Proceedings of the Nutrition Society (2002), **61**, 165–171 DOI:10.1079/PNS2002144

The Diamond Jubilee Summer Meeting of the Nutrition Society was held at the University of Sheffield on 10–12 July 2001

The Boyd Orr Lecture

Nutrition interventions in aging and age-associated disease

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Aging is a complex biological process, which usually is accompanied by changes in socio-economic status, which may have a great impact on the physical and nutritional status of the elderly. Decreased food intake and a sedentary lifestyle in the growing numbers of the elderly increase their risk for malnutrition, decline of bodily functions and developing chronic diseases. Oxidative stress is believed to be an important factor in aging and many age-associated degenerative diseases. Modulation of oxidative stress by energy restriction in animals has been shown to be one of the mechanisms for retarding the aging process. Dietary antioxidants are regarded as being important in modulating oxidative stress of aging and age-associated diseases. Supplementation of the elderly with vitamin E has been shown to enhance immune response, delay onset of Alzheimer's disease, and increase resistance to oxidative injury associated with exercise. Vitamin E, in comparison with other antioxidants, is also effective in reducing viral titres, but not the longevity of middle-aged mice. Our studies have indicated that polyphenols or vitamin E may assist in preventing cardiovascular disease, in part by decreasing expression by endothelial cells of proinflammatory cytokines, adhesion molecules, and monocyte adhesion. Most recently, we have found that some of these antioxidants may prevent tumour growth by inhibiting angiogenesis via suppression of interleukin 8 and modulation of the cell junction molecule, VE-cadherin. These findings provide further support for the consumption of fruit and vegetables, which contain several forms of phytochemicals with antioxidant activity, in order to reduce the risk of cardiovascular disease and cancer, the leading causes of morbidity and mortality among the elderly.

Oxidative stress: Antioxidants: Vitamin E

The population of elderly persons over 65 years of age is rising in the USA and other countries. The number of older Americans has increased by 3·2 million in the last decade. This increase will be even greater in the coming years; by the year 2030 it is estimated that there will be about 70 million elderly persons over the age of 65 years, or one-fifth of the whole US population (Fowles, 1999). A variety of factors, such as improved health care and diet, vaccinations and new drugs have made a major contribution to the growth of the elderly population in the US and elsewhere.

Aging is a complex biological phenomenon often accompanied by various socio-economic changes that have a great impact on the nutritional status and needs of the elderly individual. The incidence of disability increases with aging. Over one-third of elderly persons are limited by chronic conditions and are unable to carry on major activities. According to recent data (Alaimo *et al.* 1998) more than 50 % of the elderly over 65 years of age suffer from one form of disability, and 33 % of the elderly suffer from at least one type of severe disability. Arthritis, hypertension, heart disease, hearing impairments, orthopaedic impairments, cataracts, sinusitis and diabetes are the most frequent health problems that pose difficulties for the elderly in carrying out activities of daily living. Thus, it is expected that the prevalence of elderly individuals with disabilities will increase concomitantly with the rise in the elderly population to more than 30 million in the USA by

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the first decade of new millennium. Thus, strategies to prevent an age-related decline in mobility and reduce the prevalence of chronic disease are recognized to be important for healthy aging and for maintaining elderly independence and the ability to carry out activities of daily living.

Nutrition and aging

A time-dependent increase in oxidative stress and dysregulation of cellular function is the basis for the free radical theory of aging (Yu, 1993). This theory is commonly manifested with phenotypic changes and functional deterioration in later life. A variety of factors including genetics, environment and lifestyle is believed to play important roles in the rate of increase in oxidative stress and, thus, the rates of aging and age-associated diseases (Fig. 1). Mounting evidence suggests that the generation of free radicals and oxidative stress is a major player in the aging process and age-associated diseases. Cutler (1991) has demonstrated the association of antioxidant capacity and oxidative stress with longevity of mammalian species. He has shown that the maximum lifespan potential among the mammalian species directly correlates with the level of endogenous antioxidant enzymes such as superoxide dismutase, and with vitamin E concentration per specific metabolic rate in tissue or plasma. For example, human subjects, with the highest lifespan potential, have a relatively greater antioxidant superoxide dismutase capacity per specific metabolic rate compared with small mammals, such as the field mouse (*Apodemus sylvaticus*), with a lower specific metabolic rate, and thus having a very short maximum lifespan potential. Furthermore, the longer-lived species such as man have been shown to produce a lower level of steady-state oxidative damage to DNA compared with mice. Thus, eliminating free radicals formation and reducing oxidative stress, and increasing antioxidant defences, is considered one way of reducing the rate of aging and the risk of chronic disease.

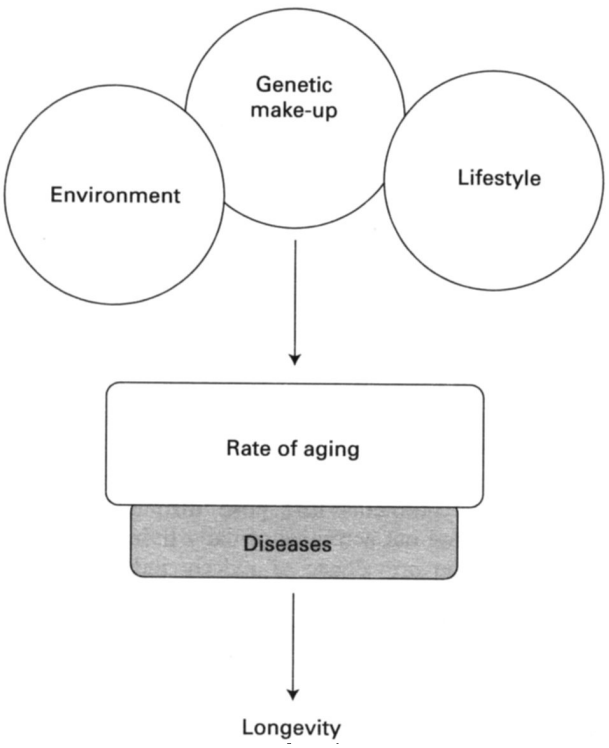

Fig. 1. Factors affecting longevity.

Decreased food intake, a sedentary lifestyle and reduced energy expenditure together, in older adults, are the risk factors for malnutrition, particularly for protein and micronutrients, and may further contribute to the decline in bodily functions and the development of chronic age-associated degenerative diseases. The recent survey of 5000 elderly from age 60 years to 80+ years in the third National Health and Nutrition Examination Survey in USA (National Center for Health Statistics, 1994; US Department of Health and Human Services, 1994) provided for the first time a cross-sectional health and nutrition status in the aging US population (Burt & Harris, 1994). The report indicated that the median intake of total energy in elderly subjects, in general, was lower than the recommended intake of 9660 kJ (2300 kcal) for men and 7980 kJ (1900 kcal) for women (Marwick, 1997). The survey found that elderly Americans consumed sufficient vitamins C and A, micronutrients important for maintenance of healthy life, to meet recommended daily allowance levels. However, the survey revealed that elderly Americans do not consume sufficient Ca to meet the recommended level of 800 mg/d, which is important for bone health and reducing the risk of osteoporosis and bone fracture. The survey also reported that the intake of vitamin E is lower than the current recommended level (for the natural form of vitamin E), which is 15 mg/d. Vitamin E is an important antioxidant for preventing lipid peroxidation and maintaining cellular membrane integrity. The third National Health and Nutrition Examination Survey clearly demonstrated that food insufficiency exists among the US elderly population, and that its prevalence is associated with the income status of the elderly (Alaimo *et al.* 1998). In addition to inadequate food intake and malnutrition due to income limitations, other factors including diseases, physical disability, inability to chew adequately and the intake of multiple drugs may contribute to the risk of food insufficiency among the elderly.

Nutrition interventions

It has been recognized that in many age-associated diseases food and nutrition play important roles (Table 1). Chronic conditions may also increase the requirements for certain nutrients due to changes in absorption and metabolism. Traditionally, nutrition has been recognized as an important

Table 1. Several age-related diseases are associated with nutrition

Cancer
Cardiovascular disease
Diabetes
Osteoporosis
Sarcopenia
Cataract
Macular degeneration
Infection

https://doi.org/10.1079/PNS2002144 Published online by Cambridge University Press

factor in the modulation of disease and longevity. However, experimentally, the only intervention shown to be effective in retarding the aging process is energy restriction, which has been demonstrated in several animal models. Energy restriction has been proven to be an effective dietary intervention to reduce oxidative stress, improve the antioxidant defence system and extend both median and maximum lifespans in several species (Weindruch, 1996). Energy restriction has also been shown to slow the age-associated decline of bodily functions, such as those of the immune and neuronal systems (Fernandes *et al.* 1997; Bruce-Keller *et al.* 1999) and to delay the onset of age-related diseases such as cancer, diabetes and cataracts (Weindruch, 1992; Taylor *et al.* 1995; Novelli *et al.* 1998). Energy restriction in rodent models has been shown to increase longevity when energy restriction is introduced at any time after the animal has matured (Yu, 1995). Evidence suggests that the mechanism of action of dietary restriction is mainly the reduction in oxidative stress and an increase in endogenous levels of antioxidant enzymes. Restriction of energy intake by 30–40 % in human subjects, however, appears to be difficult, as it would require drastic behavioural modifications. Thus, practically speaking, it is not a plausible option for increasing longevity or reducing disease risk in a population. However, in a clinical setting energy restriction to reduce body weight has been shown to be beneficial for reducing an individual's risk for diseases such as diabetes and cardiovascular disease.

The reduction in oxidative stress appears to be one of the main mechanisms of action in dietary restriction models, and is in accordance with the free radical theory of aging. Thus, it was proposed that increasing antioxidant status by feeding animals with natural or synthetic antioxidants would reduce oxidative stress and thus contribute to their longevity. In the earlier studies, however, these endeavours were not as successful as the results obtained from food restriction paradigms (Harman, 1968, 1980; Comfort, 1971; Kohn, 1971). Interestingly, a relatively recent study has shown that feeding animals with a diet containing a mixture of several dietary antioxidants, if begun early in life, might extend the longevity of animals (Bezlepkin *et al.* 1996). Although the results are promising, this observation needs to be confirmed by other laboratories. Extension of this observation to human subjects, i.e. long-term supplementation with antioxidants to examine longevity, would be of great value. It would be very interesting to prove that high antioxidant capacity and low oxidative stress are major contributing factors in slowing down the aging process in the human population. Modification of diet without drastic reductions in energy intake, together with changes in lifestyle, such as exercising, abstaining from smoking and moderating alcohol intake, along with maintaining ideal body weight, are the main recommendations for reducing the risk of chronic diseases and contributing to healthy aging.

Nutrition and age-associated chronic diseases

Several observational studies have shown that supplemental intake of antioxidant vitamins such as vitamins E and C is associated with reduced risk of age-associated chronic diseases such as cardiovascular disease, certain forms of cancer, cataracts and cognitive impairment, which in turn might have contributed to the longevity and growth of the elderly population. Thus, it would be of great value to examine the potential role of supplemental intake of antioxidant vitamins in relation to the increased life expectancy observed in recent decades in the US population and other parts of the world.

Dietary components of foods containing antioxidant activity, such as vitamin E, or non-nutritive components with antioxidant activity such as polyphenols in fruit and vegetables, have received particular attention due to their potential role in modulating the oxidative stress associated with aging and age-related chronic diseases. Several studies have shown a potential role for these components of the diet in the modulation of a variety of bodily functions, such as immune and cognitive functions, and their importance in prevention and reduction of risks of several degenerative diseases in the elderly, including cardiovascular disease, cancer, infections and Alzheimer's disease.

Atherosclerosis, the main cause of CHD, manifests its symptoms usually at middle and later ages. It is a multifactorial process involving the interplay of lipid metabolism, oxidative stress, mononuclear leucocytes, coagulation proteins, cytokines, extracellular matrix and homodynamic forces. The role of diet and lifestyle has been well recognized in the prevalence and risk for morbidity and mortality with this disease. Several observational, experimental and clinical trials have investigated the association between dietary antioxidants and risk of cardiovascular disease. Scores of observational and clinical trials have shown that the increased intake or plasma level of vitamin E is associated with reduced risk of cardiovascular disease (Table 2; Meydani, 1995, 1998). Some large clinical trials have found no benefits from vitamin E supplementation for patients with established disease (Table 3). However, mounting evidence indicates that supplemental levels of vitamin E have a great potential in preventing the development of cardiovascular disease through several mechanisms,

Table 2. Studies showing beneficial effects of dietary or high serum vitamin E on cardiovasculars disease

Study	Reference
Edinburgh case-controlled study	Riemersma *et al.* (1991)
Cross-cultural survey of sixteen European populations	Gey (1993)
Basel prospective study	Gey (1993)
Nurses' health study, USA	Stampfer *et al.* (1993)
Health professionals' follow-up study	Rimm *et al.* (1993)
Linxian China study	Blot *et al.* (1993)
Finnish men's and women's follow-up study	Knekt *et al.* (1994)
Cambridge heart antioxidant study (CHAOS)	Stephens *et al.* (1996)
Vitamin E and lesion progression study	Hodis *et al.* (1995)
Antioxidant vitamins and CHD in women	Kushi *et al.* (1996)
Vitamin E and coronary mortality in elderly	Losonczy *et al.* (1996)
Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE)	Boaz *et al.* (2000)

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Table 3. *Studies showing no clear association between serum vitamin E and cardiovascular disease*

Study	Reference
Eastern Finland heart survey	Salonen *et al.* (1985)
Dutch case–control follow-up	Kok *et al.* (1987)
Nested case–control study (MONICA Augsburg Project)	GISSI-Prevenzione Investigators (1999)
Gruppo Italiano per lo Studio Della Sopravvivnza Nell'Infarto (GISSI-Prevention trial)	
Heart outcome prevention evaluation (HOPE)	The Heart Outcomes Prevention Evaluation Study (1999)
Primary prevention project (PPP)	Palumbo *et al.* (2000)

including reducing the susceptibility of LDL to oxidation (Jialal *et al.* 1995), reducing the expression of chemokines and adhesion molecule expression and monocyte adhesion (Wu *et al.* 1999), decreasing smooth muscle proliferation (Azzi *et al.* 1995), improving vessel relaxation (Keaney *et al.* 1993; Green *et al.* 1998; Neunteufl *et al.* 1998), and decreasing platelet aggregation (Steiner, 1999). It appears that dietary vitamin E supplements are more effective in preventing the development of the disease rather than curing the established lesions in patients with cardiovascular disease.

Several observational studies have indicated that the consumption of fruit and vegetables is associated with a lower risk of cancer (Ames *et al.* 1993). Antioxidants present in fruit and vegetables in the form of antioxidant vitamins or non-nutritive polyphenols may contribute to their effect in reducing the cancer risk. The metabolic conversion of polyphenols following absorption from the gastrointestinal tract may modulate their biological efficacy (Koga & Meydani, 2001). Suppression of oxidative stress and prevention of DNA damage and mutation have been suggested as one of the mechanisms by which these compounds may affect cancer reduction.

Another potential mechanism, which has been discovered recently, is that the polyphenols of fruit and vegetables may modulate cancer development through inhibition of tumour growth by suppressing angiogenesis. Angiogenesis is the formation of new blood vessels from existing ones, which are needed for providing nutrients and O_2 to support tumour growth. Since aging and cancer development are associated with an increase in oxidative stress, we have tested the role of small increases in oxidative stress on angiogenesis. We have made *in vitro* observations that angiogenesis can be induced by H_2O_2-induced oxidative stress, while supplementing the microvascular endothelial cells with vitamin E or green-tea catechins (polyphenols with antioxidant activity) inhibits angiogenesis. (Tang & Meydani, 2001). Both vitamin E and regular consumption of green tea have been reported to be associated with reduced risk of cancer (Attar, 1992; Das, 1994; Mukhtar *et al.* 1994; Shklar & Schwartz, 1996; Nakachi *et al.* 1998; Fleshner *et al.* 1999). Green-tea catechins have been shown to be effective in reducing angiogenesis in *in vivo* animal models (Cao & Cao, 1999). Our *in vitro* studies have indicated that the reduction in interleukin 8 production and a disturbance in the assembly of VE-cadherin with intracellular β-catenins are some of the mechanisms by which these antioxidants modulate angiogenesis (Tang & Meydani, 1999, 2001).

Dietary vitamin E has been shown to be an effective antioxidant micronutrient to boost the immune function in the elderly. Earlier, Meydani *et al.* (1986) reported that supplementation of aged mice (24 months old) with dietary vitamin E (500 mg/kg) improved several indices of the immune system to levels comparable with those seen in young animals. Supplementation of aged mice with this vitamin also increased clearance of influenza virus from the lung compared with animals supplemented with other antioxidants such as melathonine, glutathione or strawberry extract containing a high level of flavonoids with antioxidant activity (Han *et al.* 2000). In a double-blind placebo-controlled study Meydani *et al.* (1990, 1997) also reported that supplementation of elderly subjects with vitamin E for a short (1 month) or long (4·5 months) period of time also improved several *in vitro* and *in vivo* indices of immune response. The optimal immune response was observed with 200 mg vitamin E/d in the long-term study. It is worth noting that this level of vitamin E has been also reported to be the optimal level for reducing plasma F_2-isoprostane, a reliable index of lipid peroxidation (Dillon *et al.* 1998). Improving the immune response in the elderly may result in a lower incidence of infections, which are prevalent among the elderly, and thus may contribute to a longer and healthier life.

The decline in cognitive function with age is another factor that hinders independence and activity in the elderly. Current evidence indicates that both increased oxidative stress and an imbalance in antioxidant status contribute to the decline in cognitive function with age. Several studies have found associations between the decline in memory performance with age and lower status of dietary antioxidants (Perrig *et al.* 1997; Perkins *et al.* 1999). The effect of dietary antioxidants on prevention of vascular dementia, stroke and atherosclerosis are other mechanisms by which dietary antioxidants may reduce the risk of dementia associated with vascular dysfunction, and probably Alzheimer's disease.

In the recent NHANES III study elderly subjects over the age of 60 years were tested for their cognitive function in relation to plasma antioxidant status. The study reported that levels of vitamins C, E and A, carotenoids and Se were correlated with memory function (Perkins *et al.* 1999).

The survey reported that about 7 % of elderly Americans suffer from poor memory, which is in agreement with the findings of other earlier reports (Graham *et al.* 1997; Hendrie, 1998). This survey indicated that only an increase of one unit in plasma vitamin E, but not vitamin C or Se, was associated with less memory impairment. Experimental animal studies have also indicated that antioxidants present in fruit and vegetables can improve cognitive function (Joseph *et al.* 1998, 1999). These authors found that feeding rats extracts of strawberry, spinach (*Spinacia oleracea*) or blueberry was effective in reversing age-related deficits in several neuronal and behavioural variables. However, feeding middle-aged mice (18 months) with vitamin E, strawberry extract or melatonin for 6 months had no effect

on their psychomotor performances, whereas supplemental glutathione was effective (Shukitt-Hale *et al.* 1999).

Experimental and clinical data have indicated that dietary antioxidants may play an important role in retarding several cognitive disorders associated with neuronal diseases, such as Alzheimer's disease. Since oxidative stress and a decrease in the antioxidant defence system in brain neuronal cells are believed to be major factors in the development and progression of Alzheimer's disease, several recently-developed drugs with antioxidant properties have been suggested to be effective. Thus, in the first double-blind placebo-controlled randomized multicentre clinical trial with patients with moderately-severe Alzheimer's disease, Sano *et al.* (1997) tested the efficacy of daily intake of either 2000 mg vitamin E or 10 mg selegiline, a monoamine oxidase inhibitor (Eldepryl; Somerset Pharmaceuticals, Tampa, FL, USA), or both, on the progression of the disease in 342 patients. Treatment with vitamin E alone significantly delayed the primary outcome by 670 d ($P=0{\cdot}001$). Selegiline significantly delayed the primary outcome by 655 d ($P=0{\cdot}012$), and combination therapy was significantly effective in delaying the primary outcome by 585 d ($P=0{\cdot}049$). Thus, both vitamin E and selegiline appear to be effective in reducing oxidative stress, to which the neuronal cell population in Alzheimer's disease is suggested to be more sensitive than in other neuro-degenerative diseases. The findings from this study were encouraging, and ongoing clinical trials will further confirm the efficacy of vitamin E in the prevention of this disease. Thus, the available evidence indicates that dietary antioxidants and non-nutritive antioxidants or polyphenols present in fruit and vegetables may provide protection against oxidative damage in neuronal tissue and prevent deterioration of the neuronal system with aging.

Conclusion

Compelling evidence from dietary restriction studies in animal models and clinical and observational studies have indicated that free radicals are involved in both aging and the pathology of many age-associated diseases. The contribution of dietary or supplemental antioxidants during the past decades to the increase in life expectancy and growth of the elderly population is not known. However, evidence indicates that adopting a healthy lifestyle, including adopting a balanced diet, physical activity and abstaining from smoking, together with better medical care most probably contributes to increased life expectancy. Emerging data from epidemiological and clinical studies also emphasize the importance of micronutrients in increasing the vigour of several bodily functions, such as immune, cognitive and cardiovascular, in the elderly. In addition, supplemental intake of antioxidants and other micronutrients appears to be important in preventing or delaying the onset of several age-associated chronic diseases such as cardiovascular disease, cancer, dementia and infections, the major causes of morbidity and mortality among the elderly. Nutritional interventions are more practical, cost-effective and can be implemented more easily in a large population.

References

Alaimo K, Briefel RR, Frongillo EA & Olson CM (1998) Food insufficiency exists in the United States: Results from the third National Health and Nutrition Examination Survey (NHANES III). *American Journal of Public Health* **88**, 419–426.

Ames BN, Shigenaga MK & Hagen TM (1993) Oxidants, antioxidants, and the degenerative diseases of aging. *Proceedings of the National Academy of Sciences USA* **90**, 7915–7922.

Attar EL (1992) Effect of vitamin C and vitamin E on prostaglandin synthesis by fibroblasts and squamous carcinoma cells. *Prostaglandins Leukotrienes and Essential Fatty Acids* **47**, 253–257.

Azzi A, Boscoboinik D, Marilley D, Ozer NK, Stable B & Tasinato A (1995) Vitamin E: A sensor and an information transducer of the cell oxidation state. *American Journal of Clinical Nutrition* **62**, Suppl., 1337S–1346S.

Bezlepkin VG, Siroat NP & Gaziev AI (1996) The prolongation of survival in mice by dietary antioxidants depends on their age by the start of feeding this diet. *Mechanisms of Ageing and Development* **92**, 227–234.

Blot W, Li J-Y, Taylor PR, Guo W, Dawsey S, Wang G-Q, Yang CS, Zheng S-F, Sun Y-H, Liu F, Fraumeni JF, Zhang Y-H & Li B (1993) Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence and disease-specific mortality in the general population. *Journal of the National Cancer Institute* **85**, 1483–1492.

Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Laina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M & Green MS (2000) Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* **356**, 1213–1218.

Bruce-Keller AJ, Umberger G, McFall R & Mattson MP (1999) Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Annals of Neurology* **45**, 8–15.

Burt VL & Harris T (1994) The third National Health and Nutrition Examination Survey: contributing data on aging and health. *Gerontologist* **34**, 486–490.

Cao Y & Cao R (1999) Angiogenesis inhibited by drinking tea. *Nature* **398**, 381.

Comfort A (1971) Effect of ethoxyquin on the longevity of C3H mice. *Nature* **229**, 254–255.

Cutler RG (1991) Antioxidants and aging. *American Journal of Clinical Nutrition* **53**, 373S–379S.

Das S (1994) Vitamin E in the genesis and prevention of cancer. *Acta Oncologica* **33**, 615–619.

Dillon G, Vita JA, Leeuwenburgh C, Olesiak M, Heinecke JW & Frei B (1998) α-Tocopherol supplementation reduces systemic markers of oxidative damage in healthy adults. *Circulation* **17**, Suppl., 6711.

Fernandes G, Venkatraman JT, Turturro A, Attwood VG & Hart RW (1997) Effect of food restriction on life span and immune functions in long-lived Fischer-344 x Brown Norway F1 rats. *Journal of Clinical Immunology* **17**, 85–95.

Fleshner N, Fair WR, Huryk R & Heston WD (1999) Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice. *Journal of Urology* **161**, 1651–1654.

Fowles DG (1999) A profile of older Americans: 2000. www.aoa.dhhs.gov/aoa/stats/profile/

Gey KF (1993) Prospects for the prevention of free radical disease, regarding cancer and cardiovascular disease. *British Medical Bulletin* **49**, 679–699.

GISSI-Prevenzione Investigators (1999) Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after

https://doi.org/10.1079/PNS2002144 Published online by Cambridge University Press

myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* **354**, 447–455.
Graham JE, Rockwood K, Beattie BL, Gauthier ERS, Tuokko H & McDowell I (1997) Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* **349**, 1793–1796.
Green D, O'Driscoll G, Rankin JM, Maiorana AJ & Taylor RR (1998) Beneficial effect of vitamin E administration on nitric oxide function in subjects with hypercholesterolaemia. *Clinical Science* **95**, 361–367.
Han SN, Meydani M, Wu D, Bender BS, Smith DE, Vina J, Cao G, Prior RL & Meydani SN (2000) Effect of long-term dietary antioxidant supplementation on influenza virous infection. *Journal of Gerontology* **55**A, B1–B8.
Harman D (1968) Free radical theory of aging: effect of free radical inhibitors on the mortality rate of male LFA mice. *Journal of Gerontology* **23**, 476–482.
Harman D (1980) Free radical theory of aging: beneficial effect of antioxidants on the lifespan of male NZB mice; role of free radical reactions in the deterioration of the immune system with age and in the pathogenesis of systemic lupus erythematosus. *Age* **3**, 64–73.
Hendrie HC (1998) Epidemiology of dementia and Alzheimer's disease. *American Journal of Psychiatry* **6**, S3–S18.
Hodis HN, Mack WJ, LaBree L, Cashin-Hemphill L, Sevanian A, Johnson R & Azen AP (1995) Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *Journal of the American Medical Association* **273**, 1849–1854.
Jialal I, Fuller CJ & Huet BA (1995) The effect of alpha-tocopherol supplementation on LDL oxidation. *Arteriosclerosis Thrombosis and Vascular Biology* **15**, 190–198.
Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ & Bickford PC (1999) Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberries, spinach, or strawberry dietary supplementation. *Journal of Neuroscience* **19**, 8114–8121.
Joseph JA, Shukitt-Hale B, Denisova NA, Prior RL, Cao G, Martin A, Taglialatela G & Bickford PC (1998) Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. *Journal of Neuroscience* **18**, 8047–8055.
Keaney JFJ, Gaziano MJ, Xu A, Frei B, Curran-Celentano J, Shwaery GT, Loscalzo J & Vita JA (1993) Dietary antioxidants preserve endothelium-dependent vessel relaxation in cholesterol-fed rabbits. *Proceedings of the National Academy of Sciences USA* **90**, 11880–11884.
Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M & Aromaa A (1994) Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *American Journal of Epidemiology* **139**, 1180–1189.
Koga T & Meydani M (2001) Effect of plasma metabolites of (+)-catechin and quercetin on monocyte adhesion to human aortic endothelial cells. *American Journal of Clinical Nutrition* **73**, 941–948.
Kohn RR (1971) Effect of antioxidants on life-span of C57/BL mice. *Journal of Gerontology* **26**, 376–380.
Kok FJ, de Bruijn AM, Vermeeren R, Hofman A, VanLaar A, deBruin M, Hermus RJT & Valkenberg HA (1987) Serum selenium, vitamin antioxidants and cardiovascular mortality. *American Journal of Clinical Nutrition* **45**, 462–468.
Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y & Bostock RM (1996) Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *New England Journal of Medicine* **334**, 1156–1162.
Losonczy KG, Harris TB & Havlik RJ (1996) Vitamin E and vitamin C supplementation use and risk of all-cause and coronary heart disease mortality in older persons: The Established Populations for Epidemiologic Studies of the Elderly. *American Journal of Clinical Nutrition* **64**, 190–196.
Marwick C (1997) NHANES III health data relevant for aging nation. *Journal of the American Medical Association* **277**, 100–102.
Meydani M (1995) Vitamin E. *Lancet* **345**, 170–175.
Meydani M (1998) Nutrition, immune cells, and atherosclerosis. *Nutrition Reviews* **56**, S177–S182.
Meydani SN, Barklund PM, Liu S, Meydani M, Miller RA, Cannon J, Morrow F, Rocklin R & Blumberg JB (1990) Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *American Journal of Clinical Nutrition* **52**, 557–563.
Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, Thompson C, Pedrosa MC, Diamond RD & Stollar BD (1997) Vitamin E supplementation and in vivo immune response in healthy elderly: a randomized controlled trial. *Journal of the American Medical Association* **277**, 1380–1386.
Meydani SN, Meydani M, Verdon CP, Shapiro AC, Blumberg JB & Hayes KC (1986) Vitamin E supplementation suppresses prostaglandin E2 synthesis and enhances the immune response of aged mice. *Mechanisms of Ageing and Development* **34**, 191–201.
Mukhtar H, Katiyar SK & Agarwal R (1994) Green tea and skin – anticarcinogenic effects. *Journal of Investigative Dermatology* **102**, 3–7.
Nakachi K, Suemasu K, Suga K, Takeo T, Imai K & Higashi Y (1998) Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Japanese Journal of Cancer Research* **89**, 254–261.
National Center for Health Statistics (1994) *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–1994. Vital and Health Statistics Series* no. 1 (32). Hyattsville, MD: National Center for Health Statistics. Available at http://www.cdc.gov.nchs
Neunteufl T, Kostner K, Katzenschlager R, Zehetgruber M, Maurer G & Weidinger F (1998) Additional benefit of vitamin E supplementation to simvastatin therapy on vasoreactivity of the brachial artery of hypercholesterolemic men. *Journal of the American College of Cardiology* **32**, 711–716.
Novelli M, Masiello P, Bombara M & Bergamini E (1998) Protein glycation in the aging male Sprague-Dawley rat: effects of antiaging diet restrictions. *Journal of Gerontology* **53**A, B94–B101.
Palumbo G, Avanzini F, Alli C, Roncaglioni M, Ronchi E, Cristofari M, Capra A, Rossi S, Nosotti L, Costantini C & Cavalera C (2000) Effects of vitamin E on clinic and ambulatory blood pressure in treated hypertensive patients. Collaborative Group of the Primary Prevention Project (PPP) – Hypertension study. *American Journal of Hypertension* **13**, 564–567.
Perkins A, Hendrie HC, Callahan CM, Cao S, Unverzagt FW, Xu Y, Hall K & Hui SL (1999) Association of antioxidants with memory in a multiethnic elderly sample using the Third National Health and Nutrition examination Survey. *American Journal of Epidemiology* **150**, 37–44.
Perrig WJ, Perrig P & Stavelin HB (1997) The relation between antioxdants and memory performance in the old and very old. *Journal of the American Geriatrics Society* **45**, 718–724.
Riemersma RA, Wood DA, MacIntyre CCH, Elton RA, Gey KF & Oliver MF (1991) Risk of angina pectoris and plasma concentrations of vitamins A, C, E, and carotene. *Lancet* **337**, 1–5.
Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA & Willett WC (1993) Vitamin E consumption and the risk of coronary heart disease in men. *New England Journal of Medicine* **328**, 1450–1456.

Salonen JT, Salonen R, Penttila I, Herranen J, Jauhiainen M, Kantola M, Lappentelainen R, Maenpaa P, Alfthan G & Puska P (1985) Serum fatty acids, apolipoproteins, selenium and vitamin antioxidants and risk of death from coronary artery disease. *American Journal of Cardiology* **56**, 226–231.

Sano M, Ernesto MS, Thomas RG, Klauber MR, Schafer K, Grundmer M, Woodbury P, Growder J, Cotman CW, Pfeiffer E, Schneider LS & Thal LJ (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *New England Journal of Medicine* **336**, 1216–1222.

Shklar G & Schwartz JL (1996) Vitamin E inhibits experimental carcinogenesis and tumour angiogenesis. *European Journal of Cancer* **32**, 114–119.

Shukitt-Hale B, Smith DE, Meydani M & Joseph JA (1999) The effects of dietary antioxidants on psychomotor performance in aged mice. *Experimental Gerontology* **34**, 797–808.

Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B & Willett WC (1993) Vitamin E consumption and the risk of coronary disease in women. *New England Journal of Medicine* **328**, 1444–1449.

Steiner M (1999) Vitamin E, a modifier of platelet function: rationale and use in cardiovascular and cerebrovascular disease. *Nutrition Reviews* **57**, 306–309.

Stephens NG, Parsons A, Schofield PM, Kelly F, Chessman K, Mitchinson MJ & Brown MJ (1996) Randomized, controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* **347**, 781–786.

Tang F-Y & Meydani M (1999) Green tea polyphenols and vitamin E inhibit angiogenesis by suppressing IL-8. *Free Radical Biology and Medicine* **27**, S149.

Tang F-Y & Meydani M (2001) Green tea catechins and vitamin E inhibit angiogenesis of human microvascular endothelial cells through suppression of IL-8 production. *Nutrition and Cancer* (In the Press).

Taylor A, Jahngen-Hodge J, Smith DE, Palmer VJ, Dallal GE, Lipman RD, Padhye N & Frei B (1995) Dietary restriction delays cataract and reduces ascorbate levels in Emory mice. *Experimental Eye Research* **61**, 55–62.

The Heart Outcomes Prevention Evaluation Study (1999) Vitamin E supplementation and cardiovascular events in high-risk patients. *New England Journal of Medicine* **342**, 154–160.

US Department of Health and Human Services (1994) *Third National Health and Nutrition Examination Survey (1988–1994). NCHS CDROM Series* 11, no. 1A, ASCII version. Hyattsville, MD: National Center for Health Statistics.

Weindruch R (1992) Effect of caloric restriction on age-associated cancers. *Experimental Gerontology* **27**, 575–581.

Weindruch R (1996) The retardation of aging by caloric restriction: studies in rodents and primates. *Toxicologic Pathology* **24**, 742–745.

Wu D, Koga T, Martin KR & Meydani M (1999) Effect of vitamin E on human aortic endothelial cell production of chemokines and adhesion to monocytes. *Atherosclerosis* **147**, 297–307.

Yu BP (editor) (1993) Oxidative damage by free radicals and lipid peroxidation in aging. In *Free Radicals in Aging*, pp. 57–88. Boca Raton, FL: CRC Press.

Yu BP (1995) Modulation of oxidative stress as a means of life prolonging action of dietary restriction. In *Oxidative Stress and Aging*, pp. 331–342 [RG Cuttler, L Packer, J Bertram and A Mori, editors]. Basel: Birkhauser Verlag.