Cured Meat Consumption, Lung Function, and Chronic Obstructive Pulmonary Disease among United States Adults

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Rationale: Cured meats are high in nitrites. Nitrites generate reactive nitrogen species that may cause nitrative and nitrosative damage to the lung resulting in emphysema.

Objective: To test the hypothesis that frequent consumption of cured meats is associated with lower lung function and increased odds of chronic obstructive pulmonary disease (COPD).

Methods: Cross-sectional study of 7,352 participants in the Third National Health and Nutrition Examination Survey, 45 years of age or more, who had adequate measures of cured meat, fish, fruit, and vegetable intake, and spirometry.

Results: After adjustment for age, smoking, and multiple other potential confounders, frequency of cured meat consumption was inversely associated with FEV₁ and FEV₁/FVC but not FVC. The adjusted differences in FEV₁ between individuals who did not consume cured meats and those who consumed cured meats 1 to 2, 3 to 4, 5 to 13, and 14 or more times per month were -37.6, -11.5, -42.0, and -110 ml, respectively (*p* for trend < 0.001). Corresponding differences for FEV₁/FVC were -0.91, -0.54, -1.13, and -2.13% (*p* for trend = 0.001). These associations were not modified by smoking status. The multivariate odds ratio for COPD (FEV₁/FVC ≤ 0.7 and FEV₁ < 80% predicted) was 1.78 (95% confidence interval, 1.29–2.47) comparing the highest with the lowest category of cured meat consumption. The corresponding odds ratios for mild, moderate, and severe COPD were 1.11, 1.46, and 2.41, respectively.

Conclusions: Frequent cured meat consumption was associated independently with an obstructive pattern of lung function and increased odds of COPD. Additional studies are required to determine if cured meat consumption is a causal risk factor for COPD.

Keywords: cured meats; nitrites; lung function; chronic obstructive pulmonary disease; emphysema

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the United States (1, 2). The death rate from COPD doubled between 1970 and 2002, in contrast to an overall decline in mortality in the United States (3). COPD prevalence and mortality continue to rise, such that COPD is projected to become the third leading cause of death worldwide by 2020 (4). Despite the magnitude of the problem,

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Experiential and animal studies suggest that nitrite exposure may cause lung damage. Cured meats are high in nitrite; however, no epidemiologic data are available for the association between consumption of cured meats and chronic obstructive pulmonary disease (COPD).

What This Study Adds to the Field

Frequent cured meat consumption is associated with increased risk for developing COPD.

preventive strategies for COPD are limited to avoidance of cigarette smoking.

Nitrites generate reactive nitrogen species that may cause nitrative and nitrosative damage to the lung, producing structural changes resembling emphysema. In 1968, a rodent model of experimental emphysema was described in which rats exposed to 10 to 25 ppm of ambient nitrogen dioxide (NO₂, a nitrite gaseous precursor) developed emphysematous changes in their lungs (5–7). In 1972, Shuval and Gruener added 1,000 to 3,000 mg/L sodium nitrite to the drinking water of rats for a 2-year period (8). The authors intended to study the carcinogenic effects of long-term nitrite intake, which leads to production of nitrosamine and nitrosamide compounds, but instead observed dilated coronary arteries and pulmonary emphysema.

Cured meats, such as bacon, sausage, luncheon meats, and cured hams, are high in nitrites, which are added to meat products as a preservative, an antimicrobial agent, and a color fixative (9). Although these rodent studies suggest that inhalation of NO₂ and ingestion of sodium nitrite may contribute to emphysema, no human studies have examined the relationship between consumption of cured meats and COPD. We therefore tested the hypothesis that frequent consumption of cured meats would be associated with an obstructive pattern of spirometry and increased odds of COPD in a large, representative sample of U.S. adults. Some results in this article were presented in abstract form at the 2006 meeting of the European Respiratory Society (10).

METHODS

Study Population

The Third National Health and Nutrition Examination Survey (NHANES III) was a cross-sectional survey conducted from 1988 through 1994 by the National Center for Health Statistics. Approximately 33,994 noninstitutionalized U.S. civilians aged 2 months or older were selected via a stratified multistage probability sampling design.

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Detailed description of the methodology of NHANES III has been previously published (11, 12). For the present study, we restricted the sample to 9,787 participants aged 45 years or older because COPD is rare before that age and because the association of cured meat and COPD is less likely to be subject to misclassification with asthma. We excluded participants who were missing measures of cured meat consumption ($n = 38$), fish, fruit, or vegetable consumption ($n = 80$), or lung function ($n = 2,143$). One author (J.L.H.) supervised measurement of spirometry in NHANES III, reviewed all spirometry results, and excluded a further 174 participants who did not have acceptable spirometry curves.

Dietary Assessment

Frequency of food consumption was collected by food frequency questionnaire (13). Respondents were asked how often over the past month they had consumed selected food items, including meats, fish, fruits, and vegetables. Cured meat consumption was defined as the total consumption of bacon, sausage, and luncheon meats, which was ascertained as a single food item on the questionnaire. Ham was not included in cured meat consumption because it was only ascertained in combination with pork as a single food item on the questionnaire (pork is not a cured meat).

Outcome Assessment

Lung function was measured using a dry rolling-seal spirometer (Ohio SensorMed model 827; Ohio Medical Instruction Co., Cincinnati, OH) according to the 1987 American Thoracic Society (ATS) recommendations. (14, 15) The highest value of FEV₁ and FVC from the acceptable maneuvers was used in this analysis. Further details are described in the online supplement.

We defined COPD for this study *a priori* as prebronchodilator FEV₁/FVC ≤ 0.7 and FEV₁ $< 80\%$ of predicted since post-bronchodilator measures were not available and the relevance of ATS/European Respiratory Society-defined mild COPD continues to be debated. To address possible misclassification of COPD in older adults from the use of the fixed FEV₁/FVC threshold, we performed a sensitivity analysis defining COPD based on lower limit of normal (LLN) criteria (FEV₁/FVC $< [\text{FEV}_1/\text{FVC}]_{\text{LLN}}$ and FEV₁ $< [\text{FEV}_1]_{\text{LLN}}$) (15).

Statistical Analysis

We divided participants into five categories approximating quintiles according to their frequency of cured meat consumption: never, 1–2 times/month, 3–4 times/month, 5–13 times/month, or ≥ 14 times/month. We examined the associations between frequency of cured meat consumption and FEV₁, FVC, and FEV₁/FVC with linear regression and between cured meat consumption and prevalent cases of COPD with logistic regression. In multivariate models, we controlled for multiple potential confounders shown in the footnotes of Tables 2–4. To reduce residual confounding by smoking history, we included a set of spline terms generated from restricted cubic spline regressions (16–18) for pack-years and serum cotinine levels. Spline terms were also used for body mass index due to its U-shaped relationship with spirometry measures. The regression coefficient for the continuous measure indicates the change in lung function or odds ratio (OR) associated with an average increment of one time per month of cured meat consumption. To account for the stratified multistage survey design in NHANES III, we applied the sampling weights in all the analyses to yield population estimates by using SAS (version 9; SAS Institute, Inc., Cary, NC) and SUDAAN (version 9; RTI International, Research Triangle Park, NC). Spline plots were created in R (version 2.0.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study sample included 7,352 NHANES III participants 45 years of age or older with adequate information on meat consumption and lung function. The mean age was 64.5 years and 48.0% were male. Those excluded because of missing measures of cured meat, fish, fruit and vegetable consumption, or lung function were older (mean age = 71.0 yr) and had a higher prevalence of physician-diagnosed emphysema or chronic bron-

chitis (12.8 vs. 9.54% in the study sample). The distributions of sex, race/ethnicity, and smoking status were similar between the two groups. Those missing lung function data had cured meat consumption similar to participants in the study sample.

The study sample represented 68.2 million adults aged 45 years or older in the United States. The characteristics of this population, stratified by frequency of cured meat consumption are shown in Table 1. Individuals who consumed cured meats frequently were more likely to be male, of lower socioeconomic status, and tobacco users, and were less likely to report physician-diagnosed asthma than individuals who never consumed cured meats. Those who consumed cured meats more frequently had lower intakes of vitamin C, β -carotene, fish, fruits, vegetables, and vitamin or mineral supplements; had higher intakes of vitamin E and total calories; and had lower serum levels of vitamin C and E and β -carotene. The distributions of age, body mass index, and total:high-density lipoprotein cholesterol ratio were similar across categories of cured meat consumption.

Greater frequency of cured meat consumption was associated with lower FEV₁, FVC, and FEV₁/FVC after adjustment for demographics and height (Table 2, model 1). After controlling for smoking status, pack-years, cotinine levels, and household environmental tobacco smoke (ETS) exposure, these inverse associations were attenuated, but remained statistically significant (Table 2, model 2). After simultaneous adjustment for multiple additional confounding variables, individuals who ate cured meat consumption 14 times/month or more had a significantly lower FEV₁ (-110 ml; p for trend < 0.001) and FEV₁/FVC (-2.13% ; p for trend < 0.001) compared with those who never ate cured meats. FVC did not differ significantly across categories of cured meat consumption. Each time-per-month increase in cured meat consumption was associated with a 3.85 ml decrease in FEV₁ and -0.07% decrease in FEV₁/FVC.

The frequency of cured meat consumption was positively associated with odds of COPD (Table 3). The OR for COPD among individuals who consumed cured meat 14 times or more per month was 1.93 (95% confidence interval [CI], 1.41–2.64; p for trend = 0.001) compared with those who did not consume cured meats, after adjustment for age, sex, race/ethnicity, height, and smoking variables. Further adjustment for other confounding variables yielded similar results. Each time-per-month increase in cured meat consumption was associated with a 2% increased risk for COPD (multivariate OR, 1.02; 95% CI, 1.01–1.03). Figure 1 shows a monotonic increase in OR for mild, moderate, severe, and severe or very severe COPD across these categories. Severe and very severe COPD categories were combined because of the small number of participants with very severe COPD ($n = 34$) in this study. The separate ORs were 2.51 for severe COPD and 352 for very severe COPD; both ORs were statistically significant.

The sensitivity analysis using the LLN definition of COPD (FEV₁/FVC $< [\text{FEV}_1/\text{FVC}]_{\text{LLN}}$ and FEV₁ $< [\text{FEV}_1]_{\text{LLN}}$) yielded similar results (15). The multivariate-adjusted OR for COPD in this analysis was 1.67 (95% CI, 1.04–2.69; p for trend = 0.01) comparing the highest to the lowest category of cured meat consumption after adjustment for all the potential confounding factors.

Multivariate analyses stratified by smoking status showed that the inverse associations of cured meat consumption with FEV₁ and FEV₁/FVC persisted among 2,823 never-smokers, 2,155 past smokers, and 1,929 current smokers (Table 4), although the standard threshold of statistical significance was not met for current smokers. There was no apparent modification of the relations between cured meat consumption and lung function by smoking status (p for interaction was 0.64 for FEV₁, 0.94 for FVC, and 0.66 for FEV₁/FVC).

TABLE 1. CHARACTERISTICS OF U.S. POPULATION (AGE $\geq$ 45 YR) ACCORDING TO FREQUENCY OF CURED MEAT CONSUMPTION (BACON/SAUSAGE/PROCESSED MEATS)

	Frequency of Cured Meat Consumption				
	Never	1–2 Times/mo	3–4 Times/mo	5–13 Times/mo	$\geq$ 14 Times/mo
Sample size	1,711	1,402	1,499	1,631	1,109
Estimated population (weighted), millions	15.0	14.1	14.5	15.0	9.60
Age, mean (SE), yr	62.4 (0.52)	61.1 (0.47)	59.8 (0.45)	60.0 (0.50)	61.2 (0.55)
Male, %	34.0	38.5	48.6	52.3	64.8
Race/ethnicity, %					
Non-Hispanic white	75.1	85.4	85.2	84.0	85.2
Non-Hispanic black	7.19	6.59	7.83	9.45	11.6
Mexican-American	4.07	2.87	3.14	2.80	1.82
Other	13.6	5.18	3.85	3.76	1.31
Family income, %					
< \$10,000	16.9	10.1	10.6	9.88	15.6
\$10,000–29,999	39.4	40.7	37.8	38.6	39.5
\$30,000–49,999	19.0	22.2	25.3	27.5	24.7
$\geq$ \$50,000	24.7	27.0	26.3	23.9	20.1
Education (yr), %					
< 9	20.0	13.9	15.3	15.6	22.0
9–11	12.5	13.7	15.9	14.4	20.4
12	28.9	35.0	36.2	35.2	30.5
$\geq$ 13	38.6	37.5	32.7	34.9	27.1
Height, mean (SE), cm	163 (0.37)	166 (0.30)	168 (0.39)	168 (0.35)	170 (0.40)
BMI, mean (SE), kg/m ²	27.1 (0.19)	27.6 (0.18)	27.3 (0.22)	27.5 (0.18)	27.5 (0.27)
Smoking status, %					
Never*	48.1	42.5	37.1	37.3	27.4
Past*	34.9	36.3	32.6	29.4	29.9
Current*	17.0	21.2	30.4	33.3	42.7
Pack-years of smoking among ever smokers, median (25th–75th percentile)	22.8 (8.24, 46.1)	27.8 (9.26, 50.5)	31.4 (9.92, 51.1)	33.8 (14.8, 55.2)	35.3 (15.3, 55.7)
Cotinine, median (25th–75th percentile), ng/ml	0.15 (0.07, 0.72)	0.17 (0.07, 1.30)	0.31 (0.09, 115)	0.37 (0.10, 140)	1.17 (0.12, 216)
Household ETS exposure, %	21.9	22.7	33.9	33.6	38.8
Asthma (physician diagnosis), %	6.65	7.17	5.94	6.32	5.32
Acetaminophen use, %	30.1	32.6	37.6	35.1	27.6
Aspirin use, %	39.9	45.7	41.1	42.9	43.1
Ibuprofen use, %	16.6	19.4	20.5	19.1	17.2
Total to HDL cholesterol ratio, median (25th–75th percentile)	4.44 (3.49, 5.63)	4.42 (3.49, 5.47)	4.49 (3.55, 5.59)	4.49 (3.53, 5.64)	4.63 (3.66, 5.76)
Diet, median (25th–75th percentile)					
Vitamin C, mg/d	92.0 (41.4, 165)	81.5 (38.9, 153)	70.6 (34.8, 140)	73.6 (33.9, 139)	73.0 (36.3, 128)
Vitamin E, α -tocopherol equivalents	6.41 (4.17, 10.1)	6.60 (4.34, 9.98)	6.82 (4.58, 11.3)	7.15 (4.52, 11.4)	7.51 (4.87, 11.0)
β -carotene, mg	1.67 (0.73, 4.62)	1.45 (0.65, 3.39)	1.31 (0.60, 3.62)	1.32 (0.63, 3.45)	1.19 (0.63, 3.61)
Fish, times/mo	3.33 (0.94, 8.35)	3.18 (0.93, 8.01)	3.09 (1.02, 4.09)	3.12 (1.08, 4.97)	3.09 (0.81, 4.00)
Fruits, times/mo	60.3 (34.3, 89.3)	48.1 (29.1, 73.9)	39.3 (18.8, 64.4)	41.0 (21.6, 64.6)	39.5 (19.4, 65.8)
Vegetables, times/month	82.3 (56.2, 115)	75.3 (50.1, 104)	66.7 (44.0, 97.8)	72.8 (50.2, 99.7)	76.3 (51.1, 108)
Total energy, kcal/d	1592 (1,184, 2,050)	1667 (1,263, 2,230)	1903 (1,397, 2,444)	1910 (1,474, 2,551)	2021 (1,455, 2,713)
Serum levels, median (25th–75th percentile)					
Vitamin C, mg/dl	0.91 (0.65, 1.15)	0.87 (0.51, 1.13)	0.80 (0.42, 1.11)	0.75 (0.40, 1.06)	0.59 (0.25, 0.99)
Vitamin E, μ g/dl	1355 (1,074, 1,749)	1256 (1,018, 1,567)	1214 (990, 1,494)	1180 (995, 1,465)	1095 (915, 1,386)
β -carotene, μ g/dl	22.6 (14.2, 36.7)	18.7 (11.6, 31.6)	16.4 (9.64, 26.5)	15.9 (8.97, 25.1)	13.5 (8.48, 22.4)
Selenium, ng/ml	126 (115, 136)	125 (115, 134)	124 (114, 135)	124 (114, 136)	122 (113, 135)
Vitamin or mineral supplement use, %	51.1	52.2	45.2	44.5	35.8

Definition of abbreviations: BMI = body mass index; ETS = environmental tobacco smoke; HDL = high-density lipoprotein.

* Never-smokers: report of never having smoked 100 cigarettes and cotinine levels < 30 ng/ml; past smokers: report of having smoked at least 100 cigarettes and having stopped smoking and cotinine levels < 30 ng/ml; and current smokers: report of having smoked at least 100 cigarettes and currently smoking, or cotinine levels $\geq$ 30 ng/ml.

TABLE 2. MEAN DIFFERENCE IN LUNG FUNCTION ACCORDING TO CURED MEAT CONSUMPTION

	Frequency of Cured Meat Consumption					p Value for Trend	Difference per 1 Time/mo Increase
	Never	1–2 Times/mo	3–4 Times/mo	5–13 Times/mo	≥ 14 Times/mo		
Estimated population (weighted), millions	15.0	14.1	14.5	15.0	9.60		
FEV ₁ , mean difference (SE), ml							
Model 1*	0 (ref)	−56.4 (19.7) [†]	−60.4 (22.2) [†]	−97.7 (20.7) [†]	−201 (33.0) [†]	< 0.001	−6.80 (1.14) [†]
Model 2 [‡]	0 (ref)	−41.0 (18.7) [§]	−24.5 (24.9)	−54.8 (21.5) [§]	−132 (28.9) [†]	< 0.001	−4.44 (1.00) [†]
Model 3	0 (ref)	−37.6 (18.2) [§]	−11.5 (23.6)	−42.0 (22.2)	−110 (27.0) [†]	< 0.001	−3.85 (1.00) [†]
FVC, mean difference (SE), ml							
Model 1*	0 (ref)	−21.8 (22.3)	−37.8 (24.8)	−54.1 (24.0) [§]	−124 (38.1) [†]	0.002	−4.19 (1.10) [†]
Model 2 [‡]	0 (ref)	−16.7 (22.4)	−16.4 (28.2)	−29.8 (25.7)	−84.3 (35.3) [§]	0.01	−2.76 (1.01) [†]
Model 3	0 (ref)	−11.3 (20.0)	−0.33 (23.9)	−11.0 (23.1)	−55.2 (34.0)	0.09	−2.05 (1.12)
FEV ₁ /FVC, mean difference (SE), %							
Model 1*	0 (ref)	−1.26 (0.44) [†]	−1.16 (0.46) [§]	−1.82 (0.39) [†]	−3.20 (0.54) [†]	< 0.001	−0.11 (0.02) [†]
Model 2 [‡]	0 (ref)	−0.91 (0.40) [§]	−0.56 (0.45)	−1.09 (0.35) [†]	−2.05 (0.51) [†]	0.002	−0.07 (0.02) [†]
Model 3	0 (ref)	−0.97 (0.40) [§]	−0.54 (0.41)	−1.13 (0.38) [†]	−2.13 (0.45) [†]	< 0.001	−0.07 (0.02) [†]

* Results were adjusted for age, age squared, sex, race/ethnicity, and height squared.

[†] p < 0.01 (in comparison with individuals who did not consume cured meats).

[‡] Results were adjusted for all the variables in model 1 plus smoking variables: smoking status (see Table 1 footnote), pack-years of smoking, serum cotinine concentration, and household environmental tobacco smoke.

[§] 0.01 ≤ p < 0.05 (in comparison with individuals who did not consume cured meats).

^{||} Results were adjusted for all the variables in model 2 plus education, family income, body mass index, physician diagnosis of asthma, use of acetaminophen, aspirin, and ibuprofen, serum total:high-density lipoprotein cholesterol ratio, serum levels of vitamins C, D, and E, β-carotene, and selenium, dietary intake of vitamin C, vitamin E, β-carotene, fish, fruits, vegetables, and total calories, and use of vitamin or mineral supplements.

Consumption of ham and pork (e.g., cured and noncured meats, respectively) was inversely associated with lung function but these associations did not attain statistical significance. The multivariate differences between individuals consuming ham and pork five times or more per month (the highest two categories were combined because of less consumption of ham and pork) and those who never ate cured meats were −40.1 ml (p = 0.12) for FEV₁, −49.7 ml (p = 0.09) for FVC, and −0.11% (p = 0.82) for FEV₁/FVC. The multivariate OR for COPD comparing the two extreme categories (highest vs. lowest) of ham and pork consumption was 1.18 (95% CI, 0.80–1.73).

According to the ATS standard, we did not exclude participants with a nonreproducible test from the study. Sensitivity analyses for cured meats excluding 104 individuals with only one acceptable curve (n = 7,248) showed similar differences in lung function and in risk of COPD in the main analyses. Compared with those who did not consume cured meats, individuals who consumed cured meats 14 times or more per month had a significantly lower FEV₁ (−107 ml; p for trend < 0.001) and FEV₁/FVC (−2.08%; p for trend < 0.001) after adjustment for all the potential confounders. The multivariate OR for COPD compar-

ing the highest to the lowest category of cured meat consumption was 1.78 (95% CI, 1.28–2.46) in this sensitivity analysis.

DISCUSSION

This study of a representative sample of U.S. population aged 45 years or older showed that frequent consumption of cured meats was associated with lower FEV₁ and FEV₁/FVC and an increased odds of COPD after adjustment for multiple known risk factors. The magnitude of the risk of COPD increased with severity of COPD.

Cured meats may contribute to the development of COPD because of their high content of nitrites (9, 19). Nitrites are prooxidants and are involved in the formation of reactive nitrogen species that include both nitrating (i.e., NO₂) as well as nitrosating (i.e., nitrosonium + NO or dinitrogen trioxide [N₂O₃]) agents (20, 21). Reactions of nitrite with H₂O₂/myeloperoxidase (22), H₂O₂/Fe²⁺ (23), and H₂O₂/hypochlorous acid (24) all result in protein tyrosine nitration. 3-Nitro-tyrosine, which has been used as a biomarker for studying disease states associated with nitrate/nitrosative stress, is elevated in the inflammatory cells

TABLE 3. ODDS RATIO OF CHRONIC PULMONARY OBSTRUCTIVE DISEASE ACCORDING TO CURED MEAT CONSUMPTION

	Frequency of Cured Meat Consumption					p Value for Trend	OR per 1 Time/mo Increase
	Never	1–2 Times/mo	3–4 Times/mo	5–13 Times/mo	≥ 14 Times/mo		
No. of COPD cases (weighted), millions	1.42	1.90	1.83	2.35	1.93		
Estimated population (weighted), millions	15.0	14.1	14.5	15.0	9.60		
COPD prevalence, %	9.47	13.5	12.6	15.7	20.1		
OR (95% CI), model 1*	1.00 (ref)	1.55 (1.00–2.40)	1.51 (1.07–2.15)	1.92 (1.36–2.71)	2.41 (1.81–3.21)	< 0.001	1.02 (1.02–1.03)
OR (95% CI), model 2 [†]	1.00 (ref)	1.45 (0.91–2.32)	1.25 (0.82–1.89)	1.60 (1.09–2.35)	1.93 (1.41–2.64)	0.001	1.02 (1.01–1.03)
OR (95% CI), model 3 [‡]	1.00 (ref)	1.42 (0.86–2.34)	1.14 (0.74–1.74)	1.50 (0.95–2.35)	1.78 (1.29–2.47)	0.002	1.02 (1.01–1.03)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

* Results were adjusted for age, sex, and race/ethnicity.

[†] Results were adjusted for all the variables in model 1 plus smoking variables: smoking status (see Table 1 footnote), pack-years of smoking, serum cotinine concentration, and household environmental tobacco smoke.

[‡] Results were adjusted for all the variables in model 2 plus education, family income, body mass index, physician diagnosis of asthma, use of acetaminophen, aspirin, and ibuprofen, serum total:high-density lipoprotein cholesterol ratio, serum levels of vitamins C, D, and E, β-carotene, and selenium, dietary intake of vitamin C, vitamin E, β-carotene, fish, fruits, vegetables, and total calories, and use of vitamin or mineral supplements.

Figure 1. Odds ratios of chronic obstructive pulmonary disease (COPD) comparing individuals who consumed cured meat 14 times or more per month with those who did not consume cured meats according to COPD severity. Error bars are 95% confidence intervals for the estimated values. The results were adjusted for the following: age; sex; race/ethnicity; smoking status; pack-years of smoking; serum cotinine concentration; household environmental tobacco smoke; education; family income; body mass index; physician diagnosis of asthma; use of acetaminophen, aspirin, and ibuprofen; serum total:high-density lipoprotein cholesterol ratio; serum levels of vitamins C, D, and E, β -carotene, and selenium; dietary intake of vitamin C, vitamin E, β -carotene, fish, fruits, vegetables, and total calories; and use of vitamin or mineral supplements.

(25) and bronchial submucosa (26) of patients with COPD, suggesting that nitrating and nitrosating reactions may be increased in COPD.

Paik and colleagues showed that nitrating and nitrosating reactions induce extracellular matrix protein changes that include covalent nonenzymatic collagen cross-linking (27, 28) and elastin fragmentation in model system experiments paralleling the aging/diabetes model system of nonenzymatic glycation (29). Such *in vitro* findings are pertinent to COPD because both biochemical and histopathologic studies indicate that collagen and elastin damage occurs during the development of human pulmonary emphysema (30–32). These findings are also consistent with animal studies that demonstrated that rats fed long term with dietary nitrite developed dilated coronary arteries and pulmo-

nary emphysema (8). Elastin and collagen integrity are principally responsible for the maintenance of both long-term coronary vessel diameter and alveolar airspace size, suggesting that supraphysiologic nitrite supplementation damages the connective tissue matrix. Although these experimental and animal studies suggest that nitrite exposure may cause lung damage through its effects on connective tissues in the lung, this is the only article of which we are aware that has examined the association between a principal source of dietary nitrite, cured meat intake, with lung function or COPD in humans.

Tobacco smoke is another major source of nitrite in the body. Of the approximately 4,000 different compounds in tobacco smoke, several compounds are present in relatively high amounts and include carbon monoxide, nicotine, and nitrogen oxides

TABLE 4. MEAN DIFFERENCE IN LUNG FUNCTION ACCORDING TO FREQUENCY OF CURED MEAT CONSUMPTION BY SMOKING STATUS

	Frequency of Cured Meat Consumption					p Value for Trend
	Never	1–2 Times/mo	3–4 Times/mo	5–13 Times/mo	≥ 14 Times/mo	
Sample size (unweighted)						
Never-smokers	777	584	546	596	320	
Former smokers	519	443	447	443	303	
Current smokers	281	296	418	513	421	
FEV ₁ , mean difference (SE), ml*						
Never-smokers	0 (ref)	–11.6 (32.0)	15.1 (35.9)	4.53 (33.2)	–89.1 (29.9) [†]	0.01
Former smokers	0 (ref)	–44.9 (40.1)	–23.4 (44.5)	–30.9 (53.0)	–121 (50.8) [‡]	0.02
Current smokers	0 (ref)	–99.3 (49.8)	–118 (49.7) [‡]	–127 (44.9) [†]	–155 (48.2) [†]	0.08
FVC, mean difference (SE), ml*						
Nonsmokers	0 (ref)	–2.09 (34.3)	31.5 (40.9)	55.6 (34.8)	–35.2 (32.1)	0.35
Former smokers	0 (ref)	–14.6 (43.6)	–1.87 (45.2)	–66.6 (52.2)	–94.6 (54.7)	0.05
Current smokers	0 (ref)	–61.2 (59.7)	–117 (67.3)	–77.2 (58.7)	–109 (66.7)	0.43
FEV ₁ /FVC, mean difference (SE), %*						
Nonsmokers	0 (ref)	–0.55 (0.46)	–0.21 (0.50)	–1.21 (0.58) [‡]	–1.93 (0.72) [†]	0.01
Former smokers	0 (ref)	–0.74 (0.80)	–0.47 (0.79)	0.34 (0.67)	–1.98 (0.73) [†]	0.04
Current smokers	0 (ref)	–1.61 (0.96)	–1.41 (0.78)	–2.30 (0.78) [†]	–1.98 (0.71) [†]	0.21

* Results were adjusted for age, age squared, sex, race/ethnicity, height squared, pack-years of smoking (former and current smokers only), serum cotinine concentration, household environmental tobacco smoke, education, family income, body mass index, physician diagnosis of asthma, use of acetaminophen, aspirin, and ibuprofen, serum total:high-density lipoprotein cholesterol ratio, serum levels of vitamins C, D, and E, β -carotene, and selenium, dietary intake of vitamin C, vitamin E, β -carotene, fish, fruits, vegetables, and total calories, and use of vitamin or mineral supplements. Smoking status (see Table 1 footnote) used for stratification was not included in the model. Participants with missing cotinine levels were excluded from the analyses (n = 542).

[†] p < 0.01 (in comparison with individuals who did not consume cured meats).

[‡] p < 0.05 (in comparison with individuals who did not consume cured meats).

(NO_x) (33). NO_x comprise mainly nitric oxide (NO) and NO₂, and almost all of the NO_x inhaled in cigarette smoke are retained in the body (34). NO_x gas is converted exclusively to nitrite (NO₂⁻) as it enters the pulmonary circulation (35), and inhaled NO results in marked increases in serum nitrite and nitrate (36, 37). Although the precise mechanisms underlying the tissue damage by cigarette smoking are poorly understood, nitrite precursors in cigarette smoke may contribute mechanistically to lower lung function through these mechanisms.

Prior epidemiologic studies have reported an inverse association between intake of fish, fruits, vegetables, and antioxidant vitamins (e.g., vitamins C and E, β-carotene) and FEV₁ or COPD (38). According to our data, those who consumed cured meats more frequently had lower intakes of fish, fruits, vegetables, vitamin C, β-carotene, and vitamin or mineral supplements, but had higher intake of vitamin E. Adjustment for these dietary factors in our analyses did not appreciably change the findings, suggesting the observed association between cured meats and lung function was unlikely to be explained by these potential dietary confounding factors reported in previous studies.

The major strength of this study was its large representative sample and multiple measures of smoking, including serum cotinine levels and ETS exposure. A limitation of the study was its cross-sectional design, which may introduce reverse causation and selection bias. Reverse causation was unlikely in that COPD probably did not cause participants to increase their cured meat consumption. Selection bias was minimized by the population-based, representative sampling of NHANES III participants. Cross-sectional studies of lung function can also yield different results from longitudinal studies of lung function for other reasons, including effect size, which was modest in this study. Smoking is the primary cause of COPD, so residual confounding by smoking was a potential concern. We adjusted, however, not only for self-report of smoking status, pack-years, and household ETS but also for serum cotinine levels as a biomarker of current smoking dose and current ETS exposure. In addition, we used cotinine levels to correct self-reported smoking status. Finally, the lack of effect modification by smoking status of the association of cured meats with lung function and the statistically significant inverse associations among never-smokers suggested true independent associations. We cannot rule out the possibility that unmeasured aspects of an unhealthy lifestyle may have caused the lower lung function and increased risk of COPD in those who ate cured meats frequently, although we adjusted for multiple dietary variables considered to be correlated with cured meat consumption in our multivariate analyses. We also lacked robust measures of dietary nitrite intake, post-bronchodilator lung function, and occupational exposures. Because food intake was self-reported and cured meats with varying nitrite content were grouped together in NHANES III, misclassification of nitrite consumption was inevitable and could bias the observed associations. Lack of post-bronchodilator measures can inflate prevalence estimates of COPD (39), but was unlikely to affect our results unless bronchodilator responsiveness was appreciably greater in those with high cured meat consumption. However, self-reported asthma was less frequent in those with high cured meat consumption, and we used relatively conservative definitions of COPD in the main and sensitivity analysis.

In conclusion, frequent cured meat consumption was associated with an obstructive pattern of lung function and increased odds of COPD independent of other major risk factors. High dietary nitrite intake warrants further evaluation in prospective, longitudinal studies as a novel risk factor for COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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