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Processed meat intake and risk of chronic obstructive pulmonary disease among middle-aged women

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Research in context

Evidence before this study

Chronic obstructive pulmonary disease (COPD), once considered mainly a consequence of tobacco smoking, is still a burden worldwide despite tobacco control measures. Although the Lancet has just launched a Commission on COPD to identify new risk factors, the impact of diet remains largely unknown by the scientific community, health care specialists, and lay people.

More than a decade ago, our group (and others) hypothesised that processed meat intake might be an independent dietary risk factor for the development of COPD. To the best of our knowledge, six studies have since been conducted (all confirming our hypothesis), either with cross-sectional or longitudinal designs and in different countries, but none specifically in participants under 40 years.

The exact role of processed meat in the pathogenesis of COPD remains unclear but the most likely mechanism is the nitrites added to meat products. Nitrites may react with amines and amides to form reactive nitrogen species (RNS), which can amplify inflammatory processes in the airways and lung parenchyma, contributing to progressive deterioration of pulmonary function and COPD pathogenesis. Indeed, the magnitude of the association between processed meat consumption and COPD may depend on other factors, which influence pulmonary oxidant/antioxidant balance and inflammation, such as smoking or unhealthy diet. To our knowledge, only one study has assessed the modifying effects of antioxidant and oxidant intake in the association between processed meat and lung function, but using a cross-sectional design and without including the combined effect of unhealthy diet and smoking.

Added value of this study

In more than 87,000 women, we confirmed that higher processed meat intake was associated with a greater risk of newly-diagnosed COPD. Our study extends previous findings by examining, for the first time, processed meat intake in relation to the risk of developing COPD in a considerably younger cohort (age 36.8 years).

When assessing the modulating role of smoking and unhealthy diet on the association between processed meat and COPD, we observed that the impact of processed meat was significant only among ever smokers and among women with unhealthy diet (e.g., a low diet quality). We also observed that adherence to high-risk lifestyle factors – high processed meat intake, smoking and low diet quality, strongly increased the risk of COPD. These findings support the hypothesis that both smoking and diet are important target for effective primary prevention of COPD.

Implications of all the available evidence

The association between diet and the risk of COPD in a younger cohort is likely to provide earlier recognition, higher sensitivity, and will further encourage a shift in the paradigm of lung health research toward earlier in adult life.

From a public health perspective, preventing smoking initiation is still more important than stopping intake of processed meat, but, based on the current evidence, we encourage cutting down of processed meat intake, and choosing a healthy diet. Our findings support the importance of multi-interventional programs for the primary prevention of COPD, including smoking education and nutrition counselling. Moreover, they should encourage researchers to study dietary interventions as an underutilised approach to promote lung health.

Abstract

Background: Processed meat intake may increase the risk of chronic obstructive pulmonary disease (COPD). However, the magnitude of this association may depend on smoking and unhealthy diet. Our aims were to determine whether processed meat intake increased the risk of COPD among middle-aged women, and to estimate the combined impact of high processed meat intake, smoking and unhealthy diet on the risk of COPD.

Methods: Analyses included 87,032 registered nurses from the Nurses' Health Study II (baseline mean age 36.8 years). Over 2,296,894 person-years (1991-2017), we documented 634 incident cases of COPD. Cumulative average of processed meat intake (every 4 years) was divided into never/almost never, <1 or ≥ 1 servings/week. A score was created to study the impact of 3-risk lifestyle factors.

Findings: In multivariable-adjusted Cox proportional hazards models, after careful adjustment for smoking and unhealthy diet, we observed a positive association between processed meat intake and the risk of COPD: Hazard Ratio (HR, 95%CI) for ≥ 1 servings/week vs. never/almost never=1.29 (1.00-1.65). In analyses stratified according to smoking or unhealthy diet, processed meat intake was associated with increased risk of COPD only among ever smokers (HR 1.37 [1.01-1.86]), and among women with unhealthy diet (HR 1.39 [1.04-1.85]). The multivariable-adjusted HR for COPD in participants with all 3 high-risk lifestyle factors compared with none was 6.32 (3.67-10.87).

Interpretation: Processed meat intake was associated with elevated risk of developing COPD in middle-aged women, especially in presence of other high-risk lifestyle factors (smoking, unhealthy diet).

Fundings: US CDC and NIH.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem that is characterised by progressive airflow limitation and an inflammatory process in the lungs. In 2016, COPD was the third most common cause of death worldwide.¹ Although COPD typically presents among men and in late adulthood, COPD has become increasingly prevalent among women² and can also be diagnosed at much younger age.³ The clinical characterisation of this subgroup (young women) has not been well established. The predominant risk factor for COPD in developed countries is cigarette smoking, but more than half smokers do not develop COPD,⁴ suggesting that other factors are involved. Up to now, there is still an incomplete understanding of the natural course of the disease and of global pattern of COPD risk factors. In this context, the Lancet has just launched a new Commission to develop transformational recommendations for COPD prevention by identifying, besides smoking, major risk factors for COPD.⁵ One of such factor may relate to diet.

More than a decade ago, our group (and others) hypothesised that processed meat intake might be an independent dietary risk factor for the development of COPD.^{6,7} Six studies have since been conducted, either among women or men, and they all confirmed that frequent processed meat intake was associated with decreased lung function^{8,9} and greater COPD symptoms,¹⁰ exacerbations,¹¹ or incidence.^{12,13} To the best of our knowledge, this association has never been investigated in a younger cohort. Furthermore, since foods are consumed in a form of complex combination (i.e. dishes and meals), dietary scores have been proposed to study the combined effect of foods and/or nutrients. Using the Alternate Healthy Eating Index 2010 (AHEI-2010) - an overall measure of diet quality reflecting high intakes of whole grains, polyunsaturated fatty acids, nuts, and long chain omega-3 fats and low intakes of red/processed meats, refined grains, and sugar sweetened drinks – we previously reported that a greater adherence to this score was associated with a lower risk of COPD in both women and men.¹⁴

Relatively little attention has been paid to diet in the primary prevention of COPD, and how interrelationships between protective and/or deleterious dietary factors with smoking might

contribute to COPD risk. Indeed, the magnitude of the association between processed meat consumption on COPD may depend on other factors, which influence pulmonary oxidant/antioxidant balance and inflammation.⁹ A comprehensive analysis of the impact of high-risk modifiable lifestyle factors, such as processed meat intake, smoking and unhealthy diet, on COPD risk is warranted. To our knowledge, these factors have not been examined using a longitudinal design, nor using an overall measure of unhealthy diet (for example, as defined by the AHEI-2010 diet score), alone or in combination.

In the context of preventing chronic diseases, public health initiatives to improve lung function through dietary advice are particularly relevant and timely. Our aims were to determine whether processed meat intake increased the risk of COPD among middle-aged women, and to estimate the combined impact of high-risk lifestyle factors (e.g., high processed meat intake, smoking and unhealthy diet) on the risk of COPD.

Methods

Study population

The Nurses' Health Study II (NHSII) began in 1989 when 116,429 female registered nurses from 14 US states, aged 25-44 years, completed a mailed questionnaire on their medical history and lifestyle characteristics.¹⁵ Follow-up questionnaires have been sent every 2 years since. Information on diet was collected for the first time in 1991, which was defined as baseline for the current study. This investigation was approved by the Institutional Review Board at the Brigham and Women's Hospital (Boston, MA), and participants provided written informed consent.

After the exclusion of participants with missing or unreasonable information on diet or who reported a physician diagnosis of asthma or COPD in 1991, the final baseline population included 87,032 women (see Appendix Methods, Appendix Table 1 and Appendix Figure 1).

Processed meat and healthy diet assessment

Dietary intake information was collected by using a semi quantitative validated food frequency questionnaires (FFQ) designed to assess average food intake over the previous 12 months in 1991, 1995, 1999, 2003, 2007, 2011 and 2015.¹⁶ To reduce measurement errors and to represent long term dietary intake, we calculated the cumulative average of processed meat and of unhealthy diet, used as a time-dependent variable (Appendix Methods).

Processed meat consumption was defined as the total consumption of processed meats (including sausages, bacon and hot dogs), which was asked as three separate questions in FFQ sent in 1991 and in 1995, and in four separate questions in FFQ sent since 1999. Cumulative average of processed meat consumption was divided into three categories: never/almost never (never or less than once per month), <1 serving/week, ≥ 1 servings/week.

The AHEI-2010, designed to target food choices and macronutrient sources associated with reduced chronic disease risk, is based on 11 components, ranging from 0 to 110 with a lower score representing a less healthy diet¹⁴. In present analyses, we calculated a modified AHEI-2010 including all the components except for the red/processed meat component (highest value=100), divided into quintiles.

COPD assessment

Women who reported COPD in biennial questionnaires were categorised on the basis of a supplemental COPD questionnaire sent between 2015 and 2017, as described and validated previously.¹⁷ In the current study, we selected participants who reiterated a physician diagnosis of chronic bronchitis, emphysema, or COPD on the supplemental questionnaire (Appendix Methods). In addition, women with COPD listed as the main cause of death (International Statistical Classification of Diseases, Ninth Revision codes; codes 491, 492 and 496; n=16) were further classified as COPD cases.

Statistical analysis

We analysed the association between the cumulative average of processed meat intake (time varying exposure) and the risk of COPD by using a stratified proportional Cox hazards model adjusted for time varying variables – e.g., smoking status (never, former, current smokers), pack years of smoking and pack years of smoking squared (among ever-smokers; continuous), body mass index (<25.0, 25.0–29.9, ≥30.0 kg/m²), physical activity (metabolic equivalents per week; quintiles), total energy intake (kilocalories per day; continuous), and the modified AHEI-2010 (continuous), and fixed variables – e.g., US region (West, Midwest, South, Northeast) and race (white, nonwhite) (Appendix Methods). The proportional hazards assumption was met, and model was stratified according to age to provide finer control for age. All hazard ratios (HRs) are reported with 95% confidence interval (CI).

As smoking is the major risk factor for COPD, we further investigated the association according to smoking status and formally tested the interaction between processed meat intake and smoking (never vs. ever). We also investigated the association according to unhealthy diet in 2 categories (the healthiest diet [$\geq 80\%$ of the distribution, i.e. 5th quintile], vs. the less healthy diet [$< 80\%$, e.g., 1st to 4th quintiles]), and formally tested the interaction between processed meat intake and unhealthy diet (continuous).

To study the impact of 3-risk lifestyle factors (high intake of processed meat, smoking, and unhealthy diet) on the risk of COPD, we created a score by dichotomising processed meat into highest intake (≥ 1 servings/month) vs. lowest (never/almost never), smoking into ever vs. never smokers, and diet quality in two categories (see above; less healthy vs. healthy). Summing up these values led to an unhealthy lifestyle score ranging from 0 (e.g., no unhealthy lifestyle) to 3. Participants with no unhealthy lifestyle were taken as reference. Because the binary variables could not account for the gradient in COPD risk with more extreme levels of these lifestyle factors, we conducted a sensitivity analysis in which we calculated an expanded high-risk score (Appendix Table 2). We assigned scores of 0 (most healthy) to 2 or 4 (unhealthy) to the categories of each lifestyle factor, and summed the points across all three factors as below (score for each category is listed in the bracket following): Processed meat intake: never/almost never (0), < 1 serving/week (1), ≥ 1 servings/week (2); Smoking: never (0), former (1), current (2); modified AHEI-2010: quintile 1 (4), quintile 2 (3), quintile 3 (2), quintile 4 (1), quintile 5 (0). The expanded high-risk score ranges from 0 to 8.

We also performed “lagged analyses” (Appendix Methods).

We calculated a test for trend across the categories of processed meat intake by treating the categories as an ordinal variable in a proportional hazards model. All analyses were performed using SAS version 9.3 (Cary, NC).

Role of Funding Sources

The study was funded by the Centers for Disease Control and Prevention (R01 OH-10359) and the National Institutes of Health (UM1 CA-176726), neither of which had a role in the conception, design, analysis, or conduct of the study.

Data Statement

Further information including procedure to obtain and access data from the Nurses' Health Studies is described at http://www.channing.harvard.edu/nhs/?page_id=471)

Results

Characteristics of the population

Table 1 shows characteristics of women according to the intake of processed meat. In 1991, 56% of women almost never ate processed meat, 32% reported <1 serving/week, and 12% ≥ 1 servings/week. Women with the highest intake of processed meat (≥ 1 servings/week) were more likely to be obese and follow unhealthy diet, and less likely to be physically active, and live in the Western US, as compared to women with the lowest intake of processed meat (never/almost never). In 1991, women were aged 36.8 years in average, and 66% were never smokers, 22% former smokers and 12% current smokers.

Processed meat intake and COPD

Among 2,296,894 person-years of follow-up, we documented 634 cases of COPD between 1991 and 2017. The incidence rate for newly-diagnosed COPD was 28 per 100,000 person-years. Processed meat intake was positively associated with risk of COPD: age-adjusted HR (95% CI) for the highest compared with lowest intake of processed meat was 2.39 (1.89 to 3.01), P for trend <0.001. After controlling for smoking variables (Table 2), the magnitude of the association decreased but the risk of COPD remained higher in women with the highest intake of processed meat compared to those with the lowest intake. Further adjustments for several potential confounders (model 3) and for

adherence to the modified AHEI-2010 (model 4) led to similar results: the risk of COPD was 29% higher among women with the highest intake of processed meat compared to those with the lowest intake: multivariable HR (95% CI) 1.29 (1.00 to 1.65); P for trend=0.05.

We performed lagged analyses, first by excluding cases occurring on the first 8 years (n=82). We again observed a similar association between processed meat intake and the risk of COPD: multivariable HR for the highest compared with lowest intake of processed meat was 1.32 (1.00 to 1.73); P for trend=0.04. When we excluded COPD cases occurring within the first twelve years (n=162), we again observed a positive association: multivariable HR for the highest compared with lowest intake of processed meat was 1.31 (0.97 to 1.76); P for trend=0.07.

Processed meat intake, smoking and unhealthy diet on the risk of COPD

The interaction between processed meat intake and smoking was statistically significant (P=0.02). After control for potential confounders, processed meat intake was positively and significantly associated with risk of COPD among ever smokers (Table 3): multivariable HR for the highest compared with lowest intake of processed meat was 1.37 (1.01 to 1.86); P for trend=0.05. The risk of COPD was not increased in never smokers: the corresponding figure was 1.08 (0.68 to 1.71), P for trend=0.78.

The interaction term between processed meat and the modified AHEI-2010 score had a P-value of 0.06. After control for potential confounders, processed meat intake was positively and significantly associated with risk of COPD among women with unhealthy diet only (Table 4): multivariable HR for the highest compared with lowest intake of processed meat was 1.39 (1.04 to 1.85); P for trend=0.04; corresponding figure was 1.15 (0.61 to 2.18) in women with a healthy diet.

The incidence rate for newly-diagnosed COPD was 10 per 100,000 person-years among women who never smoked, had a healthy diet and avoided processed meat; the corresponding figure in women

who smoked, had an unhealthy diet and ate at least one serving/month of processed meat was more than 8x higher (81/100,000 person-years).

In our study, 7% of women reported no unhealthy lifestyle, 27% only one unhealthy lifestyle, 48% two unhealthy lifestyles, and 18% the three unhealthy lifestyles. Among participants who reported only 1 unhealthy lifestyle, 20% reported “high processed meat intake”, 15% reported “smoking” and 65% “unhealthy diet”. The multivariable-adjusted HR for COPD in women with 3 (e.g., high processed meat intake, smoking and unhealthy diet) compared with zero risk factors was 6.32 (3.67 to 10.87) (Table 5).

Using the expanded high-risk score, 7% of women had a score of 0, 13% a score of 1, 17% a score of 2, 19% a score of 3, 19% a score of 4, 15% a score of 5, 7% a score of 6, 2% a score of 7 and 1% a score of 8. We also reported a strong and positive association between the expanded high-risk score and the risk of COPD, with multivariable-adjusted HRs (95% CI) increasing till 24.01 (15.50 to 46.15) among women with a score of 8 compared to women with a score of 0, with a significant dose-response association (P for trend<0.0001) (Figure 1).

Discussion

In this prospective cohort analysis of more than 87,000 middle-aged US women, we confirmed that higher processed meat intake was associated with a greater risk of newly-diagnosed COPD. The association was consistent after adjustment for smoking, unhealthy diet and several potential confounders. When assessing the modulating role of smoking and unhealthy diet on the association between processed meat and COPD, we observed that the impact of processed meat was significant only among ever smokers and among women with an unhealthy diet. We also observed that adherence to high-risk lifestyle factors – high processed meat intake, smoking and unhealthy diet, strongly increased the risk of COPD. These findings support the hypothesis that smoking and diet are important target for effective primary prevention of COPD.

Processed meat was recently classified as carcinogenic by the International Agency for Research on Cancer (WHO-IARC).¹⁸ High processed meat intake is a risk factor not only for cancer, but also for several chronic diseases and all-cause mortality.^{19,20} Regarding lung health, eight studies have reported that frequent processed meat intake was associated with decreased lung function^{6,7} and greater COPD symptoms,¹⁰ exacerbations,¹¹ or incidence.^{6,7,12,13} These eight studies have been published either with cross-sectional or longitudinal designs, in different countries, among men or women with a mean age greater than 65 years, and they are all concordant with our findings. Our study extends previous findings by examining, for the first time, processed meat intake in relation to the risk of developing COPD in a considerably younger cohort (age 36.8 years). Although there is no biological reason to believe that processed meat intake would be risk factor in women and not in men, there have been studies in the literature on sex differences in eating habits, and in general, men are more likely to report eating meat (including processed meat), whereas women are more likely to report eating fruits and vegetables.²¹ Once thought of primarily as a disease of older male smokers, COPD has become increasingly prevalent among women. Although increasing tobacco consumption among women over the last decades is linked to the rising prevalence of COPD in women, sex differences in susceptibility to COPD are probably multifactorial, and many unanswered questions remain.²² Our findings in a younger cohort of women is likely to provide earlier recognition, higher sensitivity, and will further encourage a shift in the paradigm of lung health research toward women and earlier adult life.²³

Our findings in this large longitudinal cohort that the magnitude of the association between processed meat consumption and COPD is modified by exposure to other modifiable lifestyle factors that influence pulmonary oxidant/antioxidant balance and inflammation, such as smoking and unhealthy diet, as reflected by a low AHEI-2010 diet score, may have major public health implications. Besides avoidance of direct and indirect exposure to tobacco smoke, there is no effective measure of primary prevention for COPD. To our knowledge, only one cross-sectional study

has assessed the modifying effects of antioxidant and oxidant intake in the association between processed meat and lung function, but without including the combined effect of unhealthy/healthy diet and smoking.⁹ Using data from 2,942 men and women from UK aged 65 years on average, Okubo et al. reported that higher processed meat consumption was associated with poorer lung function only in men with lower fruit and vegetable intake, or in men who are current smokers (no modifying effect among women). This result is difficult to compare with our findings since we included only women, and we used longitudinal and repeated data, as well as on overall estimate of diet. Our analysis to estimate the combined impact of high-risk lifestyle factors further indicated that combinations of high processed meat intake, smoking and unhealthy diet were particularly powerful: the larger the number of high-risk factors, the greater the risk of COPD, regardless of the combined factors.

The exact role of processed meat in the pathogenesis of COPD remains unclear and mechanistic studies are lacking.²⁴ The most likely mechanism is the nitrites added to meat products.²⁵ Nitrites are rapidly absorbed both in the small intestine and in the stomach, where they may react with secondary or tertiary amines and amides to reactive nitrogen species (RNS) such as N-nitroso compounds. With specific regard to the lung, the reactive oxygen species (ROS) and RNS can amplify inflammatory processes in the airways and lung parenchyma causing lipid peroxidation, DNA damage, inhibition of mitochondrial respiration, and inactivation of proteins.²⁶ Positive associations have also been observed between processed meat intake and several biological markers involved in the inflammatory pathway, such as high-sensitivity C-reactive protein (hsCRP)²⁷ and advanced glycation end-products (AGE),²⁸ which in turn have been associated with higher risk of COPD and COPD exacerbations.^{29,30} The long-term persistence of nitrosative stress and of inflammation may contribute to progressive deterioration of pulmonary function and COPD pathogenesis.³¹ In addition to the antioxidant/anti-inflammatory hypothesis in the diet-COPD association, it is reasonable to posit that an imbalance in the gut microbiome caused by changes in the diet over the last decades,

may lead to the development of COPD.³² Tobacco smoke is another source of nitrites as well as oxidants. Finally, using data from the same cohort, it was reported that lower dietary quality, as assessed by AHEI-2010, was associated with significantly higher plasma concentrations of inflammatory cytokines.³³ Hence the interaction between processed meat consumption with smoking and unhealthy diet is biologically plausible.

Strengths and limitations of study

Our study has several potential limitations. First, newly-diagnosed COPD was defined by a self-reported physician's diagnosis of COPD, and lung function measures were not available for this large national cohort. However, our questionnaire based definition of newly-diagnosed COPD was validated in a subset of registered nurses¹⁷ and has been used in several publications.^{6,7,14,34,35} The main source of disease misclassification is probably misdiagnosis of asthma; however, we excluded women with asthma at baseline, and during the follow-up using a validated case definition in the NHSII.³⁶ Second, we acknowledge the potential role of residual confounding in all observational studies. Regarding smoking, the association between processed meat and COPD may be due, in part, to a residual confounding by cigarette smoking, which is a powerful risk factor. To minimise this possibility, multivariable models were adjusted with multiple time varying measures of tobacco exposure (smoking habits, pack years, and pack years²), which were assessed biennially from 1991. A positive association between processed meat and risk of COPD remained even after we controlled for all of these factors. To address residual confounding by diet, our analyses were further adjusted for the modified AHEI-2010 as a continuous variable, and again, associations remained. Another risk factor of concern is certainly alcohol, either as a surrogate for an additional smoking effect or as a potential mechanism for the release of greater quantity of nitrorosamines.³⁷ However, the modified version of the AHEI-2010 included "alcohol" as an item (moderate intake as ideal). At last, exposure to air pollution could also have an effect on the diet-COPD association, its impact is most likely much less important than the role of smoking.^{38,39} Third, we also acknowledge that misclassification of diet

assessed by the FFQ intake is likely. For the combined effect of lifestyle factors, due to a limited sample size, we dichotomised value for smoking, healthy/unhealthy diet and processed meat intake, which is somewhat simplistic approach. However, our analysis based on the expanded score allowing to consider different levels of each risk factor, yielded similar results. Finally, with regard to the sample, we note that they are all female health professionals and predominantly white. The relatively homogeneity of the group (e.g., regarding education level), actually helps with causal inferences about the relation between processed meat intake and risk of developing COPD. However, we also recognise that our results obtained among health professionals are not necessarily generalisable to the whole population, as differences in health awareness, socioeconomic status, and smoking behaviour might differ significantly between the general population and our study population. Likewise, our study population was mainly non-Hispanic white, which might limit generalisability of our results to other racial/ethnic populations. We encourage replication of our prospective findings in other populations.

Conclusion

Processed meat intake increased the risk of developing COPD. Furthermore, adherence to a high-risk lifestyle combining processed meat intake, smoking and unhealthy diet, appeared to strongly impact lung health. From a public health perspective, preventing smoking initiation is still more important than stopping intake of processed meat, but, based on the current evidence, we encourage cutting down of processed meat intake, and choosing a healthy diet, as already recommended by several national dietary guidelines.⁴⁰ The Lancet Commission on COPD has called to develop actionable recommendations to drive transformational change.⁵ In this context, our findings support the importance of multi-interventional programs for the primary prevention of COPD, including smoking education and nutrition counselling. Moreover, they should encourage researchers to study dietary interventions as an underutilised approach to promote lung health.

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Author Contributions:

Dr Varraso had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

Study concept and design: Varraso, Willett, Speizer, Camargo.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Varraso, Camargo.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Varraso

Obtained funding: Willett, Camargo.

Administrative, technical, or material support: Boggs, Dumas

Study supervision: Willett, Camargo.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Table 1 Age-standardised baseline characteristics in women from the Nurses' Health Study II (n=87,032), according to intake of processed meat.

	Processed meat intake			Missing, %
	Never / almost never	<1 serving/week	≥1 serving/week	
Age, mean (SD), years*	36.3 (4.6)	35.9 (4.7)	36.0 (4.7)	0.0
Smoking				
Never smokers	66	66	66	0.1
Former smokers	24	21	20	
Current smokers	10	12	14	
Pack-years in ever smokers, mean (SD)†	10.8 (8.2)	11.0 (8.3)	11.9 (8.9)	0.0
Body mass index, mean (SD), kg/m ²	23.8 (4.7)	24.6 (5.2)	25.4 (6.0)	2.8
Body mass index, kg/m ²				
< 25.0	72	66	60	2.8
25 - 29.9	18	21	22	
≥ 30.0	10	13	18	
Physical activity, mean (SD), METs/week‡	23.8 (30.0)	19.7 (25.7)	19.2 (26.2)	0.3
Total energy intake, mean (SD), kcal/day	1,627 (500)	1,833 (530)	2,030 (590)	2.3
US region				
West	21	13	11	0.0
Midwest	29	34	35	
South	19	21	23	
Northeast	31	32	31	
White race	96	97	95	0.0
Modified AHEI-2010 score, mean (SD)	46.7 (9.6)	42.9 (8.9)	41.4 (9.1)	2.3
Unhealthy diet§	70	85	88	2.3

Values are percentages (standardised to age distribution of study population) unless stated otherwise. Values of polytomous variables may not sum to 100% due to rounding. SD: standard deviation.

* Value is not age adjusted.

† Number of packs smoked per day multiplied by number of years smoked, among ever smokers.

‡ Sum of average time per week spent in each activity multiplied by metabolic equivalent (MET) value of each activity.

§ Unhealthy diet was defined as a cumulative average of the modified AHEI-2010 (e.g., including all the items except for the red and processed meat item) <

80% of the distribution, e.g., 1st to 4th quintiles

Table 2 Processed meat intake and the risk of newly-diagnosed chronic obstructive pulmonary disease*

	No	Person years	Age-adjusted model 1, HR (95% CI)	Multivariable-adjusted model 2, HR (95% CI)†	Multivariable-adjusted model 3, HR (95% CI)‡	Multivariable-adjusted model 4, HR (95% CI)§
Processed meat intake						
Never/almost never	134	839,753	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<1 serving/week	338	1,097,825	1.67 (1.37 to 2.05)	1.39 (1.13 to 1.70)	1.23 (1.00 to 1.52)	1.17 (0.94 to 1.44)
≥ 1 serving/week	162	359,316	2.39 (1.89 to 3.01)	1.69 (1.34 to 2.14)	1.45 (1.13 to 1.85)	1.29 (1.00 to 1.65)
P for trend			<.001	<.001	.003	.05

Abbreviations: HR, hazard ratio.

* A total of 634 COPD cases occurred during 26 years of follow-up (1991-2017) in the Nurses' Health Study II (n = 87,032).

† Multivariable-adjusted model 2 includes age, smoking (never, former, current), pack -years of smoking (continuous), and pack-years² of smoking (continuous).

‡ Multivariable-adjusted model 3 includes model 2 variables (see above) plus body mass index (< 25 kg/m², 25-29.9 kg/m², or ≥ 30.0 kg/m²), physical activity (metabolic equivalent task-hours/week, in quintiles), total caloric intake (continuous), US region (West, Midwest, South, or Northeast) and race (white, or non-white).

§ Multivariable-adjusted model 4 includes model 3 variables (see above) plus the modified AHEI-2010 (continuous variable).

|| Test for trend using categories of processed meat intake as an ordinal variable.

Table 3 Processed meat intake and the risk of newly-diagnosed chronic obstructive pulmonary disease, according to smoking status*

Processed meat intake	No	Person years	Multivariable-adjusted model 1, HR (95% CI)†	Multivariable-adjusted model 2, HR (95% CI)‡	Multivariable-adjusted model 3, HR (95% CI)§
Among never smokers					
Never/almost never	50	551,895	1.00 (ref)	1.00 (ref)	1.00 (ref)
<1 serving/week	83	715,833	1.24 (0.87 to 1.78)	1.05 (0.73 to 1.51)	0.95 (0.65 to 1.37)
≥ 1 serving/week	38	230,539	1.77 (1.15 to 2.72)	1.35 (0.87 to 2.11)	1.08 (0.68 to 1.71)
P for trend			.01	.21	.78
Among ever smokers					
Never/almost never	83	278,759	1.00 (ref)	1.00 (ref)	1.00 (ref)
<1 serving/week	249	372,208	1.43 (1.11 to 1.84)	1.29 (0.99 to 1.67)	1.24 (0.95 to 1.60)
≥ 1 serving/week	122	124,593	1.68 (1.26 to 2.24)	1.47 (1.09 to 1.99)	1.37 (1.01 to 1.86)
P for trend			<.001	.01	.05

Abbreviations: HR, hazard ratio.

Interaction term between processed meat intake (≥1 servings/month vs. never/almost never) and smoking (ever vs. never): P=0.02.

* A total of 171 cases in never smokers, and 454 in ever smokers occurred during 26 years of follow-up (1991-2017) in the Nurses' Health Study II.

† Multivariable-adjusted model 1 includes age, current smoking (in ever smokers only), pack -years of smoking (in ever smokers only; continuous), and pack-years² of smoking (in ever smokers only; continuous).‡ Multivariable-adjusted model 2 includes model 1 variables (see above) plus body mass index (< 25 kg/m², 25-29.9 kg/m², or ≥ 30.0 kg/m²), physical activity (metabolic equivalent task-hours/week, in quintiles), total caloric intake (continuous), US region (West, Midwest, South, or Northeast) and race (white, or non-white).

§ Multivariable-adjusted model 3 includes model 2 variables (see above) plus the modified AHEI-2010 (continuous variable).

|| Test for trend using categories of processed meat intake as an ordinal variable.

Table 4 Processed meat intake and the risk of newly-diagnosed chronic obstructive pulmonary disease, according to unhealthy diet*

Processed meat intake	No	Person years	Multivariable-adjusted model 1, HR (95% CI)†	Multivariable-adjusted model 2, HR (95% CI)‡	Multivariable-adjusted model 3, HR (95% CI)§
Among women with healthy diet					
Never/almost never	39	238,883	1.00 (ref)	1.00 (ref)	1.00 (ref)
<1 serving/week	39	168,509	0.99 (0.63 to 1.57)	0.80 (0.50 to 1.28)	0.80 (0.49 to 1.28)
≥ 1 serving/week	15	42,395	1.44 (0.78 to 2.64)	1.16 (0.61 to 2.18)	1.15 (0.61 to 2.18)
P for trend			.37	.95	.96
Among women with unhealthy diet					
Never/almost never	88	584,289	1.00 (ref)	1.00 (ref)	1.00 (ref)
<1 serving/week	292	909,158	1.51 (1.18 to 1.92)	1.31 (1.02 to 1.68)	1.29 (1.01 to 1.65)
≥ 1 serving/week	137	298,467	1.77 (1.34 to 2.32)	1.43 (1.07 to 1.91)	1.39 (1.04 to 1.85)
P for trend			<.001	.02	.04

Abbreviations: HR, hazard ratio.

Interaction term between processed meat intake (≥1 servings/month vs. never/almost never) and healthy diet (continuous): P=0.06.

* A total of 93 cases in women with healthy diet (≥ 80% of the distribution of the cumulative average of the modified AHEI-2010, i.e. ≥ 5th quintile), and 517 in women with unhealthy diet (< 80%, e.g., 1st to 4th quintiles) occurred during 26 years of follow-up (1991-2017) in the Nurses' Health Study II.

† Multivariable-adjusted model 1 includes age, smoking (never, former, current), pack -years of smoking (in ever smokers only; continuous), and pack-years² of smoking (in ever smokers only; continuous).

‡ Multivariable-adjusted model 2 includes model 1 variables (see above) plus body mass index ($< 25 \text{ kg/m}^2$, $25\text{-}29.9 \text{ kg/m}^2$, or $\geq 30.0 \text{ kg/m}^2$), physical activity (metabolic equivalent task-hours/week, in quintiles), total caloric intake (continuous), US region (West, Midwest, South, or Northeast) and race (white, or non-white).

§ Multivariable-adjusted model 3 includes model 2 variables (see above) plus the modified AHEI-2010 (continuous variable).

|| Test for trend using categories of processed meat intake as an ordinal variable.

Table 5 Unhealthy lifestyle factors and the risk of newly-diagnosed chronic obstructive pulmonary disease

	No	Person years	Age-adjusted model, HR (95% CI)	Multivariable-adjusted model 2, HR (95% CI)*
Unhealthy lifestyle factors†				
0	14	145,608	1.00 (ref)	1.00 (ref)
1	71	612,454	1.28 (0.72 to 2.27)	1.21 (0.68 to 2.15)
2	195	1,063,056	1.93 (1.12 to 3.32)	1.63 (0.94 to 2.81)
3	322	399,072	7.77 (4.55 to 13.27)	6.32 (3.67 to 10.87)
P for trend			<.001	<.001

Abbreviations: HR, hazard ratio.

A total of 602 COPD cases occurred during 26 years of follow-up (1991-2017) in the Nurses' Health Study II (n = 84,898).

* Multivariable-adjusted model 2 includes age, body mass index (< 25 kg/m², 25-29.9 kg/m², or ≥ 30.0 kg/m²), physical activity (metabolic equivalent task–hours/week, in quintiles), total caloric intake (continuous), US region (West, Midwest, South, or Northeast) and race (white, or non-white).

† High-risk lifestyle factors included intake of processed meat (≥1 servings/month vs. never/almost never), cigarette smoking (ever vs. never smoking), and unhealthy diet (lower 80% of modified AHEI-2010).

Figure Legends:

Figure 1 Expanded high-risk score and the risk of newly-diagnosed chronic obstructive pulmonary disease

A total of 602 COPD cases occurred during 26 years of follow-up (1991-2017) in the Nurses' Health Study II (n = 84,898).

* Multivariable-adjusted model includes age, body mass index (< 25 kg/m², 25-29.9 kg/m², or ≥30.0 kg/m²), physical activity (metabolic equivalent task hours/week, in quintiles), total caloric intake (continuous), US region (West, Midwest, South, or Northeast) and race (white, or non-white). P for trend<0.0001.

We assigned scores of 0 (most healthy) to 2 or 4 (unhealthy) to the categories of each lifestyle factor, and summed the points across all three factors as below (score for each category is listed in the bracket following): Processed meat intake: never/almost never (0), < 1 serving/week (1), ≥1 servings/week (2); Smoking: never (0), former (1), current (2); modified AHEI-2010: quintile 1 (4), quintile 2 (3), quintile 3 (2), quintile 4 (1), quintile 5 (0). The expanded high-risk score ranges from 0 to 8 (see Appendix Table 2).

Figure 1 Expanded high-risk score and the risk of newly-diagnosed chronic obstructive pulmonary disease

