American Journal of Epidemiology

Vol. 184, No. 11
DOI: 10.1093/aje/kww101
Advance Access publication:
October 27, 2016

## Original Contribution

# Consumption of Unprocessed and Processed Red Meat and the Risk of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study of Men

**Joanna Kaluza*, Susanna C. Larsson, Anders Linden, and Alicja Wolk**

* Correspondence to Joanna Kaluza, Department of Human Nutrition, Warsaw University of Life Sciences, 159C Nowoursynowska Street, 02-776 Warsaw, Poland (e-mail: joanna_kaluza@sggw.pl).

*Initially submitted September 15, 2015; accepted for publication March 14, 2016.*

Consumption of both processed and unprocessed red meat has been associated with a higher risk of major chronic diseases. However, only processed meat consumption has been studied in relation to chronic obstructive pulmonary disease (COPD). Therefore, we endeavored to determine the association between the risk of COPD and consumption of processed and unprocessed red meat while taking into account smoking status. The population-based prospective Cohort of Swedish Men included 43,848 men who were 45–79 years of age and had no history of COPD or cancer at baseline. Meat consumption was assessed using a self-administered questionnaire in 1997. During 13.2 years of follow-up, 1,909 COPD cases were ascertained. Consumption of processed meat was associated with risk of COPD: Compared with men who consumed less than 25 g/day of processed meat, men who consumed 75 g/day or more had a multivariable-adjusted hazard ratio of 1.21 (95% confidence interval: 1.02, 1.44; $P$ for trend = 0.03). The positive association was confined to current smokers ($P$ for interaction = 0.003); among smokers who consumed 75 g/day or more of processed red meat, the hazard ratio was 1.26 (95% confidence interval: 1.00, 1.60) when compared with persons who consumed less than 25 g/day. Consumption of unprocessed red meat was not associated with COPD incidence. Findings from this prospective study indicate that high consumption of processed red meat is associated with an increased COPD risk among smokers.

chronic obstructive pulmonary disease; processed meat; prospective cohort study; red meat

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

According to the World Health Organization, chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide in 2012, after ischemic heart disease and stroke (1). Researchers in the Global Burden of Disease Study 2013 classified COPD as the sixth leading cause of disability-adjusted life years in developed countries (2) and the third leading cause of disability-adjusted life years in the United States and the United Kingdom. The estimated number of global age-standardized disability-adjusted life years for COPD was 1,138 cases per 100,000 population (1, 2).

Genetic predisposition and exposure to environmental pollution, including cigarette smoking and presence of dust in occupational settings, are important risk factors for COPD (3). In addition, recent evidence indicated that diet may play an important role in the development of COPD. A "prudent" dietary pattern (i.e., high consumption of fruit, vegetables, fish, and whole-grain cereals) has been observed to be associated with a lower risk of impaired lung function and COPD, whereas a "Western" dietary pattern (i.e., high consumption of processed meat, white bread, added sugar, full-fat dairy products, and chips) has been associated with a higher risk of COPD (4–6). It has been suggested that high consumption of processed meat is associated with impaired lung function because of the high nitrite content in these products (7). This hypothesis is plausible, given that nitrites lead to the generation of reactive nitrogen species and an antioxidant-oxidant imbalance (3, 8, 9). In prospective studies of women (7) and men (10), a positive association between processed meat consumption and COPD was observed. Although the association was observed only in ever smokers, there was no significant interaction with smoking status, probably because of the

limited number of never smokers. Studies of the association between unprocessed red meat consumption and COPD are lacking. However, consumption of both processed and unprocessed red meat has been associated with a higher risk of major chronic diseases, such as diabetes (11, 12), cardiovascular diseases (13–15), and cancers (16).

Therefore, we investigated the associations of processed meat consumption and unprocessed red meat consumption with the risk of COPD in the Cohort of Swedish Men (COSM), a large, population-based, prospective study. We assessed whether smoking status modified the associations.

## METHODS

### Study population

The Cohort of Swedish Men was established in central Sweden (Västmanland and Örebro Counties) in 1997. Questionnaires were sent to all men who were 45–79 years of age and lived in this area. Of the 48,850 men who returned a completed questionnaire, we excluded those with a missing or incorrect national identification number ($n = 297$), those who died before baseline ($n = 55$), and those with a previous cancer diagnosis (other than nonmelanoma skin cancer) ($n = 2{,}592$). Moreover, men with a history of COPD ($n = 281$), those with implausible values for total energy intake (>3 standard deviations from the mean value for log-transformed energy; $n = 567$); and those for whom data on red meat consumption were missing ($n = 1{,}210$) were excluded. After these exclusions, 43,848 men remained for the analysis. The original and analytical cohort was representative of the population of Swedish men in 1997 in terms of age, educational level, and proportion with obesity as compared with the Official Statistic of Sweden (17, 18) (Web Table 1, available at http://aje.oxfordjournals.org/). The study was approved by the Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden).

### Assessment of diet and other exposures

Diet was assessed using a 96-item food frequency questionnaire. The food frequency questionnaire included 3 questions about consumption of unprocessed red meat (pork, beef/veal, and minced meat) and 4 questions about consumption of processed meat (sausages, cold cuts/ham/salami, blood pudding/sausages, and liver paté). Participants were asked to indicate how often, on average, they had consumed each food item over the past year, using 8 predefined categories: never/seldom, 1–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, once per day, 2 times per day, and ≥3 times per day. The frequencies of red meat consumption were converted to grams per day by multiplying the frequency of consumption of each food item by the appropriate age-specific portion size.

The food frequency questionnaire has been validated in 248 Swedish men using fourteen 24-hour recall interviews over a year as the reference method (19). The Spearman correlation coefficients for the associations between estimates obtained from the food frequency questionnaire and those from the repeated recall interviews were, on average, 0.65 for macronutrients and 0.62 for micronutrients.

We assessed dietary patterns based on 2 measurements of diet quality, the Recommended Food Score and modified Non-Recommended Food Score, which were developed and described previously (20). Based on global dietary guidance (21), the Recommended Food Score included 36 food items: 13 vegetables (carrot, beetroot, cabbage/red cabbage, cauliflower, broccoli/Brussels sprouts, tomatoes/tomato juice, pepper, lettuce/iceberg lettuce, spinach, onion/leek, green peas, soy bean products, and mixed vegetables), 6 fruits (apples/pears, bananas, berries, oranges/citrus fruits, other fruits, and orange/grapefruit juice), 7 cereal products (whole grain bread, crispbread/crackers, oatmeal, gruel/other porridge, cereals/muesli, rice, and oat/wheat bran), 5 types of fish and seafood (herring/mackerel, salmon, cod/saithe/fish fingers, caviar, and shellfish), 3 different low-fat dairy products (low-fat (≤0.5% fat) and medium-fat (1.5%) milk, low-fat sour milk/yoghurt, and low-fat cheese (10%–17%)), nuts/almonds, and olive oil. One point was assigned for each recommended food item that was consumed at least 1–3 times per month. People could receive maximum 36 points, and a higher score indicated a better-quality diet. The Non-Recommended Food Score included 9 food items (we omitted 3 unprocessed and 4 processed red meat food items included in the original score) that are not recommended from health point of view: 3 high-fat dairy products (cheese (28% fat), butter (80% fat), and cream/crème fraiche), white bread, sweets (combined buns/cakes, biscuits/wafers/rusks, and gateau/pastries), and 4 other products (combined potato chips/popcorn and fried potatoes/French fries, unprocessed offal, mayonnaise, ice cream). Participants were assigned 1 point if they consumed of any of these nonrecommended food items 3 times per week or more; otherwise, they received 0 points. Subjects could receive a maximum of 9 points, with a higher number of points corresponding to a lower-quality diet (20).

Information about educational level, body weight and height, physical activity level, smoking status, alcohol consumption, and history of hypertension were obtained in the baseline self-administered questionnaire. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters. Assessment of total physical activity estimated as metabolic equivalents (metabolic equivalent of energy expenditure × hours/day) was based on 6 questions described previously by Norman et al. (22). Pack-years of smoking history were calculated by multiplying the number of cigarettes smoked per day by the number of years of smoking.

### Case ascertainment

Date of the first registered diagnosis of COPD and date of death from COPD were ascertained by linkage of the study cohort with the Swedish Patient Register (in-patient and out-patient registers) and the Cause of Death Register at the Swedish National Board of Health and Welfare. Events of COPD were defined according to the *International Classification of Diseases and Related Health Problems, 10th Revision* (code J44). In the present study, a COPD event was defined as the first diagnosis of COPD (listed either as the primary diagnosis or at any

diagnosis position) in the Swedish Patient Register or in the Cause of Death Register (COPD as the primary diagnosis only). It was reported that in the period from 1999 to 2009, a higher proportion of patients with COPD were detected and diagnosed in primary care than in the beginning of the study period (81% vs. 59%) (23). On average, patients who were diagnosed with COPD in 2009 were 7 years younger than those diagnosed at the start of the study in 1999 (66 vs. 73 years of age) (23).

### Statistical analysis

Study participants were followed from January 1, 1998, to the date of COPD diagnosis, death, or the end of the study follow-up period (December 31, 2012), whichever came first. Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals for COPD. We categorized participants into quintiles of consumption of unprocessed, processed, and total red meat, as well as into 4 categories of consumption of unprocessed and processed red meat (<25.0, 25.0–49.9, 50.0–74.9, and ≥75.0 g/day). The categorization simplifies the interpretation in relation to portion sizes and facilitates communication of results.

Multivariable hazard ratios were adjusted for age (continuous), educational level (less than high school, high school graduate, or university), body mass index (<18.5, 18.5–24.9, 25–29.9, or ≥30), total physical activity (metabolic equivalent of energy expenditure × hours/day, in quintiles), smoking status and pack-years of smoking (never; former smoker for <20, 20–39, or ≥40 pack-years; or current smoker for <20, 20–39, or ≥40 pack-years), energy intake (kcal/day, in quintiles), consumption of alcohol (g/day, in quintiles), Recommended Food Score (continuous), and Non-Recommended Food Score (continuous). We mutually adjusted for unprocessed red meat consumption and processed red meat consumption through inclusion in the same multivariable model. The covariates were chosen because they were either a known risk factor for COPD or potentially related to both COPD and red meat consumption (3, 24, 25).

The proportional hazards assumption was tested by regressing scaled Schoenfeld residuals against survival time. There was no evidence of departure from the assumption. To calculate $P$ values for trend, the median values of quintiles and categories of unprocessed, processed, and total red meat consumption were used as continuous variables. Using the likelihood ratio test, we tested statistical interactions of unprocessed and processed red meat consumption with smoking status in predicting the risk of COPD.

The statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). All reported $P$ values are 2-sided; $P$ values ≤0.05 were considered to be statistically significant.

## RESULTS

### Characteristics of the cohort

During a mean follow-up of 13.2 years (578,109 person-years; 1998–2012), 1,909 cases of COPD were ascertained. The Spearman correlation coefficient for the association between consumption of unprocessed red meat and consumption of processed red meat was 0.30. The median consumption of unprocessed red meat differed 4.4-fold between the highest and the lowest quintiles and 4.9-fold between the highest and the lowest categories (≥75 g/day vs. <25 g/day). For processed red meat consumption, the corresponding differences were 6.5-fold and 5.9-fold, respectively. Compared with men in the lowest quintiles of unprocessed and processed red meat consumption, those in the highest quintiles were younger, had higher intakes of energy, and consumed more products from nonrecommended list (Table 1). Moreover, men with a high intake of unprocessed red meat had higher alcohol consumption, whereas those with a high intake of processed meat were less likely to have a university education.

### Red meat consumption and risk of COPD

We observed a positive association between consumption of processed (but not unprocessed) red meat and the risk of COPD. Compared with men in the lowest category of processed meat consumption (<25 g/day), those in the highest category (≥75 g/day) had a 21% (95% confidence interval (CI): 2, 44) higher risk of COPD (Table 2). In the dose-response analysis, the risk of COPD increased statistically significantly by 9% (95% CI: 2, 17%) for each 50-g/day (about 2–3 slices of processed meat) increase in processed meat consumption. For quintiles of processed red meat consumption, compared with being in the lowest quintile of processed meat consumption, being in the highest quintile was associated with a 21% (95% CI: 4, 41) higher risk of COPD (Web Table 2). After excluding the first year of follow-up, the result did not change substantially; the highest category of processed red meat consumption (≥75 g/day) was associated with a 20% (95% CI: 0, 43; $P$ for trend = 0.05) higher risk of COPD when compared with the lowest category of consumption (<25 g/day).

We observed a statistically significant interaction between processed red meat consumption and smoking status ($P$ for interaction = 0.003). Among current smokers, those in the highest category of processed meat consumption had a 26% (95% CI: 0, 60) higher risk of COPD compared with those in the lowest category (Table 3). For each 50-g/day increase in processed meat consumption, the risk of COPD increased by 13% (95% CI: 3, 23) among current smokers. Moreover, we performed a sensitivity analysis excluding current smokers with a diagnosis of asthma before baseline or during follow-up (252 cases of asthma), and the results did not change essentially: The hazard ratio for COPD in men who consumed 50 g/day or more of processed red meat was 28% (95% CI: 7, 54; $P$ for trend = 0.008) compared with those who consumed less than 25 g/day. There was no relation between processed red meat consumption and COPD risk among former smokers and never smokers.

We also investigated whether specific processed meat items were associated with COPD in current smokers (Table 4). Consumption of blood pudding/sausages and liver paté was statistically significantly positively associated with COPD; for the highest category of consumption, the risks of COPD were increased by 35% (95% CI: 7, 69) and

**Table 1.** Age-Standardized Participant Characteristics by Category of Unprocessed and Processed Red Meat Consumption at Baseline ($n$ = 43,848), Cohort of Swedish Men, 1998

| Characteristic | Unprocessed Red Meat Consumption, g/day[a] | | | | | | | | Processed Red Meat Consumption, g/day[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <25.0 ($n$ = 4,902) | | 25.0–49.9 ($n$ = 14,986) | | 50.0–74.9 ($n$ = 10,942) | | ≥75.0 ($n$ = 13,018) | | <25.0 ($n$ = 12,607) | | 25.0–49.9 ($n$ = 19,601) | | 50.0–74.9 ($n$ = 7,673) | | ≥75.0 ($n$ = 3,967) | |
| | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) |
| Age, years | | 67.8 (9.2) | | 60.2 (9.3) | | 60.3 (9.8) | | 56.4 (8.1) | | 62.1 (10.0) | | 59.4 (9.6) | | 59.4 (9.2) | | 58.5 (8.7) |
| University education | 15.5 | | 14.9 | | 16.5 | | 17.8 | | 21.2 | | 15.7 | | 14.5 | | 11.2 | |
| BMI[c] | | 25.9 (3.5) | | 25.8 (3.2) | | 25.7 (3.3) | | 25.9 (3.4) | | 25.7 (3.3) | | 25.8 (3.3) | | 25.8 (3.3) | | 26.1 (3.7) |
| Total physical activity[d] | | 42.0 (4.9) | | 41.7 (4.8) | | 41.5 (4.9) | | 41.4 (5.0) | | 41.3 (4.8) | | 41.5 (4.9) | | 41.6 (5.0) | | 42.1 (5.3) |
| Current smoker | 25.6 | | 23.4 | | 24.3 | | 25.2 | | 24.5 | | 24.0 | | 23.7 | | 26.5 | |
| Former smoker | 36.7 | | 39.4 | | 38.6 | | 38.5 | | 38.1 | | 38.8 | | 39.4 | | 37.8 | |
| Alcohol consumption, g/day | | 8.0 (10.1) | | 9.6 (9.6) | | 10.7 (10.2) | | 11.7 (11.0) | | 9.9 (10.4) | | 10.5 (10.0) | | 10.8 (10.1) | | 11.1 (11.7) |
| Energy consumption, kcal/day | | 2,327 (751) | | 2,531 (755) | | 2,726 (758) | | 2,972 (876) | | 2,390 (755) | | 2,643 (746) | | 2,901 (793) | | 3,309 (986) |
| RFS | | 20.6 (6.9) | | 23.8 (5.7) | | 24.3 (5.7) | | 24.0 (5.6) | | 22.9 (6.5) | | 24.3 (5.5) | | 24.5 (5.6) | | 23.2 (6.2) |
| NRFS | | 2.9 (1.1) | | 3.1 (1.0) | | 3.2 (1.0) | | 3.4 (1.1) | | 2.9 (1.1) | | 3.2 (1.0) | | 3.4 (1.0) | | 3.6 (1.1) |

Abbreviations: BMI, body mass index; MET, metabolic equivalent of energy expenditure; NRFS, Non-Recommended Food Score; RFS, Recommended Food Score.

[a] The median ranged from 17.0 to 83.2 g/day.

[b] The median ranged from 15.6 to 91.2 g/day.

[c] Weight (kg)/height $(m)^2$.

[d] Total physical activity is given as MET-hours (kcal/kg × hour) per day.

**Table 2.** Hazard Ratios for Chronic Obstructive Pulmonary Disease by Category of Unprocessed and Processed Red Meat Consumption in Study Participants ($n$ = 43,848), Cohort of Swedish Men, 1998–2012

| Red Meat Type and Intake, g/day | No. of Men | Person-Years | No. of Cases | Age Adjusted | | Multivariate Adjusted[a,b] | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR | 95% CI |
| Unprocessed red meat[c] | | | | | | | |
| <25.0 | 4,902 | 56,468 | 337 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 14,986 | 199,557 | 610 | 0.84 | 0.73, 0.96 | 0.92 | 0.80, 1.06 |
| 50.0–74.9 | 10,942 | 142,743 | 497 | 0.90 | 0.78, 1.03 | 0.97 | 0.84, 1.13 |
| ≥75.0 | 13,018 | 179,342 | 465 | 0.98 | 0.84, 1.14 | 1.00 | 0.85, 1.17 |
| *P* for trend | | | | | 0.51 | | 0.61 |
| Processed red meat[d] | | | | | | | |
| <25.0 | 12,607 | 162,311 | 605 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 19,601 | 261,533 | 793 | 0.99 | 0.89, 1.10 | 1.07 | 0.96, 1.20 |
| 50.0–74.9 | 7,673 | 101,866 | 317 | 1.05 | 0.92, 1.20 | 1.10 | 0.96, 1.27 |
| ≥75.0 | 3,967 | 52,399 | 194 | 1.36 | 1.16, 1.61 | 1.21 | 1.02, 1.44 |
| *P* for trend | | | | | 0.001 | | 0.03 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age (continuous), educational level (less than high school, high school graduate, or university), body mass index (weight (kg)/height (m)$^2$; <18.5, 18.5–24.9, 25.0–29.9, or ≥30.0), total physical activity (metabolic equivalent of energy expenditure hours per day, in quintiles), smoking status and pack-years of smoking (never; former smoker for <20, 20–39, or ≥40 pack-years; or current smoker for <20, 20–39, or ≥40 pack-years), intake of energy (kcal/day, quintiles), alcohol consumption (g/day, in quintiles), Recommended Food Score (continuous), and Non-Recommended Food Score (continuous).

[b] Unprocessed and processed red meat were included in the same multivariable model.

[c] The median ranged from 17.0 to 83.2 g/day.

[d] The median ranged from 15.6 to 91.2 g/day.

31% (95% CI: 5, 62), respectively. Consumption of cold cuts/ham/salami was associated with a statistically nonsignificant increased risk of COPD, whereas no association was observed for consumption of sausages.

## DISCUSSION

In the present large, population-based, prospective cohort of men, consumption of processed red meat, but not of unprocessed red meat, was positively associated with a higher risk of COPD. Compared with men who consumed less than 25 g of processed meat daily, men who consumed 75 g or more had a statistically significant 21% higher risk of COPD. The observed association was confined to current smokers, among whom the risk of COPD was 26% higher for those in the highest category of processed meat consumption.

Our findings are consistent with results from 2 earlier published prospective studies (the Health Professionals Follow-up Study (10) and the Nurses' Health Study (7)) and 2 cross-sectional studies (24, 26), in which positive associations between consumption of cured meats and risk of COPD were found. The inverse associations of frequency of cured meat consumption with forced expiratory volume in 1 second and with the ratio of forced expiratory volume in 1 second to forced vital capacity were observed in participants in the Third National Health and Nutrition Examination Survey (26), and associations with forced expiratory volume in 1 second, forced vital capacity, and ratio of forced expiratory volume in 1 second to forced vital capacity were observed in participants in the Hertfordshire Cohort Study (24). Moreover, results from a study conducted among 274 COPD patients indicated that high consumption of cured meats (more than the median value in the study population) was associated with a 2-fold increased risk of COPD hospital readmission (27).

It seems feasible that the observed association between processed meat consumption and COPD may be related to the potentially pro-inflammatory properties of processed meat (28, 29), as well as to the high content of food additives, particularly nitrites (which are added during the manufacturing process as a preservative, antimicrobial agent, and color fixative), in these products (30). The fact that nitrites generate reactive nitrogen species such as peroxynitrite, which can impair lung antioxidant status and promote an inflammatory process causing DNA damage, inhibition of mitochondria respiration, protein modification, and cell dysfunction, makes their involvement as causative compounds credible (8). Moreover, the analysis of bronchial biopsies from 51 patients has demonstrated that "nitrosative stress" is associated with the pathogenesis of severe COPD (31). Furthermore, in patients with COPD, the number of myeloperoxidase-positive cells was significantly correlated with the number of neutrophils in bronchial submucosa, and patients with severe COPD had a significantly higher number of nitrotyrosine-positive and myeloperoxidase-positive cells compared with patients with mild-to-moderate COPD, smokers with normal lung function,

**Table 3.** Hazard Ratios for Chronic Obstructive Pulmonary Disease by Category of Processed Red Meat Consumption and Smoking Status in Study Participants, Cohort of Swedish Men, 1998–2012

| Smoking Status and Processed Meat Consumption, g/day | No. of Men | Person-Years | No. of Cases | Age Adjusted | | Multivariate Adjusted | |
|---|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | HR[a] | 95% CI |
| Ever smokers[b,c] | | | | | | | |
| <25.0 | 7,879 | 99,514 | 541 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 12,326 | 161,574 | 729 | 1.02 | 0.92, 1.15 | 1.10 | 0.98, 1.24 |
| 50.0–74.9 | 4,833 | 62,926 | 293 | 1.06 | 0.92, 1.23 | 1.14 | 0.98, 1.32 |
| ≥75.0 | 2,549 | 32,948 | 175 | 1.32 | 1.11, 1.57 | 1.20 | 1.00, 1.44 |
| *P* for trend | | | | | 0.004 | | 0.03 |
| Current smokers[b] | | | | | | | |
| <25.0 | 3,044 | 37,424 | 299 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 4,746 | 60,747 | 396 | 1.00 | 0.86, 1.16 | 1.06 | 0.90, 1.24 |
| 50.0–74.9 | 1,822 | 22,862 | 188 | 1.25 | 1.04, 1.50 | 1.27 | 1.04, 1.53 |
| ≥75.0 | 1,057 | 13,216 | 110 | 1.35 | 1.08, 1.68 | 1.26 | 1.00, 1.60 |
| *P* for trend | | | | | 0.001 | | 0.01 |
| Former smokers[b] | | | | | | | |
| <25.0 | 4,835 | 62,091 | 242 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 7,580 | 100,827 | 333 | 1.09 | 0.92, 1.29 | 1.14 | 0.96, 1.36 |
| 50.0–74.9 | 3,011 | 40,064 | 105 | 0.89 | 0.71, 1,12 | 0.96 | 0.76, 1.22 |
| ≥75.0 | 1,492 | 19,732 | 63 | 1.24 | 0.94, 1,64 | 1.09 | 0.81, 1.47 |
| *P* for trend | | | | | 0.51 | | 0.80 |
| Never smokers | | | | | | | |
| <25.0 | 4,558 | 60,756 | 56 | 1.00 | Referent | 1.00 | Referent |
| 25.0–49.9 | 7,037 | 96,961 | 50 | 0.70 | 0.47, 1.02 | 0.69 | 0.47, 1.03 |
| 50.0–74.9 | 2,749 | 37,732 | 19 | 0.74 | 0.44, 1.25 | 0.69 | 0.40, 1.19 |
| ≥75.0 | 1,363 | 18,747 | 17 | 0.69 | 0.86, 2.57 | 1.22 | 0.67, 2.22 |
| *P* for trend | | | | | 0.54 | | 0.95 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age (continuous), educational level (less than high school, high school graduate, or university), body mass index (weight (kg)/height (m)$^2$; <18.5, 18.5–24.9, 25.0–29.9, or ≥30.0), total physical activity (metabolic equivalent of energy expenditure hours per day, in quintiles), intake of energy (kcal/day, in quintiles), consumption of alcohol (g/day, in quintiles), Recommended Food Score (continuous), Non-Recommended Food Score (continuous), and consumption of unprocessed red meat (<25, 25–44.9, 45–74.9,or ≥75.0 g/day).

[b] Additionally adjusted for pack-years of smoking (<20, 20–39, or ≥40 pack-years).

[c] Ever smokers included both current and former smokers.

and nonsmokers. Interestingly, among those COPD patients, the number of nitrotyrosine-positive and myeloperoxidase-positive cells negatively correlated with the postbronchodilatory forced expiratory volume in 1 second, which suggests the possibility that nitrosative stress relates to irreversible airway obstruction. Another potential mechanism whereby processed red meat consumption may increase the risk of COPD is through advanced glycation end-products, which are formed through heat processing and also may have pro-inflammatory properties (32).

Just like the investigators in the 2 preceding prospective studies of processed meat and COPD (7, 10), we found that the positive association of processed red meat consumption with risk of COPD was confined to current and former smokers. Indeed, this is compatible with an imbalance between free radicals and antioxidant status. Moreover, because cigarette smoke contains approximately 5,000 different chemical compounds and is a major source of nitrites, there is a plethora of mechanistic opportunities for harmful and toxic effects on the lung via generated production of reactive oxygen species, including reactive nitrogen species, and via other mechanisms (9). In fact, the results of several studies highlight that cigarette smoke leads to a high oxidative burden and a decreased antioxidant capacity in blood (33–35). In addition, impaired antioxidant status was positively correlated with severity of COPD in 1 clinical study (34). Specifically, higher plasma lipid peroxidation (measured as malondialdehyde) was associated with higher risk of COPD progression. On the other hand, higher catalase and erythrocyte glutathione activities were associated with a decreased risk of progression of this disease.

**Table 4.** Hazard Ratios for Chronic Obstructive Pulmonary Disease by Category of Processed Red Meat Consumption in Current Smokers ($n$ = 10,669), Cohort of Swedish Men, 1998–2012

| Type of Processed Meat and Consumption, g/day | Median | No. of Men | No. of Cases | Multivariate Adjusted[a] | |
|---|---|---|---|---|---|
| | | | | HR | 95% CI |
| Sausages | | | | | |
| 0.0 | 0.0 | 764 | 93 | 1.00 | Referent |
| 0.1–24.9 | 18.6 | 7,033 | 718 | 0.85 | 0.68, 1.07 |
| ≥25.0 | 27.0 | 2,872 | 182 | 0.91 | 0.69, 1.19 |
| *P* for trend | | | | 0.42 | |
| Cold cuts/ham/salami | | | | | |
| 0.0 | 0.0 | 1,252 | 126 | 1.00 | Referent |
| 0.1–24.9 | 5.4 | 8,268 | 762 | 1.12 | 0.91, 1.36 |
| ≥25.0 | 35.9 | 1,149 | 105 | 1.26 | 0.96, 1.65 |
| *P* for trend | | | | 0.12 | |
| Blood pudding/sausages | | | | | |
| 0.0 | 0.0 | 5,667 | 498 | 1.00 | Referent |
| 0.1–24.9 | 10.0 | 4,323 | 404 | 1.15 | 1.00, 1.32 |
| ≥25.0 | 31.1 | 679 | 91 | 1.35 | 1.07, 1.69 |
| *P* for trend | | | | 0.004 | |
| Liver paté | | | | | |
| 0.0 | 0.0 | 3,134 | 304 | 1.00 | Referent |
| 0.1–9.9 | 1.6 | 6,446 | 559 | 1.17 | 1.00, 1.36 |
| ≥10 | 14.9 | 1,089 | 130 | 1.31 | 1.05, 1.62 |
| *P* for trend | | | | 0.02 | |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age (continuous), educational level (less than high school, high school graduate, or university), body mass index (weight (kg)/height (m)$^2$; <18.5, 18.5–24.9, 25.0–29.9, or ≥30.0), total physical activity (metabolic equivalent of energy expenditure hours per day, in quintiles), pack-years of smoking (<20, 20–39, or ≥40), intake of energy (kcal/day, in quintiles), consumption of alcohol (g/day, in quintiles), Recommended Food Score (continuous), Non-Recommended Food Score (continuous), and consumption of unprocessed red meat (<25, 25–44.9, 45–74.9, or ≥75.0 g/day). The model included mutual adjustment for consumption of sausages, cold cuts/ham/salami, blood pudding/sausages, and liver paté.

The present study has several strengths, including the population-based and prospective design, the detailed information on diet, and the large number of incident COPD cases. In addition, the available data on potential risk factors for COPD allowed us to extensively adjust for confounders. However, as in all observational studies, unmeasured or residual confounding cannot be disregarded. Although the food frequency questionnaire used in this study had a relatively high validity for intake of macronutrients and micronutrients, misclassification of unprocessed, processed, and total red meat consumption is inevitable. Because of the prospective design, any misclassification of processed and unprocessed red meat consumption would be nondifferential and would most likely have attenuated rather than exaggerated the true associations. Finally, in our study of COPD, we cannot rule out that some patients classified as COPD had obtained the diagnosis without the correct spirometry assessment, even though this investigation is formally required for setting the diagnosis of COPD. Ideally, new studies in this research area should include this type of verifying spirometry, which would presumably further strengthen the validity of the data. Presumably, such new prospective studies in this area will also benefit in accuracy from the fact that a higher proportion of patents with COPD are now identified compared with what was the case at the turn of the century (23).

In conclusion, consumption of processed, but not unprocessed, red meat was positively associated with the risk of COPD, particularly among current smokers. We speculate that this finding relates to the high contents of nitrites in processed meat and their role in oxidative stress and inflammatory processes in the lung cells. Hypothetically, this type of nitrite exposure may enhance the detrimental effects of smoking. Our findings may be of importance for public health because they indicate that not only smoking but also processed red meat consumption might be modifiable risk factors for COPD.

## ACKNOWLEDGMENTS

Author affiliations: Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Joanna Kaluza, Susanna C. Larsson, Alicja Wolk); Department of Human Nutrition, Warsaw University of Life Sciences-SGGW, Warsaw, Poland (Joanna Kaluza); and Unit for Lung and Airway Research, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Anders Linden).

This study was supported by a research grant from the Swedish Research Council/Infrastructure to A.W., the Karolinska Institutet's Distinguished Professor Award to A.W., a project grant from the Swedish Heart Lung Foundation to A.L., a project grant from King Gustav V's and Queen Victoria's Freemason Research Foundation to A.L. Federal funding was obtained from the Stockholms Läns Landsting (ALF) and the Västra Götaland Region (LUA), both to A.L.

Conflict of interest: none declared.

## REFERENCES

1. World Health Organization. *Health Statistics and Information Systems. Estimates for 2000–2012. Cause-Specific Mortality: Global Summary Estimates*. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html. Accessed June 15, 2015.
2. GBD 2013 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145–2191.
3. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of*

*Chronic Obstructive Pulmonary Disease*. http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/. Accessed October 18, 2016.
4. Varraso R, Fung TT, Barr RG, et al. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US women. *Am J Clin Nutr*. 2007;86(2):488–495.
5. Shaheen SO, Jameson KA, Syddall HE, et al. The relationship of dietary patterns with adult lung function and COPD. *Eur Respir J*. 2010;36(2):277–284.
6. Varraso R, Fung TT, Hu FB, et al. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US men. *Thorax*. 2007;62(9):786–791.
7. Jiang R, Camargo CA Jr, Varraso R, et al. Consumption of cured meats and prospective risk of chronic obstructive pulmonary disease in women. *Am J Clin Nutr*. 2008;87(4):1002–1008.
8. Ricciardolo FL, Di Stefano A, Sabatini F, et al. Reactive nitrogen species in the respiratory tract. *Eur J Pharmacol*. 2006;533(1–3):240–252.
9. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD–implications and relevance for treatment. *Int J Chron Obstruct Pulmon Dis*. 2014;9:1207–1224.
10. Varraso R, Jiang R, Barr RG, et al. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007;166(12):1438–1445.
11. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *Am J Clin Nutr*. 2011;94(4):1088–1096.
12. Feskens EJ, Sluik D, van Woudenbergh GJ. Meat consumption, diabetes, and its complications. *Curr Diab Rep*. 2013;13(2):298–306.
13. Bernstein AM, Sun Q, Hu FB, et al. Major dietary protein sources and risk of coronary heart disease in women. *Circulation*. 2010;122(9):876–883.
14. Kaluza J, Wolk A, Larsson S. Red meat consumption and risk of stroke: a meta-analysis of prospective studies. *Stroke*. 2012;43(10):2556–2560.
15. Haring B, Misialek JR, Rebholz CM, et al. Association of dietary protein consumption with incident silent cerebral infarcts and stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2015;46(12):3443–3450.
16. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16(16):1599–1600.
17. Official Statistics of Sweden. *Statistisk Årsbok 1999, Statistical Yearbook of Sweden 1999*. Vol 85. Örebro, Sweden: Statistics Sweden; 1999.
18. Johansson SE, Qvist J. Fetma en tickande bomb också i Sverige? *Välfärdsbulletinen*. 1998;4:14–16.
19. Messerer M, Johansson SE, Wolk A. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. *J Nutr*. 2004;134(7):1800–1805.
20. Kaluza J, Håkansson N, Brzozowska A, et al. Diet quality and mortality: a population-based prospective study of men. *Eur J Clin Nutr*. 2009;63(4):451–457.
21. World Health Organization/Food and Agriculture Organization. *Diet, Nutrition and the Prevention of Chronic Diseases*. WHO Technical Report Series 916. Geneva, Switzerland: World Health Organization; 2002. http://apps.who.int/iris/bitstream/10665/42665/1/WHO_TRS_916.pdf. Accessed October 18, 2016.
22. Norman A, Bellocco R, Bergström A, et al. Validity and reproducibility of self-reported total physical activity–differences by relative weight. *Int J Obes Relat Metab Disord*. 2001;25(5):682–688.
23. Ställberg B, Janson C, Johansson G, et al. Management, morbidity and mortality of COPD during an 11-year period: an observational retrospective epidemiological register study in Sweden (PATHOS). *Prim Care Respir J*. 2014;23(1):38–45.
24. Okubo H, Shaheen SO, Ntani G, et al. Processed meat consumption and lung function: modification by antioxidants and smoking. *Eur Respir J*. 2014;43(4):972–982.
25. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010;182(5):693–718.
26. Jiang R, Paik DC, Hankinson JL, et al. Cured meat consumption, lung function, and chronic obstructive pulmonary disease among United States adults. *Am J Respir Crit Care Med*. 2007;175(8):798–804.
27. de Batlle J, Mendez M, Romieu I, et al. Cured meat consumption increases risk of readmission in COPD patients. *Eur Respir J*. 2012;40(3):555–560.
28. Ley SH, Sun Q, Willett WC, et al. Associations between red neat intake and biomarkers of inflamation and glucose metabolism in women. *Am J Clin Nutr*. 2014;99(2):352–360.
29. Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA*. 2013;309(22):2353–2361.
30. Walters C. Nitrate and nitrite in food. In: Hill M, ed. *Nitrates and Nitrites in Food and Water*. West Sussex, England: Ellis Horwood Limited; 1991:93–112.
31. Ricciardolo FL, Caramori G, Ito K, et al. Nitrosative stress in the bronchial mucosa of severe chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2005;116(5):1028–1035.
32. Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: cause, effect, or both? *Curr Diab Rep*. 2014;14(1):453.
33. Bloomer RJ. Decreased blood antioxidant capacity and increased lipid peroxidation in young cigarette smokers compared to nonsmokers: impact of dietary intake. *Nutr J*. 2007;6:39.
34. Alberg A. The influence of cigarette smoking on circulating concentrations of antioxidant micronutrients. *Toxicology*. 2002;180(2):121–137.
35. Chiu YW, Chuang HY, Huang MC, et al. Comparison of plasma antioxidant levels and related metabolic parameters between smokers and non-smokers. *Kaohsiung J Med Sci*. 2009;25(8):423–430.