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Fatty acid intake and the risk of community-acquired pneumonia in US women

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Abstract

Objective—Despite substantial progress in the treatment of community-acquired pneumonia, there are limited data on dietary risk factors. Fatty acid intake may influence community-acquired pneumonia risk by modulating the immune system. Our study prospectively examined the association between fatty acid intake and community-acquired pneumonia risk.

Research Methods & Procedures—The study population included 83,165 women from the Nurses' Health Study II cohort who were between the ages of 27 and 44 in 1991. The women reported lifestyle habits on biennial questionnaires and dietary intake every four years by validated semiquantitative food frequency questionnaires (FFQ). There were 925 pneumonia cases over 10 years of follow-up. We examined independent associations for six fatty acids using Cox proportional hazards regression.

Results—Women in the highest quintile of palmitic acid intake had a 54% greater risk of pneumonia compared to the lowest quintile: multivariate relative risk (RR)=1.54; 95% confidence interval (CI): 1.12, 2.12; *p* for trend = 0.002. Oleic acid intake was inversely associated with pneumonia risk (highest quintile multivariate RR=0.75; 95% CI: 0.55, 1.04; *p* for trend = 0.02). Women in the highest quintile of docosahexanoic acid (DHA) and eicosapentanoic acid (EPA) intake had a 24% greater risk of community-acquired pneumonia than the lowest quintile (multivariate RR=1.24; 95% CI: 1.00, 1.55; *p* for trend = 0.08). No significant associations were found for linoleic acid, alpha-linolenic acid, or DHA alone.

Conclusions—Fatty acid intake may affect the risk of community-acquired pneumonia in young and middle-aged women. Higher dietary intake of palmitic acid and possibly DHA and EPA may increase the risk of community-acquired pneumonia in women while higher oleic acid intake may decrease the risk.

Keywords

fatty acid intake; pneumonia; prospective study; women

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INTRODUCTION

Community-acquired pneumonia is one of the most common infectious diseases and is associated with high rates of morbidity and mortality. Five to 6 million cases of community-acquired pneumonia are diagnosed annually in the United States.[1] Furthermore, pneumonia is responsible for 15 percent of all infections treated in the hospital in the US and for over 1 million hospitalizations.[1,2] Although the majority of pneumonia cases nationally affect the elderly, very little research exists about pneumonia risk in middle-aged women. Risk factors for pneumonia include smoking, chronic obstructive pulmonary disease, alcohol abuse, and age.[3] Surprisingly, little research exists on the dietary risk factors that may impact on community-acquired pneumonia risk other than malnutrition.[3–5]

Essential fatty acids (alpha-linolenic and linoleic acids), non-essential fatty acids (palmitic and oleic acids), eicosapentanoic acid or EPA, and docosahexanoic acid or DHA may impact the risk of community-acquired pneumonia. Essential fatty acids may modulate inflammation and immunity.[6] EPA inhibits the conversion of arachidonic acid to leukotriene B4 and prostaglandin E2, two mediators of inflammation.[7] Additionally, EPA suppresses the production of the pro-inflammatory cytokines interleukin-1 β and TNF- α . [7] Alpha-linolenic acid is the precursor of EPA and may produce effects similar to that of other omega-3 fatty acids.[8] Respiratory infections were decreased in children with recurrent respiratory infections using dietary supplements containing linoleic and alpha-linolenic acids.[9] Finally, the levels of palmitic and oleic acids within pulmonary surfactant have both been found to be predictors of respiratory disease.[10] Patients with pneumonia had lower ratios of palmitic acid to oleic acid in lung surfactant compared to healthy controls.[10] To investigate the role of fatty acids further, we performed a prospective study of fatty acid intake and risk of pneumonia in 83,165 participants in the Nurses' Health Study II.

MATERIALS AND METHODS

Study population

The source population consisted of 116,671 women from the Nurses' Health Study II, an ongoing cohort study that began in 1989.[11] In 1991, when diet was first assessed, the women ranged in age from 27 to 44 years. Participants have provided detailed information on medical history and lifestyle habits on biennial questionnaires.[12] Women were excluded from the analysis if they had incomplete dietary information (12,360 women), had pneumonia prior to the baseline in 1991 (14,156 women), died prior to the start of the study period (37 women), or if they suffered from conditions known to affect pneumonia risk prior to the start of the study period, such as cancer, cardiovascular disease (myocardial infarction, stroke, or arterial surgery), or asthma (6,953 women). This study was approved by the Human Subjects Committee at the Harvard School of Public Health.

Identification of cases of pneumonia

Only the first report of community-acquired pneumonia that developed in women between June 1, 1991 and May 31, 2001 was considered. Women who reported pneumonia were sent a supplementary questionnaire asking whether the pneumonia diagnosis had been confirmed by x-ray. To examine the validity of self-reported pneumonia during the first two years, a study physician, who was blinded to exposure status, examined the medical records of 76 women who had reported pneumonia. A radiology report of a pulmonary infiltrate confirmed the presence of pneumonia in 82 percent of the cases.[3] After the first two years of this study, medical records were obtained from all women who reported radiologically diagnosed pneumonia. After reviewing records from a sample of 99 confirmed cases, only one was

potentially hospital-acquired. Therefore, we considered all the cases to have community-acquired pneumonia.

Ascertainment of dietary data

A semiquantitative food frequency questionnaire was used to estimate nutrient intake. Diet was first assessed in 1991 and updated in 1995 and 1999. We excluded women if they reported implausible or incomplete dietary data. For each food, the women indicated how often they consumed a specified portion of food (e.g. 6–8 ounces of fish). The nine potential response categories ranged from “almost never” to “6 or more times per day.” Nutrient intake was calculated by the intake frequency of each food, its serving size, and the nutrient content of the food.[13] Nutrient content was determined from the Harvard University Food Composition database, which is based on the US Department of Agriculture and manufacturer information. [14,15] The validity of the food frequency questionnaire has been demonstrated in the Nurses’ Health Study I cohort.[15] The corrected correlation coefficients between four one-week dietary records and a food frequency questionnaire administered after the dietary records were 0.66 for fish, 0.46 for meat, 0.67 for chicken without skin, 0.58 for chicken with skin, and 0.76 for margarine.[16]

Fatty acids that could be assessed included palmitic acid, oleic acid, linoleic acid, alpha-linolenic acid, DHA, and EPA. The major sources of both palmitic and oleic acids were beef, chicken and pork. Linoleic and alpha-linolenic acid were derived mainly from foods containing vegetable oils. The major sources of DHA and EPA intake were tuna and other fish.

Assessment of other covariates

Covariates considered in the multivariate model included age, body mass index, cigarette smoking, physical activity, alcohol intake, and total energy intake.[17] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared using the reported height of the women at the start of the study and updated weight. Cigarette smoking was assessed on the basis of whether the woman smoked and the amount smoked. Moderate to vigorous physical activity was assessed as the number of MET-hours per week, calculated as sum of the time invested in each activity every week multiplied by the energy expenditure required by the activity.[18]

Data analysis

Person-time of follow-up was calculated from the return of the 1991 questionnaire until the first report of community-acquired pneumonia, death, or the end of the study period (May 31, 2001). We first examined age-adjusted models for the association between fatty acid intake and the risk of pneumonia. Cox proportional hazards multivariate models with updating of exposure variables were used to estimate multivariate relative risks (RR). Variables considered in the models were: age; BMI (<21 kg/m², 21–22.9, 23–24.9, 25–29.9, 30–31.9, and 32+ and continuous); alcohol consumption (non-drinker, 0.1–4.9 grams/day, 5.0–14.9, 15.0–29.9, and 30.0+); cigarette smoking (non-smoker, past smoker, current smoker at 1–14 cigarettes per day, 15–24 cigarettes per day, and 25 or more cigarettes per day); physical activity (quintiles and continuous); and total energy (continuous). Fatty acid intake was divided into quintiles.

RESULTS

From 1991 through 2001, there were 925 confirmed pneumonia cases spanning 650,377 person years of follow-up. The characteristics of the women according to quintile of intake for palmitic and oleic acids are summarized in tables 1a and 1b.

Women who consumed more palmitic acid were slightly younger, had a higher BMI, smoked more, were less active, and consumed less alcohol (table 1a). Women with higher palmitic acid intake consumed on average more linoleic acid, alpha-linolenic acid and oleic acid and less DHA and EPA (table 1a). Women with higher intake of oleic acid were slightly older, had a higher BMI, smoked more, were less active, and consumed less alcohol (table 1b). Women with higher oleic acid intake had greater intake of linoleic acid, alpha-linolenic acid and palmitic acid and less DHA and EPA (table 1b).

After adjusting for age, women in the highest quintile of palmitic acid intake had an increased risk of community-acquired pneumonia compared with women in the lowest quintile (RR=1.35; 95 percent confidence interval (CI): 1.11–1.66; *p* for trend < 0.001) (table 2a). After adjusting for six covariates, the results were attenuated yet still significant (RR=1.24; 95 percent CI: 1.00–1.53; *p* for trend = 0.03) (table 2a). After further adjusting for oleic acid, women in the highest quintile of palmitic acid intake had a 54 percent greater risk of community-acquired pneumonia compared with women in the lowest quintile (RR=1.54; 95 percent CI: 1.12–2.12; *p*-value for trend = 0.002) (table 2a).

After adjusting for age, there was no significant association between oleic acid intake and community-acquired pneumonia (RR=1.16; 95 percent CI: 0.95–1.43; *p* for trend = 0.18) (table 2b). After further adjustment for the initial six covariates, oleic acid was still not associated with risk of community-acquired pneumonia. However, after additionally adjusting for palmitic acid intake, the trend for decreased risk was significant (RR=0.75; 95 percent CI: 0.55–1.04; *p* for trend = 0.02) (table 2b).

The results of the age-adjusted and multivariate models for the other four fatty acids tested are presented in table 3. After adjusting for age, none of these fatty acids (linoleic acid, alpha-linolenic acid, DHA and EPA, and DHA alone) were associated with risk of pneumonia. After further adjusting for BMI, alcohol, physical activity, smoking, total energy intake, and palmitic and oleic acid intake, women in the highest quintile of DHA and EPA intake had a 24 percent greater risk of pneumonia (RR=1.24, 95 percent CI: 1.00–1.55; *p* for trend = 0.08) (table 3). DHA alone was not significantly associated with the risk of community-acquired pneumonia.

DISCUSSION

We found that palmitic acid intake was positively associated with the risk of developing community-acquired pneumonia. Conversely, higher oleic acid intake was associated with a lower risk of community-acquired pneumonia. Women in the highest quintile of DHA and EPA intake also appeared to be at greater risk, although the overall trend was not significant. Linoleic acid and alpha-linolenic acid intake were not associated with pneumonia risk.

Prior studies have examined palmitic and oleic acid levels in the lung surfactant of patients with pneumonia. One prior investigation found a lower ratio of palmitic acid to oleic acid in bronchoalveolar lavage fluid obtained from patients with pneumonia compared to those without pulmonary disease.[10] While that study examined fatty acid levels in surfactant of patients with known pneumonia, our study examined dietary intake prior to the development of pneumonia, and in contrast found that higher dietary intake of palmitic acid was associated with a greater risk of pneumonia while higher oleic acid intake had a lower risk. One potential explanation for our observations is that exogenous palmitic acid intake may decrease palmitic acid biosynthesis,[19,20] the main source of palmitic acid in the lung.[21] Palmitic acid is important for properly functioning surfactant,[22] and poorer functioning surfactant may increase the risk of pneumonia.[23] Although *in vitro*[24] and *in vivo*[25] studies have examined de novo fatty acid synthesis after exogenous palmitate, the conflicting results warrant further study.

Higher oleic acid levels may lead to greater surfactant production. Surfactant is composed of apoproteins, which have an immune function, and phospholipids, which lower surface tension. [26] Oleic acid increases the activity of an enzyme, cytidyltransferase, which is integral in the biosynthesis of a main surfactant phospholipid, phosphatidylcholine (PC). [27,28] Lower proportions of the phospholipid PC have been found in patients with pneumonia. [29] In addition to negatively impacting surface tension, decreased levels of PC may also affect the levels of surfactant protein A, which binds PC. [30] Surfactant protein A is important for promoting phagocyte chemotaxis and enhancing phagocyte destruction of bacteria and viruses. [31]

After adjusting for palmitic and oleic acids, women in the highest quintile of DHA and EPA intake had a 24 percent greater risk of pneumonia. Although DHA and EPA are generally regarded as anti-inflammatory, [32,33] at high levels they may be immunosuppressive as evidenced by *in vitro* [6] and *in vivo* [34–38] studies. We found that the essential fatty acids, linoleic and alpha linolenic acids, were not associated with risk of pneumonia.

Prior studies have examined dietary supplements as a way to reduce pneumonia risk. [5,39] Our results raise the possible protective benefit of supplementing a diet with olive oil or other products high in oleic acid. Furthermore, our study demonstrates the importance of controlling for the non-essential fatty acids in future studies examining DHA and EPA.

Recent findings in the Health Professionals Follow-Up Study cohort found that EPA and DHA intake was not associated with pneumonia risk, and that men in the highest quintile of linoleic and linolenic acid were at lower risk of developing community acquired pneumonia. [5] The population of men studied was significantly older and had more co-morbidities than the women included in our study. Whereas we studied a population of women who were between the ages of 27 and 44 at the outset, the Health Professionals study followed a population of men ages 44–79 at the outset. Furthermore, EPA and DHA have additional benefit among persons with chronic diseases, [40,41] which are more prevalent in the Health Professionals Follow-Up Study. Therefore, any immunosuppressive risk from high EPA and DHA intake in the elderly may have been balanced by the fatty acids' benefit in chronic disease yielding no association in the Health Professionals Follow-Up Study.

Limitations of this study should be noted. We cannot exclude the possibility that one or more of the significant associations may have been a consequence of chance. All pneumonia cases were confirmed by an infiltrate on a chest x-ray, but we could not distinguish between bacterial and viral pneumonia. However, the etiologic agent responsible for pneumonia is rarely identified, even in rigorous epidemiologic studies of community-acquired pneumonia. [42–44] Because some of the nurses were working in a hospital setting, it is possible that more than 1 percent of the cases may have been “hospital-acquired pneumonia.” Although unlikely, it is possible that one or more of the associations found were due to chance, as multiple associations were studied. Finally, our study population may be more health-conscious since it is composed of nurses.

We found that dietary intake of fatty acids may play a role in the development of community-acquired pneumonia; however, the etiology of this disease is multi-factorial. Further research is needed in this area prior to the consideration of dietary modification to alter disease risk. Our results are generalizable to healthy, young and middle-aged women.

CONCLUSION

Dietary fatty acid intake appears to influence the risk of community acquired pneumonia in women. Palmitic acid intake was associated with an increased risk while oleic acid intake had

a reduced risk. Although DHA and EPA are often viewed as “healthy” fatty acids, our results suggest that higher intake may actually increase risk in some populations.

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TABLE 1

TABLE 1a. Age-standardized characteristics of Nurses' Health Study II participants by quintile of palmitic acid intake in 1991*

TABLE 1b. Age-standardized characteristics of Nurses' Health Study II participants by quintile of oleic acid intake in 1991*

	Quintiles				
	1	2	3	4	5
Palmitic acid (g/d)	10.3	12.8	14.3	15.8	18.6
Age (years)	36.2	36.1	35.9	35.8	35.8
Body mass index (kg/m ²)	23.3	24	24.5	24.9	25.5
Smoking – past smoker	24%	22%	22%	21%	20%
– current 1–14 cigs/day	5%	5%	5%	5%	6%
– current 15–24 cigs/day	3%	4%	4%	5%	7%
– current 25+ cigs/day	1%	1%	1%	2%	3%
Total energy (kcal/day)	1775	1801	1803	1790	1757
Physical activity (METs/wk)	28.9	22.3	19.5	18.1	16.2
Alcohol intake (g/d)	3.8	3.3	3.1	2.8	2.5
Linoleic acid (g/d)	8.71	9.51	9.91	10.24	10.44
Alpha-linolenic acid (g/d)	0.92	0.95	0.98	0.99	1.0
Oleic acid (g/d)	16.9	20.3	22.3	24.3	27.1
DHA (g/d)	0.15	0.13	0.11	0.10	0.09
DHA and EPA (g/d)	0.26	0.22	0.20	0.18	0.16

	Quintiles				
	1	2	3	4	5
Oleic acid (g/d)	15.8	19.7	22.2	24.6	28.7
Age (years)	35.8	35.8	35.8	36	36.4
Body mass index (kg/m ²)	23.5	24	24.4	24.8	25.5
Smoking – past smoker	23%	23%	22%	22%	19%
– current 1–14 cigs/day	5%	5%	6%	6%	6%
– current 15–24 cigs/day	3%	4%	4%	5%	6%
– current 25+ cigs/day	1%	1%	2%	2%	3%
Total energy (kcal/day)	1757	1796	1807	1810	1753
Physical activity (METs/wk)	29	22.6	19.6	18	15.6
Alcohol intake (g/d)	3.5	3.4	3.3	3	2.4
Linoleic acid (g/d)	7.82	9.04	9.75	10.5	11.7
Alpha-linolenic acid (g/d)	0.84	0.92	0.96	1.01	1.10
Palmitic acid (g/d)	11.0	13.2	14.5	15.7	17.5
DHA (g/d)	0.15	0.13	0.11	0.10	0.09
DHA and EPA (g/d)	0.26	0.22	0.20	0.18	0.16

* Data are means except where noted. The values were standardized according to the age distribution of the cohort.

TABLE 2

TABLE 2a. Age-adjusted and multivariate relative risks for community-acquired pneumonia by quintile of palmitic acid intake in Nurses' Health Study II participants

TABLE 2b. Age-adjusted and multivariate relative risks for community-acquired pneumonia by quintile of oleic acid intake in Nurses' Health Study II participants

	Quintiles					P, trend
	1	2	3	4	5	
Cases	167	170	169	194	225	
Person-yr	129,367	130,512	131,436	129,986	129,076	
Age-adjusted RR	1.00	1.02	1.00	1.16	1.35	<0.001
95% CI	Referent	0.82, 1.26	0.81, 1.24	0.94, 1.43	1.11, 1.66	
Multivariate RR*	1.00	1.02	0.96	1.06	1.24	0.03
95% CI	Referent	0.81, 1.27	0.77, 1.20	0.85, 1.32	1.00, 1.53	
Multivariate RR [†]	1.00	1.05	1.05	1.24	1.54	0.002
95% CI	Referent	0.82, 1.35	0.79, 1.39	0.92, 1.67	1.12, 2.12	
	Quintiles					P, trend
Cases	1	2	3	4	5	
Person-yr	173	184	181	187	200	
Age-adjusted RR	129,828	130,268	131,420	130,264	128,597	
95% CI	1.00	1.06	1.04	1.08	1.16	0.18
Multivariate RR*	Referent	0.86, 1.31	0.84, 1.28	0.87, 1.32	0.95, 1.43	
95% CI	1.00	1.05	0.99	1.02	1.04	0.87
Multivariate RR [†]	Referent	0.85, 1.30	0.80, 1.24	0.82, 1.27	0.84, 1.29	
95% CI	1.00	1.00	0.89	0.82	0.75	0.02
	Referent	0.78, 1.28	0.67, 1.17	0.61, 1.11	0.55, 1.04	

* Multivariate RR: Adjusted for age, BMI, alcohol intake, physical activity, total energy intake and smoking.

[†] Multivariate RR: The palmitic acid results were additionally adjusted for oleic acid and the oleic acid results adjusted for palmitic acid intake.

Age-adjusted and multivariate relative risks for community-acquired pneumonia according to quintiles of linoleic acid, alpha-linolenic acid, DHA, and omega-3 intake in Nurses' Health Study II participants

TABLE 3

	Quintiles					P, trend
	1	2	3	4	5	
Linoleic acid (g/d)						
Age-adjusted RR	6.67	8.34	9.51	10.8	13.5	
95% CI	1	1.21	1.06	1.19	1.11	0.45
Multivariate RR *	Referent	0.98, 1.49	0.86, 1.31	0.97, 1.47	0.90, 1.37	
95% CI	1	1.23	1.08	1.18	1.15	0.67
Alpha-Linolenic acid (g/d)						
Age-adjusted RR	0.63	0.98, 1.53	0.85, 1.36	0.93, 1.50	0.90, 1.48	
95% CI	1	0.79	0.91	1.07	1.44	
Multivariate RR *	Referent	0.83, 1.24	0.86, 1.29	0.81, 1.22	0.82, 1.24	1
95% CI	1	1	1.09	1	1.02	0.89
DHA (g/d)						
Age-adjusted RR	0.02	0.81, 1.24	0.88, 1.34	0.80, 1.24	0.82, 1.27	
95% CI	1	0.05	0.09	0.14	0.28	
Multivariate RR *	Referent	0.71, 1.08	0.84, 1.26	0.90, 1.34	0.81, 1.23	0.35
95% CI	1	0.9	1.06	1.14	1.11	0.12
DHA and EPA (g/d)						
Age-adjusted RR	0.05	0.72, 1.12	0.86, 1.30	0.92, 1.40	0.89, 1.37	
95% CI	1	0.1	0.16	0.24	0.47	
Multivariate RR *	Referent	0.91, 1.38	0.89, 1.34	0.96, 1.45	0.90, 1.36	0.3
95% CI	1	1.17	1.13	1.21	1.24	0.08

For illustrative purposes, the listed quintile means for fatty acid intake were derived from responses to the 1991 dietary questionnaire. However, the period specific values were used in the 1991–2001 analyses.

* Multivariate RR: Adjusted for age, BMI, alcohol intake, hours of physical activity, total energy intake, cigarette smoking, palmitic acid and oleic acid.