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Meta-analyses

Processed red meat intake and risk of COPD: A systematic review and dose-response meta-analysis of prospective cohort studies

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SUMMARY

Background & aims: No earlier study has summarized findings from previous publications on processed red meat intake and risk of Chronic Obstructive Pulmonary Disease (COPD). This systematic review and meta-analysis was conducted to examine the association between processed red meat intake and COPD risk.
Methods: We searched in PubMed/Medline, ISI Web of Knowledge, Scopus, EMBASE and Google Scholar up to April 2018 to identify relevant studies. Prospective cohort studies that considered processed red meat as the exposure variable and COPD as the main outcome variable or as one of the outcomes were included in the systematic review. Publications in which hazard ratios (HRs) were reported as effect size were included in the meta-analysis. Finally, five cohort studies were considered in this systematic review and meta-analysis.
Results: In total, 289,952 participants, including 8338 subjects with COPD, aged ≥27 years were included in the meta-analysis. These studies were from Sweden and the US. Linear dose response meta-analysis revealed that each 50 gr/week increase in processed red meat intake was associated with 8% higher risk of COPD (HR: 1.08; 95% CI: 1.03, 1.13). There was an evidence of non-linear association between processed red meat intake and risk of COPD ($P < 0.001$).
Conclusions: In this systematic review and meta-analysis, we found a significant positive association between processed red meat intake and risk of COPD.
PROSPERO registration number: CRD42017077971.

1. Introduction

According to the World Health Organization, Chronic Obstructive Pulmonary Disease (COPD) was the third leading cause of death worldwide in 2012 [1]. Several factors including genetic, smoking and exposure to environmental pollutants might contribute to COPD incidence [2]. Diet has also been reported to play an important role in the prevention or progression of COPD. Previous studies

Abbreviations: COPD, Chronic obstructive pulmonary disease; HR, Hazard ratio; CI, Confidence interval; NOS, Newcastle-Ottawa scale; SE, Standard error; FFQ, Food frequency questionnaire; GLST, Generalized least squares trend estimation.

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have assessed the association between dietary intake of fiber, fruit and vegetables, fish and risk of COPD [3–5]. Processed red meat consumption has also been investigated in relation to COPD in earlier studies. Prospective studies on dietary patterns and COPD among US men and women suggested that adherence to a western dietary pattern (greatly loaded with high intakes of cured and red meats, refined grains, desserts and French fries) was positively linked to COPD [6,7]. Some studies have reported a direct positive association between consumption of processed red meat and risk of COPD. In a cross-sectional study, frequent cured meat intake was associated with lower lung function and increased odds of COPD [8]. In a population-based cohort study on Swedish men, despite a direct association between processed meat intake and odds of COPD, no significant association was observed between consumption of unprocessed red meat and COPD [9]. Another study reported that cured meat consumption was associated with increased risk of COPD readmission [10].

In spite of several studies on the association between processed red meat intake and COPD, we are aware of no previous comprehensive study that summarized findings in this regard. Therefore, we aimed to conduct a comprehensive systematic review and meta-analysis to summarize available data on the association between processed red meat intake and risk of COPD.

2. Materials and methods

2.1. Search strategy

A systematic search on all published papers until April 2018 was conducted in PubMed/Medline, ISI Web of Knowledge, Scopus, EMBASE and Google Scholar by two separate investigators using the following keywords: ((“Pulmonary Disease” AND “Chronic Obstructive”) OR COPD OR “Chronic Obstructive Pulmonary Disease” OR COAD OR COBD OR AECB OR “Chronic Obstructive Airway Disease” OR “Chronic Obstructive Lung Disease” OR “chronic obstructive respiratory disease” OR “chronic obstructive airflow disease” OR “chronic obstructive bronchitis disease” OR “acute exacerbation of chronic bronchitis” OR (“Airflow Obstruction” AND Chronic) OR “Chronic Airflow Obstruction” OR emphysema OR “lung disease” OR “chronic bronchitis”) in combination with (“Red meat” OR (Meat AND Red) OR Pork OR Beef OR “Cured meat” OR “Processed meat” OR Diet OR Lifestyle OR Food OR Meat OR “Risk factor” OR N-nitroso OR “Nitroso compounds” OR Nitrates OR Nitrosamines). Our search had no time and language restrictions. In addition, gray literature including reports and conference papers were searched for additional studies. We also examined the reference lists of included studies. When data were ambiguous or missing from any published study, we contacted corresponding authors for key information. Two reviewers independently screened the output of the search to identify potentially eligible studies.

2.2. Inclusion criteria

Each title and abstract was reviewed to clarify whether the articles were relevant or not. Papers' full-texts were reviewed if the abstract indicated that the article reported the association between processed red meat intake and risk of COPD. Studies were eligible for inclusion in the current research if they met the following criteria: 1) all prospective cohort studies that considered processed red meat as the exposure variable and COPD as the main outcome variable or as one of the outcomes were included in the systematic review; 2) publications in which hazard ratios (HRs) were reported as effect size were included in the meta-analysis.

2.3. Exclusion criteria

We excluded letters, comments, reviews and animal studies. In total, 16,502 articles were found in our initial search. After elimination of duplicates, 9893 articles remained. On the basis of title and abstract screening, 9879 studies were excluded and finally 14 potential relevant articles remained for further assessment. The other 9 papers were excluded because of the following reasons: One paper had reported the association between processed red meat intake and forced expiratory volumes, not COPD [11]. Another paper had reported the association between cured meat intake and risk of readmission in COPD patients [10]. Four other papers had examined dietary patterns rather than processed red meat as the main exposure [6,7,12,13]. Three papers had studied the same population [14–16]; of them we selected two papers that had separately reported hazard ratios for men and women [15,16]. Two meeting abstracts were found in our search [17,18]. One abstract was in Chinese language [18]. We used Google translate to convert the language to English. Then, this publication was screened for eligibility criteria. After this assessment, we decided to exclude that study because of its case–control design. Another meeting abstract that had reported our required information was included in the current analysis [17]. Yung et al. conducted two independent case–control studies in southern and eastern China [19]. Therefore, these studies were not included in the meta-analysis due to their study design. In the study of Kaluza et al., data from both cross-sectional and longitudinal phases were reported [20]. Therefore, we used longitudinal findings of that study in our meta-analysis and findings from the cross-sectional phase were not considered. After these exclusions, 5 cohort studies [9,15–17,20] were considered for inclusion in this systematic review and meta-analysis (Fig. 1).

2.4. Data extraction

Two independent reviewers extracted the data regarding first author's last name, publication date, country, study design, participant's age range, sex, follow up duration, number of cases/cohort size, exposure, methods used for assessing exposure and outcome, the reported HRs with the corresponding 95% CIs, adjustments for confounders and quality scores (Table 1). The estimates used in this study were those that were maximally adjusted for confounding variables. Any disagreements between the two reviewers were consulted by principal investigator (AE).

2.5. Quality assessment of studies

The quality of included studies was examined by the Newcastle-Ottawa Scale (NOS) [21]. Based on NOS method, the maximum of nine score can be awarded to each study. In the current analysis, we considered the quality scores of $\geq$6 as high-quality publications and those with the score of <6 were considered as low-quality publications.

2.6. Statistical analysis

All reported hazard ratios (HRs) and 95% CIs for the risk of COPD were used to calculate log HR and its standard errors (SEs). Using the random effects model that incorporates between-study heterogeneity, the overall effect size was calculated. Between-study heterogeneity was examined using Cochran's Q test and I-squared. We performed linear dose-response meta-analysis per 50 gr/week increment of processed red meat intake using generalized least squares trend estimation (GLST). These methods require the number of cases or person-year and total number of

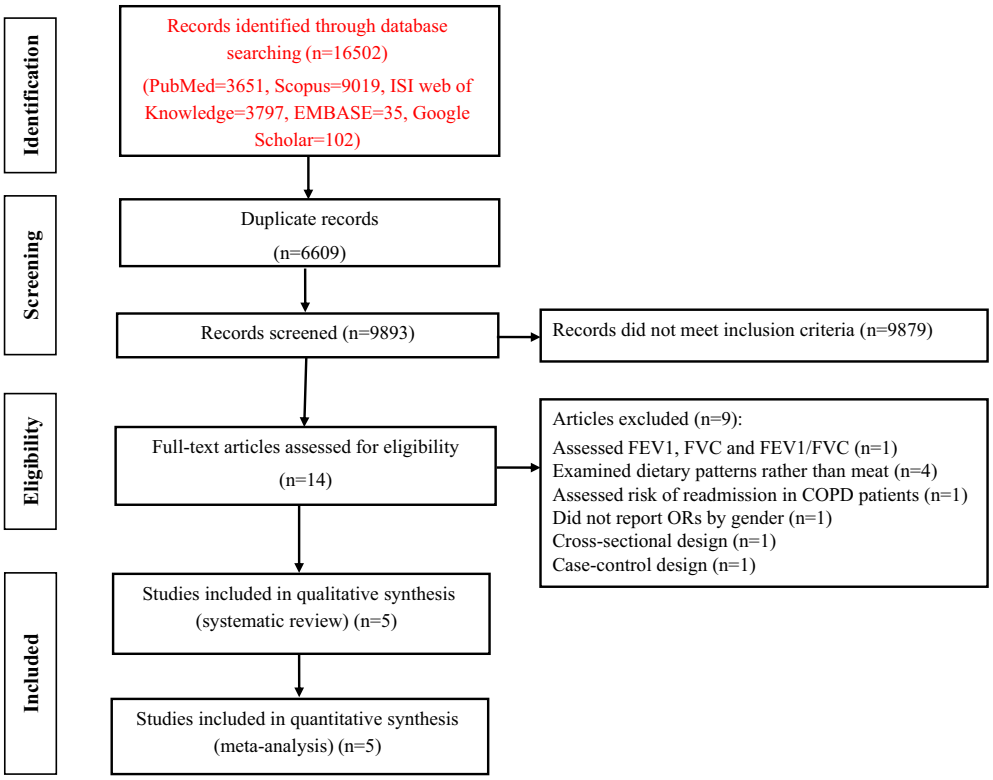

Fig. 1. Flowchart of study selection process.

subjects for at least three quantitative exposure categories. GLST also requires mean intake for each category of exposure levels. When the range of processed red meat intake was available rather than mean intake, we chose the midpoint of the upper and lower limits in each category as the assigned dose. For open-ended categories, we defined the lowest limits as zero and upper limits as 1.5 times the lower limit [22]. Then, a two-stage random-effects dose-response meta-analysis was conducted to examine linear trend between processed red meat intake and COPD risk. At first, we used Greenland and Longnecker [23] and Orsini et al. [24] method to calculate the correlation within each study. Secondly, study-specific estimates were combined by using a random-effects meta-analysis. For non-linear dose-response relationship between processed red meat intake and risk of COPD, restricted cubic splines with 4 knots at 5%, 35%, 65% and 95% percentiles of the distribution were used [25]. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. Publication bias was assessed by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was done with Egger's regression asymmetry test. Statistical analyses were done by the use of Stata, version 11.2 (Stata Crop). Values of <0.05 were considered statistically significant.

3. Results

3.1. Study characteristics

Out of 16,502 retrieved papers, 5 cohort studies were included in this systematic review and meta-analysis. The studies included in this systematic review are provided in Table 1. These studies included 289,952 participants aged ≥27 years. Total number of subjects with COPD was 8338, varied from 111 to 4080 between studies. These studies were published between 2007 and 2018; three of them were conducted in USA [15–17] and two studies conducted in Sweden [9,20]. Three studies performed among women [15,17,20] and two studies performed among men [9,16]. Processed red meat intake was measured by FFQ in all studies. Types of processed red meat in eligible studies including sausages, cold cuts/ham/salami, blood pudding/sausages, and liver pate [9,20] or cured meat, bacon, hot dogs [17] or bacon, hog dogs, sausages, salami, bologna [15,16]. For outcome assessment, the included studies had used different methods including linkage to national registry [9,20], self-reported [16,17] and questionnaire [15].

All studies had controlled the analyses for age and BMI. Most studies had controlled for smoking [9,15–17,20], smoking pack-years [9,15–17,20], physical activity [9,15–17,20], race/ethnicity [15–17] and energy intake [9,15,16,20]. Other studies did further adjustments for US region ($n = 3$), dietary intake of fish ($n = 2$), fruit ($n = 2$), vegetables ($n = 2$), sex ($n = 2$), educational experience ($n = 2$), pack-years squared ($n = 2$), alcohol consumption ($n = 2$), Recommended Food Score ($n = 2$), Non-Recommended Food Score ($n = 2$), unprocessed meat ($n = 2$), processed meat ($n = 2$), exposure to secondhand tobacco ($n = 1$), menopausal status ($n = 1$) and postmenopausal hormone use ($n = 1$). Based on the New-Castle Ottawa Scale, all of the included studies were high quality studies (Table 1).

Processed red meat intake was associated with increased risk of COPD in all cohort studies. The risk estimates for COPD in these studies ranged from 0.95 to 2.64.

3.2. Findings from the meta-analysis

The meta-analysis was done on 5 prospective cohort studies. In total, 289,952 participants aged ≥27 years were studied in these 5 cohort studies. Combining 5 effect sizes, we found that the highest

Table 1
Main characteristics of cohort studies examined the association between processed red meat intake and COPD.

First author (year)	Country/cohort name	Age range	Sex	Follow up duration (y)	Number of cases/ cohort size	Exposure	Exposure assessment	Outcome assessment	Comparison	HR (95% CI)	Adjustments	Quality score
Cohort												
Kaluza et al. (2018)	Sweden/SMC	48–83	F	11.6	1488/34,053	Processed red meat (sausages, cold cuts/ ham/salami, blood pudding/sausages, and liver pate)	FFQ	Linkage to National Registry	<25 g/day 25–49.9 g/day ≥50 g/day	HR: 1.00 0.95 (0.84–1.07) 1.36 (1.03–1.79)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	9
Kaluza et al. (2016)	Sweden/COSM	45–79	M	13.2	1909/43,848	Processed red meat (sausages, cold cuts/ ham/salami, blood pudding/sausages, and liver pate)	FFQ	Linkage to National Registry	<25 g/day 25–49.9 g/day 50–74.9 g/day ≥75 g/day	HR: 1.00 1.07 (0.96–1.20) 1.10 (0.96–1.27) 1.21 (1.02–1.44)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	9
Varraso et al. (2016)	USA/NHSII	27–44	F	17	4080/97,605	Processed meat (cured meat, bacon, hot dogs)	FFQ	Self-reported	Never <1 serving/week 1–2 servings/week >2 servings/week	HR: 1.00 1.12 (1.04–1.21) 1.11 (0.99–1.25) 1.45 (1.26–1.66)	1, 3, 4, 5, 6, 13, 14	6
Jiang et al. (2008)	USA/NHS	38–63	F	16	750/71,531	Cured meat (bacon, hog dogs, sausages, salami, and bologna)	FFQ	Questionnaire	Never or almost never 1–3 servings/month 1 serving/week 2–3 servings/week ≥4 servings/week	HR: 1.00 1.14 (0.78–1.66) 1.15 (0.79–1.69) 1.40 (0.96–2.05) 1.51 (1.00–2.27)	1, 3, 4, 5, 6, 7, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25	8
Varraso et al. (2007)	USA/HPFS	40–75	M	12	111/42,915	Cured meat (bacon, hog dogs, sausages, salami, and bologna)	FFQ	Self-reported	None <1 serving/week 1–3 servings/week 4–6 servings/week ≥1 serving/day	HR: 1.00 1.29 (0.69–2.42) 0.97 (0.46–2.04) 1.57 (0.79–3.11) 2.64 (1.39–5.00)	1, 3, 4, 5, 6, 7, 13, 14, 15	8

M: Male; F: Female; FFQ: Food Frequency Questionnaire; NR: Not Reported; OR: Odds Ratio; RR: Risk Ratio; HR: Hazard Ratio; COPD: Chronic Obstructive Pulmonary Disease; NR: Not Reported; NA: Not Applicable; SMC: Swedish Mammography Cohort; COMS: Cohort of Swedish Men; NHSII: Nurses' Health Study II; NHS: Nurses' Health Study; HPFS: Health Professional Follow-up Study.
1: age; 2: educational level; 3: BMI, 4: physical activity; 5: smoking status; 6: pack-years of smoking; 7: intake of energy; 8: alcohol consumption; 9: Recommended Food Score; 10: Non-Recommended Food Score; 11: unprocessed meat; 12: processed red meat; 13: race/ethnicity, 14: US region, 15: pack-years squared, 16: exposure to secondhand tobacco, 17: menopausal status, 18: postmenopausal hormone use, 19: spouse's educational attainment, 20: physician visits, 21: multivitamin use, 22: dietary intake of fish, 23: fruit, 24: vegetables, 25: sex.

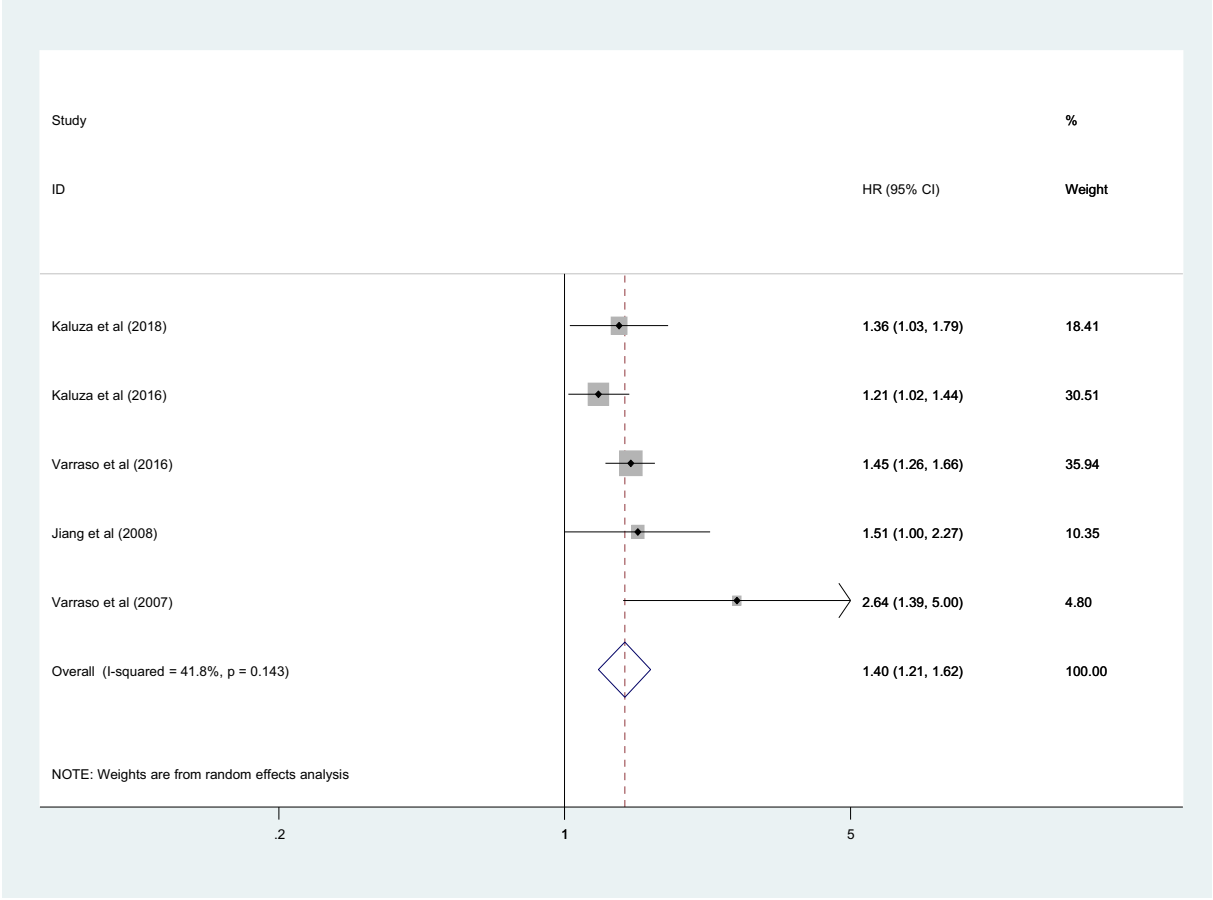

Fig. 2. Forest plot of prospective cohort studies that examined the association between processed red meat intake and COPD according to highest vs. lowest analysis.

(≥75–787.5 gr/week) versus the lowest (0–175 gr/week) categories of processed red meat intake was associated with 40% increased risk of COPD (HR: 1.40; 95% CI: 1.21, 1.62) (Fig. 2). No significant between-study heterogeneity was seen (I^2 = 41.8%, P = 0.143). In a sensitivity analysis, we found that no particular study significantly influenced the findings. In addition, no evidence of significant publication bias was found (Egger's test = 0.33).

3.3. Findings from the dose-response meta-analysis

Five prospective cohort studies were included in the dose-response meta-analysis on processed red meat intake and risk of COPD. Linear dose response meta-analysis showed that each 50 gr/week increase in processed red meat intake was associated with 8% higher risk of COPD (HR: 1.08; 95% CI: 1.03, 1.13), with an evidence of a considerable heterogeneity (I^2 = 90.6%, P < 0.001) (Fig. 3). We did not perform meta-regression to find sources of heterogeneity due to limited number of studies.

In the non-linear dose-response meta-analysis, we found an association between processed red meat intake and risk of COPD (P < 0.001). Visual inspection of the curve suggested that risk of COPD was significantly increased with the processed red meat consumption of 0–100 gr/week. Then, the risk was attenuated by the consumption of 100–250 gr/week. An increasing trend in the risk of COPD was also observed after 250 gr/week intake (Fig. 4).

4. Discussion

This meta-analysis of prospective cohort studies showed that higher intakes of processed red meat were associated with 40% increased risk of COPD. To the best of our knowledge, this is the first systematic review and dose-response meta-analysis that examined the association between processed red meat intake and risk of COPD.

COPD is an important cause of morbidity and mortality [26,27]. Among several factors that might influence the risk of COPD, recent evidence emphasis the importance of diet as a modifiable risk factor for COPD [28]. Therefore, particular attention has been paid to the dietary intakes, including processed red meat consumption in relation to COPD. As pooling information can provide more precise findings than those obtained from individual studies, we conducted a meta-analysis to summarize findings from previous studies in this regard. In this systematic review and meta-analysis, we observed that higher intakes of processed red meat were significantly associated with increased risk of COPD. Our findings were in line with earlier studies. A cross-sectional study among US adults, reported that frequent cured meat intake was linked to increased odds of COPD [8]. Yang et al. conducted two case–control studies in southern and eastern China and found that cured meat consumption was associated with increased risk of COPD [19]. Our findings were also in line with previous review studies that reported the same association [28,29]. However, these studies

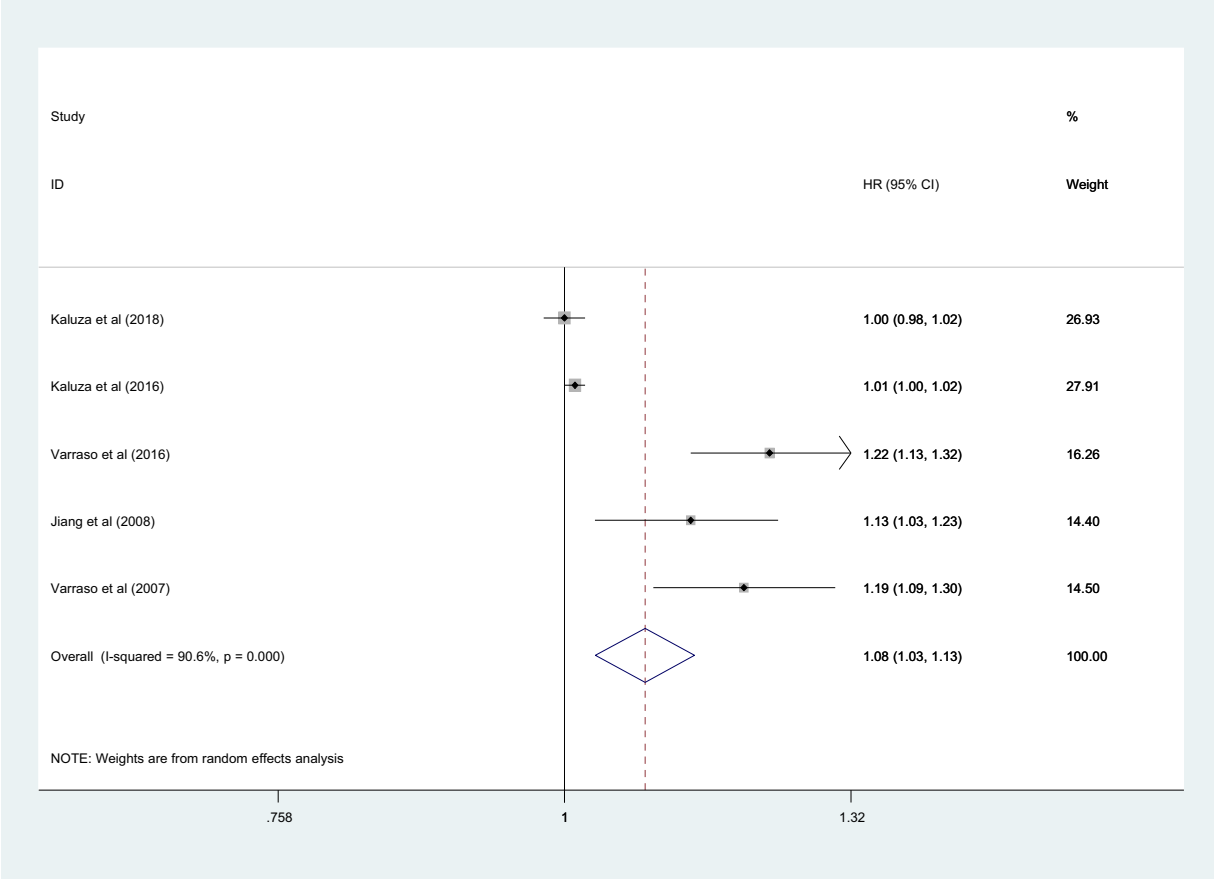

Fig. 3. Linear dose-response meta-analysis of prospective cohort studies that examined the association between processed red meat intake and COPD. The overall estimate indicates the risk of COPD by 50 gr/week increase in processed red meat intake.

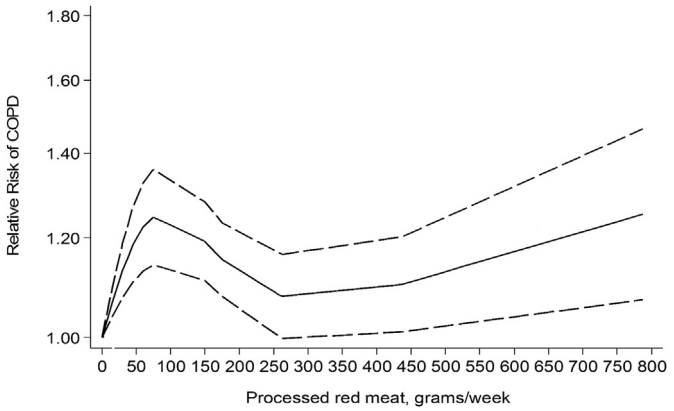

Fig. 4. Non-linear dose-response association between processed red meat intake and risk of COPD (per 50 gr/week increment).

conducted a narrative review and did not report any effect size or dose-response analysis. We conducted a dose-response meta-analysis and observed that each 50 gr/week increase in processed red meat intake was associated with 8% higher risk of COPD. The risk was attenuated by the consumption of 100–250 gr/week; however, the association was still positive. Above this range, the risk was slightly increased by processed red meat intake. A possible explanation for N-shape association might be that the magnitude of the association between processed red meat intake and COPD depend on other dietary factors, such as dietary antioxidant and anti-inflammatory intakes that influence pulmonary oxidant/anti-oxidant balance and inflammation [11].

Consumption of processed red meat was linked with a greater risk of colorectal cancer, obesity, cardiovascular disease and diabetes [30–33]. In addition, in a cohort study with a 10-year follow-up period, processed red meat intake was associated with modest increases in total mortality, cancer and cardiovascular mortality [34]. Processed red meat is one of the components of western dietary patterns [33]. Findings from a recent meta-analysis revealed that adherence to western dietary patterns were associated with greater risk of COPD [35]. Combining these findings, it seems that higher intakes of processed red meat were associated with higher chance of COPD; therefore, to prevent COPD condition, it should be advised to confine consumption of processed red meats.

The mechanisms through which processed red meat might affect the risk of COPD are largely unclear and mechanistic studies are lacking in this regard. Processed red meat contains a high amount of nitrates, nitrites and nitrosamine compounds [36]. It has been proposed that these compounds may have a potential role in oxidative stress and inflammatory processes involved in lung cells [9]. Another suggested mechanism is that processed red meat consumption may damage lung tissue by influencing connective tissue protein collagen and elastin in the lung by its nitrate content [15].

This study has some strengths as well as limitations. The strengths include that the present study was the first systematic review and dose-response meta-analysis that examined the association between processed red meat intake and risk of COPD. In addition, we searched gray literature to find unpublished studies. We also examined the linear and non-linear relationship between

processed red meat intake and risk of COPD. However; some points need to be considered when interpreting our results. We conducted this systematic review and meta-analysis on observational studies. Therefore, it is difficult to make a conclusive decision about the causal association between processed red meat and risk of COPD. As processed red meat intake was assessed by FFQ in most included studies, measurement errors and misclassification of participants in terms of processed red meat intake is possible. Residual confounders in primary studies are also of concern. Another limitation is that we could not perform meta-regression to find possible sources of heterogeneity due to limited number of studies. It must also be taken into account that as the number of studies was rather small, the significance of I-squared estimate is less relevant that the actual estimate of the heterogeneity. Perhaps the associations in the studies went in the same direction and that heterogeneity is mostly due to the size of association rather than the direction. Included studies came from western countries and no information is available in this regard from non-western nations. Given the emerging phenomenon of nutrition transition in these countries that is associated with increased consumption of processed meats [37], it seems that having data from such countries would move the field forward.

In conclusion, summarizing earlier findings, we found a significant positive association between processed red meat intake and risk of COPD. We also found a significant linear and non-linear dose-response association between processed red meat intake and risk of COPD. However, due to limited information in this field, further studies are required to confirm our results.

Conflicts of interest

ASM, AM, BL and AE declared no potential personal or financial conflicts of interest.

Author's contribution

ASM and AM contributed in conception, design, search, statistical analyses, data interpretation and manuscript drafting. BL contributed in design, data interpretation and manuscript drafting. AE contributed in conception, design, statistical analyses, data interpretation and manuscript drafting. AE supervised the study. All authors approved the final manuscript for submission.

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