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Vitamin and Micronutrient Intake and the Risk of Community-Acquired Pneumonia in US Women

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Abstract

Background—There are limited data regarding the role of dietary and supplemental vitamin intake and the risk of community-acquired pneumonia.

Methods—We prospectively examined, during a 10-year period, the association between dietary and supplemental vitamin intake and the risk of community-acquired pneumonia among 83,165 women in Nurses' Health Study II who were between the ages of 27 and 44 years in 1991. We excluded women who had pneumonia prior to 1991, those who did not provide complete dietary information, or those with a history of cancer, cardiovascular disease or asthma. Self-administered food frequency questionnaires were used to assess dietary and supplemental vitamin intake. Cases of pneumonia required a diagnosis by a physician and confirmation with a chest radiograph. The independent associations between specific vitamins and pneumonia risk were evaluated.

Results—There were 925 new cases of community-acquired pneumonia during 650,377 person-years of follow up. After adjusting for age, cigarette smoking, body mass index, physical activity, total energy intake, and alcohol consumption, there were no associations between dietary or total intake of any individual vitamin and risk of community-acquired pneumonia. Specifically, women in the highest quintile of vitamin A intake did not have a significantly lower risk of pneumonia than women in the lowest quintile (multivariate RR= 0.88; 95% confidence interval [CI] 0.70–1.09, p for trend=0.16). Similarly, vitamin C (RR=0.94; 95% CI 0.76–1.16, p for trend=0.81) and E (RR=0.95; 95% CI 0.76–1.17, p for trend=0.74) intake did not alter risk of pneumonia.

Conclusions—Higher vitamin intake from diet and supplements is unlikely to reduce pneumonia risk in well-nourished women.

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Clinical Significance

- In well-nourished women, dietary and total intake of individual vitamins do not influence risk of community-acquired pneumonia.
- Multivitamin use did not lower the risk of community-acquired pneumonia.
- Among smokers, women in the top quintile of vitamin E intake from food sources had a lower risk of community-acquired pneumonia than women in the lowest quintile.

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Keywords

vitamin; micronutrient; diet; pneumonia

Background

Community-acquired pneumonia is a common illness associated with significant morbidity and mortality.^{1–4} Many factors, particularly waning immune responses and the onset of age-associated organ dysfunction, account for an increase in susceptibility to respiratory tract infection in older adults.^{5–7} Nutritional factors play a major role in the immune responses, and may impact the risk of development of respiratory infections, particularly community-acquired pneumonia.^{5, 8, 9} There is a lack of information regarding the risk factors for the development of pneumonia, particularly in well nourished individuals.

Individuals with vitamin deficiencies have been shown to be at increased risk for respiratory infections,¹⁰ and vitamin supplementation, with particular vitamins such as C and E, have been shown to decrease the rate of respiratory infections in certain populations.^{11–16} Other studies have found no benefit with vitamin supplementation in reducing the rate of respiratory infections.^{6, 17–20} Merchant and colleagues demonstrated that vitamin E intake from food sources, but not total intake, was inversely associated with pneumonia risk in US men.^{15, 17} We prospectively studied over 80,000 well-nourished women to determine whether vitamin intake alters risk of community-acquired pneumonia.

Methods

Study Population

Details of the study design and data collection used in the NHS II have been previously published.²¹ The NHS II study began in 1989 when 116,671 US female registered nurses aged 25 to 42 years returned a mailed questionnaire. At the time of enrollment, participants provided a detailed medical history including diagnosed diseases, medications, and information on lifestyle factors including smoking, physical activity, and alcohol use. Information on dietary and supplemental vitamin intake was first ascertained in 1991 and updated every 4 years using a semi-quantitative food frequency questionnaire. Women were excluded from the analysis if they had incomplete questionnaires (12,360), had pneumonia prior to the baseline in 1991 (14,156), died prior to 1991 (37), or if they had a history of conditions known to affect pneumonia risk (6,953), including cancer, cardiovascular disease (MI, stroke, or arterial surgery), or asthma diagnosed either prior to or during the study period.

Identification of Cases of Pneumonia

We considered a case to be physician-diagnosed pneumonia confirmed by chest radiography, and included only the first documented event of community-acquired pneumonia occurring between June 1, 1991, and May 31, 2001. 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 of follow-up, a study physician 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% of the cases.²² After the first two years of follow-up, medical records were obtained from all women who reported radiologically diagnosed pneumonia. We reviewed records from a sample of 99 confirmed cases and found only one that was potentially hospital-acquired. Therefore, we considered all the cases to have community-acquired pneumonia.

Ascertainment of Vitamin Intake

A semi-quantitative food frequency questionnaire was used to estimate vitamin and nutrient intake every four years starting in 1991. For each food, the participant indicated how often they consumed a specified portion of food (e.g. 6 to 8 ounces of fish). The nine potential response categories ranged from “never, or less than once per month” to “6 or more times per day.” Specific nutrient intakes were computed from the reported frequency of consumption of each specified unit of food or beverage using published data on the nutrient content of the specified portions.²³ Because total energy intake for a given person tends to be fixed within a narrow range, variations in nutrient intake are largely attributable to changes in diet composition, not total food consumption. Therefore, all computed nutrient intakes were adjusted for total energy intake.²⁴ Energy adjustment also reduces variation introduced by questionnaire responses that under-report or over-report intake, thus improving the accuracy of nutrient measurements.

The validity of the self-reported data from the food frequency questionnaire has been demonstrated in the Nurses’ Health Study I and Health Professionals Follow-Up Study cohorts.^{25–27} Compared with diet records, the food frequency questionnaire was a good measure of specific vitamin intake (correlation coefficients range from 0.52 to 0.85).^{23, 28, 29} We assessed the following nutrients: thiamine, riboflavin, niacin, pyridoxine, folate, vitamins B12, A, C, D, E, total carotenoids, alpha-carotene, beta-carotene, beta-cryptoxanthine, lycopene, lutein and zeaxanthin.

To account for wide ranges in supplemental vitamin intake, specific vitamins were further categorized; pyridoxine (< 1.5 mg, 1.5–4 mg, 5–9 mg, 10–39 mg, 40–99 mg, 100+ mg/day), vitamin B12 (< 2.6 mg, 2.6–7.9 mg, 8–10 mg, 11–13 mg, 14+ mg/day), vitamin A (< 5000 IU, 5000–7499 IU, 7500–9999 IU, 10,000–14,999 IU, and 15,000+ IU/day), vitamin C (<90 mg, 90–249 mg, 250–499 mg, 500–999 mg, 1000–1499 mg, and 1500+ mg/day).

Assessment of Other Covariates

Covariates considered in the multivariate model included age, body mass index, cigarette smoking, physical activity, and alcohol intake. 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. Physical activity was assessed as the number of MET-hours per week, the time invested in an activity every week multiplied by the energy expenditure required by the activity. Alcohol intake was classified by amount the participant consumed per day.

Data Analysis

Person-time of follow-up was calculated as the time between 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 vitamin intake and the risk of pneumonia. Cox proportional hazards multivariate models with updating of exposure variables were used to estimate multivariate relative risks (RR). The age-adjusted relative risk of pneumonia was calculated per quintile of specific vitamin intake, with the referent group being the first quintile. Additionally, due to wide variation in specific vitamin intake, we evaluated the association between pyridoxine, vitamins B12, A, and C and pneumonia risk by further categorizing these variables into wider contrasting groups.

The multivariate model adjusted for age, body mass index (<21 kg/m², 21–22.9, 23–24.9, 25–29.9, 30+), alcohol intake (0 gm/day, 0.1–5 gm, 5–9.9 gm, 10–14.9 gm, 15–29.9 gm, 30+ gm), cigarette smoking (never, past, current smoker of 1–14 cigarettes per day, 15–24 per day, or

25+ per day), and physical activity (in quintiles of metabolic equivalents (METs) per day. Additionally, to assess for possible confounding, we further adjusted for multivitamin use (0, 1–2, 3–5, 6–9, ≥ 10 multivitamin tablets per week).

We further analyzed the association between dietary vitamin intake (excluding supplements) and the risk of community-acquired pneumonia. We also studied the association between vitamin E intake (total intake, as well as diet alone) and risk of community-acquired pneumonia among smokers, as vitamin E intake has been shown to decrease the risk of pneumonia in laboratory animals exposed to smoke.³⁰ This analysis was further adjusted for intake of vegetable fat (in quintiles), as vegetable fat may also rich in vitamin E. Lastly, we studied the association between multivitamin use (0, 1–2, 3–5, 6–9, ≥ 10 multivitamin tablets per week) and the risk of community-acquired pneumonia.

We used the Mantel extension test to calculate tests for trends across quintiles of intake using the respective median values.³¹ SAS statistical software was used for all analyses. Two-sided p-values <0.05 were considered significant.

This study was approved by the Human Subjects Committee of the Harvard School of Public Health.

Results

During 10 years of follow up (650,377 person-years), there were 925 new cases of non-fatal community acquired pneumonia. Women with higher vitamin intake were less likely to be current smokers, and exercised more at baseline in 1991 than women with lower vitamin intake. (Table 1) Forty-two percent of participants reported the use of supplemental multivitamins: 1–2 per week (7%), 3–5 (12%), 6–9 (21%), and 10+ per week (2%).

After adjusting for age, women in the highest quintile of total vitamin A intake were less likely to develop pneumonia than women in the lowest quintile (RR=0.79; 95% CI 0.64–0.98; p for trend = 0.02) (Table 2). This association was no longer significant after further adjusting for smoking, BMI, alcohol use, and physical activity (RR=0.88; 95% CI 0.70–1.09; p for trend = 0.16). After multivariate adjustment, there were no significant associations between vitamin C intake (p, trend =0.81) or vitamin E intake (p, trend =0.74) and risk of community-acquired pneumonia. There were also no significant associations between intake of other vitamins and micronutrients and community-acquired pneumonia risk. Inclusion of women with cancer, cardiovascular disease and asthma did not materially change our results.

There were no associations between vitamin intake from diet alone (excluding intake of supplements) and risk of community-acquired pneumonia (data not shown). Additionally, even after classification of specific vitamins into categories (e.g. vitamin C < 90 mg vs. 1500+ mg) there were no associations with risk of community-acquired pneumonia for pyridoxine (p value comparing extreme categories = 0.29), vitamin B12 (p = 0.34), vitamin A (p = 0.15), and vitamin C (p = 0.67).

Among smokers, total vitamin E intake did not impact risk of community-acquired pneumonia (multivariate p for trend 0.40). Among smokers, after we excluded those who took vitamin E supplements, women in the top quintile of vitamin E intake from food sources had a lower risk of community-acquired pneumonia (multivariate RR=0.46; 95% CI 0.23–0.90; p for trend = 0.04). (Table 3). There was no material change after further adjusting for vegetable fat (RR=0.45; 95% CI 0.21–0.93; p for trend = 0.055).

Multivitamin use did not lower the risk of community-acquired pneumonia. Compared to nonusers, the multivariate RR for women taking 10 or more multivitamin tablets per week was 0.75 (95% CI 0.45–1.26; *p* for trend = 0.84). (Table 4).

Discussion

We found that vitamin intake was not associated with community-acquired pneumonia in well-nourished, young and middle-aged adult US women. Additionally, dietary vitamin intake as well as multi-vitamin use did not appear to alter risk. Although many studies have found that intakes of specific vitamins reduce risk of pneumonia and respiratory infections, these studies have been primarily conducted in the elderly or poorly nourished individuals.

Nutritional status is an important determinant of immune function.^{32, 33} The beneficial effects of adequate nutrition appear to be mediated through mechanisms such as increasing the number of T-cell subsets and natural killer cells, improved lymphocyte proliferation response to mitogens, interleukin-2 production and antibody response to natural killer cell activity.^{17, 34} Individuals with vitamin deficiencies are at increased risk for respiratory infections,¹⁰ and vitamin supplementation has been shown to decrease the rate of respiratory infections in certain populations.^{11–16, 18–20}

Micronutrients can improve cell-mediated immunity and reduce oxidative stress.³⁵ Vitamin E supplementation in healthy, well-nourished adults increased delayed hypersensitivity responses, response to hepatitis B vaccine, lymphocyte proliferation, and decreased formation of immunosuppressive prostaglandins.^{17, 36} Vitamin C regenerates the antioxidant form of vitamin E and is critical for the killing of pathogens by neutrophils.¹⁷ Vitamin B6 (pyridoxine) supplementation enhanced lymphocyte proliferation and interleukin-2 levels in young women.³⁷

Merchant and colleagues reported that vitamin E intake from food sources was inversely associated with pneumonia risk among US men (multivariate relative risk comparing extreme quintiles=0.58, 95% CI 0.39–0.86, *p*-value for trend=0.01), but no association was observed when vitamin E from supplements was included.¹⁷ In contrast, we found that dietary vitamin E intake was not associated with community-acquired pneumonia in healthy, well-nourished women. Both of these large prospective cohort studies found that intake of other vitamins (including dietary and supplemental intake) was not associated with risk of pneumonia. Additionally, both studies found that multivitamin use was not associated with pneumonia risk. Although certain factors, such as excessive weight gain and cigarette smoking have been found to increase the risk of community-acquired pneumonia in both men and women, other factors, such as sedentary lifestyle and obesity were associated with pneumonia risk only among women.²² There might be differences between males and females that may affect susceptibility to pneumonia, however there is insufficient information available. Our results in women, along with Merchant's study of pneumonia in older men, suggest that higher vitamin intake is unlikely to reduce the risk of community-acquired pneumonia in well-nourished adults.¹⁷

Pacht et al found a deficiency of vitamin E in the alveolar fluid of cigarette smokers,³⁰ and a recent laboratory-based study showed that vitamin E supplementation was protective against the development of pneumonia among rats exposed to cigarette smoke.³⁸ We found that among smokers, dietary, but not total, intake of vitamin E was inversely associated with risk of community-acquired pneumonia. A possible reason for this observation is that foods containing vitamin E may have some other beneficial nutrient. Vitamin E-rich foods (i.e. nuts) also contain fatty acids, which have been shown to modulate inflammation and immunity, and may alter risk of respiratory infections and pneumonia.^{39–42}

Dietary information is unlikely to be influenced by recall bias since it was gathered prospectively. Misclassification of the diagnosis of community-acquired pneumonia is certainly possible, however we included only participants with physician diagnosed and radiographically confirmed pneumonia. We were unable to distinguish bacterial and viral pneumonia, but even in the best of circumstances, the microbiological etiology of pneumonia is difficult to establish.^{43–45} Additionally, because some of the nurses were working in a hospital setting, it is possible that more than 1% of the cases may have been “hospital-acquired pneumonia”. Lastly, our results are generalizable to healthy, young and middle-aged women.

In conclusion, vitamin intake does not alter community-acquired pneumonia risk in healthy young and middle-aged women. Among smokers, higher intake of foods rich in vitamin E may reduce the risk of community-acquired pneumonia.

References

1. National-Center-for-Injury-Prevention-and-Control. Activity Report 2001: CDC's Unintentional Injury and Prevention Program. Atlanta: 2002.
2. American-Lung-Association. Pneumonia Fact Sheet. 2002.
3. File TM Jr, Tan JS. Pneumonia in older adults: reversing the trend. *Jama* 2005;294(21):2760–3. [PubMed: 16333013]
4. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *Jama* 2005;294(21):2712–9. [PubMed: 16333006]
5. Miller RA. The aging immune system: primer and prospectus. *Science* 1996;273(5271):70–4. [PubMed: 8658199]
6. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *Jama* 2002;288(6):715–21. [PubMed: 12169075]
7. Meyer KC. Lung infections and aging. *Ageing Res Rev* 2004;3(1):55–67. [PubMed: 15163102]
8. Lesourd B, Mazari L. Nutrition and immunity in the elderly. *Proc Nutr Soc* 1999;58(3):685–95. [PubMed: 10604204]
9. Mazari L, Lesourd BM. Nutritional influences on immune response in healthy aged persons. *Mech Ageing Dev* 1998;104(1):25–40. [PubMed: 9751430]
10. Reyes H, Villalpando S, Perez-Cuevas R, et al. Frequency and determinants of vitamin A deficiency in children under 5 years of age with pneumonia. *Arch Med Res* 2002;33(2):180–5. [PubMed: 11886719]
11. Hemila H. Vitamin C supplementation and respiratory infections: a systematic review. *Mil Med* 2004;169(11):920–5. [PubMed: 15605943]
12. Hemila H, Douglas RM. Vitamin C and acute respiratory infections. *Int J Tuberc Lung Dis* 1999;3(9):756–61. [PubMed: 10488881]
13. Hemila H, Kaprio J. Vitamin E and respiratory tract infections in elderly persons. *Jama* 2004;292(23):2834. [PubMed: 15598911]author reply 2834
14. Hemila H, Virtamo J, Albanes D, Kaprio J. Vitamin E and beta-carotene supplementation and hospital-treated pneumonia incidence in male smokers. *Chest* 2004;125(2):557–65. [PubMed: 14769738]
15. Meydani SN, Han SN, Hamer DH. Vitamin e and respiratory infection in the elderly. *Ann N Y Acad Sci* 2004;1031:214–22. [PubMed: 15753147]
16. Sempertegui F, Estrella B, Camaniero V, et al. The beneficial effects of weekly low-dose vitamin A supplementation on acute lower respiratory infections and diarrhea in Ecuadorian children. *Pediatrics* 1999;104(1):e1. [PubMed: 10390287]
17. Merchant AT, Curhan G, Bendich A, Singh VN, Willett WC, Fawzi WW. Vitamin intake is not associated with community-acquired pneumonia in U.S. men. *J Nutr* 2004;134(2):439–44. [PubMed: 14747686]

18. Fawzi WW, Mbise R, Spiegelman D, Fataki M, Hertzmark E, Ndossi G. Vitamin A supplements and diarrheal and respiratory tract infections among children in Dar es Salaam, Tanzania. *J Pediatr* 2000;137(5):660–7. [PubMed: 11060532]
19. Fawzi WW, Mbise RL, Fataki MR, et al. Vitamin A supplementation and severity of pneumonia in children admitted to the hospital in Dar es Salaam, Tanzania. *Am J Clin Nutr* 1998;68(1):187–92. [PubMed: 9665113]
20. Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr* 1995;126(5 Pt 1):807–12. [PubMed: 7752011]
21. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. *Circulation* 1996;94(6):1310–5. [PubMed: 8822985]
22. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch Intern Med* 2000;160(20):3082–8. [PubMed: 11074737]
23. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122(1):51–65. [PubMed: 4014201]
24. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124(1):17–27. [PubMed: 3521261]
25. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol* 1989;18(4):858–67. [PubMed: 2621022]
26. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135(10):1114–26. [PubMed: 1632423]discussion 1127–36
27. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993;93(7):790–6. [PubMed: 8320406]
28. Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *Am J Epidemiol* 1988;127(2):283–96. [PubMed: 3257350]
29. Jacques PF, Sulsky SI, Sadowski JA, Phillips JC, Rush D, Willett WC. Comparison of micronutrient intake measured by a dietary questionnaire and biochemical indicators of micronutrient status. *Am J Clin Nutr* 1993;57(2):182–9. [PubMed: 8424386]
30. Pacht ER, Kaseki H, Mohammed JR, Cornwell DG, Davis WB. Deficiency of vitamin E in the alveolar fluid of cigarette smokers. Influence on alveolar macrophage cytotoxicity. *J Clin Invest* 1986;77(3):789–96. [PubMed: 3949977]
31. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc* 1963;58:690–700.
32. Hamer DH, Meydani SN. Immune function in the elderly. *Arch Intern Med* 2001;161(3):482–3. [PubMed: 11176778]
33. Meydani SN, Leka LS, Fine BC, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *Jama* 2004;292(7):828–36. [PubMed: 15315997]
34. Pike J, Chandra RK. Effect of vitamin and trace element supplementation on immune indices in healthy elderly. *Int J Vitam Nutr Res* 1995;65(2):117–21. [PubMed: 7591530]
35. Evans P, Halliwell B. Micronutrients: oxidant/antioxidant status. *Br J Nutr* 2001;85 (Suppl 2):S67–74. [PubMed: 11509092]
36. Meydani SN, Meydani M, Blumberg JB, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. *Jama* 1997;277(17):1380–6. [PubMed: 9134944]
37. Bendich, A.; Zilberboim, R. Drug/Nutrient interactions and immune function. In: Armente, V., editor. *Handbook of Drug-Nutrient Interactions*. 5. Totowa, NJ: Humana Press; 2003.
38. Ozlu T, Cay M, Akbulut A, Yekeler H, Naziroglu M, Aksakal M. The facilitating effect of cigarette smoke on the colonization of instilled bacteria into the tracheal lumen in rats and the improving

- influence of supplementary vitamin E on this process. *Respirology* 1999;4(3):245–8. [PubMed: 10489666]
39. Baughman RP, Stein E, MacGee J, Rashkin M, Sahebji H. Changes in fatty acids in phospholipids of the bronchoalveolar fluid in bacterial pneumonia and in adult respiratory distress syndrome. *Clin Chem* 1984;30(4):521–3. [PubMed: 6705194]
40. Calder PC, Davis J, Yaqoob P, Pala H, Thies F, Newsholme EA. Dietary fish oil suppresses human colon tumour growth in athymic mice. *Clin Sci (Lond)* 1998;94(3):303–11. [PubMed: 9616265]
41. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71(1 Suppl):343S–8S. [PubMed: 10617994]
42. Venuta A, Spano C, Laudizi L, Bettelli F, Beverelli A, Turchetto E. Essential fatty acids: the effects of dietary supplementation among children with recurrent respiratory infections. *J Int Med Res* 1996;24(4):325–30. [PubMed: 8854285]
43. Korppi M. Non-specific host response markers in the differentiation between pneumococcal and viral pneumonia: what is the most accurate combination? *Pediatr Int* 2004;46(5):545–50. [PubMed: 15491381]
44. Swingle GH. Radiologic differentiation between bacterial and viral lower respiratory infection in children: a systematic literature review. *Clin Pediatr (Phila)* 2000;39(11):627–33. [PubMed: 11110362]
45. Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. *Pediatr Radiol* 1988;18(6):453–4. [PubMed: 3186320]

Table 1

Age-adjusted characteristics of women in the top, middle and bottom quintiles of specific vitamin intake at baseline (1991)

	Median Intake ¹	Smoking Current Smokers	Alcohol Intake ²	Physical Activity ²	BMI ²
		%	g/d	MET/wk	kg/m ²
Thiamine (mg/day)					
Quintile 1	1.3	18.8	4.0	18.4	24.7
Quintile 3	1.8	8.7	2.7	20.8	24.3
Quintile 5	5.1	10.6	2.8	23.8	24.1
Riboflavin (mg/day)					
Quintile 1	1.4	17.6	3.6	17.7	24.5
Quintile 3	2.3	10.1	2.8	20.8	24.5
Quintile 5	6.0	10.6	2.8	23.8	24.2
Niacin (mg/day)					
Quintile 1	19.2	14.3	2.9	18.4	24.3
Quintile 3	27.8	11.4	3.3	20.3	24.6
Quintile 5	55.9	11.4	3.1	24.7	24.2
Pyridoxine (mg/day)					
Quintile 1	1.7	17.0	3.0	16.5	24.5
Quintile 3	2.5	9.9	3.2	22.0	24.4
Quintile 5	8.8	10.6	3.0	24.0	24.3
Vitamin B12 (mcg/day)					
Quintile 1	4.0	13.1	3.4	20.1	24.1
Quintile 3	7.0	11.8	3.1	19.9	24.7
Quintile 5	17.0	12.0	2.7	22.9	24.4
Vitamin A (IU/day)					
Quintile 1	5288	16.4	3.3	16.0	24.9
Quintile 3	11095	11.0	3.2	20.6	24.4
Quintile 5	21512	9.7	2.8	27.7	24.1
Vitamin C (mg/day)					
Quintile 1	75	16.4	3.2	15.7	24.9
Quintile 3	158	10.3	3.1	21.1	24.4
Quintile 5	525	11.3	3.3	26.0	23.9
Vitamin E (mg/day)					
Quintile 1	4.9	15.8	3.2	16.9	24.5
Quintile 3	8.1	11.3	3.3	21.6	24.7
Quintile 5	45.9	10.4	3.0	24.3	24.1
Total Carotenoids (IU/day)					
Quintile 1	3130	15.5	3.1	16.0	24.9
Quintile 3	7540	11.3	3.2	20.1	24.4
Quintile 5	16456	9.8	3.0	27.9	24.1
Alpha-carotene (mcg/day)					
Quintile 1	160	15.3	3.4	17.9	24.7
Quintile 3	577	12.0	3.2	19.8	24.4
Quintile 5	1544	9.3	2.8	26.1	24.2
Beta-carotene (mcg/day)					
Quintile 1	1554	15.2	2.9	15.6	24.8
Quintile 3	3578	11.0	3.2	20.1	24.3
Quintile 5	7432	10.6	3.1	28.4	24.1
Beta-cryptoxanthine (mcg/day)					
Quintile 1	6.4	16.5	3.5	18.0	24.6
Quintile 3	35.5	11.0	3.2	20.8	24.4
Quintile 5	103.9	9.6	2.6	24.9	24.2
Lycopene (mcg/day)					
Quintile 1	3305	12.9	2.8	19.1	24.8
Quintile 3	7227	12.0	3.1	20.6	24.3
Quintile 5	15917	11.8	3.4	23.8	24.4
Lutein and Zeaxanthin (mcg/day)					
Quintile 1	942	12.9	2.4	15.6	24.9
Quintile 3	2566	11.4	3.2	20.4	24.4
Quintile 5	5968	12.3	3.7	28.0	24.0
Folate (mcg/day)					
Quintile 1	224	17.8	3.1	15.9	25.0
Quintile 3	371	10.2	3.3	22.3	24.2
Quintile 5	866	9.0	2.6	24.0	24.2
Vitamin D (IU/day)					
Quintile 1	128	16.7	3.5	17.9	24.7
Quintile 3	316	10.6	3.1	21.4	24.4

	Median Intake¹	Smoking Current Smokers	Alcohol Intake²	Physical Activity²	BMI²
		%	g/d	MET/wk	kg/m²
Quintile 5	742	9.2	2.5	23.9	24.2

¹ Based in intake from food and supplements in 1991

² Values are means

Table 2
Relative risks (RR) for total vitamin intake and community-acquired pneumonia

	Quintile of intake from all sources					P-value, test for trend
	1	2	3	4	5	
Thiamine						
No. of cases (n)	181	174	212	192	166	
Age adjusted RR ¹	Ref	0.94(.76–1.16)	1.14(.94–1.40)	1.06(.86–1.30)	0.92(.75–1.14)	0.33
Multivariate adjusted RR ²	Ref	0.96(.78–1.20)	1.22(.99–1.50)	1.14(.92–1.41)	0.98(.79–1.22)	0.60
Riboflavin						
No. of cases (n)	176	188	213	170	178	
Age adjusted RR ¹	Ref	1.05(.85–1.29)	1.17(.96–1.43)	0.96(.77–1.18)	1.02(.83–1.25)	0.61
Multivariate adjusted RR ²	Ref	1.07(.86–1.32)	1.21(.98–1.49)	1.03(.83–1.29)	1.07(.86–1.33)	0.99
Pyridoxine						
No. of cases (n)	176	191	200	178	180	
Age adjusted RR ¹	Ref	1.08(.88–1.32)	1.13(.93–1.39)	1.02(.83–1.25)	1.05(.85–1.29)	0.93
Multivariate adjusted RR ²	Ref	1.10(.89–1.36)	1.17(.95–1.44)	1.08(.87–1.34)	1.11(.89–1.37)	0.72
Niacin						
No. of cases (n)	182	184	200	195	164	
Age adjusted RR ¹	Ref	1.01(.82–1.24)	1.09(.89–1.33)	1.07(.87–1.31)	0.93(.76–1.15)	0.50
Multivariate adjusted RR ²	Ref	0.98(.79–1.21)	1.05(.86–1.30)	1.08(.88–1.33)	0.94(.75–1.17)	0.69
Vitamin B12						
No. of cases (n)	198	179	198	191	159	
Age adjusted RR ¹	Ref	0.90(.73–1.10)	1.00(.82–1.21)	0.98(.80–1.19)	0.83(.67–1.02)	0.17
Multivariate adjusted RR ²	Ref	0.89(.72–1.10)	0.98(.80–1.20)	0.96(.78–1.18)	0.85(.69–1.06)	0.30
Vitamin A						
No. of cases (n)	201	191	197	184	152	
Age adjusted RR ¹	Ref	0.96(.79–1.17)	0.99(.81–1.12)	0.94(.77–1.15)	0.79(.64–.98)	0.02
Multivariate adjusted RR ²	Ref	1.01(.83–1.24)	1.08(.88–1.32)	1.02(.82–1.25)	0.88(.70–1.09)	0.16
Vitamin C						
No. of cases (n)	204	178	189	184	170	
Age adjusted RR ¹	Ref	0.87(.71–1.06)	0.92(.76–1.12)	0.93(.76–1.13)	0.88(.72–1.08)	0.56
Multivariate adjusted RR ²	Ref	0.90(.73–1.11)	1.00(.82–1.23)	1.02(.83–1.26)	0.94(.76–1.16)	0.81
Vitamin E						
No. of cases (n)	204	171	182	194	170	
Age adjusted RR ¹	Ref	0.85(.69–1.04)	0.89(.73–1.09)	0.96(.79–1.17)	0.88(.72–1.08)	0.51
Multivariate adjusted RR ²	Ref	0.87(.71–1.07)	0.95(.77–1.16)	1.01(.82–1.24)	0.95(.76–1.17)	0.74
Total Carotenoids						
No. of cases (n)	193	203	191	174	164	
Age adjusted RR ¹	Ref	1.04(.86–1.27)	1.00(.81–1.22)	0.92(.75–1.13)	0.88(.71–1.08)	0.06
Multivariate adjusted RR ²	Ref	1.08(.88–1.33)	1.06(.86–1.30)	1.00(.81–1.24)	0.97(.78–1.20)	0.34
Alpha-carotene						
No. of cases (n)	190	203	163	193	176	
Age adjusted RR ¹	Ref	1.17(.96–1.42)	0.97(.78–1.19)	1.07(.87–1.31)	0.99(.80–1.22)	0.51
Multivariate adjusted RR ²	Ref	1.23(1.00–1.51)	1.01(.81–1.25)	1.16(.94–1.43)	1.05(.85–1.31)	0.94
Beta-carotene						
No. of cases (n)	196	194	208	160	167	
Age adjusted RR ¹	Ref	1.02(.84–1.25)	1.01(.83–1.23)	0.92(.75–1.13)	0.90(.73–1.11)	0.13
Multivariate adjusted RR ²	Ref	1.08(.88–1.32)	1.07(.87–1.32)	1.01(.82–1.22)	0.98(.79–1.22)	0.45
Beta-cryptoxanthine						
No. of cases (n)	198	180	202	167	178	
Age adjusted RR ¹	Ref	0.99(.81–1.21)	1.00(.82–1.22)	0.85(.69–1.05)	0.94(.76–1.15)	0.36
Multivariate adjusted RR ²	Ref	1.04(.84–1.28)	1.03(.84–1.27)	0.91(.73–1.13)	1.03(.83–1.27)	0.99
Lycopene						
No. of cases (n)	178	198	174	180	195	
Age adjusted RR ¹	Ref	1.04(.84–1.27)	1.00(.82–1.24)	1.01(.82–1.24)	1.08(.88–1.33)	0.50
Multivariate adjusted RR ²	Ref	1.08(.88–1.34)	1.04(.84–1.29)	1.07(.86–1.32)	1.12(.91–1.39)	0.35
Lutein + Zeaxanthine						
No. of cases (n)	183	192	211	164	175	
Age adjusted RR ¹	Ref	1.04(.85–1.27)	1.14(.94–1.40)	0.95(.77–1.17)	1.04(.85–1.29)	0.98
Multivariate adjusted RR ²	Ref	1.08(.88–1.33)	1.22(.99–1.50)	1.04(.83–1.29)	1.17(.94–1.45)	0.31
Folate						
No. of cases (n)	182	193	176	189	181	
Age adjusted RR ¹	Ref	1.07(.88–1.32)	0.95(.77–1.17)	1.05(.85–1.28)	1.01(.82–1.24)	0.98
Multivariate adjusted RR ²	Ref	1.13(.92–1.40)	1.03(.83–1.28)	1.15(.93–1.42)	1.13(.91–1.40)	0.36

	Quintile of intake from all sources					
	1	2	3	4	5	P-value, test for trend
Vitamin D						
No. of cases (<i>n</i>)	197	177	187	182	182	
Age adjusted RR ¹	Ref	0.88(.72–1.08)	0.93(.76–1.13)	0.91(.74–1.10)	0.92(.76–1.13)	1.0
Multivariate adjusted RR ²	Ref	0.91(.74–1.12)	0.97(.79–1.20)	0.96(.78–1.18)	1.02(.83–1.26)	1.0

¹ RR denotes Relative Risk (95% confidence interval [CI])

² Multivariate model adjusted for age in months, smoking (never smokers, past smokers and current smokers who smoked 1–14, 15–24, or ≥ 25 cigarettes/d), BMI (<21, 21–22.9, 23–24.9, 25–29.9, and ≥ 30 kg/m²), alcohol use (never, 0.1–4.9, 5.0–14.9, 15.0–29.9, and ≥ 30 gm/d), and physical activity (quintiles of MET).

Dietary information for vitamin E and folate were missing for 4 participants from 1999 questionnaire preceding the development of pneumonia.

Table 3

Relative risks (RR) for dietary vitamin E intake and community-acquired pneumonia among current smokers (n=12,003)

	Quintile of Vitamin E Intake from diet only					P-value, test for trend
	1	2	3	4	5	
Age adjusted RR	Ref	0.68(.40–1.18)	0.58(.32–1.03)	0.64(.37–1.13)	0.44(.23–.84)	0.01
Multivariate adjusted RR ^a	Ref	0.62(.35–1.11)	0.57(.31–1.05)	0.72(.41–1.28)	0.46(.23–.90)	0.04

^aMultivariate model adjusted for age in months, BMI (<21, 21–22.9, 23–24.9, 25–29.9, and ≥ 30 kg/m²), alcohol use (never, 0.1–4.9, 5.0–14.9, 15.0–29.9, and ≥ 30 gm/d), and physical activity (quintiles of MET).

Table 4
Relative risks (RR) for multivitamin intake and community-acquired pneumonia

	Multivitamin intake (# of tablets) per week					P-value, test for trend
	0	1-2	3-5	6-9	10+	
Age adjusted RR	Ref	0.97(.76–1.25)	1.01(.83–1.23)	1.03(.88–1.21)	0.75(.45–1.23)	0.95
Multivariate adjusted RR ^a	Ref	0.97(.75–1.26)	0.99(.80–1.21)	1.05(.90–1.24)	0.75(.45–1.26)	0.84

^aMultivariate model adjusted for age in months, smoking (never smokers, past smokers and current smokers who smoked 1–14, 15–24, or ≥ 25 cigarettes/d), BMI (<21, 21–22.9, 23–24.9, 25–29.9, and ≥ 30 kg/m²), alcohol use (never, 0.1–4.9, 5.0–14.9, 15.0–29.9, and ≥ 30 gm/d), and physical activity (quintiles of MET).