles and reviews were checked for further relevant studies. Such systematic review was carried out and reported following the quality standards of reporting meta-analysis [42].

Selection of studies

Criteria for including a study in the meta-analysis were as follows: 1) case control or cohort design; 2) comparing the quantitative intake of red and/or processed meat 3) reporting the outcome NHL or major histological subtypes and 4) presented an association estimate with 95% confidence interval (CI). If the same data from the same study were reported in different articles, only the publication with the largest sample size was included.

Quality assessment

Full texts of studies were independently assessed by 2 authors for methodological quality, using the Newcastle-Ottawa Scale (Wells et al., 2008), which is indicated among the tools for assessing methodological quality or risk of bias in non-randomized studies [44]. The Newcastle-Ottawa Scale contains eight items, categorized into three dimensions including selection, comparability, and outcome (cohort studies) or exposure (case-control studies) and ranges between 0 (worst quality) to

10 (best quality). In case of disagreements in the scores between the 2 reviewers, a third author was involved and the scoring was solved by consensus. Studies with a score of => 7 were considered as adequately conducted.

Data extraction

Data extraction was carried out independently by two authors and disagreements resolved by consensus. The following data were extracted from each study: first author's name, year of publication, country where the study was conducted, study period, number of cases, type and number of controls (case control studies), cohort size and length of follow-up (cohort studies), dietary assessment method, type of meat, consumption categories, histological subtype of NHL (if available), the most fully adjusted ORs, RRs, or HRs with 95% CI, and covariate list. Available major histological subtypes were: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). Type of meat was either red or processed, as defined in each study. Usually, red meat was described in the studies as the total intake of beef, veal, pork, mutton and lamb while processed meat was intake of bacon, ham, sausages, cured or preserved meats.

Statistical analysis

Meta-analysis was based on reported NHL relative risk when comparing the highest with the lowest intake category of red and processed meat. The study-specific most adjusted estimates were used as the common measure of association across studies. If only separate risks for men and women were available in the original report, we pooled sex specific risks for subsequent meta-analysis using the fixed effect model. Subgroup analysis of red/processed meat was conducted by study design (cohort studies and case-control studies, divided further into population and hospital based), histological subtype, geographic area (Europe, North America, South America), and study adjustments (smoking, alcohol, total energy, fruit and vegetable intakes). Random-effects model was used to estimate the pooled RR with 95%CI using the DerSimonian-Laird estimator of inter-study variance. Forest plots were generated to visualize the study specific effect size and 95%CI. Heterogeneity was assessed with Q and I^2 statistics. Sensitivity analysis was carried out by excluding one study at a time and examining each study impact on the summary result. Publication bias was evaluated with Begg's funnel plots and Egger's regression asymmetry test.

For dose-response meta-analyses, we used the method proposed by Orsini and co-workers [45] and by Greenland and Longnecker [46] to study the relationship of (correlated) RR estimates with categories of consumption (servings per day) [47]. This method could only be applied to studies reporting association estimates with 95%CI and the proportion of cases in each consumption category for at least 3 categories [48]. Random-effects model was fitted through restricted maximum likelihood using centred dose levels (each original non-reference dose minus the reference dose within a study) as described in [49] and [50]. Heterogeneity was assessed with Q and I^2 statistics. Meat intake was modelled with restricted cubic splines with 3 knots (at 25%, 50% and 75% percentiles) to examine potential nonlinear relationship and overall P value obtained as described in [51]. When daily intake was expressed in grams/1000 kcal, we converted it into servings/day using the daily average energy intake reported in the article. As a standard portion size we used 120 g for red and 50 g for processed meat ([52, 53]). Following similar meta-analyses ([47, 48]), midpoint of each intake category was used when median intake per category was not reported. When the lowest and/or the highest category of intake were open-ended, we used the width of the adjacent close-ended category to estimate the midpoints ([47, 48]).

All statistical analyses were carried out using R packages metafor [54] and dosresmeta [50] in R 2.14.1.

Results

Literature search and study characteristics

The search strategy generated 1682 citations (Pubmed: 255, Scopus: 1427). After a first examination of titles and abstracts to remove irrelevant articles and duplicates, we obtained 28 articles potentially relevant for the present meta-analysis. Additionally, 2 more articles were identified from reference lists. In total 30 full texts were assessed for eligibility (Figure 1). A further examination led to exclude one study because it reported associations of meat consumption with malignant lymphoma [55], and 6 more studies because they reported NHL associations with specific types of meat (e.g. hamburger, bacon etc.) or with dietary intakes of no interests for the present meta-analysis [5, 56–60]. In 2 studies the 95%CI of the measured association was not deducible [61, 62]. Seven more studies were eventually identified as duplicated reports of larger studies [32, 41, 63–67].

In this meta-analysis we included 14 studies in total, 13 reporting the association of NHL with red meat and 11 reporting the association of NHL with processed meat (Table 1). Two studies refer to women cohorts [30, 31], 3 studies report NHL association with red meat only [31, 68, 69], 1 with processed meat only [24], and 2 case control studies report OR separately for men and women [24, 70]. All of the studies were published between 1994 -2013; 8 were from North America, 4 from Europe and 2 from South America. Meat intake and diet were estimated once during the study period (at baseline for cohort studies) with food frequency questionnaires (FFQ) with different number of items (Table 1). The 4 cohort studies involved a total of 5,181 NHL cases and 1,026,849 participants with a mean follow up length of 7-14 years (Table 1). The 10 case control studies involved a total of 4,940 cases and 21,031 control subjects, 6 were hospital and 4 population based (Table 1). Most of the studies adjusted the effect measure for gender, age, total energy intake and other risk factors. All studies resulted in Newcastle-Ottawa Score ≥7 and could be considered as adequately conducted (Supplemental content, table S1-S2).

Five studies could not be included in the dose-response meta-analysis (2 cohort and 3 case control) because the proportion of cases in each exposure category was not reported [31, 36, 39, 40, 71]. For the same reason we used in dose-response meta-analysis associations reported in [41], that refers to the same dataset of [72]. The latter article was included in the highest versus lowest meat intake meta-analysis because providing NHL cases registered through a time frame longer than the one used in [41]. Therefore, for the dose-response analysis we used a total of 8 studies for red meat (2 cohort, 6 case-control; Supplemental table S3) and 6 studies for processed meat (1 cohort, 5 case-control; Supplemental table S4).

Red and processed meat intake

Association between red meat intake and NHL was presented in 13 studies (4 cohort and 9 case control). The pooled RR for the highest versus lowest red meat intake was 1.14 (95%CI, 1.03-1.26; Figure 2), with non-significant heterogeneity (I^2= 24.2%, *P*=0.20; Table 2). The 4 cohort studies contributed to 55.6% of the overall RR, with 2 cohort ([35, 36]) and 1 case-control study ([72]) having relative stronger effects (supplemental table S5). Analysis of processed meat intake and NHL included 11 studies (3 cohort and 8 case control) and the pooled RR for the highest versus lowest intake was 1.06 (95%CI, 0.98-1.15; Figure 3), with non-significant heterogeneity (I^2= 3.6%, *P* =0.41; Table 2). The 3 cohort studies contributed to 60.8% of the overall RR, with 1 cohort ([35]) and 1 case-control study ([72]) having relative stronger effects (supplemental table S6).

In dose-response meta-analysis, NHL risk was associated with red meat consumption non linearly (*P*=0.04), with moderate not significant heterogeneity (I^2= 29.8%, *P*=0.12). Compared with no red meat consumption, the predicted NHL relative risk was 1.01 (95% CI: 0.91, 1.12) for 0.5 serving/day, 1.11 (95% CI: 0.96, 1.33) for 1 serving/day and 1.46 (95% CI: 1.07, 2.00) for 1.5 serving/day. The NHL risk increased with processed meat consumption too, but the non-linear term was not significant (*P*=0.088) and the model showed moderate not significant heterogeneity (I^2= 39.4%, *P*=0.06). Compared with no consumption, the predicted NHL relative risk for processed meat was 1.48 (95% CI: 1.18, 1.84) for 0.5 serving/day and 1.60 (95% CI: 1.08, 2.38) for 1 serving/day.

Subgroup, sensitivity analysis and publication bias

In subgroup analyses regarding highest versus lowest red meat intake and NHL, there were significant associations for case-control studies, those that were adjusted for total energy intake and not adjusted for smoking, alcohol, fruit and vegetable intake (Table 2). In subgroup analyses regarding highest versus lowest processed meat intake and NHL, there were significant associations for case-control studies and those that were not adjusted for smoking and fruit and vegetable intake (Table 2). Only 5 studies analysed NHL by major histological subtype (Supplemental table S7) and no significant associations were found (Table 3).

In sensitivity analysis, when excluding one study per time the pooled RR ranged from 1.09 to 1.18 for red meat- NHL and from 1.04 to 1.08 for processed meat- NHL (Supplemental material, tables S8-S9).

In publication bias analysis, the funnel plot for red meat intake and NHL (Supplemental material, figure S1) showed moderate asymmetry (Egger test p <0.05). On the contrary, analogous analysis of funnel plot for processed meat – NHL (Supplemental material, figure S2) showed no evidence of publication bias (Egger test P = 0.75).

Discussion

Previous research showed that increased meat consumption was associated with increased risk of many chronic diseases such as type 2 diabetes [73], stroke [74], gastric [75, 76], colorectal, colon and rectal cancers [53], all cause mortality [48]. Several authors have also investigated the possible association between diet and NHL development but with inconsistent results [8]. Animal studies showed already long ago that malignant lymphomas were predominant in rats with high protein

intake and that diets rich in polyunsaturated fatty acids enhanced carcinogenesis [26]. Excessive meat consumption might lead to chronic stimulation of immune system and subsequent higher risk of lymphomas or increased susceptibility to pathogens whose infections constitute a risk factor for NHL. Recently, a biological mechanism that links meat consumption to NHL involving phytanic acid, a saturated fatty acid obtained primarily through the consumption of ruminant meat and dairy products, was also suggested [66]. Additionally, depending on the cooking technique and conservation methods, several known mutagens, including nitrate, nitrite and N-nitroso compounds, heterocyclic amines and polycyclic aromatic hydrocarbons can also originate from ingested red and processed meats [38, 77, 78].

Our highest versus lowest intake meta-analysis suggests that increased consumption of red meat is associated with a 14% increased risk of NHL but no significant association was found for processed meat. Qualitative analysis of the shape of the relationship between NHL risk and red meat intake suggests an increase of relative risk at high doses while the NHL-processed meat curve seems to level off (figure 4 and 5). Those data together may suggest that NHL risk increases only at higher daily intakes of red meat while the interpretation of the effect of processed meat intake is less clear. However, the small number of available primary studies and the fact that significant associations rely on the results of case-control studies, while the few prospective studies have provided negative results, should suggest caution in making those results conclusive.

The low number of studies conducted so far hinders a proper statistical screening of the multiple sources of heterogeneity that affect the present analysis. Those include the lack of information on the number of cases by NHL subtype, study design (cohort, hospital and population based case-control studies), method of meat consumption assessment, categories of meat intake and covariates used to adjust the risk estimates.

First, red and processed meat intake may have different impacts on the development of lymphoma depending on NHL histological subtype [5]. NHL subtypes develop from different stages of lymphocyte differentiation and current understanding of the etiology of lymphomas points to different role of the various known risk factors [7]. Therefore, the result of associations reported in primary studies could be influenced by the relative frequencies of NHL subtypes among cases in the studied populations, making the use of all NHL as outcome questionable. Unfortunately, very few studies reported separate risk estimates by histological subtype and we did not find any significant association between DLBCL, FL and SLLCLL and red and processed meat intake, possibly because of the low statistical power.

Second, the subgroup analysis showed that the overall pooled association is mainly due to the results of population based case-control studies that might be affected by exposure misclassification (see below), despite the higher weight of 2 cohort studies [35, 36] that have reported not significant associations between NHL and red meat consumption. Additionally, although the Egger test has little statistical power when applied to small sample sizes [48], we cannot exclude the presence of publication bias.

Third, the accuracy of the meat intake assessment in the component studies may vary, depending on the instrument used and timing of its administration. The food frequency questionnaires (FFQs) are usually adopted in dietary assessment studies but those instruments are subject to random or systematic errors [79]. Most of the published studies are case–control studies prone to recall and interviewer bias that might result in misclassification of exposure. On the other hand, the assessment of meat intake in cohort studies relies on the assumption that a baseline diet assessment reflects the individual long-term dietary behaviour, excluding eventual diet shifts. Moreover, the type of FFQ used, the food items classified as red or processed meats, the intake quantities compared, and the measurement units used were different between individual studies (see table 1). Finally, most studies report only intake class boundaries and not the medians, simplifying the exposure distribution in the examined population. Hence, the precision in quantifying individual meat intake in primary studies is probably low and different between them and might have affected the overall estimates of this meta-analysis.

Fourth, important confounding factors might not have been measured with sufficient precision (or not have been measured at all) in primary studies included in this meta-analysis. Despite almost all studies adjusted for energy intake, few did for smoking, physical activity and alcohol consumption or obesity that may be confounders in the association of increased meat intake with NHL risk, limiting our ability to discern the role of confounders in subgroup analysis. Furthermore, only 6 studies included in this meta-analysis controlled for fruit and/or vegetable consumption. Since fruits and vegetables have antioxidants protecting against the oxidative damage, joint intake of those foods may significantly reduce the NHL risk [28] and the lack of inclusion of those confounders in primary studies might have resulted into biased estimation of NHL risk attributable to meat consumption.

In conclusion, the results of this meta-analysis provided mixed and inconclusive evidences on the relationship between red and processed meat consumption and NHL. The observed positive association between red meat consumption and NHL was mainly supported by the effect estimates coming from case-control studies and several additional caveats were present in our analysis. Given

the multiple sources of heterogeneity noticed in the current published literature, future prospective studies should focus on NHL major subtypes and perform a more precise quantitative assessment of diet.

References

1. Evans LS, Hancock BW (2003) Non-Hodgkin lymphoma. Lancet 362:139–146.
2. Ferlay J, Soerjomataram I, Ervik M, et al. (2013) GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. In: Lyon, Fr. Int. Agency Res. Cancer. http://globocan.iarc.fr. Accessed 5 May 2014
3. AmericanCancerSociety Cancer Statistics Center. cancerstatisticscenter.cancer.org. Accessed 1 Oct 2016
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49:1374–1403.
5. Morton LM, Wang SS, Cozen W, et al. (2008) Etiologic heterogeneity among non-Hodgkin lymphoma subtypes. Blood 112:5150–5160.
6. Morton LM, Sampson JN, Cerhan JR, et al. (2014) Rationale and Design of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014:1–14.
7. Morton LM, Slager SL, Cerhan JR, et al. (2014) Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014:130–44.
8. Alexander DD, Mink PJ, Adami H-O, et al. (2007) The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer 120 Suppl :1–39.
9. Smedby KE, Vajdic CM, Falster M, et al. (2008) Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 111:4029–4038.
10. Matsuo K, Kusano A, Sugumar A, et al. (2004) Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: A meta-analysis of epidemiological studies. Cancer Sci 95:745–752.
11. Castillo JJ, Mull N, Reagan JL, et al. (2012) Increased incidence of non-Hodgkin lymphoma , leukemia , and myeloma in patients with diabetes mellitus type 2: a meta-analysis of observational studies. Blood 119:4845–4850.
12. Chao C, Page JH (2008) Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. Am J Epidemiol 168:471–480.
13. Castillo JJ, Dalia S, Pascual SK (2010) Association between red blood cell transfusions and development of non-Hodgkin lymphoma: a meta-analysis of observational studies. Blood 116:2897–2907.
14. Cerhan J (1997) New epidemiologic leads in the etiology of non-Hodgkin lymphoma in the elderly: the role of blood transfusion and diet. Biomed Pharmacother 51:200–207.
15. Bassig BA, Lan Q, Rothman N, et al. (2012) Current understanding of lifestyle and environmental factors and risk of non-hodgkin lymphoma: an epidemiological update. J

Cancer Epidemiol 2012:978930.

16. Morton LM, Hartge P, Holford TR, et al. (2005) Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). Cancer Epidemiol Biomarkers Prev 14:925–933.
17. Morton LM, Zheng T, Holford TR, et al. (2005) Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. Lancet Oncol 6:469–476.
18. McMichael A, Giles G (1996) Have increases in solar ultraviolet exposure contributed to the rise of incidence of non-Hodgkin's lymphoma? Br J Cancer 73:945–950.
19. Armstrong BK, Kricker A (2007) Sun exposure and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 16:396–400.
20. Castillo JJ, Ingham RR, Reagan JL, et al. (2014) Obesity is associated with increased relative risk of diffuse large B-cell lymphoma: a meta-analysis of observational studies. Clin Lymphoma Myeloma Leuk 14:122–130.
21. Larsson SC, Wolk A (2007) Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis. Int J Cancer 121:1564–1570.
22. Willett E V, Morton LM, Hartge P, et al. (2008) Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. Int J Cancer 122:2062–70.
23. Renehan AG, Tyson M, Egger M, et al. (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371:569–578.
24. Ward MH, Zahm SH, Weisenburger DD, et al. (1994) Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). Cancer causes Control 5:422–432.
25. Skibola CF (2007) Obesity, diet and risk of non-Hodgkin lymphoma. Cancer Epidemiol biomarkers Prev 16:392–395.
26. Davis S (1992) Nutritional factors and the development of non-Hodgkin's lymphoma: a review of the evidence. Cancer Res 52:5492s–5495s.
27. Thompson C a, Habermann TM, Wang AH, et al. (2010) Antioxidant intake from fruits, vegetables and other sources and risk of non-Hodgkin's lymphoma: the Iowa Women's Health Study. Int J Cancer 126:992–1003.
28. Chen G-C, Lv D-B, Pang Z, Liu Q-F (2013) Fruits and vegetables consumption and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. Int J Cancer 133:190–200.
29. Holtan SG, O'Connor HM, Fredericksen ZS, et al. (2012) Food-frequency questionnaire-based estimates of total antioxidant capacity and risk of non-Hodgkin lymphoma. Int J Cancer 131:1158–68.
30. Chiu BC-H, Cerhan JR, Folsom AR, et al. (1996) Diet and risk of Non-Hodgkin Lymphoma in older women. JAMA 275:1315–1321.
31. Zhang S, Hunter DJ, Rosner BA, et al. (1999) Dietary Fat and Protein in Relation to Risk of Non-Hodgkin ' s Lymphoma Among Women. J Natl Cancer Inst 91:1751–1758.
32. Cross AJ, Leitzmann MF, Gail MH, et al. (2007) A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 4:e325.
33. Cunningham AS (1976) Lymphomas and animal-protein consumption. Lancet 308:1184–1186.
34. Cross AJ, Sinha R (2004) Meat-related mutagens/carcinogens in the etiology of colorectal

cancer. Environ Mol Mutagen 44:44–55.

35. Daniel CR, Sinha R, Park Y, et al. (2012) Meat Intake Is Not Associated with Risk of Non-Hodgkin Lymphoma in a Large Prospective Cohort of U . S . Men and Women. J Nutr 142:1074–1080.

36. Rohrmann S, Linseisen J, Jakobsen MU, et al. (2011) Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 128:623–634.

37. Erber E, Maskarinec G, Gill J, et al. (2009) Dietary Patterns and the Risk of Non-Hodgkin Lymphoma: The Multiethnic Cohort. Leuk Lymphoma 50:1269–1275.

38. Aschebrook-Kilfoy B, Ollberding NJ, Kolar C, et al. (2012) Meat intake and risk of non-Hodgkin lymphoma. Cancer Causes Control 23:1681–1692.

39. De Stefani E, Ronco AL, Deneo-Pellegrini H, et al. (2013) Meat, milk and risk of lymphoid malignancies: a case-control study in Uruguay. Nutr Cancer 65:375–383.

40. Cross AJ, Ward MH, Schenk M, et al. (2006) Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: results from a NCI-SEER case-control study. Carcinogenesis 27:293–7.

41. Purdue MP, Bassani DG, Klar NS, et al. (2004) Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. Cancer Epidemiol biomarkers Prev 13:1665–1676.

42. Liberati A, Altman DG, Tetzlaff J, et al. (2009) The PRiSMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Br Med J 339:b2700.

43. Wells G, Shea B, O'Connell D, et al. (2008) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 2 May 2014

44. Higgins J, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration

45. Orsini N, Li R, Wolk A, et al. (2012) Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 175:66–73.

46. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135:1301–1309.

47. Wallin a, Orsini N, Wolk a (2011) Red and processed meat consumption and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. Br J Cancer 104:1196–201.

48. Larsson SC, Orsini N (2014) Red meat and processed meat consumption and all-cause mortality: a meta-analysis. Am J Epidemiol 179:282–289.

49. Liu Q, Cook NR, Bergström A, Hsieh C-C (2009) A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose–response data. Comput Stat Data Anal 53:4157–4167.

50. Crippa A (2014) Package "dosresmeta". Performing multivariate dose-response meta-analysis (Version 1.3.0). http://cran.r-project.org/web/packages/dosresmeta/. Accessed 30 Jun 2014

51. Crippa A, Discacciati A, Larsson SC, et al. (2014) Systematic Reviews and Meta- and Pooled Analyses Coffee Consumption and Mortality From All Causes , Cardiovascular Disease , and Cancer : A Dose-Response Meta-Analysis. Am J Epidemiol 180:763–775.

52. World Cancer Research Fund / American Institute for Cancer Research (2007) Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. AICR, Washington DC

53. Chan DSM, Lau R, Aune D, et al. (2011) Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 6:e20456.

54. Viechtbauer W (2014) Package "metafor". Meta-Analysis Package for R (Version 1.9.3). http://www.metafor-project.org/. Accessed 30 Jun 2014

55. Matsuo K, Hamajima N, Hirose K, et al. (2001) Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: results of a hospital-based case-control study at Aichi Cancer Center. Jpn J Cancer Res 92:1011–1017.

56. Zheng T, Holford T, Leaderer B, et al. (2004) Diet and Nutrient Intakes and Risk of Non-Hodgkin's Lymphoma in Connecticut Women. Am J Epidemiol 159:454–466.

57. Ali A, Al-Belushi BS, Waly MI, et al. (2013) Dietary and Lifestyle Factors and Risk of Non-Hodgkin's Lymphoma in Oman. Asian Pacific J Cancer Prev 14:841–848.

58. Mozaheb Z, Aledavood A, Farzad F (2012) Diet and non-Hodgkin's lymphoma risk. Pan Afr Med J 12:53.

59. Balasubramaniam G, Saoba S, Sarade M, Pinjare S (2013) Case-control study of risk factors for Non-Hodgkin lymphoma in Mumbai, India. Asian Pac J Cancer Prev 14:775–780.

60. De Stefani E, Aune D, Boffetta P, et al. (2009) Salted meat consumption and the risk of cancer: a multisite case-control study in Uruguay. Asian Pac J Cancer Prev 10:853–857.

61. Tavani A, Pregnolato A, Negri E, et al. (1997) Diet and risk of lymphoid neoplasms and soft tissue sarcomas. Nutr Cancer 27:256–260.

62. Franceschi S, Serraino D, Carbone A, et al. (1989) Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. Nutr Cancer 12:333–341.

63. Aune D, Ronco A, Boffetta P, et al. (2009) Meat consumption and cancer risk : a multisite case- control study in Uruguay. Cancer Ther 7:174–187.

64. Chiu BC-H, Dave BJ, Ward MH, et al. (2008) Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. Cancer Causes Control 19:859–867.

65. Hu J, La Vecchia C, Morrison H, et al. (2011) Salt, processed meat and the risk of cancer. Eur J Cancer Prev 20:132–139.

66. Ollberding NJ, Aschebrook-Kilfoy B, Caces DBD, et al. (2013) Phytanic acid and the risk of non-Hodgkin lymphoma. Carcinogenesis 34:170–175.

67. Tsai H-T, Cross AJ, Graubard BI, et al. (2010) Dietary factors and risk of chronic lymphocytic leukemia and small lymphocytic lymphoma: a pooled analysis of two prospective studies. Cancer Epidemiol Biomarkers Prev 19:2680–2684.

68. Chang ET, Smedby KE, Zhang SM, et al. (2005) Dietary factors and risk of non-hodgkin lymphoma in men and women. Cancer Epidemiol biomarkers Prev 14:512–520.

69. Tavani A, La Vecchia C, Gallus S, et al. (2000) Red meat intake and cancer risk: a study in Italy. Int J cancer 86:425–428.

70. De Stefani E, Fierro L, Barrios E, Ronco A (1998) Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. Leuk Res 22:445–452.

71. Talamini R, Polesel J, Montella M, et al. (2006) Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. Int J Cancer 118:2871–2876.

72. Hu J, La Vecchia C, DesMeules M, et al. (2008) Meat and fish consumption and cancer in

Canada. Nutr Cancer 60:313–24.

73. Micha R, Michas G, Mozaffarian D (2012) Unprocessed red and processed meats and risk of coronary artery disease and type 2 diabetes--an updated review of the evidence. Curr Atheroscler Rep 14:515–524.

74. Kaluza J, Wolk A, Larsson SC (2012) Red meat consumption and risk of stroke: a meta-analysis of prospective studies. Stroke 43:2556–2560.

75. Zhu H, Yang X, Zhang C, et al. (2013) Red and processed meat intake is associated with higher gastric cancer risk: a meta-analysis of epidemiological observational studies. PLoS One 8:e70955.

76. Bonequi P, Meneses-González F, Correa P, et al. (2013) Risk factors for gastric cancer in Latin America: a meta-analysis. Cancer Causes Control 24:217–231.

77. Aschebrook-Kilfoy B, Ward MH, Zheng T, et al. (2012) Dietary nitrate and nitrite intake and non-Hodgkin lymphoma survival. Nutr Cancer 64:488–492.

78. Domingo JL, Nadal M (2016) Carcinogenicity of consumption of red and processed meat: What about environmental contaminants? Environ Res 145:109–115.

79. Willett WC (1998) Nutritional epidemiology, 2nd ed. Oxford University Press, New York, NY

80. Charbonneau B, O'Connor HM, Wang AH, et al. (2013) Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-hodgkin lymphoma. J Nutr 143:672–681.

Table 1. Characteristics of the cohort and case-control studies on red meat and processed meat and non-Hodgkin lymphoma

First author, year (reference)	Study location	No. of cases / Cohort size or No. of controls (type)	Study period or mean follow-up (years)	Dietary assessment method (number of items)	Meat lowest intake category	Meat highest intake category	RR/HR/OR (95%CI) highest versus lowest intake category	Adjustments
Case-control studies								
Ward, 1994 [24]	Nebraska (USA)	385/1432 (hospital)	1983-1986	FFQ-30	Processed meat <2 times/wk	Processed meat >6 times/wk (men) >4 times/wk (women)	OR(men)=0.6(0.4,1.1) OR(women)=1.2(0.7,2.1)	Age
De Stefani, 1998 [70]	Uruguay	52/163 (hospital)	1988-1995	FFQ	Red meat ≤7.7servings/wk (men) ≤6.0servings/wk (women) Processed meat ≤0.2servings/wk	Red meat ≥12.7servings/wk (men) ≥9.3 servings/wk (women) Processed meat ≥1.1 servings/wk	OR(men)=2.53(1.01,6.34) OR(women)=2.45(0.88,6.82) OR(men)=1.03(0.43,2.42) OR(women)=1.9 (0.66,5.45)	Age, residence, urban/rural, diagnosis year, parity
Tavani, 2000 [69]	Italy	200/7990 (hospital)	1983-1996	FFQ-40	Red meat ≤3 portions/wk	Red meat ≥6 portions/wk	OR=1.2(0.8,1.7)	Age, recruitment year, sex, education, smoking, alcohol, fat, fruit, vegetable intakes
Talamini, 2006 [71]	Italy	190/484 (hospital)	1999-2002	FFQ-63	Red meat 1.5 servings/wk Processed meat <1.3 servings/wk	RM >3.25 servings/wk Processed meat ≥3.5 servings/wk	OR=0.93(0.56,1.55) OR=1.1(0.67,1.81)	Age, gender, center, education, place of birth, hepatitis C, total energy intake
Chang, 2005 [68]	Sweden Denmark	597/467 (population)	2000-2002	FFQ-137	Red meat <0.8 servings/dd	Red meat >1.6 servings/dd	OR=1.2(0.8,1.7)	Age, sex
Cross, 2006 [40]	4 US geographic areas (USA)	458/383 (population)	1998-2000	FFQ-117	Red meat: quartile 1 Processed meat: quartile 1	Red meat: quartile 4 Processed meat: Quartile 4	OR=1.10(0.67,1.81) OR=1.18(0.74,1.89)	Gender, location, physical activity, total intake, alcohol
Hu, 2008 [72]	Canada	1666/5039 (population)	1994-1997	FFQ-69	Red meat ≤2 servings/wk	Red meat ≥5.1 servings/wk	OR=1.1(0.9,1.3)	Age, province, sex, education, BMI, smoking, alcohol, total energy, vegetable and fruit intake

					Processed meat ≤0.9 servings/wk	Processed meat ≥5.4 servings/wk	OR=1.2(0.9,1.4)	
Aschebrook-Kilfoy, 2012 [38]	Nebraska (USA)	335/459 (population)	1999-2002	FFQ-117	Red meat <41.2 g/1000kcal	Red meat ≥61.8 g/1000kcal	OR=1.5(1.1,2.2)	Age, sex, total energy intake
					Processed meat <6.2 g/1000kcal	Processed meat ≥13.1 g/1000kcal	OR=1.3(0.9,1.9)	
De Stefani, 2013 [39]	Uruguay	697/3606 (hospital)	1996-2004	FFQ	Red meat: terzile 1	Red meat: terzile 3	OR= 1.25(0.92-1.69)	Age, sex, residence, urban/rural, education, body mass index (BMI), smoking, alcohol, mate, fruit, vegetable intakes, total energy
					Processed meat: terzile 1	Processed meat: terzile 3	OR=0.95(0.72,1.25)	
Charbonneau, 2013 [80]	3 US states (USA)	603/1007 (hospital)	2002-2008	FFQ-103	Red meat ≤19.5 servings/mo	Red meat >50.1 servings/mo	OR=1.07 (0.75,1.53)	Age, sex, residence, total energy
					Processed meat ≤0.9 servings/mo	Processed meat >6.0 servings/mo	OR=1.37(1.02,1.83)	
Cohort studies								
Chiu, 1996 [30]	Iowa (USA)	104/35156 women aged 55-69y	7 y	FFQ-126	Red meat <22 servings/mo	Red meat: >36 serving / mo	RR=1.00(0.97,1.73)	Age, total energy intakes.
					Processed meat <4 servings/mo	Processed meat: >6 serving / mo	RR= 1.11(0.68,1.79)	
Zhang, 1999 [31]	11 US states (USA)	199/88410 women aged 30-55 y	14 y	Semiquantitative FFQ	Red meat <3 times/mo	Red meat: >6 times/wk	RR=2.2(1.1,4.4)	Age, total energy, follow-up length, region, smoking, height
Rohrmann, 2010 [36]	9 European countries	1267/411097	8.5 y	Country–specific validated FFQ	Red meat <20 g/dd	Red meat ≥ 80 g/dd	HR=1.95(0.73,5.21)	Age, centre, sex, education, smoking, energy, alcohol, fruit, vegetable intakes
					Processed meat <20 g/dd	Processed meat ≥ 80 g/dd	HR=1.06(0.82,1.37)	
Daniel, 2012 [35]	6 US states + 2 Metropolitan areas (USA)	3611/492186	9 y	FFQ-124	Red meat: mean quartile 1= 9.7 g/1000kcal	Red meat: mean quartile 4= 66.8 g/1000kcal	HR=1.01(0.90,1.14)	Age, sex, education, cancer family history, race, BMI, smoking, physical activity, alcohol, fruit, vegetable, total energy intakes.
					Processed meat mean quartile 1= 5.3 g/1000kcal	Processed meat mean quartile 4= 19.1 g/1000kcal	HR= 0.99(0.89,1.34)	

Table 2. Random-effect summary estimates of the relative risk (RR) for the associations of non-Hodgkin's lymphoma, red meat and processed meat highest versus lowest intake comparison for all studies and by subgroup. Heterogeneity estimated with the I^2 and Q statistics.

		N	RR	95% CI	*P* value	I^2	Q (*P* value Q-test)
Red meat	All studies	13	1.14	1.03,1.26	0.008	24.2	15.8 (0.20)
Study design	Cohort	4	1.08	0.92,1.26	0.365	33.0	4.5 (0.21)
	Case control	9	1.19	1.06,1.34	0.003	4.1	8.3 (0.40)
	Hospital based	5	1.22	0.97,1.52	0.085	31.1	5.8 (0.21)
	Population based	4	1.17	1.02,1.35	0.028	0.0	2.5 (0.48)
Geographic areas	North America	7	1.13	1.00,1.28	0.051	26.5	8.2 (0.23)
	South America	2	1.64	0.85,3.18	0.141	69.5	3.3 (0.07)
	Europe	4	1.07	0.91,1.25	0.436	0.0	1.3 (0.73)
Adjusted for energy intake	Yes	10	1.09	1.00,1.19	0.042	7.9	9.8 (0.37)
	No	3	1.39	0.97,1.99	0.074	47.5	3.8 (0.15)
Adjusted for alcohol	Yes	6	1.06	0.97,1.15	0.202	0.0	2.5 (0.77)
	No	7	1.32	1.08,1.61	0.006	26.7	8.2 (0.22)
Adjusted for smoking	Yes	5	1.05	0.96,1.15	0.302	0.0	3.0 (0.56)
	No	8	1.23	1.05,1.45	0.012	30.6	10.1 (0.18)
Adjusted for fruit/vegetable intakes	Yes	4	1.04	0.95,1.15	0.390	0.0	2.3 (0.52)
	No	9	1.23	1.06,1.43	0.005	21.4	10.2 (0.25)
Processed meat	All studies	11	1.06	0.98,1.15	0.147	3.6	10.4 (0.41)
Study design	Cohort	3	1.01	0.91,1.11	0.921	0.0	0.4 (0.82)
	Case control	8	1.14	1.00,1.30	0.049	6.4	7.5 (0.38)
	Hospital based	5	1.05	0.83,1.33	0.701	36.5	6.3 (0.18)
	Population based	3	1.22	1.02,1.45	0.028	0.0	0.2 (0.93)
Geographic areas	North America	7	1.12	0.97,1.29	0.128	38.3	9.7 (0.14)
	South America	2	0.96	0.74,1.24	0.761	0.0	0.1 (0.82)
	Europe	2	1.07	0.85,1.34	0.570	0.0	0.1 (0.90)
Adjusted for total energy intake	Yes	9	1.07	0.98,1.15	0.114	0.0	7.6 (0.47)
	No	2	0.78	0.46,1.34	0.375	19.1	1.2 (0.27)
Adjusted for alcohol	Yes	5	1.03	0.94,1.12	0.514	0.0	3.0 (0.55)
	No	6	1.17	0.97,1.42	0.095	7.5	5.4 (0.37)
Adjusted for smoking	Yes	3	0.99	0.90,1.09	0.909	0.0	0.3 (0.84)
	No	8	1.19	1.04,1.36	0.010	0.0	5.4 (0.61)
Adjusted for fruit/vegetable intakes	Yes	3	0.99	0.90,1.09	0.909	0.0	0.3 (0.84)
	No	8	1.19	1.04,1.36	0.014	0.0	5.4 (0.61)

Table 3. Random-effect summary estimates of the relative risk (RR) for the associations of non-Hodgkin's lymphoma by histological subtype, red meat and processed meat highest versus lowest intake comparison for all studies and by subgroup. Heterogeneity was estimated with the I^2 and Q statistics. DLBCL: large B-cell lymphoma, FL: follicular lymphoma, SLLCLL: small lymphocytic lymphoma/chronic lymphocytic leukemia.

		N	RR	95%CI	*P* value	I^2	Q (*P* value Q-test)
Red meat	DLBCL	5	1.13	0.94,1.32	0.20	0.00	4.7 (0.31)
	FL	5	1.08	0.79,1.47	0.63	43.0	6.9 (0.14)
	SLLCLL	5	1.00	0.84,1.19	0.97	0.00	1.6 (0.81)
Processed meat	DLBCL	4	1.18	0.95,1.45	0.13	5.6	1.9 (0.59)
	FL	4	0.89	0.59,1.35	0.59	59.0	7.5 (0.06)
	SLLCLL	4	1.29	0.86,1.93	0.22	67.4	9.4 (0.03)

Figure captions

Figure 1. Flowchart of selection of studies for inclusion in meta-analysis.

Figure 2. Relative risk (RR) of non-Hodgkin lymphoma for the comparison of highest versus lowest intake of red meat. Squares represent study –specific relative risk estimates, the size of the squares are proportional to the study weight (i.e. the inverse of the variance), horizontal lines represent 95% confidence intervals, diamonds represent random effect pooled estimates with 95% confidence intervals.

Figure 3. Relative risk (RR) of non-Hodgkin lymphoma for the comparison of highest versus lowest intake of processed meat. Squares represent study –specific relative risk estimates, the size of the squares are proportional to the study weight (i.e. the inverse of the variance), horizontal lines represent 95% confidence intervals, diamonds represent random effect pooled estimates with 95% confidence intervals.

Figure 4. Association of relative risk for NHL with red meat intake. The relationship was modelled with restricted cubic splines in a random-effects dose response model.

Figure 5. Association of relative risk for NHL with processed meat intake. The relationship was modelled with restricted cubic splines in a random-effects dose response model.

Figure 1

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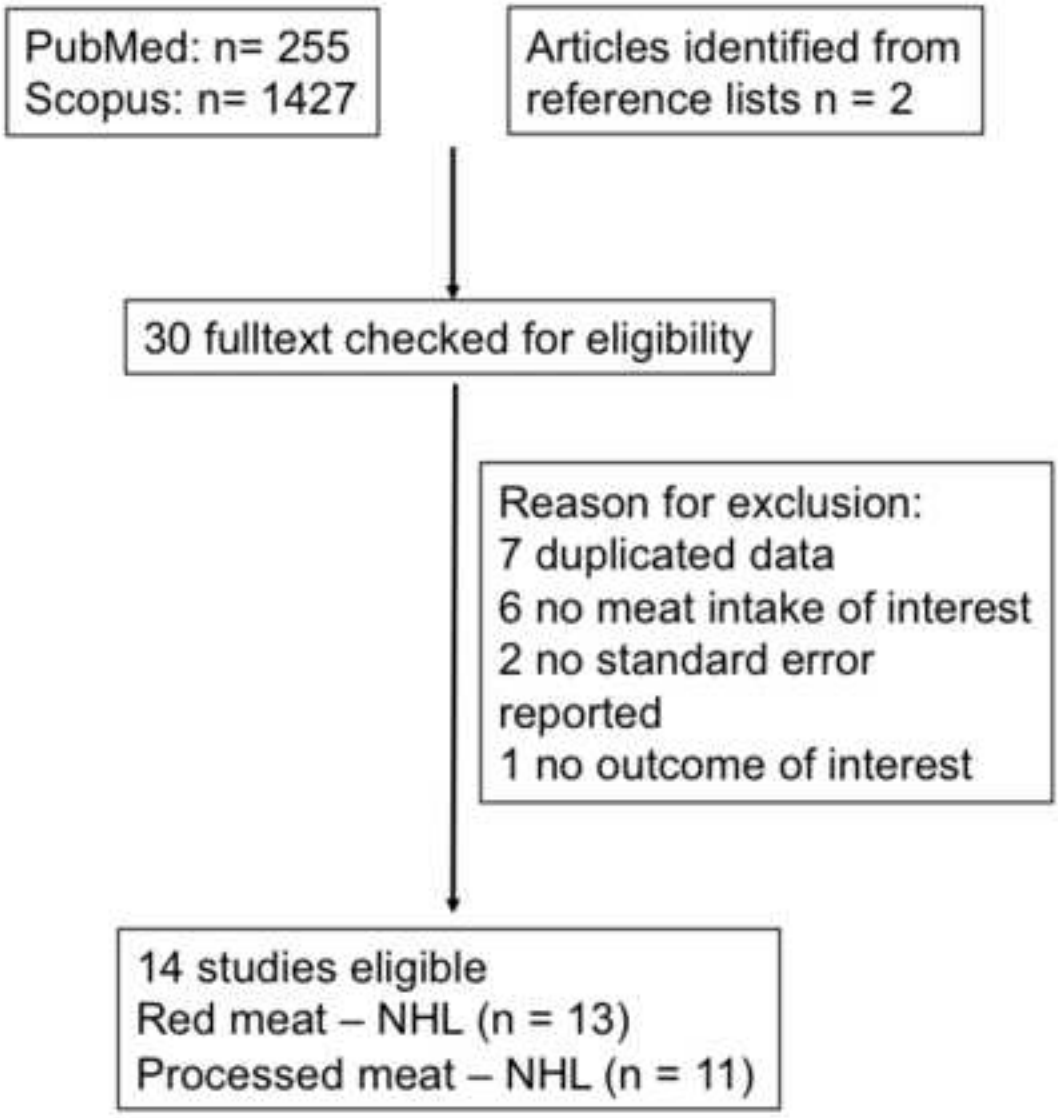

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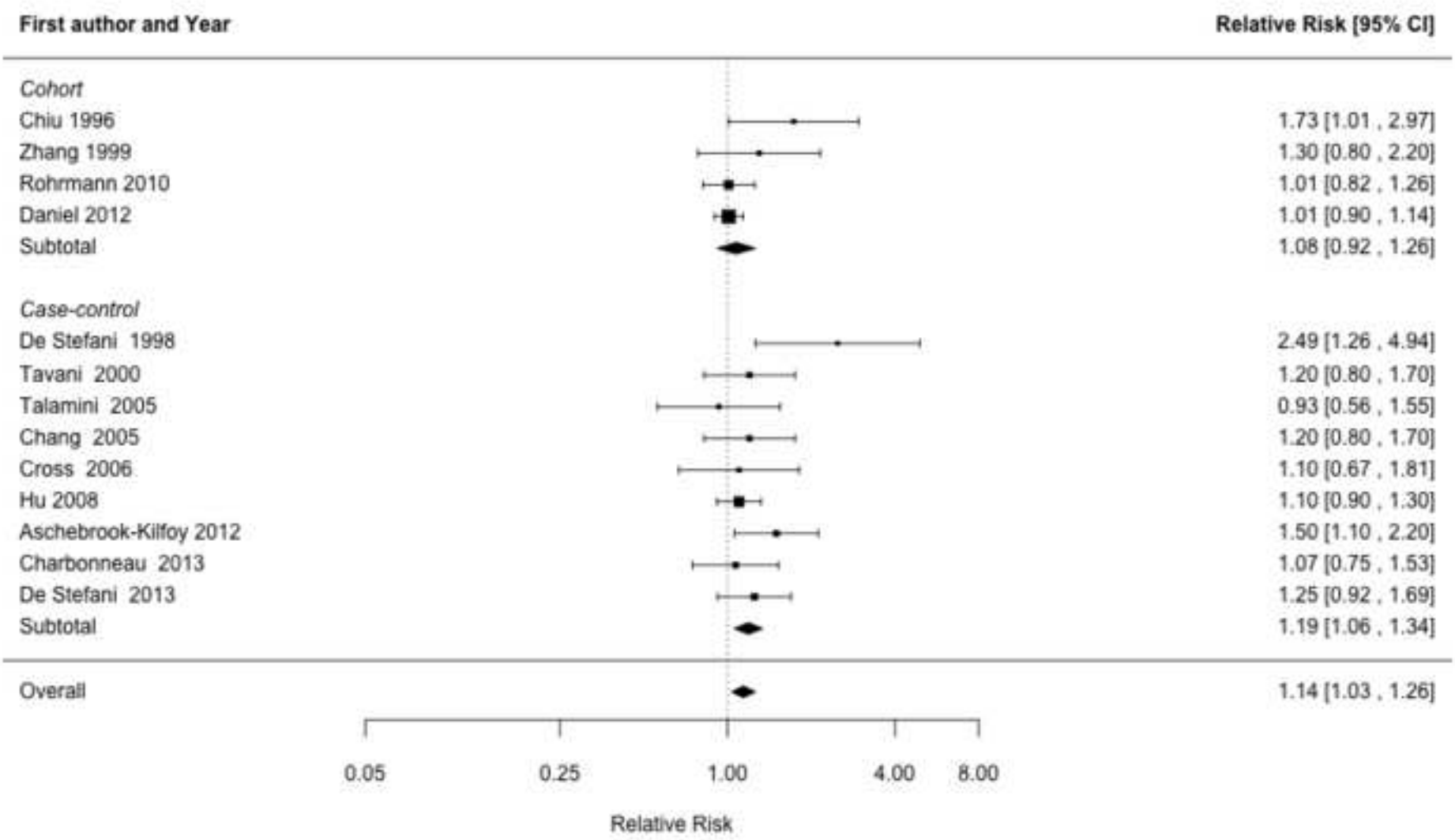

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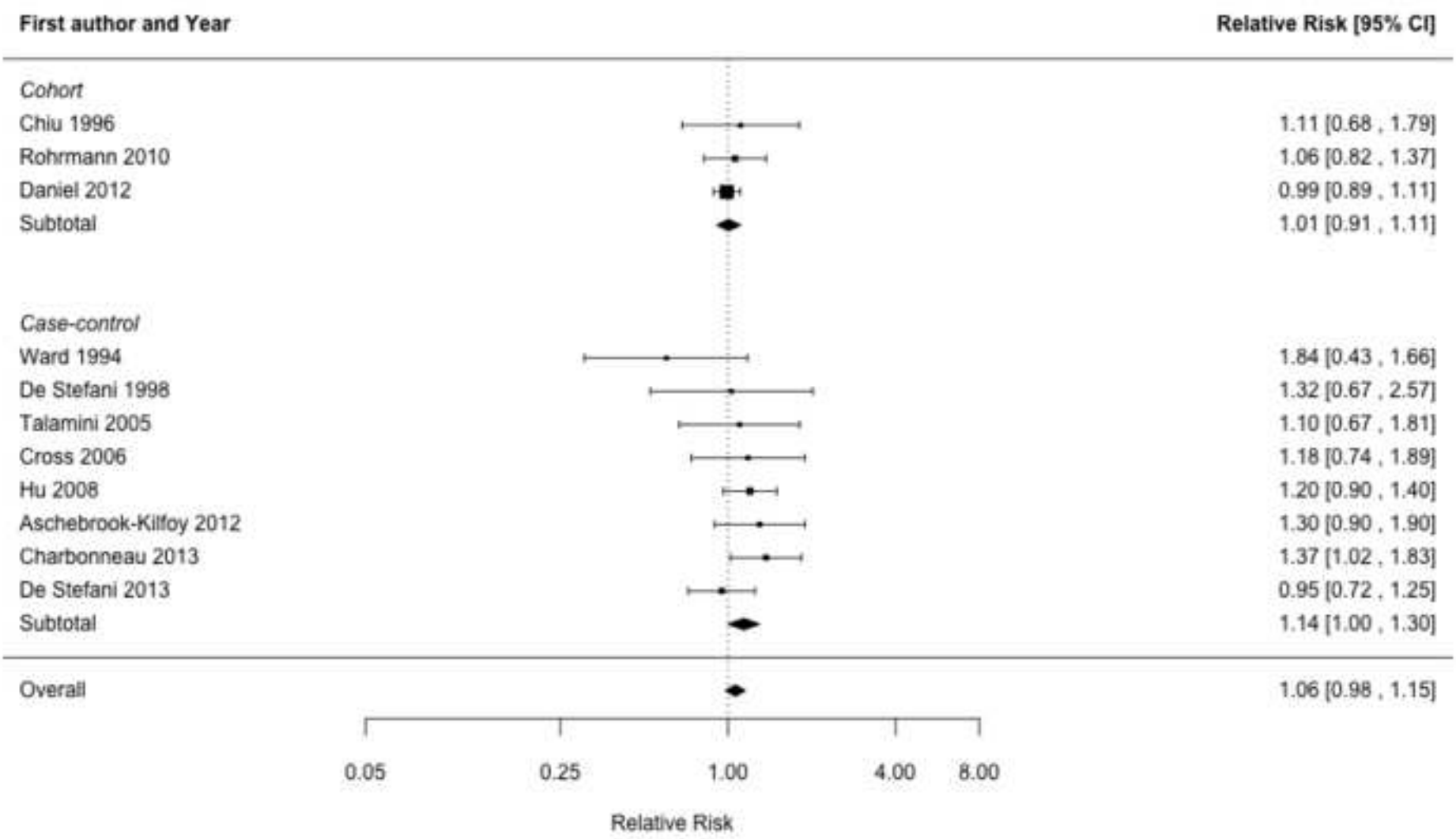

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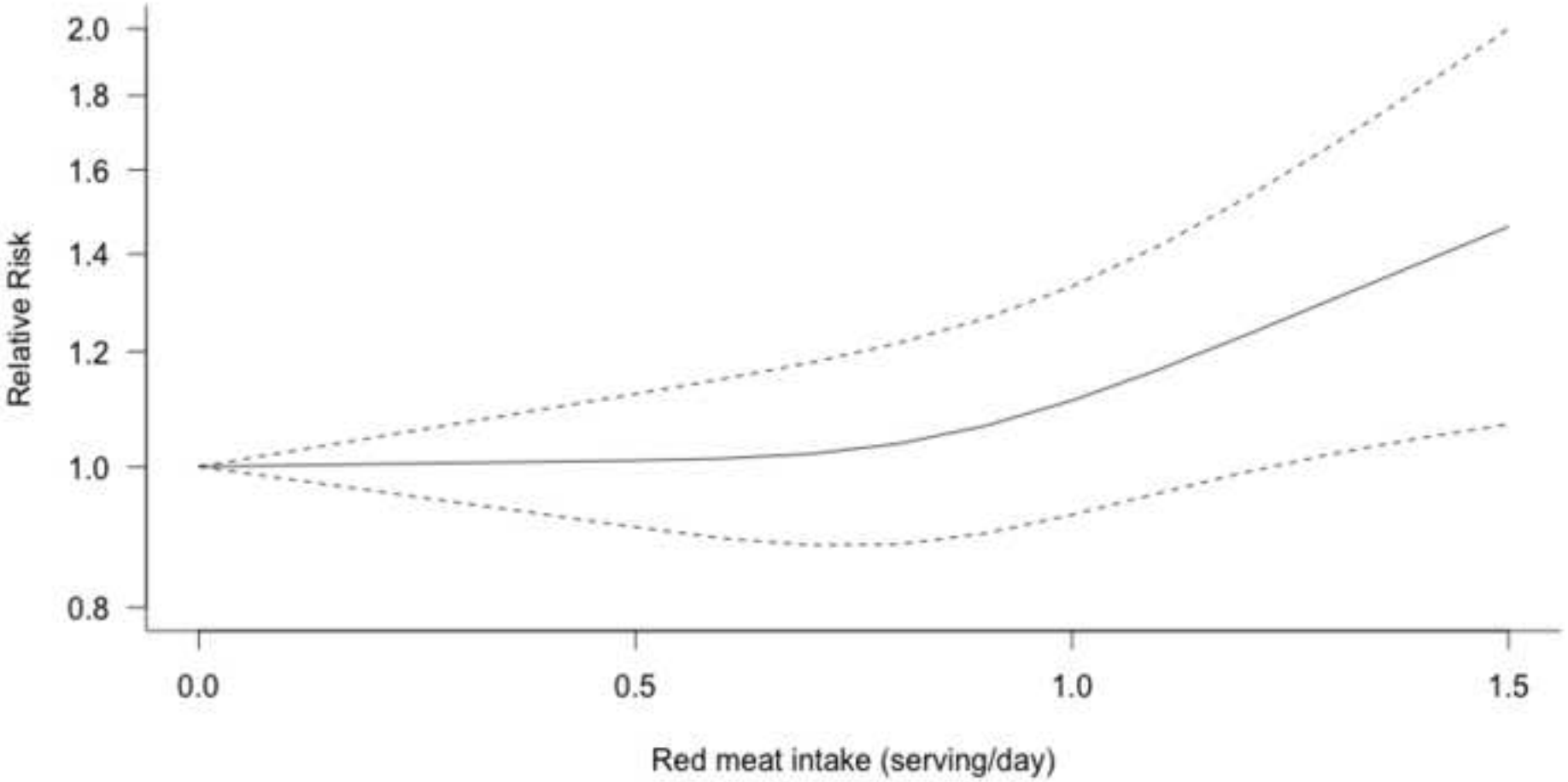

Figure5

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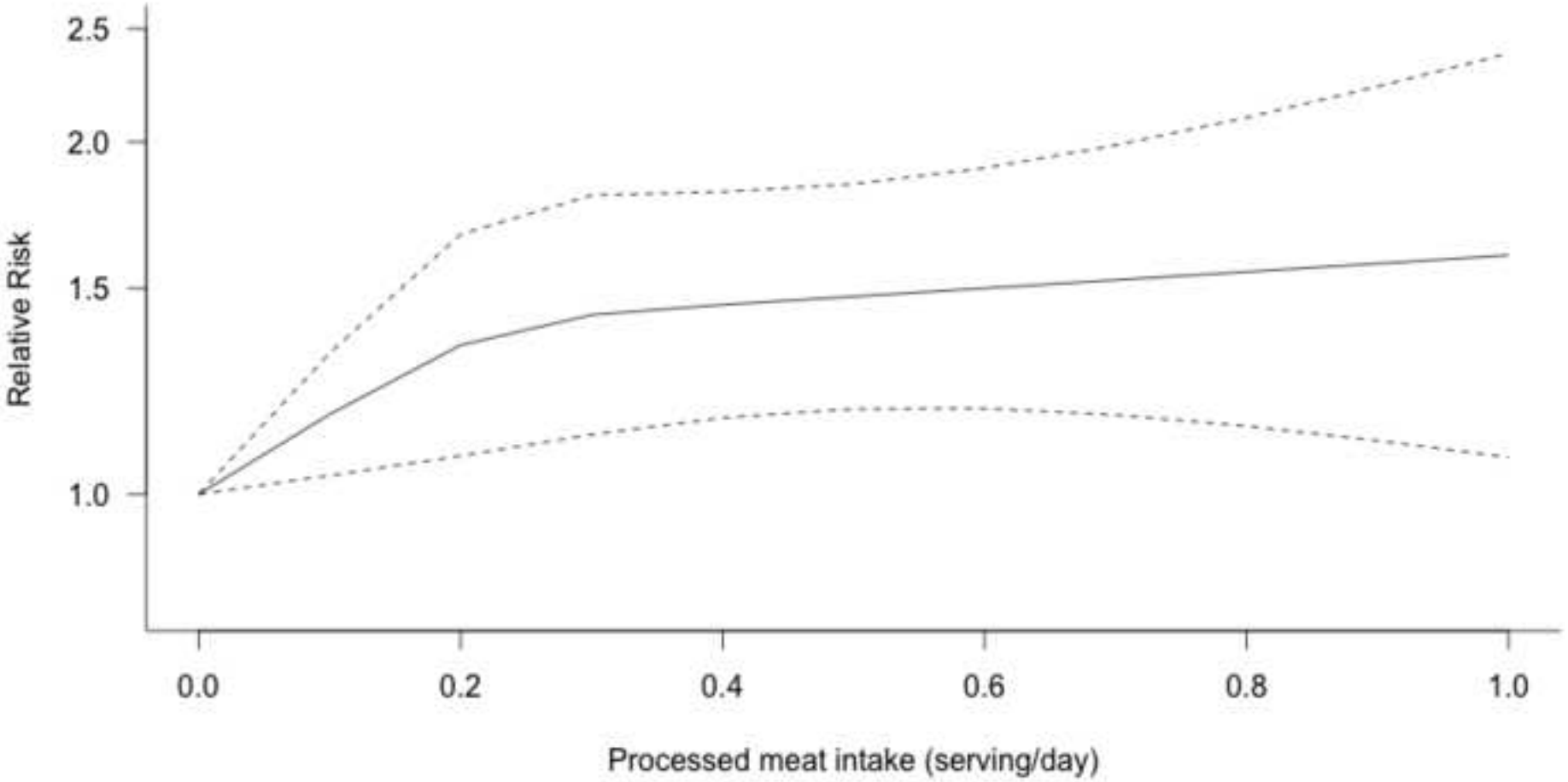

SUPPLEMENTAL MATERIAL

Table S1. Scores of the Newcastle-Ottawa scale for case control studies [1].

First author, year	1. Case definition	2. Case representativeness	3.Control selection	4. Control definition	5a. Comparability	5b. Comparability	6. exposure ascertainment	7. Same methods	8. Non response rate	Total score
Ward, 1994	1	0	1	1	1	1	0	1	1	7
De Stefani, 1998	1	1	0	1	1	1	1	1	1	8
Tavani, 2000	1	1	0	1	1	1	0	1	1	7
Talamini, 2005	1	1	0	1	1	1	0	1	1	7
Chang, 2005	1	1	1	1	1	1	0	1	1	8
Cross, 2006	1	1	1	1	1	1	0	1	1	8
Aschebrook-Kilfoy, 2012	1	1	1	1	1	1	0	1	1	8
Hu, 2008	1	1	1	0	1	1	0	1	1	7
De Stefani, 2013	1	1	0	1	1	1	0	1	1	7
Charbonneau, 2013	1	1	0	1	1	1	0	1	1	7

Table S2. Scores of the Newcastle-Ottawa scale for cohort studies [1].

First author, year	1. Representativeness exposed	2.Selection non exposed	3. Exposure ascertainment	4. No outcome initially present	5a. Comparability	5b. Comparability	6. Outcome assessment	7. follow-up length	8. Loss at follow-up	Total Score
Chiu, 1996	1	1	0	1	1	1	1	1	1	8
Zhang, 1999	0	1	0	1	1	1	1	1	1	7
Rohrman, 2010	1	1	0	1	1	1	1	1	1	8
Daniel, 2012	1	1	0	1	1	1	1	1	0	7

S3. Studies included into red meat – NHL dose-response meta-analysis. (^) Median class intake; (§) Relative Risk

First author, year	Study type	Intake units	Gender	Intake class	OR	95% CI
Chiu, 1996	Cohort	servings/month	Women	<22		
				22-36	1.11	(0.64,1.91)
				>36	1.98	(1.13,3.47)
Daniel, 2012	Cohort	g/1000Kcal	Both	9.8^		
				21.4^	1.08§	(0.97,1.2)
				31.6^	1.12§	(1.01,1.25)
				42.9^	0.97§	(0.87,1.09)
				62.7^	1.01§	(0.9,1.14)
De Stefani, 1998	Case-control	servings/week	Men	<7.7		
				7.8-12.6	1.09	(0.46,2.61)
				>=12.7	2.53	(1.01,6.34)
			Women	>6		
				6.1-9.2	1.22	(0.5,3.01)
				>=9.3	2.45	(0.88,6.82)
				>=61.8	1.5	(1.1,2.2)
Tavani, 2000	Case-control	portions/week	Both	<3		
				4-6	1	(0.7,1.4)
				>6	1.2	(0.8,1.7)
Purdue, 2004	Case-control	servings/week	Both	0-1.9		
				2-3.9	1.14	(0.95,1.36)
				>=4	1.11	(0.93,1.33)
Chang, 2005	Case-control	servings/day	Both	0.0-0.8		
				>0.8-1.1	0.8	(0.5,1.1)
				>1.1-1.6	1	(0.7,1.14)
				>1.6	1.2	(0.8,1.7)
Aschebrook-Kilfoy, 2012	Case-control	g/1000 kcal	Both	<41.2		
				41.2-61.8	1.2	(0.9,1.8)
				>=61.8	1.5	(1.1,2.2)
Charbonneau, 2013	Case-control	servings/month	Both	<19.5		
				19.6-32.4	0.98	(0.72,1.32)
				32.4-50.1	0.96	(0.7,1.33)
				>50.1	1.07	(0.75,1.53)

S4. Studies included into processed meat – NHL dose-response meta-analysis. (^) Median class intake

First author, year	Study type	Intake units	Gender	Intake class	OR	95% CI
Chiu, 1996	Cohort	servings/month	Women	<4		
				4-6	0.94	(0.57,1.55)
				>6	1.11	(0.68,1.79)
Ward, 1994	Case-control	times/week	Men	<2		
				2-3	0.6	(0.3,1)
				4-6	0.8	(0.4,1.3)
				>6	0.6	(0.4,1.1)
	Case-control	times/week	Women	<2		
				2-3	0.9	(0.5,1.6)
				3-4	1.1	(0.7,1.9)
				>4	1.2	(0.7,2.1)
De Stefani, 1998	Case-control	interquartile servings/week	Men	<=0.2		
				0.3-1.0	0.44	(0.19,1.02)
				>1.1	1.03	(0.43,2.42)
	Case-control	servings/week	Women	<=0.2		
				0.3-1.0	3.19	(1.32,7.74)
				>1.1	1.9	(0.66,5.45)
Purdue, 2003	Case-control	servings/week	Both	0-1.3		
				1.4-3.9	1.19	(0.99,1.43)
				>=4	1.49	(1.24,1.8)
Aschebrook-Kilfoy, 2012	Case-control	g/1000 kcal	Both	<6.2		
				6.2-13.1	1.4	(1,2.1)
				>=13.1	1.3	(0.9,1.9)
Charbonneau, 2013	Case-control	servings/month	Both	<0.9		
				1.0-2.1	1.05	(0.77,1.43)
				2.2-6.0	1.21	(0.92,1.59)
				>6.0	1.37	(1.02,1.83)

Table S5. Highest versus lowest red meat intake category: study contributions (%) to the overall RR.

First author, year		Contribution (%)
Chiu, 1996		1.9
Zhang, 1999		2.2
Rohrmann, 2010		12
Daniel, 2012		39.5
	Total cohort studies	55.6
De Stefani, 1998		1.2
Tavani, 2000		3.9
Talamini, 2005		2.1
Chang, 2005		3.9
Cross, 2006		2.2
Hu, 2008		16.3
Aschebrook-Kilfoy, 2012		4.6
Charbonneau, 2013		4.2
De Stefani 2013		6.0
	Total case-control studies	44.4

Table S6. Highest versus lowest processed meat intake category: study contributions (%) to the overall RR.

First author, year		Contribution (%)
Chiu, 1996		2.6
Rohrmann, 2010		9.1
Daniel, 2012		49.1
	Total cohort studies	60.8
Ward, 1994		1.3
De Stefani, 1998		1.3
Talamini, 2005		2.4
Cross, 2006		2.7
Hu, 2008		12.3
Aschebrook-Kilfoy, 2012		4.3
Charbonneau, 2013		7.0
De Stefani, 2013		7.9
	Total case-control studies	39.2

Table S7. Studies included in the analysis by NHL subtype.

First author, year	Study type	Outcome	No. cases / cohort size or No. controls	Meat type	RR (95%CI)
Rohrmann, 2010	Cohort	DLBCL	159 / 411097	Red	0.87 (0.47,1.61)
				Processed	1.37 (0.68, 2.76)
		FL	140 / 411097	Red	0.85 (0.43,1.68)
				Processed	0.31 (0.10, 0.94)
		SLLCLL	234 / 411097	Red	1.13 (0.69,1.85)
				Processed	2.19 (1.27, 3.77)
Daniel, 2012	Cohort	DLBCL	888 / 492186	Red	1.11 (0.88, 1.40)
				Processed	1.07 (0.86, 1.34)
		FL	612 / 492186	Red	0.94 (0.71, 1.25)
				Processed	0.83 (0.63, 1.10)
		SLLCLL	979 / 492186	Red	0.93 (0.75, 1.16)
				Processed	0.93 (0.75, 1.15)
Chang, 2005	Case control	DLBCL	128 / 467	Red	1.1 (0.6, 1.9)
		FL	105 / 467		1.3 (0.7, 2.4)
		SLLCLL	147 / 467		1.1 (0.6, 2.0)
Aschebrook-Kilfoy, 2012	Case control	DLBCL	87 / 459	Red	2.1 (1.1, 3.9)
				Processed	1.5 (0.8, 2.8)
		FL	106 / 459	Red	1.9 (1.1, 3.3)
				Processed	0.9 (2.5, 1.6)
		SLLCLL	26 / 459	Red	1.5 (0.6, 4.2)
				Processed	1.1 (0.4, 3.2)
Charbonneau, 2013	Case control	DLBCL	105 / 1007	Red	0.92 (0.46, 1.83)
				Processed	1.45 (0.80, 2.64)
		FL	146 / 1007	Red	0.75 (0.40, 1.43)
				Processed	1.47 (0.89, 2.42)
		SLLCLL	218 / 1007	Red	1.12 (0.67, 1.88)
				Processed	1.35 (0.89, 2.05)

Table S8. Highest versus lowest red meat intake category pooled relative risks when excluding one study per time.

First author, year of excluded study	RR	95%CI
Cohort		
Chiu, 1996	1.12	(1.02, 1.20)
Zhang, 1999	1.14	(1.03, 1.26)
Rohrmann, 2010	1.17	(1.05, 1.31)
Daniel, 2012	1.18	(1.06, 1.31)
Case-control		
De Stefani, 1998	1.09	(1.01, 1.18)
Tavani, 2000	1.14	(1.03, 1.27)
Talamini, 2005	1.15	(1.04, 1.28)
Chang, 2005	1.14	(1.03, 1.27)
Cross, 2006	1.15	(1.04, 1.28)
Hu, 2008	1.16	(1.04, 1.31)
Aschebrook-Kilfoy, 2012	1.11	(1.01, 1.21)
Charbonneau, 2013	1.15	(1.04, 1.28)
De Stefani, 2013	1.14	(1.02, 1.26)

Table S9. Highest versus lowest processed meat intake category pooled relative risks when excluding one study per time.

First author, year of excluded study	RR	95% CI
Cohort		
Chiu, 1996	1.07	(0.98, 1.18)
Rohrmann, 2010	1.08	(0.97, 1.19)
Daniel, 2012	1.13	(1.01, 1.25)
Case-control		
Ward, 1994	1.06	(0.98, 1.15)
De Stefani, 1998	1.07	(0.98, 1.18)
Talamini, 2005	1.07	(0.98, 1.18)
Cross, 2006	1.07	(0.97, 1.17)
Hu, 2008	1.04	(0.96, 1.13)
Aschebrook-Kilfoy, 2012	1.05	(0.97, 1.14)
Charbonneau, 2013	1.04	(0.96, 1.12)
De Stefani, 2013	1.08	(0.99, 1.19)

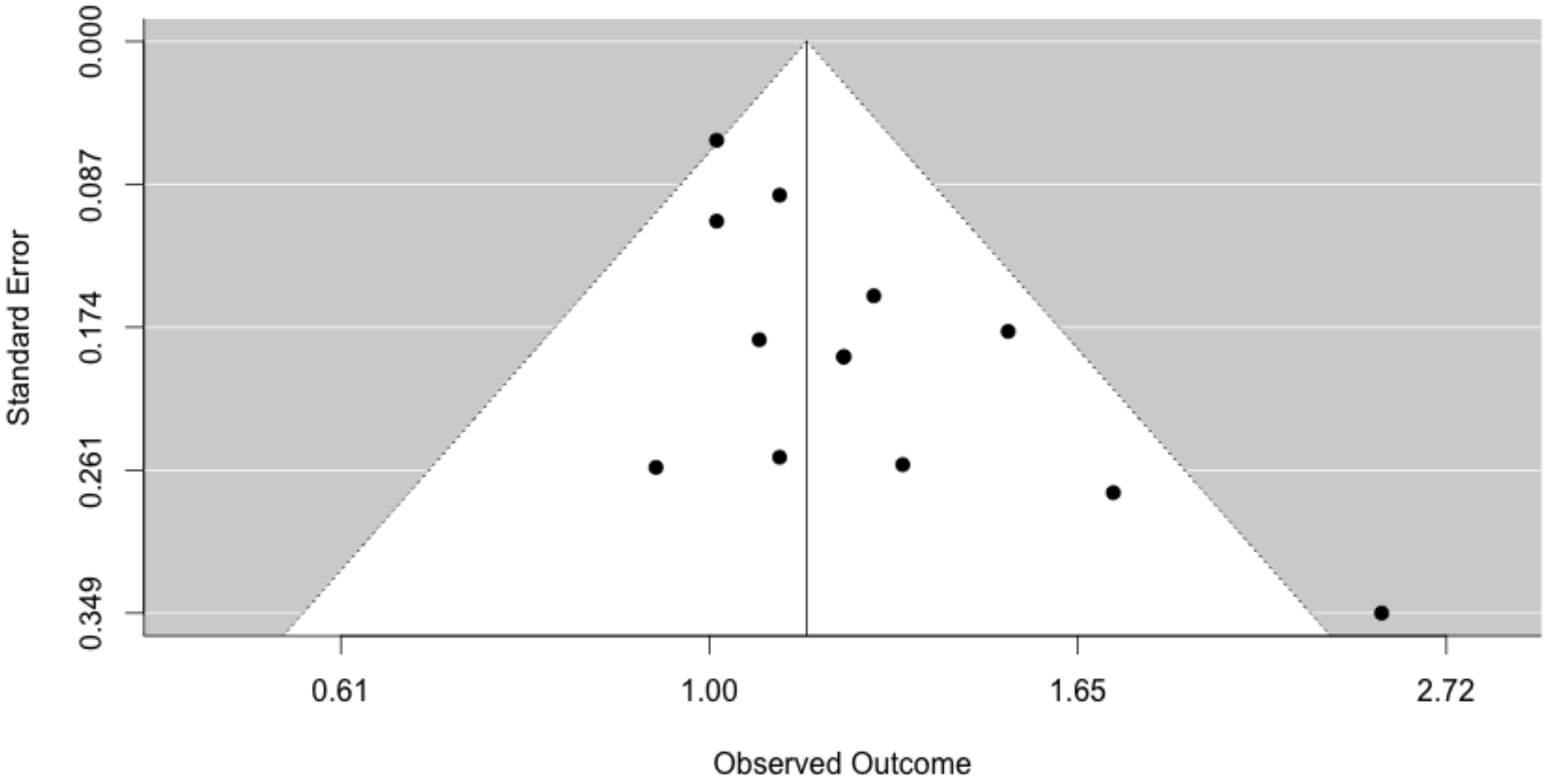

Figure S1- Funnel plot of the meta-analysis of highest versus lowest intake of red meat and NHL risk

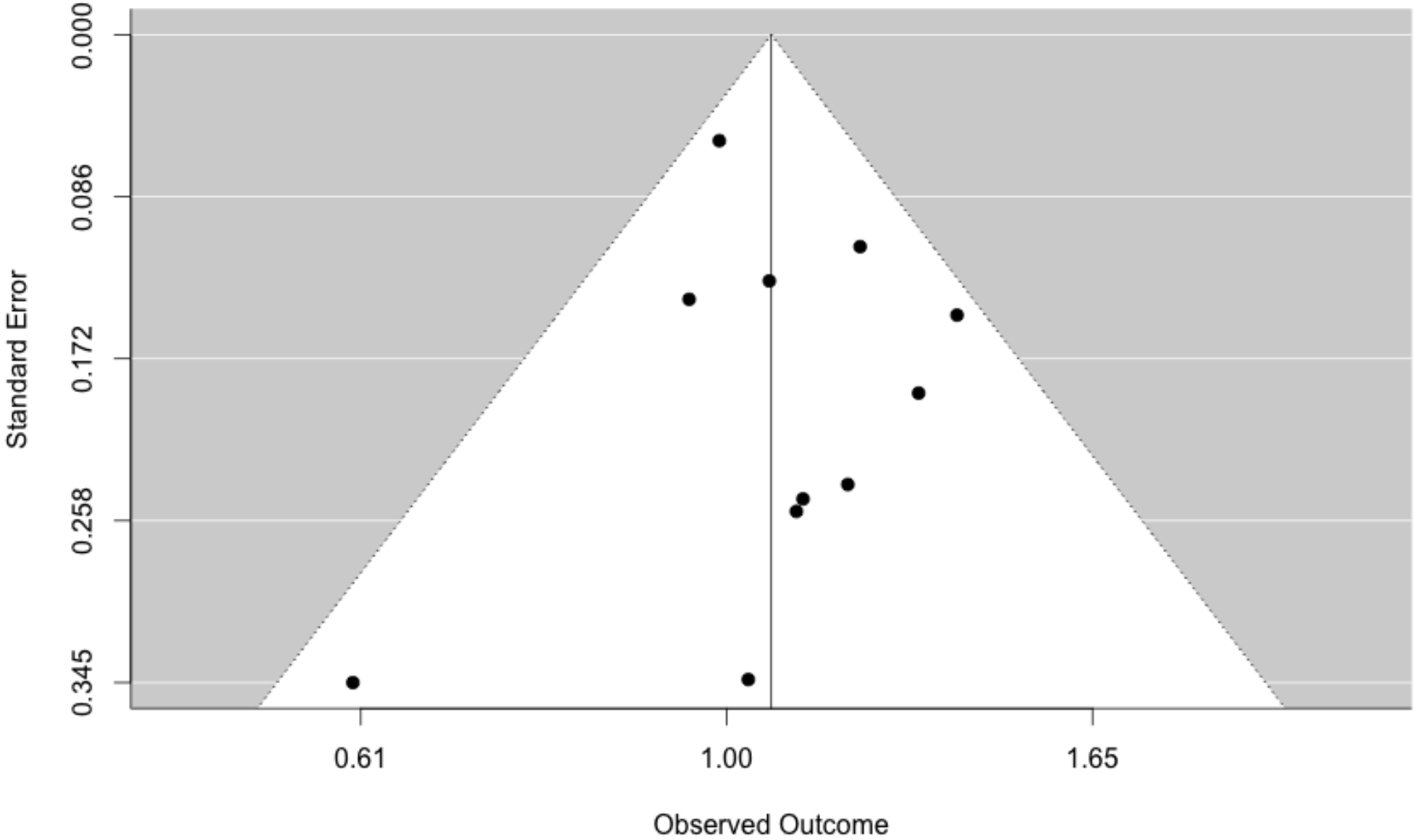

Figure S2- Funnel plot of the meta-analysis of highest versus lowest intake of processed meat and NHL risk