PRISM

Promoting Research into Supplementation with Micronutrients

2/2009

In this issue

DHA – the new essential fatty acid?

Editorial

The impact of n-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), on health has been ignored until the end of the 20th century. In the 9th edition of the Recommended Dietary Allowances (RDA) 1980, long-chain polyunsaturated fatty acids derived from α-linolenic acid (ALA) are mentioned to have specific functions not met by linoleic acid (LA)

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and its metabolites. Nine years later, in the 10th edition 1989, the nutritional value of n-3 PUFAs has been acknowledged, especially the contribution of DHA to the structure of retina- and brain membranes.

ALA is obviously not an adequate source for the functional n-3 long chain PUFAs EPA and DHA; only about 1 % of ALA is converted to DHA in infants and considerably less in adults (International Society for the Study of Fatty Acids and Lipids (ISSFAL) 5th statement 2009; http://www.issfal.org.uk/). Metabolic studies clearly show health benefits of EPA and DHA that are not obtained with ALA. The Food and Nutrition Board in the latest evaluation of dietary requirements acknowledged the contribution of EPA/DHA towards the risk reduction for cardiovascular diseases and cancer, but suggested merely a ratio LA/ALA of 5:1 to allow an optimum conversion of ALA to EPA/DHA (Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). 2002. National Academy of Sciences Washington, D.C. http://www.nap.edu/catalog/10490.html).

Supportive data for the favorable impact of EPA/DHA on cardiovascular events and the safety and tolerability profile of these compounds led to the realization of a large randomized, double-blind, placebo-controlled multi center trial involving 7046 patients with clinical evidence of heart failure. They were randomly assigned to receive 1 g of n-3 PUFA (850-882 mg EPA+DHA) daily for 3-9 years besides standard treatment. 27% of the patients in the PUFA group died from any cause, and 29 % in the placebo group (p=0.124). Admission to the hospital for cardiovascular reasons occurred in 57% of the patients of the PUFA group and in 59 % in the placebo group (p=0.059), whereby the Kaplan-Maier curves started to diverge after 2 years. There was a significant reduction of the number of patients in the PUFA group who died of a cardiovascular cause, and who were admitted for cardiovascular reasons (Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. GISSI-HF Investigators, Lancet 2008; 372: 1223-30).

Such convincing results, together with data from other studies as well as from animal and cellular models, encouraged authorities to revise the recommended intake values for polyunsaturated fatty acids. The European Food Safety Authority (EFSA) adopted the labeling reference intake value for EPA+DHA on June 30, 2009 to 250 mg/day (http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/nda_op_ej1176_labelling_reference_intake_values_PUFA_en.pdf?ssbinary=true). This is still less than the 500 mg EPA+DHA per day recommended by ISSFAL for cardiovascular health in 2004. In a recent state of the art paper CJ Lavie et al came to a similar conclusion as ISSFAL: 'The target EPA + DHA consumption should be at least 500 mg/day for individuals without underlying overt cardiovascular disease and at least 800 to 1,000 mg/day for individuals with known coronary heart disease and heart failure' (CJ Lavie et al. Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Diseases. Am Coll Cardiol, 2009; 54:585-594).

Thus, taking into account the accumulating science regarding DHA throughout the last 30 years, DHA should be considered as 3rd essential fatty acid besides ALA and LA in order to establish a RDA similar to the ones for vitamins.

U. Moser, Editor

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n-3 PUFAs reduce risk of atrial fibrillation

Observation

The relationship between omega-3 fatty acids (n-3 PUFA) and atrial fibrillation (AF) occurrence has been assessed in post-myocardial infarction (MI) patients since current strategies for avoiding AF are of limited value. A population study, linking hospital discharge records, prescription databases, and vital statistics, was conducted and included all consecutive patients with MI (ICD-9: 410) in six Italian local health authorities over a 3-year period. One prescription of n-3 PUFAs qualified patients as exposed to these agents. A propensity score (PS)-based, 5-to-1, greedy 1:1 matching algorithm was used to check consistency of results. Sensitivity analysis was performed to assess the robustness of findings. 3242 patients were included in the analysis. N-3 PUFA reduced the relative risk of the hospitalization for AF [hazard ratio (HR) 0.19, 95% CI 0.07-0.51] and was associated with a further and complementary reduction in all-cause mortality (HR 0.15, 95% CI 0.05-0.46). PS-based matched analysis and sensitivity analysis confirmed the main results.

Conclusion

n-3 PUFA reduced both all-cause mortality and incidence of 1-year AF in patients hospitalized with MI. Although the number of patients exposed to n-3 PUFAs was very low and participants differed in demographic an clinical characteristics from their unexposed counterparts, the conclusions from the analysis are strengthened by a sensitivity analysis showing that an unmeasured confounder should have a hypothetical hazard ratio of at least 3.0.

Editor's comment

Although not mentioned by the authors, the dosage of n-3PUFAs taken by the patients could be in the order of 1 g per day as can be concluded from the available supplements in Italy.

Source

Omega-3 fatty acid supplementation reduces one-year risk of atrial fibrillation in patients hospitalized with myocardial infarction. Macchia A, Monte S, Pellegrini F, Romero M, Ferrante D, Doval H, D'Ettorre A, Maggioni AP, Tognoni G. Eur J Clin Pharmacol. 2008; 64: 627-34.

n-3 PUFAs improve heart rate variability and heart rate responses

Intervention

Dietary fish oil supplementation and regular physical activity can improve outcomes in patients with established CVD. Exercise has been shown to improve heart rate variability (HRV), a predictor of cardiac death, but whether fish oil benefits HRV is controversial. Obese adults at risk of future coronary disease have impaired HRV and may benefit from these interventions. The outcome of DHA-rich tuna fish oil supplementation with and without regular exercise on HRV in sedentary, overweight adults with risk factors for coronary disease has been evaluated in a randomized, double-blind, parallel comparison. Sixty-five volunteers consumed 6 g fish oil/d (DHA 1.56 g/d, EPA 0.36 g/d) or sunflower-seed oil (placebo) for 12 weeks. Half of each oil group also undertook regular moderate physical activity (3 d/week for 45 min, at 75 % of age-predicted maximal heart rate (HR)). Resting HR and the HR response to sub maximal exercise were measured at weeks 0, 6 and 12. In forty-six subjects, HRV was also assessed by power spectrum analysis of 20 min electrocardiogram recordings

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taken supine at baseline and 12 weeks. Fish oil supplementation improved HRV by increasing high-frequency power, representing parasympathetic activity, compared with placebo (P = 0.01; oil x time interaction). It also reduced HR at rest and during sub maximal exercise (P = 0.008; oil x time interaction). There were no significant fish oil x exercise interactions. Dietary supplementation with DHA-rich fish oil reduced HR and modulated HRV in keeping with an improved parasympathetic-sympathetic balance in overweight adults with risk factors for future coronary disease.

Conclusion

Fish oil supplementation delivering 1.56 g DHA/d and 0.36 g EPA/d increased parasympathetic measures of HRV and lowered the HR response to exercise in subjects with risk factors for coronary artery disease. This provides further evidence that all those at risk of CVD benefit from fish oil supplements, not only patients with established coronary disease.

Source

Docosahexaenoic acid-rich fish oil improves heart rate variability and heart rate responses to exercise in overweight adults. Ninio DM, Hill AM, Howe PR, Buckley JD, Saint DA. Br J Nutr. 2008; 100: 1097-103.

n-3 PUFAs and cardiovascular diseases: the science behind

Review

Fats in fish and marine animals are rich in highly unsaturated fatty acids (FA with 5 or more double bonds) of the Omega 3 series. These FA, present in aquatic animals as an adaptation to the environmental conditions, reached the human diet through the food chain, with a significant impact on nutrition, life style and cultural conditions. Studies in the 70's showed that high fish consumption is associated with better cardiovascular health and this observation was subsequently confirmed in many studies (epidemiological, cohort, case-control). The evidence is stronger for secondary prevention and when the intakes of fish or omega 3 FA are assessed, rather than just estimated. The major effects are reduction of cardiac, especially sudden, death. Underlying mechanisms concern the antiarrhythmic activities, reduction of thrombotic and inflammatory processes and of serum triacylglycerol levels. Therefore, the consumption of fish and its components should be promoted on a global scale especially in the case of subjects with cardiovascular problems. Although still some issues need to be faced especially in large scale interventions (i.e. the assessment of the omega 3 fatty acid status, correlations between levels and cardiovascular indexes and bioavailability of different forms of administration), these recommendations are highly valuable.

Conclusion

The intake of n-3PUFAs of about 1 g/d (e.g. fatty fish twice a week) protects the cardiovascular system at several sites.

Source

Fish consumption, omega 3 fatty acids and cardiovascular disease. The science and the clinical trials. Galli C, Risé P. Nutr Health. 2009; 20: 11-20.

N-3 PUFAS IMPROVE BRAIN HEALTH

Docosahexaenoic acid alleviates depressive symptoms

Intervention

The antidepressant efficacy and dose-response pattern of docosahexaenoic acid (DHA) has been examined in thirty-five depressed adult outpatients (46% women; mean age 42+/-14 years) with a 17-item Hamilton-Depression

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Scale (HAM-D-17) score of >or=18. They were randomized into one of three double-blind dosing arms for 12 weeks. Group A (n=14): 1 g/day of oral DHA; Group B (n=11): 2 g/day; and Group C (n=10): 4 g/day. HAM-D-17 scores, plasma DHA, eicosapentaenoic acid (EPA), and n-6/n-3 ratio were measured. Completer response rates (≥ 50% decrease in HAM-D-17 score) were 83% for Group A (n=5/6), 40% for Group B (n=2/5), and 0% for Group C (n=0/3); Groups A and B had significant decreases in HAM-D-17 scores: from 21.50±2.88 to 6.00±6.07 (p=0.028) in group A; from 21.80±2.78 to 12.60±7.64 (p=0.043) in group B and from 20.67±2.52 to 14.00±3.61 (p=0.109) in group C. For completers and intent-to-treat subjects, plasma DHA increased significantly (p<0.05), EPA had little change (p>0.05), and n-6/n-3 decreased significantly (p<0.05).

Conclusion

DHA at a dose of ≤ 1 g/d may be a potential therapeutic agent for Major Depressive Disorder. However, the results must be interpreted with caution, in view of the small, uncontrolled sample and the limited statistical power.

Source

A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu SL, Papakostas GI, Dording CM, Sonawalla SB, Nierenberg AA, Alpert JE, Fava M. Eur Neuropsychopharmacol. 2008; 18: 639-45.

n-3 PUFAs alleviate depressive symptoms in Parkinson's disease

Intervention

The effect of fish oil supplementation in parkinsonian patients with depression measured by Montgomery-Asberg Rating Scale (MADRS), the Clinical Global Impressions Scale (CGI) and Beck Depression Inventory (BDI) has been evaluated in a double-blind, placebo-controlled study in 31 patients with Parkinson's Disease and Major Depression (DSM-IV). The patients were double-blind separated in 2 groups that received fish oil (containing 720 mg EPA plus 480 mg DHA) or mineral oil capsules for 3 months; each group was separated in 2 new groups: one taking antidepressant medication and another one not taking it. 29 patients completed the 12-week trial, 58% were female and the mean age was 64.4 years old. Patients supplemented with fish oil showed a significant decrease in MADRS and CGI-Depression scores, and there was no difference among groups in BDI. 14 patients (42%) met criteria for ≥ 50% reduction in MADRS score, 7 patients (22%) met criteria for remission (final MADRS total score ≤ 12), and 2 patients (6%) discontinued supplementation of fish oil. HPLC analysis of fatty-acid profile showed increase of omega-3 fatty acid in the erythrocyte membrane of patients taking fish oil.

Conclusion

These results reveal that PD patients taking fish oil, with or without antidepressants, presented improvement in depressive symptoms and indicate that the intake of omega-3 can be used with an antidepressant effect or as adjuvant therapy with some other medication. This is a first pilot study with parkinsonian patients and omega-3 supplementation and requires replication in a larger sample.

Source

Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss A, Andreatini R, Ferraz AC. J Affect Disord. 2008; 111: 351-9.

CAROTENOIDS PROTECT AT VARIOUS SITES

Lutein and zeaxanthin protect the skin besides the eyes

Review

This review summarizes the effects of lutein and zeaxanthin in the human eye and skin.
The human body accumulates less than 20 of the hundreds of carotenoids found in nature. Carotenoids cannot be synthesized by humans, they have to be ingested from food or dietary supplements. Among the carotenoids present in the body, only lutein and its coexistent isomer, zeaxanthin, are found in the portion of the eye where light is focused by the lens, namely, the macula lutea. Numerous studies have shown that lutein and zeaxanthin may provide significant protection against the potential damage caused by light striking this portion of the retina. In the eye, lutein and zeaxanthin have been shown to filter high-energy wavelengths of visible light and act as antioxidants to protect against the formation of reactive oxygen species and subsequent free radicals. Human studies have demonstrated that lutein and zeaxanthin are present in the skin, and animal studies have provided evidence of significant efficacy against light-induced skin damage, especially the ultraviolet wavelengths. Little was known about the protective effects of these carotenoids in human skin until recently.

Conclusion

The protective effect of lutein and zeaxanthin on human eyes is well documented and similar data are available for the skin. Oral as well as topical applications may protect against lipid peroxidation and the loss of elasticity and hydration caused by light induced damage.

Source

Lutein and zeaxanthin in eye and skin health. Roberts RL, Green J, Lewis B. Clin Dermatol. 2009; 27: 195-201.

Lycopene protects DNA from oxidative damage

Intervention

While tomato product supplementation, containing antioxidant carotenoids, including lycopene, decreases oxidative stress, the role of purified lycopene as an antioxidant remains unclear. Thus, the effects of different doses of purified lycopene supplementation on biomarkers of oxidative stress in healthy volunteers has been tested in a double-blind, randomized, placebo-controlled trial. Plasma lycopene levels, biomarkers of lipid peroxidation {LDL oxidizability, malondialdehyde & hydroxynonenals (MDA & HNE), urinary F(2)-isoprostanes}, and markers of DNA damage in urine and lymphocytes have been measured after 8-week supplementation of purified lycopene. Healthy adults (n = 77, age $\geq$ 40 years), consumed a lycopene-restricted diet for 2 weeks, and were then randomized to receive 0, 6.5, 15, or 30 mg lycopene/day for 8 weeks, while on the lycopene-restricted diet. Blood and urine samples were collected at the beginning and end of Week 2 of lycopene-restricted diet, and at end of Week 10 of the study.
Independent of the dose, plasma lycopene levels significantly increased in all lycopene supplemented groups versus placebo ($p < 0.05$). ANOVA revealed a significant decrease in DNA damage by the comet assay ($p = 0.007$), and a significant decrease in urinary 8-hydroxy deoxoguanosine (8-OHdG) at 8 weeks versus baseline ($p = 0.0002$), with 30 mg lycopene/day. No significant inter- or intra-group differences were noted for glucose, lipid profile, or other biomarkers of lipid peroxidation at any dose/time point.

Conclusion

Purified lycopene was bioavailable and was shown to decrease DNA oxidative damage and urinary 8-OHdG at the high dose that may have consequences in the prevention of various cancers. Biomarkers of lipid peroxidation were not affected neither in plasma nor in urine.

Source

A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. Devaraj S, Mathur S, Basu A, Aung HH, Vasu VT, Meyers S, Jialal I. J Am Coll Nutr. 2008; 27: 267-73.

TOLERABLE UPPER INTAKE LEVELS FOR VITAMIN A TOO CLOSE TO THE RECOMMENDED INTAKE

The low UL might prevent food fortification efforts against vitamin A deficiency

Policy

Vitamin A deficiency (VAD) is a major health problem, particularly in low-resource countries, putting an estimated 125-130 million preschool-aged children at increased risk of morbidity and mortality from infectious diseases. Vitamin A supplementation reduces VAD and increases child survival; it is complemented by fortifying foods with vitamin A. Concern over increased risk of bone fracture associated with vitamin A intakes below the tolerable upper intake level (UL) among populations in affluent countries conflicts with the need to increase intakes in less developed countries, where populations are at greater risk of VAD and intakes are unlikely to reach the UL as diets include fewer foods containing retinol while vitamin A from carotenoids poses no risk of overdose. With the implementation of recently developed risk management tools, vitamin A can be used safely in food fortification, including point-of-use fortification in the context of supplementation among specific target groups in low-resource countries.

Conclusion

Health authorities might be in favor of setting low safety barriers for nutrients; however, this policy can, as a consequence, increase the risk for deficiency in certain cases.

Source

Are low tolerable upper intake levels for vitamin A undermining effective food fortification efforts? Kraemer K, Waelti M, de Pee S, Moench-Pfanner R, Hathcock JN, Bloem MW, Semba RD. Nutr Rev. 2008; 66: 517-25.

ALPHA-TOCOPHEROL MAY IMPROVE PROSTATE CANCER SURVIVAL

Associations between α-tocopherol, β-carotene, retinol and prostate cancer survival

Observation

Previous studies suggest that carotenoids and tocopherols (vitamin E compounds) may be inversely associated with prostate cancer risk, yet little is known about how they affect prostate cancer progression and survival. We investigated whether serum alpha-tocopherol, beta-carotene, and retinol concentrations, or the alpha-tocopherol and beta-carotene trial supplementation, affected survival of men diagnosed with prostate cancer during the alpha-Tocopherol, beta-Carotene Cancer Prevention Study, a randomized, double-blind, placebo-controlled primary prevention trial testing the effects of beta-

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carotene and alpha-tocopherol supplements on cancer incidence in adult male smokers in southwestern Finland (n = 29,133). Prostate cancer survival was examined using the Kaplan-Meier method with deaths from other causes treated as censoring, and using Cox proportional hazards regression models with hazard ratios (HR) and 95% confidence intervals (CI) adjusted for family history of prostate cancer, age at randomization, benign prostatic hyperplasia, age and stage at diagnosis, height, body mass index, and serum cholesterol. As of April 2005, 1,891 men were diagnosed with prostate cancer and 395 died of their disease. Higher serum alpha-tocopherol at baseline was associated with improved prostate cancer survival (HR, 0.67; 95% CI, 0.45-1.00), especially among cases who had received the alpha-tocopherol intervention of the trial and who were in the highest quintile of alpha-tocopherol at baseline (HR, 0.51; 95% CI, 0.20-0.90) or at the 3-year follow-up measurement (HR, 0.26; 95% CI, 0.09-0.71). Serum beta-carotene, serum retinol, and supplemental beta-carotene had no apparent effects on survival. These findings suggest that higher alpha-tocopherol (and not beta-carotene or retinol) status increases overall prostate cancer survival. Further investigations, possibly including randomized studies, are needed to confirm this observation.

Conclusion

Dietary and supplemental α-tocopherol may improve prostate cancer survival.

Editor's comment

The authors report a HR of 0.73 (95% CI 0.57, 0.93; p=0.01) using a cut-off value of 10.9 mg/L serum α-tocopherol (= 25.3 µmol/L). This fits well to the 30 µmol/L concluded earlier from epidemiological studies to be protective against chronic diseases (Antioxidant vitamins in prevention. H.K. Biesalski, et al. Clinical Nutrition 1997; 16: 151-155).

Source

Associations between α-Tocopherol, β-Carotene, and Retinol and Prostate Cancer Survival. Watters JL, Gail MH, Weinstein SJ, Virtamo J, Albanes D. Cancer Res. 2009; 69: 3833-41.

VITAMIN C DEFICIENCY IN HOSPITAL PATIENTS

Vitamin C deficiency is prevalent in a Canadian teaching hospital

Observation

There is almost no information regarding the vitamin C status of patients treated in Canadian and American hospitals. Therefore, the prevalence and predictors of vitamin C deficiency in patients hospitalized on the acute-care wards of a Canadian teaching hospital have been determined, and their plasma vitamin C concentrations have been tracked while they were there. This was a population-based cross-sectional and time course survey of 149 medical patients shortly after admission to a university teaching hospital. The procedure for sample handling, storage and analysis was validated by measuring the vitamin C concentrations of a reference sample of 141 presumably well nourished people and comparing the results with published norms. In keeping with published norms, 13% of people in the reference group had a subnormal vitamin C concentration (<28.4 µmol/L) and 3% were vitamin C deficient (<11.4 µmol/L). By contrast, 60% of hospitalized patients had a subnormal vitamin C concentration and 19% were deficient. A history of inadequate nutrition or failure to use a vitamin supplement prior to admission, low serum albumin, and male sex predicted plasma vitamin C deficiency, whereas use of a vitamin supple-

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ment prior to admission was associated with adequate vitamin C status in hospital. In a second measurement, obtained in 52 patients after an average of 17 days in hospital, vitamin C status had not improved.
24 % of the participants had used a vitamin supplement that was discontinued by the medical team in most cases upon admission to the hospital.

Conclusion

Vitamin C deficiency is prevalent and sustained in patients in a Canadian teaching hospital. The abnormality can be prevented by providing a diet sufficient in vitamin C or by prescribing a multiple vitamin tablet.

Source

Vitamin C deficiency in a university teaching hospital. Gan R, Eintracht S, Hoffer LJ. J Am Coll Nutr. 2008; 27: 428-33.

FOLIC ACID, VITAMIN B_6 AND VITAMIN B_{12} BENEFICIAL FOR EYE HEALTH

Folic acid, Vitamin B_6 and Vitamin B_{12} reduce the risk of age-related macular degeneration in the Women's Antioxidant and Folic Acid Cardiovascular Study

Intervention

Observational epidemiologic studies indicate a direct association between homocysteine concentration in the blood and the risk of age-related macular degeneration (AMD), but randomized trial data to examine the effect of therapy to lower homocysteine levels in AMD are lacking. The objective of this study was to examine the incidence of AMD in a trial of combined folic acid, pyridoxine hydrochloride (vitamin B_6), and cyanocobalamin (vitamin B_{12}) therapy in a randomized, double-blind, placebo-controlled trial. 5442 female health care professionals 40 years or older with preexisting cardiovascular disease or 3 or more cardiovascular disease risk factors have been included. A total of 5205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis. Participants were randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo. Our main outcome measures included total AMD, defined as a self-report documented by medical record evidence of an initial diagnosis after randomization, and visually significant AMD, defined as confirmed incident AMD with visual acuity of 20/30 or worse attributable to this condition. After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 [P = .02]). For visually significant AMD, there were 26 cases in the combination treatment group and 44 in the placebo group (relative risk, 0.59; 95% confidence interval, 0.36-0.95 [P = .03]).

Conclusion

These randomized trial data from a large cohort of women at high risk of cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD.

Source

Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Arch Intern Med. 2009; 169: 335-41.