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Serum zinc and pneumonia in nursing home elderly

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Abstract

Background—Zinc plays an important role in immune function. The association between serum zinc and pneumonia in the elderly has not been studied.

Objective—To determine if serum zinc concentrations in nursing home elderly are associated with incidence and duration of pneumonia, total and duration of antibiotic use, and pneumonia-associated and overall deaths.

Design—This observational study was conducted in residents from 33 nursing homes in Boston, MA, who participated in a one-year randomized, double-blind, and placebo controlled vitamin E supplementation trial; all were given daily doses of ½ RDA of essential vitamins and minerals including zinc. Participants with baseline (N=578) or final (N=420) serum zinc concentrations were categorized as having low (<70 μg/dL) or normal (≥70 μg/dL) serum zinc concentrations. Outcome measures included incidence and number of days with pneumonia, number of new antibiotic prescriptions, days of antibiotic use, death due to pneumonia, and, all-cause mortality.

Results—Subjects with normal final serum zinc concentrations had lower pneumonia incidence, total antibiotic use (by almost 50%), and shorter duration of pneumonia and antibiotic use (by 3.9 and 2.6 days, respectively) (all p-values ≤0.004) relative to those with low zinc concentrations. Normal baseline serum zinc concentrations were associated with decreased all-cause mortality (p=0.049).

Conclusion—Normal serum zinc concentrations in nursing home elderly were associated with decreased incidence and duration of pneumonia, and decreased use and duration of antimicrobial therapy. Zinc supplementation to maintain normal serum zinc concentrations in the elderly may help reduce pneumonia incidence and associated morbidity.

Keywords

serum zinc; nursing home elderly; pneumonia; mortality; antibiotic use

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INTRODUCTION

Pneumonia is a major public health problem in the elderly (1). An important predisposing factor to the increased incidence of infections such as pneumonia in the elderly is the age-associated decline in immune function (2). Such changes in immune response with age, in addition to malnutrition, contribute to the increased frequency and severity of pneumonia, as well as mortality due to pneumonia in the elderly (1-4).

Zinc has been shown to play an important role in regulation of the immune response particularly T cell-mediated function (5-7). Zinc deficiency has been shown to cause thymus involution and to depress lymphocyte proliferation, interleukin-2 (IL-2) production, delayed type hypersensitivity skin responses, and antibody response to T cell-dependent antigens (5,8). Similar defects in T cell function have been observed with aging (2). Several investigators have reported low zinc status or decreased intake in elderly subjects (9-11). Furthermore, low zinc status in the elderly has been shown to contribute to age-associated dysregulation of the immune response (3,12) and zinc supplementation has been shown to improve T cell mediated function in elderly (9,12-15) . In children, low concentrations of circulating zinc have been shown to be associated with an increased risk of respiratory morbidity (16), and zinc supplementation has been shown to reduce both the risk and duration of pneumonia and deaths due to pneumonia in children (17,18). The association between serum zinc and pneumonia in the elderly, however, has not been studied.

From April 1998 to August 2001, a randomized controlled trial was carried out in order to investigate the effect of vitamin E supplementation on respiratory infections in a nursing home elderly population (19). We found a high proportion (about 30%) of nursing home elderly with low serum zinc concentrations at baseline, and after a year of follow up despite all participants' receiving ½ RDA of essential vitamins and minerals, including zinc, during the trial. Because recently published studies in children (17,18) have shown zinc supplementation to be beneficial in reducing morbidity and mortality from pneumonia and past research has demonstrated the negative impact of zinc deficiency on immune function in the elderly, we examined the relationships between serum zinc concentration and the incidence and duration of pneumonia, total antibiotic use, and duration of antibiotic use and death due to pneumonia, as well as overall deaths in this population of elderly nursing home residents.

SUBJECTS AND METHODS

Study design and intervention

A total of 617 subjects was enrolled (approximately 1/3 enrolled in each of 3 successive years) into a randomized, double-blind, placebo-controlled trial of the effect of one-year vitamin E supplementation (200 IU/day) on respiratory infections in a nursing home population (19). The Tufts-New England Medical Center Institutional Review Board approved the study protocol and informed consent form.

Nursing home residents have a heterogeneous intake of micronutrients (20), some of which are necessary for proper immune function. To reduce variability in the vitamin E trial, all subjects received a daily capsule containing 50% of the Recommended Dietary Allowance (RDA) (21) for essential micronutrients, including zinc. Fifty percent RDA was selected since few subjects meeting our eligibility criteria would have dietary intakes <50% of the RDA for micronutrients (22).

At baseline as well as at follow-up, about 30% of subjects were found to be deficient in zinc. Other micronutrient deficiencies were much less prevalent at baseline (from 0 to 10%) and their prevalence did not significantly change at follow up (19).

Selection of study subjects

Detailed information on the screening and recruitment of participants has been described previously (19). The eligibility criteria included age ≥65 y, life expectancy >6 months, no anticipated discharge within 3 months, not room-bound for the past 3 months, body mass index (BMI) ≥16 kg/m^2, serum albumin ≥3.0 g/dL, ability to swallow pills, and willingness to receive influenza vaccine and provide informed consent. Exclusion criteria included active neoplastic disease, tube feeding, kidney dialysis, intravenous or urethral catheters for the last 30 days, tracheostomy or chronic ventilator use, chronic steroid treatment >10 mg/d, use of immunosuppressive drugs, use of antibiotics within the prior 2 weeks, and >RDA level supplements of vitamins E, C, B_6, selenium, zinc, β-carotene, or fish oil.

The current analyses include all enrolled subjects with baseline (N=578) or end of study zinc measurements (N=420, including 7 subjects with only end of study zinc values). For the purposes of this study, subjects were categorized by serum zinc concentrations using cutoffs of <70 μg/dL to indicate low serum zinc concentrations and ≥70 μg/dL to indicate normal serum zinc concentrations (23).

Outcomes

Pneumonia-related outcomes included incidence of and number of days with pneumonia, new antibiotic prescriptions for pneumonia, days of antibiotic use for treatment of pneumonia, and death due to pneumonia. We also examined all-cause mortality.

Data collection

Information regarding subject characteristics, baseline diseases and medications, and vaccination history was obtained from medical records. Fasting blood was collected at baseline and at study completion for clinical chemistries, complete blood count, and nutritional status as previously described (19). Serum samples were collected using trace metal-free tubes and serum zinc concentrations were measured using the Perkin Elmer flame atomic absorption spectrometer (24) at the Nutrition Evaluation Laboratory, Human Nutrition Research Center on Aging at Tufts University.

Study nurses were trained by a study physician to identify relevant respiratory symptoms and to perform a focused physical examination of the respiratory tract. Supervised practice evaluations were repeated throughout the study to reinforce the nurses' clinical skills and to ensure consistency of the pneumonia data collection. The study nurses collected information weekly relating to infection, including symptoms of respiratory infections, temperature, respiratory and heart rate, and a physical examination focused on the respiratory system. The nurses reviewed each participant's chart for documentation of laboratory analyses, radiography, medications, micronutrient supplementation, weight, and nursing or physician descriptions of symptoms and signs relating to pneumonia and other respiratory infections. At the end of the study, data collected from the subjects were randomly assigned, by nursing home, to the two study physicians for diagnosis of infections. Infection data from any one subject were evaluated by only one physician, except for 18 subjects whose records were used to determine the concurrence of diagnoses between physicians.

Diagnosis of pneumonia

Details on how the study physicians evaluated the data to determine incidence and duration of pneumonia have been described previously (19). Briefly, clinical definitions of pneumonia were developed based on accepted definitions (25). In order to increase the specificity of the definitions, a diagnosis of pneumonia had to include at least one physical sign and thus could not be made on symptoms alone. An episode was considered resolved when all symptoms ceased. A new infection was defined as one occurring after 7 symptom-free days. Pneumonia symptoms could include cough with or without sputum production, chest pain, dyspnea, and fever. Signs of infection included elevated temperature (≥38°C), tachycardia, tachypnea, abnormal breath sounds, and dullness to percussion of the chest. The diagnosis required radiological findings of 1 or more new pulmonary infiltrates.

Statistical analysis

The demographic and clinical characteristics of participants in the low and normal serum zinc groups were compared by using Student's t-test for independent samples (continuous measures) and Fisher's exact test (categorical measures).

As noted above, all subjects received a capsule containing 50% of the RDA for essential micronutrients, including zinc. Because of this supplementation, the baseline zinc concentrations might not reflect the usual zinc status during the entire study period. Therefore, we also used zinc concentrations measured at the final study visit as a marker of zinc status. However, analyses based on final zinc concentrations were necessarily limited to those who survived or completed the trial.

Rate ratios and their confidence intervals for incidence of pneumonia and number of antibiotic prescriptions per year were modeled using Poisson regression with the natural logarithm of time as an offset (26). None of the deviance statistics from the Poisson regressions exceeded 1, which suggests that there was no overdispersion. Multiple linear regression analyses were used to determine the association between serum zinc and duration of pneumonia and antibiotic use due to pneumonia. Cox-proportional hazards models using baseline zinc concentrations were fitted to determine the hazards ratio for deaths due to pneumonia or overall deaths using baseline zinc concentrations. Except for the proportional hazards analyses, these analyses were performed by using both baseline and final zinc concentrations as predictors. Although the original study did not show a significant difference in the rate of pneumonia between the vitamin E and placebo groups (19), we nevertheless controlled for allocation to treatment and placebo groups in these analyses. We also adjusted for year of enrollment, as well as age, sex, baseline BMI, current smoking, diabetes mellitus, and chronic obstructive pulmonary disease (including bronchial asthma), which have been shown to be associated with increased risk of pneumonia and/or pneumonia-associated death (1,27,28). Analyses done comparing those with low compared to normal final serum zinc concentrations were also controlled for change in BMI between baseline and follow-up values. Additionally, in separate analyses, we also controlled for baseline serum albumin and change in serum albumin concentrations between baseline and follow-up in these models. Two-sided observed significance concentrations (*p* values) <0.050 were considered to be statistically significant. All calculations were performed by using SAS for Windows, version 9.1.2 (SAS Institute Inc, Cary, NC, USA).

RESULTS

The demographic and clinical characteristics of participants with baseline zinc (N=578) and those with final study zinc concentrations (N=420) were similar (Table 1). These characteristics were also similar in distribution to those of our original overall study population (N=617) (19).

Of the characteristics listed in Table 1, only the difference in age between those with low and normal baseline serum zinc concentrations was statistically significant (mean ± SD were 86 ± 8 and 84 ± 7 years, respectively; $p<0.001$). Elderly with low final serum zinc concentrations were older at baseline (86 ± 8 versus 84 ± 7 years; $p=0.014$), and were more likely to have had coronary artery disease (39% versus 28%; $p=0.042$) at baseline compared to those with normal final zinc concentrations. All subjects received influenza vaccine and there was no difference between the two groups in the proportion of subjects who had pneumococcal immunization.

When participants with low and normal baseline zinc concentrations were compared, differences in the incidence and duration of pneumonia, and total amount and duration of antibiotic use due to pneumonia (Table 2) were not statistically significant. Deaths due to pneumonia were 53% lower in those with normal compared to low baseline serum concentrations of zinc, but this association was not statistically significant ($p=0.198$). All-cause mortality rate was 39% lower in those with normal versus lower baseline zinc concentrations ($p=0.049$) (Table 2).

End of study serum zinc concentrations were strongly associated with the incidence and duration of pneumonia as well as antibiotic use and duration of antimicrobial therapy (Table 3; $p\leq0.004$ in all cases). The incidence of pneumonia and the total number of antibiotics used for treatment of pneumonia were about 50% lower in those with end serum zinc concentrations ≥70 μg/dL compared to those with concentrations <70 μg/dL. In addition, the duration of pneumonia was lower by 3.9 days and the duration of antibiotic use by 2.6 days in those with end serum zinc in the normal range compared to those with low concentrations (Table 3). Controlling for coronary artery disease in our multiple regression analyses model did not change the statistical significance of the differences observed. In addition, differences remained statistically significant after controlling for baseline serum albumin and change in serum albumin concentrations between baseline and follow-up. The 310 subjects with normal end zinc concentrations at completion suffered 78 cases of pneumonia while the 110 with low end zinc concentrations suffered 51. The fraction of pneumonias occurring in the final 2 months of the study was similar in those subjects with normal (14 cases out of 78) and low (8 cases out of 51) end serum zinc concentrations, i.e., 18% vs 16%, respectively.

Our findings were specific to zinc. We did not observe similar associations in our outcome variables of interest with other micronutrients that might influence immune function such as vitamins A, B6, D, E, β-carotene, and iron (data not shown). In addition, the mean changes in weight and BMI from baseline to follow-up between subjects with low and normal zinc concentrations were not significantly different; mean weight changes were −0.80 and −0.01 kg, respectively, and BMI, −0.35 and −0.01 kg/m^2, respectively.

DISCUSSION

We observed that elderly nursing home residents with low serum zinc concentrations at the end of one year of 50% RDA micronutrient daily supplementation, including zinc, had a higher risk of pneumonia and longer duration of pneumonia episodes as well as increased antibiotic use and longer duration of antibiotic use for treatment of pneumonia episodes. In addition, low baseline concentrations of serum zinc in our elderly nursing home population were associated with increased all-cause mortality.

Our finding of a significantly lower all-cause mortality rate (by 39%) between those with normal versus low baseline serum zinc concentrations among elderly in this study suggest that zinc may play a crucial role in influencing mortality in the elderly. Severe zinc deficiency can impair immunity and increase susceptibility to infectious diseases, a major cause of mortality in the elderly (1,3,29,30). Indeed, the risk of mortality was reduced by 27% in participants of

the Age-related Eye-Disease Study (aged 55 to 81 years) who received zinc supplements (RR: 0.73; 95% CI, 0.61−0.89) (31). In addition, zinc supplementation has been shown to reduce overall mortality by as much as 51% in children with diarrhea and 68% in infants born full-term and small for gestational age (32,33).

When baseline serum zinc status was used as a measure of zinc to determine if low serum zinc affects susceptibility to pneumonia, differences failed to reach statistical significance. It may be that findings using baseline zinc concentrations were attenuated due to the higher risk of death among subjects with low baseline zinc concentrations or due to loss of subjects from serious illnesses and/or hospitalizations. In addition, because all study participants were provided with ½ RDA supplement that included zinc, the baseline concentrations may not reflect zinc status during much of the study period.

Because of the potential bias introduced by zinc supplementation, we performed similar analyses using final zinc concentrations, as this measure may better reflect the zinc status of subjects during the course of the study. We observe a strong association between low final zinc concentrations with increased incidence and duration of pneumonia, as well as total and duration of antibiotic use for pneumonia treatment. As described in the results, the effects observed were specific to zinc and were not observed with other micronutrients. Furthermore, the lower incidence and morbidity of pneumonia observed in subjects with normal final zinc concentrations compared to those with low final zinc concentrations were not due to differences between the two groups in changes in weight, BMI, or other micronutrients (19) during the study period.

Zinc deficiency has been suggested to be a risk factor for immune deficiency and subsequent infection relapses in the elderly (12,29,34). Zinc is essential for membrane integrity, DNA synthesis and cell proliferation, in addition to being a cofactor to more than 300 enzymes (5, 35).

It is essential for all highly proliferating cells in the human body, especially the immune system (36). Thymus atrophy and lymphopenia, as well as other defects in T cell function have been observed in both zinc deficiency and in the elderly (2,5,8).

Low zinc consumption has been reported in the elderly (10,37). Bogden et al. reported that zinc ingestion was below the RDA in more than 90% of their 100 study subjects aged 60−89 years (37). In addition, as mentioned above, we found below normal serum zinc concentrations in approximately 30% of the nursing home elderly enrolled in our vitamin E supplementation study. This level of deficiency persisted during the study period despite giving the participants supplements with ½ RDA of zinc (19). Thus, our finding of a significant association between low serum zinc level and pneumonia could be of major importance to the health of elderly, as poor zinc status would lead to impaired immune response, which could in turn result in increased susceptibility to infections in the elderly (9,29,34). Supplementing with ½ RDA of zinc appeared to benefit many of the subjects with inadequate baseline zinc concentrations, but the results also showed that this supplementation was not adequate to maintain serum zinc concentrations in a significant proportion of subjects.

Plasma or serum zinc concentrations are also known to decrease sharply in many infections (35,38,39). The decline is part of a set of metabolic reactions to infection known as the acute phase response (40). Although one could argue that lower serum zinc concentrations might be due to a higher incidence of pneumonia, this is unlikely to be the case here as the acute effect of pneumonia on zinc is likely to be transient--approximately 2 weeks if effective therapy is provided (41). Given the similar incidence of pneumonia in our participants in the last months of the study, transient suppression of serum zinc by the acute phase response is unlikely to be responsible for the low end study zinc concentrations.

Zinc supplementation may play an important role in the prevention and/or modulation of infectious diseases in the elderly (3,9,14,29). Various studies on zinc supplementation in the elderly have observed increased circulating zinc concentrations (13,14), as well as enhanced immune status including improved cell-mediated immune response, serum thymulin activity, and IL-2 production, and increased response to skin-test antigens (12,15,42). Also, when cultures of white blood cells from elderly subjects were supplemented with 15 μM zinc (the physiologic concentration), they produced interferon-alpha in amounts comparable to those from the younger subjects (43). In a randomized, double-blind, placebo-controlled clinical trial (N=81), institutionalized elderly had a significant decrease in the mean number of respiratory infections 2 years following supplementation with micronutrients containing zinc and selenium, but not vitamins (44). In another, larger (N=725), randomized, double-blind, placebo-controlled intervention study, low-dose supplementation of zinc and selenium significantly increased the humoral response in institutionalized elderly after vaccination (45). The number without respiratory tract infections during the study was also found to be higher in elderly that received trace elements over a 2-year period (45). While these studies suggest a protective effect of zinc against respiratory infections, contribution from other nutrients present in the mixture cannot be ruled out.

The results from our current study, in addition to these earlier findings, suggest that elderly with low serum zinc concentrations might benefit from zinc supplementation. Such a measure has the potential to reduce not only the number of episodes and duration of pneumonia and the total and duration of antibiotic use due to pneumonia, but also overall deaths in the elderly. Randomized, double blind, controlled studies are needed to determine the efficacy of zinc supplementation as a potential low cost intervention to reduce morbidity and mortality due to pneumonia in this vulnerable population.

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References

1. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. Public Health Reports 1989;104:350–60. [PubMed: 2502806]
2. Miller RA. The cell biology of aging: immunological models. Journal of Gerontology 1989;44:B4–8. [PubMed: 2642937]
3. Mocchegiani E, Giacconi R, Muzzioli M, Cipriano C. Zinc, infections and immunosenescence. Mechanisms of Ageing & Development 2000;121:21–35. [PubMed: 11164457][erratum appears in Mech Ageing Dev 2001 Mar;122(3):353].
4. Riquelme R, Torres A, el-Ebiary M, et al. Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. American Journal of Respiratory & Critical Care Medicine 1997;156:1908–14. [PubMed: 9412574]

5. Fraker PJ, King LE, Laakko T, et al. The dynamic link between the integrity of the immune system and zinc status. Journal of Nutrition 2000;130:1399S–406S. [PubMed: 10801951]

6. Allen JI, Perri RT, McClain CJ, Kay NE. Alterations in human natural killer cell activity and monocyte cytotoxicity induced by zinc deficiency. Journal of Laboratory & Clinical Medicine 1983;102:577–89. [PubMed: 6604771]

7. Oleske JM, Westphal ML, Shore S, et al. Zinc therapy of depressed cellular immunity in acrodermatitis enteropathica. Its correction. American Journal of Diseases of Children 1979;133:915–8. [PubMed: 112858]

8. Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. American Journal of Physiology 1997;272:E1002–7. [PubMed: 9227444]

9. Prasad AS, Fitzgerald JT, Hess JW, Kaplan J, Pelen F, Dardenne M. Zinc deficiency in elderly patients. Nutrition 1993;9:218–24. [PubMed: 8353362]

10. Sandstead HH, Henriksen LK, Greger JL, et al. Zinc nutriture in the elderly in relation to taste acuity, immune response, and wound healing. American Journal of Clinical Nutrition 1982;36:1046–59. [PubMed: 6765070]

11. Lindeman RD, Clark ML, Colmore JP, Lindeman RD, Clark ML, Colmore JP. Influence of age and sex on plasma and red-cell zinc concentrations. Journal of Gerontology 1971;26:358–63. [PubMed: 5124516]

12. Wagner PA, Jernigan JA, Bailey LB, Nickens C, Brazzi GA. Zinc nutriture and cell-mediated immunity in the aged. International Journal for Vitamin & Nutrition Research 1983;53:94–101. [PubMed: 6853062]

13. Bogden JD, Oleske JM, Lavenhar MA, et al. Effects of one year of supplementation with zinc and other micronutrients on cellular immunity in the elderly. Journal of the American College of Nutrition 1990;9:214–25. [PubMed: 2358617]

14. Kajanachumpol S, Srisurapanon S, Supanit I, et al. Effect of zinc supplementation on zinc status, copper status and cellular immunity in elderly patients with diabetes mellitus. Journal of the Medical Association of Thailand 1995;78:344–9. [PubMed: 7658178]

15. Duchateau J, Delepesse G, Vrijens R, Collet H. Beneficial effects of oral zinc supplementation on the immune response of old people. American Journal of Medicine 1981;70:1001–4. [PubMed: 6972165]

16. Bahl R, Bhandari N, Hambidge KM, Bhan MK. Plasma zinc as a predictor of diarrheal and respiratory morbidity in children in an urban slum setting. American Journal of Clinical Nutrition 1998;68:414S–417S. [PubMed: 9701154]

17. Brooks WA, Santosham M, Naheed A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet 2005;366:999–1004. [PubMed: 16168782]

18. Brooks WA, Yunus M, Santosham M, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004;363:1683–8. [PubMed: 15158629]

19. 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;292:828–36. [PubMed: 15315997] [erratum appears in JAMA. 2004 Sep 15;292(11):1305].

20. Drinka PJ, Goodwin JS, Drinka PJ, Goodwin JS. Prevalence and consequences of vitamin deficiency in the nursing home: a critical review. Journal of the American Geriatrics Society 1991;39:1008–17. [PubMed: 1918773]

21. National Research Council (U.S.). Recommended dietary allowances. 10th ed.. National Academy Press; Washington, D.C.: 1989. Subcommittee on the Tenth Edition of the RDAs., National Institutes of Health (U.S.), National Research Council (U.S.). Committee on Dietary Allowances..

22. Fiatarone M, Fiatarone M. Nutrition in the geriatric patient. Hospital Practice (Office Edition) 1990;25:38–40.

23. Institute of Medicine (U.S.). Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc : a report of the Panel on Micronutrients ... and the Standing Committee on the Scientific Evaluation of

Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. National Academy Press; Washington, D.C.: 2002. Panel on Micronutrients..

24. Smith JC Jr. Butrimovitz GP, Purdy WC. Direct measurement of zinc in plasma by atomic absorption spectroscopy. Clinical Chemistry 1979;25:1487–91. [PubMed: 455691]
25. McGeer A, Campbell B, Emori TG, et al. Definitions of infection for surveillance in long-term care facilities. American Journal of Infection Control 1991;19:1–7. [PubMed: 1902352]
26. Ramsey, FL.; Schafer, DW. The statistical sleuth : a course in methods of data analysis. 2nd ed.. Duxbury/Thomson Learning; Australia ; Pacific Grove, CA: 2002.
27. Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clinical Infectious Diseases 2003;37:1405–33. [PubMed: 14614663][see comment].
28. Koivula I, Sten M, Makela PH. Risk factors for pneumonia in the elderly. American Journal of Medicine 1994;96:313–20. [PubMed: 8166149]
29. Mocchegiani E, Muzzioli M, Gaetti R, et al. Contribution of zinc to reduce CD4+ risk factor for 'severe' infection relapse in aging: parallelism with HIV. International Journal of Immunopharmacology 1999;21:271–81. [PubMed: 10408635]
30. Janssens J-P, Krause K-H. Pneumonia in the very old. The Lancet Infectious Diseases 2004;4:112–24. [PubMed: 14871636]
31. Clemons TE, Kurinij N, Sperduto RD, Group AR. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. Archives of Ophthalmology 2004;122:716–26. [PubMed: 15136320]
32. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002;325:1059. [PubMed: 12424162][see comment].
33. Sazawal S, Black RE, Menon VP, et al. Zinc supplementation in infants born small for gestational age reduces mortality: a prospective, randomized, controlled trial. Pediatrics 2001;108:1280–6. [PubMed: 11731649][see comment].
34. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. American Journal of Clinical Nutrition 1998;68:447S–463S. [PubMed: 9701160]
35. Rink L, Kirchner H, Rink L, Kirchner H. Zinc-altered immune function and cytokine production. Journal of Nutrition 2000;130:1407S–11S. [PubMed: 10801952]
36. Ibs KH, Rink L, Ibs K-H, Rink L. Zinc-altered immune function. Journal of Nutrition 2003;133:1452S–6S. [PubMed: 12730441]
37. Bogden JD, Oleske JM, Munves EM, et al. Zinc and immunocompetence in the elderly: baseline data on zinc nutriture and immunity in unsupplemented subjects. American Journal of Clinical Nutrition 1987;46:101–9. [PubMed: 3604960]
38. Brown KH. Effect of infections on plasma zinc concentration and implications for zinc status assessment in low-income countries. American Journal of Clinical Nutrition 1998;68:425S–429S. [PubMed: 9701156]
39. Duggan C, MacLeod WB, Krebs NF, et al. Plasma zinc concentrations are depressed during the acute phase response in children with falciparum malaria. Journal of Nutrition 2005;135:802–7. [PubMed: 15795438]
40. Kushner I, Kushner I. The phenomenon of the acute phase response. Annals of the New York Academy of Sciences 1982;389:39–48. [PubMed: 7046585]
41. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998;279:1452–7. [PubMed: 9600479]
42. Fortes C, Forastiere F, Agabiti N, et al. The effect of zinc and vitamin A supplementation on immune response in an older population. Journal of the American Geriatrics Society 1998;46:19–26. [PubMed: 9434661]
43. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. Journal of Interferon & Cytokine Research 1997;17:469–72. [PubMed: 9282827]

44. Girodon F, Lombard M, Galan P, et al. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. Annals of Nutrition & Metabolism 1997;41:98–107. [PubMed: 9267584]

45. Girodon F, Galan P, Monget AL, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. Archives of Internal Medicine 1999;159:748–54. [PubMed: 10218756]

Table 1

Characteristics of study subjects

Baseline characteristics	Participants with baseline serum zinc concentration (N=578)[χ]	Participants with final serum zinc concentration (N=420)[δ]	Participants with normal final serum zinc concentration (≥70ug/dL) (N=310)[ϕ]	Participants with low final serum zinc concentration (<70ug/dL) (N=110)[γ]
Age (y), mean (SD)	84.6 (7.6)	84.6 (7.5)	84.1 (7.1)	86.1 (7.7)
Females, n (%)	419 (72)	314 (75)	227 (73)	87 (79)
Caucasians, n (%)	544 (94)	398 (95)	291 (94)	107 (97)
Body mass index (kg/m^2), mean (SD)	25.8 (5.2)	26.0 (5.2)	26.0 (4.9)	26.0 (5.9)
Current smoker, n (%)	43 (8)	30 (7)	24 (8)	6 (6)
Vitamin E supplementation, n (%)	290 (50)	217 (52)	141 (45)	62 (56)
Serum albumin (g/dL), mean (SD)	3.76 (0.34)	3.77 (0.34)	3.80 (0.33)	3.69 (0.33)
Total cholesterol (mg/dL), mean (SD)	197 (46)	197 (45)	197 (46)	199 (43)
White Blood Count (cells/μL), mean (SD)	7.10 (2.30)	6.96 (1.78)	7.01 (1.81)	6.82 (1.69)
Total lymphocyte count (cells/μL), mean (SD)	2.12 (1.41)	2.10 (0.75)	2.15 (0.78)	1.98 (0.66)
Lymphocyte (%), mean (SD)	30.1 (9.3)	30.7 (9.0)	31.1 (9.1)	29.7 (8.8)
Pneumococcal vaccination, n (%)	53 (9)	46 (11)	33 (11)	13 (12)
Non-steroidal anti-inflammatory drug (NSAID) use, n (%)	212 (37)	158 (38)	120 (39)	38 (35)
Baseline medical conditions				
OLD, n (%)[†]	146 (25)	98 (23)	71 (23)	27 (25)
Coronary artery disease, n (%)	194 (34)	131 (31)	88 (28)	43 (39)
Congestive heart failure, n (%)	120 (21)	79 (19)	52 (17)	27 (25)
Hypertension, n (%)	297 (51)	222 (53)	162 (52)	60 (55)
Diabetes mellitus, n (%)	117 (20)	87 (21)	68(22)	19 (17)
Malignancy, n (%)	53 (9)	44 (10)	34 (11)	10 (9)
Dementia, n (%)[‡]	286 (49)	207 (49)	149 (48)	58 (53)

Comparison between those with low versus normal final serum zinc concentrations were conducted using Student's t-test for independent samples (continuous measures) and Fisher's exact test (categorical measures); p=0.014, and 0.042 between these groups for age, and coronary artery disease, respectively; all other variables were not found to be significant.

[†] obstructive lung disease (includes asthma, chronic obstructive pulmonary disease, and chronic bronchitis)

[‡] includes Alzheimer's disease

[χ]: N=563−578;

[δ]: N=412−420;

[ϕ]: N=305−310;

[γ]: N=105−110

Table 2

Pneumonia, antibiotic use and death by baseline serum zinc concentration

	Baseline Serum Zinc Groups *		Rate Ratio or Mean Difference (95% CI)†	*p*
	≥70ug/dl (N=379)	<70ug/dl (N=174)		
Incidence of pneumonia (no. per person-yr)	0.34	0.37	0.87 (0.63, 1.21)	0.414
Duration of pneumonia (days per person-yr)	4.32	5.65	−1.5 (−3.4, 0.4)	0.126
Antibiotic prescriptions for pneumonia (no. per person-yr)	0.34	0.36	0.90 (0.65, 1.25)	0.539
Duration of antibiotic use for pneumonia (days per person-yr)	3.07	3.58	−0.7 (−2.0, 0.7)	0.330
Deaths due to pneumonia (no. per person-yr)	0.02	0.04	0.47 (0.15, 1.49)	0.198
Overall deaths (no. per person-yr)	0.12	0.19	0.61 (0.37, 1.00)	0.049

*: Crude values

†: Poisson regression analyses were used for incidence of pneumonia and number of antibiotic prescriptions, least squares regression analyses for duration of pneumonia and of antibiotic use, and Cox proportional hazard regression for deaths. All analyses controlled for treatment (supplemented with vitamin E or not), age, sex, chronic obstructive lung disease, current smoking, diabetes mellitus, year of enrollment (1998−2000) and baseline BMI; additionally controlling for coronary artery disease, and, in separate models, baseline serum albumin concentrations, did not affect the observed associations. *p* values derived from Poisson, least squares and Cox proportional hazard regression analyses.

Table 3

Pneumonia and antibiotic use by final serum zinc concentration

	Final Serum Zinc Groups*		Rate Ratio or Mean Difference (95% CI) †	
	≥70ug/dl (N=310)	<70ug/dl (N=110)		*p*
Incidence of pneumonia (no. per person-yr)	0.25	0.46	0.52 (0.36, 0.76)	<0.001
Duration of pneumonia (days per person-yr)	3.19	6.82	−3.9 (−6.2, −1.6)	<0.001
Antibiotic prescriptions for pneumonia (no. per person-yr)	0.26	0.48	0.52 (0.36, 0.75)	<0.001
Duration of antibiotic use for pneumonia (days per person-yr)	2.50	4.85	−2.6 (−4.4, −0.9)	0.004

*: Crude values

†: Poisson regression analyses were used for incidence of pneumonia and number of antibiotic prescriptions and least squares regression analyses for duration of pneumonia and of antibiotic use. All analyses controlled for treatment (supplemented with vitamin E or not), age, sex, chronic obstructive lung disease, current smoking, diabetes mellitus, year of enrollment (1998−2000) and baseline and change in BMI between baseline and follow-up; additionally controlling for coronary artery disease, and, in separate models, baseline serum albumin and change in serum albumin concentrations between baseline and follow-up, did not affect the observed associations. *p* values derived from Poisson and least squares regression analyses.