

Dietary approaches that delay age-related diseases

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Abstract: Reducing food intake in lower animals such as the rat decreases body weight, retards many aging processes, delays the onset of most diseases of old age, and prolongs life. A number of clinical trials of food restriction in healthy adult human subjects running over 2–15 years show significant reductions in body weight, blood cholesterol, blood glucose, and blood pressure, which are risk factors for the development of cardiovascular disease and diabetes. Lifestyle interventions that lower energy balance by reducing body weight such as physical exercise can also delay the development of diabetes and cardiovascular disease. In general, clinical trials are suggesting that diets high in calories or fat along with overweight are associated with increased risk for cardiovascular disease, type 2 diabetes, some cancers, and dementia. There is a growing literature indicating that specific dietary constituents are able to influence the development of age-related diseases, including certain fats (trans fatty acids, saturated, and polyunsaturated fats) and cholesterol for cardiovascular disease, glycemic index and fiber for diabetes, fruits and vegetables for cardiovascular disease, and calcium and vitamin D for osteoporosis and bone fracture. In addition, there are dietary compounds from different functional foods, herbs, and nutraceuticals such as ginseng, nuts, grains, and polyphenols that may affect the development of age-related diseases. Long-term prospective clinical trials will be needed to confirm these diet–disease relationships. On the basis of current research, the best diet to delay age-related disease onset is one low in calories and saturated fat and high in wholegrain cereals, legumes, fruits and vegetables, and which maintains a lean body weight. Such a diet should become a key component of healthy aging, delaying age-related diseases and perhaps intervening in the aging process itself. Furthermore, there are studies suggesting that nutrition in childhood and even in the fetus may influence the later development of aging diseases and lifespan.

Keywords: food intake, obesity, cardiovascular disease, diabetes, cancer, osteoporosis, macular degeneration, dementia, preventive dietary therapy

Food intake, longevity, and development of age-related diseases

Due to the increased incidence with advancing age of chronic conditions, such as coronary heart disease, cancers, diabetes, and dementia, there is a need to develop primary preventive interventions to prolong the period of healthy life (Kirkland 2002; Mehr and Tatum 2002; Report of a Joint WHO/FAO Expert Consultation 2003; Eyre et al 2004; Topp et al 2004; Tse and Benzie 2004; Yamori 2004). Diet has a substantial influence on health and aging. Food intake modifies the development of age-related diseases (Weindruch and Walford 1988; Bronson and Lipman 1991; Turturro et al 1994; Masoro 2002c; Heilbronn and Ravussin 2003; Mattson and Wan 2005). The amount of food consumed has a major and well established impact, with food restriction delaying many age-related diseases and obesity predisposing to them. In

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addition, there is emerging evidence to support the association of exposure to specific food types with the development of some age-related diseases. Due to the relatively long “lag time” of effect of risk factors for age-related diseases, humans can benefit from modification of their unhealthy dietary practices of overeating and consuming unhealthy foods, along with increased physical activity which utilizes the excess food before the onset of disease (Report of a Joint WHO/FAO Expert Consultation 2003).

Food restriction in the rat

Food restriction was first clearly shown to prolong life in the rat 70 years ago (McCay et al 1935). This is a robust effect repeatedly confirmed in many laboratories, and overall calorie restriction (CR) increases the maximum lifespan by 20%–40%. Later studies found that long-term food restriction in the rat retarded most aging processes (Weindruch and Sohal 1997; Masoro 2002a; Koubova and Guarente 2003) and delayed the onset of the major age-related diseases (Berg and Simms 1960; Berg and Simms 1965; Roe et al 1995; Bronson and Lipman 1991; Turturro et al 1994; Masoro 2002c). The onset of a wide spectrum of diseases is delayed including neoplasms, degenerative diseases, and autoimmune diseases. Reduced energy intake, that is calorie restriction (CR), is believed to be the basis of the anti-aging effect in the rat and lower animals, because the life-extending effect of CR is the same regardless of the composition of the diet (Masoro 2002b). CR refers to a reduced calorie intake without malnutrition. According to Masoro (2002b), other dietary factors have only minor roles in determining lifespan in the rodent. There are studies in the rat reporting the effects of dietary constituents such as protein on the development of specific diseases, for example, kidney disease (Mattson et al 2005). The earlier studies of Masoro and colleagues (1989) showed that CR is more effective than protein restriction in retarding the age-associated progression of nephropathy in the rat. Further, there are studies in the rat showing that reducing the methionine content of the diet without reducing calories will prolong life by mechanisms not involving energy restriction (Zimmerman et al 2003). At the molecular level, CR is believed to reduce the generation of reactive oxygen species (ROS) in mitochondria during the metabolism of food, leading to tissue damage (Sastre et al 2003; Merry 2004). In this way, CR plays a major role in delaying the onset of age-related diseases (Harman 1956, 1988; Meydani 2001;

Polidori 2003). Similarly, antioxidants in foods, especially fruit and vegetable diets, may counter the oxidative damage in tissues.

Food restriction in humans

There are no life-long prospective food-restriction studies in humans. Two human studies in healthy adults have clearly shown that reducing the intake of calories by about 20% in nutritionally adequate diets over periods of 2 years (Walford et al 2002) and 3–15 years (Fontana et al 2004) lowers body weight, blood pressure, body fat, blood cholesterol, blood triglycerides, blood glucose, and blood insulin. These 2 CR studies demonstrated significant reductions in the risk factors for cardiovascular disease and diabetes. In human studies carotid artery intima-media thickness, a measure of atherosclerotic development, was markedly reduced by CR (Fontana et al 2004). The benefits of food restriction in reducing cardiovascular disease have been known since the Second World War (Strom and Jensen 1951). Similar changes in these risk factors are seen in a close human relative: the rhesus monkey, which has been maintained on 30% CR over 12 years in studies conducted at the National Institute of Aging in Baltimore (Lane et al 1999). These human CR studies, like the rhesus monkey research, clearly show that long-term reductions in food intake lower body weight and reduce the risk of cardiovascular disease and diabetes, which should delay their onset.

There is an optimal energy intake for the slowest development of age-related diseases and hence the lowest all-cause mortality. The balance between energy intake and energy expenditure in physical activity is shown in body weight and body mass index (BMI). In a study over 36 years of 1915 healthy non-smoking Japanese-American men living in Hawaii, the lowest all-cause mortality was found in those whose original energy intake was 15% below the average (Willcox et al 2004). The BMI in the longest-lived group was 24 kg/m², which is close to the BMI of those with the lowest mortality in a prospective study of 1 million non-smoking American adults (Calle et al 1999). However, another prospective study over 10 years in middle-aged men and women indicates that adults should maintain a BMI between 18.5 and 21.9 kg/m² to minimize their risk of common chronic diseases (Field et al 2002). In the two 20% CR trials running for 2–15 years (Walford et al 2002; Fontana et al 2004), so as to reduce the risk factors for cardiovascular disease and diabetes, BMI fell to about 19 kg/m², but the effect on longevity as yet is unknown. A

recent study showed that underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$) in non-smokers as in smokers is associated with significantly increased mortality (Flegal et al 2005).

Overweight and obesity

The prevalence of overweight and obesity is increasing in virtually all populations and age groups of the world (Eckel et al 2004). The per capita food consumption in industrialized countries increased from 2947 kcalories per day in 1964–1966 to 3380 in 1997–1999 (Report of a Joint WHO/FAO Expert Consultation 2003). Overweight and obesity are due to sedentary lifestyles plus high intake of energy-dense foods (fat and sugar) with a low intake of micronutrient-rich foods (fruit, vegetables, high-grain cereals). This epidemic of overweight and obesity is expected to accelerate the onset of age-related diseases (Must et al 1999; Field et al 2002; Cameron et al 2003; Eckel et al 2004), and by the middle of the 21st century will halt, and possibly reverse, the rise in life expectancy seen during the 20th century (Olshansky et al 2005). Obesity increases the risk of type 2 diabetes, hypertension, coronary heart disease, stroke, and cancers of the esophagus, endometrium, breast, prostate, kidney, and colon (Bray 1996; Must et al 1999; Field et al 2002; IARC 2002; Cameron et al 2003; Report of a Joint WHO/FAO Expert Consultation 2003). The increasing prevalence of overweight in children and the appearance of cardiovascular risk factors early in life raises the likelihood of premature development of age-related diseases in the future (Hassink 2003; Remsberg and Siervogel 2003; Wiegman et al 2003; Nesbitt et al 2004). Epidemiological studies are suggesting that poor fetal nutrition and growth resulting in low birth weight may be related to faster aging (Sayer et al 1998) and to the early development of heart disease and type 2 diabetes in adult life (Barker 1995; Robinson 2001).

Analysis of data from the Framingham study indicates that in non-smokers, life expectancy at age 40 is decreased by 3 years for the overweight (BMI of $25\text{--}30 \text{ kg/m}^2$), and by 7 years for an obese man or woman (BMI of $>30 \text{ kg/m}^2$) (Peeters et al 2003). The life-shortening effect of smoking is similar to that of obesity. At age 40 years the combined effect of smoking and obesity leads to a loss of 13–14 years (Peeters et al 2003). In a prospective study of 48 287 men and women in the Netherlands, the all-cause mortality was increased in obese men ($\text{BMI} > 30 \text{ kg/m}^2$) and underweight men ($\text{BMI} < 18.5 \text{ kg/m}^2$), but not in women (Seidel et al 1996). The increased mortality in obese men was mainly

attributable to coronary heart disease and in underweight men to lung cancer in smokers (Seidel et al 1996). In the Physicians Health Study of 85 078 men aged 40–84 years followed up for 5 years, the all-cause and cardiovascular mortality was directly related to BMI (Ajani et al 2004). Among non-smokers there was a linear relation between all cause mortality and BMI; lean men ($\text{BMI} < 20 \text{ kg/m}^2$) did not have excess mortality, although this was not confirmed in another study (Flegal et al 2005). The Report of a Joint WHO/FAO Expert Consultation (2003) recommends that to prevent diet-related disease, BMI needs to be maintained in the normal range of $18.5\text{--}24.9 \text{ kg/m}^2$ to avoid a weight gain of greater than 5 kg during adult life. The risk of weight gain and obesity is reduced by regular physical activity plus high dietary intake of non-starch polysaccharides, including fiber, wholegrain cereals, legumes, fruits, and vegetables (Report of a Joint WHO/FAO Expert Consultation 2003).

Energy intake versus dietary composition

It is known that reducing energy intake will lower risk factors for cardiovascular disease and type 2 diabetes and should thereby delay their onset. Long-term studies in the rat indicate that it is almost entirely energy intake that determines the development of age-related disease and sets the lifespan (Masoro et al 1989; Masoro 2002b). However, in humans there are many studies showing that the development of certain diseases is influenced by dietary components such as saturated fats (Weisburger 2002; Tucker et al 2005), glycemic index (Ludwig 2002; Brand-Miller 2004; Pereira et al 2004), salt (Sacks et al 2001; Weir 2004), calcium (Kulak and Bilezikian 1998; Kanis 1999), folate (Connor 2004; Strain et al 2004; Tavani et al 2004), vitamins (Fairfield and Fletcher 2002; Polidori 2003; Strain et al 2004), micronutrients (Polidori 2003; Johnson 2004), fiber (Cummings et al 2004; Pereira et al 2004), nuts (Fraser 1999; Jenkins et al 2002), meat (Singh et al 2003), fish (Nakamura et al 2005), and fruits and vegetables (Hung et al 2004; Lock et al 2005; Tucker et al 2005). Vegetarians are reported to have a lower risk of dying from ischemic heart disease (Key et al 1998) and have a reduced all-cause mortality (Genkinger et al 2004). A hypothetical polymeal (a mix of wine, fish, dark chocolate, fruits, vegetables, garlic, and almonds) has been proposed to reduce cardiovascular disease by more than 75% and increase life expectancy by 5 years (Franco et al 2004).

Delaying cardiovascular disease

During the second half of the 20th century, changes in diet and lifestyle have led to the rise in cardiovascular and other noncommunicable diseases, which have become the leading causes of death and morbidity. Cardiovascular diseases (CVD), principally cerebrovascular accidents and coronary heart disease (CHD), account for approximately 30% of mortality in the world (Srinath Reddy and Katan 2004). Risk factors for developing CVD, such as diabetes and smoking, are well known. However, the Framingham study identified old age as the biggest risk factor for developing CVD (Grundy et al 1999).

Obesity and calorie restriction

As discussed earlier, animal and human studies have shown that obesity adversely affects many risk factors for CVD and contributes to an increased rate of CVD and to a reduced life expectancy (Nicholls and Viner 2005). Reducing calorie intake in obese humans improves risk factors for CVD and cardiovascular events (Eckel et al 2005). Based on this, many public health campaigns throughout the Western world focus on reducing calorie intake to minimize CVD (Anderson 2005). In addition, surgery designed to alter the gastrointestinal tract and reduce calorie intake or absorption improves multiple CVD risk factors (Fobi et al 2005).

Cholesterol and fatty acids

Diets with a high intake of cholesterol and fatty acids adversely effect lipid profile and are associated with an increased risk of CVD (Grundy and Vega 1988; Mensink and Katan 1992; Katan et al 1995). Trans fatty acids render the lipid profile even more atherogenic than saturated fatty acids. An abnormal lipid profile, for example, one with increased levels of low-density lipoprotein (LDL) cholesterol, accelerates the progression of atherosclerotic plaques and CVD (Fulcher et al 2004). Contrastingly, diets that restrict cholesterol and trans fatty acid intake have been shown to reduce CVD in human and animal studies (Chahoud et al 2004). The American Heart Association guidelines advocate a population-wide limitation of saturated fat to <10% of caloric consumption and a cholesterol intake of less than 300 mg/day to reduce the risk of CVD (Nicolosi et al 2001).

Alcohol

Epidemiological studies have consistently shown that alcohol intake has a bi-modal dose-related relationship to

CVD. An alcohol intake of one to four standard units per day correlates with a lower rate of cardiovascular events than zero intake (Simons et al 2000; Mukamal et al 2003). However, consumption of over six units of alcohol per day increases CVD-related mortality. Mechanisms proposed for the association of mild to moderate alcohol consumption with reduced atherogenesis include beneficial effects on lipoprotein metabolism, homeostasis, insulin sensitivity, and reduced aortic stiffness and inflammatory processes (da Luz and Coimbra 2004).

Dietary antioxidants

Antioxidants have been implicated in the prevention of atherosclerosis. In animals, antioxidants have been shown to improve lipid profile, reduce blood pressure, and reduce the rate of progression of atherosclerotic plaques (Wojcicki et al 1991). Epidemiological studies in humans have also shown that a high intake of fruit and vegetables, which contain a large variety and volume of antioxidants, is associated with a reduced risk of CVD (Gaziano 2004). Conversely, low plasma levels of antioxidants, including vitamins C and E, correlate with an increased CVD risk. Therefore, many guidelines, including those of the American Heart Association, recommend high intake of fruit and vegetables to prevent CVD (Krauss et al 2000; Kris-Etherton et al 2004).

Isoflavanes, flavonoids, and polyphenols are specific antioxidants that are associated with reduced risk of CVD. Dietary isoflavanes have been associated with an improvement in lipid profile (Lichtenstein 1998). Inverse relationships between dietary flavonoid and polyphenol intakes and CHD risk have also been reported (Hertog et al 1993; Manach et al 2005). An intake of 100 g/day of dark chocolate, which contains cocoa polyphenols, has been shown to reduce blood pressure in humans (Taubert et al 2003). The favorable effects of garlic, lethicin, and curcumin-containing foods on lipid profile has been attributed to the antioxidants in these foods (Ackermann et al 2001; Nicholosi et al 2001; Miquel et al 2002; Blomhof 2005).

Despite strong observational evidence associating a low antioxidant intake with CVD, interventional studies with single antioxidants overall have not demonstrated efficacy. Several studies have shown that vitamin E supplements do not alter the risk of cardiovascular events (Blomhoff 2005). Even so, this does not exclude a role for antioxidants in preventing CVD, and it has been suggested that a cocktail

of dietary antioxidants and other nutrients is required to reduce CVD risk (Srinath Reddy and Katan 2004).

Plant fibers, fats, and proteins

Epidemiological studies have consistently identified an association between a high dietary intake of fiber, reduced blood pressure and LDL cholesterol, and reduced incidence of CVD (Bazzano et al 2003; Lupton and Turner 2003; Streppel 2005). Other foods such as mono- and polyunsaturated fats, brans, nuts, plant sterols, and soy proteins have all been shown to have a favorable effect on lipid profile and blood pressure (Jensen et al 2004; Srinath Reddy and Katan 2004). Consequently, the US Food and Drug Administration (FDA) allows foods containing viscous fibers, soy protein, plant sterols, and nuts to carry a health claim that they reduce the risk of CVD (Jenkins et al 2005).

Fish

People with a high intake of dietary fish have a low rate of CVD (Kromhout et al 1985; Daviglus et al 1997). This has been attributed to the omega-3 (n-3) fatty acids in fish. In humans, fish oil supplements have favorable effects on lipid profile and blood pressure (Durrington et al 2001; Dyerberg et al 2004) and so reduce risk factors for CVD.

Vitamins and minerals

Raised homocysteine is a risk factor for the development of CVD and osteoporotic fractures (Sato et al 2005). It can be lowered with folic acid supplements. There is an inverse relationship between folate intake and CVD risk (Bazzano et al 2002a). Vitamin B6 also assists in homocysteine metabolism and a recent study suggests that vitamin B6 intake may protect against CVD (De Caterina et al 2004).

While restricting sodium intake reduces blood pressure in hypertensive patients, the role of salt restriction in preventing hypertension in the normotensive population remains controversial (Graudal et al 1998; Sacks et al 2001; Mitka 2004). Studies have also shown an inverse relationship between magnesium intake and CVD (Tang et al 2003; Al-Delaimy et al 2004). Potassium supplements have been shown to reduce blood pressure in normotensive subjects (Whelton et al 1997) and reduce the risk of stroke (Ascherio et al 1998).

Combinations of foods

While many individual foods have been shown to reduce the risk factors for CVD, it is important to establish the effect

of a combination of these foods. A combination diet high in plant sterols, soy proteins, almonds, and viscous fibers has been shown to have a similar effect on lipid profile and C-reactive protein to a 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitor (Jenkins et al 2003, 2005) and to lower the level of small dense LDL (Lamarche et al 2004). The Dietary Approaches to Stop Hypertension (DASH) trial reported that a diet that is rich in fruit, vegetables, and low in fat dairy foods significantly lowered systolic blood pressure in patients with isolated systolic hypertension (Moore et al 2001). The combined effect of the DASH diet plus three other lifestyle changes (weight loss, increased physical activity, and reduced sodium intake) produced a greater reduction in blood pressure than the three lifestyle measures alone (McGuire et al 2004). As described previously, a hypothetical polymeal consisting of a mix of wine, fish, dark chocolate, fruits, vegetables, garlic, and almonds has been proposed to reduce CVD (Franco et al 2004).

Conclusion

In conclusion, epidemiological studies consistently demonstrate that the intake of specific foods is associated with CVD risk. The Report of a Joint WHO/ FAO Expert Consultation (2003) states that there is convincing evidence that the risk of developing cardiovascular diseases is reduced by linoleic acid, fish and fish oils, vegetables and fruits, potassium, and low to moderate alcohol intake plus regular physical activity. Interventional studies show that intake of specific foods can improve conventional risk factors for CVD such as abnormal lipid profiles and hypertension. However, a reduction in blood pressure or cholesterol with certain foods does not prove that these foods are associated with a reduction in CVD. If foods are shown to reduce cardiovascular end points effectively this could reduce the huge cost of preventing and treating CVD. Additionally, dietary interventions to prevent CVD could reduce drug use and lower the risk of drug-induced side effects, which are relatively common and make a significant contribution to morbidity and mortality, especially in the older population (Le Couteur et al 2004).

Prevention of type 2 diabetes

Type 2 diabetes is the most common metabolic disease in the world and the leading cause of blindness and end-stage renal disease. It is rapidly becoming a global pandemic, projected to afflict one in 20 people by the year 2025,

secondary to population aging and obesity (Alberti et al 2004).

Lifestyle interventions of diet and exercise

Although the primary cause of the disease is still unknown, randomized controlled trials have unequivocally proven that preventing type 2 diabetes is possible (Pan et al 1997; Tuomilehto et al 2001; Diabetes Prevention Program 2002). Both the American Diabetes Prevention Program (2002) and the Finnish Diabetes Prevention Trial (Tuomilehto et al 2001) showed that lifestyle intervention reduced or delayed the risk of diabetes by ~60% over a 3-year period in people at higher risk (ie, they had impaired glucose tolerance [IGT]). Both interventions were *intensive* lifestyle modifications, with goals of >7% loss of body weight and 150 minutes of physical activity per week. Both emphasized restriction of energy, lower fat intake, and higher fiber intake. Not everyone reached their goals, of course, but significantly, diabetes did not develop in any high-risk participant who managed to achieve them. Despite its intensive nature, lifestyle intervention was also cost-effective relative to usual care and 2 times more cost-effective than one of the cheaper drugs (Diabetes Prevention Program 2003).

These trials cannot tell us whether weight loss per se, energy restriction, or physical activity was more important, or whether they act synergistically. Similarly, they do not determine whether the composition of the diet is relevant. While new studies will be needed to answer these questions, prospective, large-scale observational studies ("natural experiments") offer valuable insights. The first is that although BMI and physical activity are independent predictors of incident diabetes and mortality, the magnitude of the association with BMI is much greater than with physical activity (Hu et al 2004). In a recent study, being overweight increased the risk of developing type 2 diabetes within 7 years by 3 times, being obese by 12 times. But being obese but active still increased the risk by 11.5 times (Weinstein 2004). In other words, fitness alone is not sufficient to prevent diabetes.

Dietary composition

While intervention studies in diabetes prevention have universally employed conventional high carbohydrate, high fiber diets, we do not know if any reduced-energy diet would suffice. The epidemiological literature provides little evidence that total carbohydrate intake is associated with

the development of type 2 diabetes (Lundgren et al 1989; Colditz et al 1992; Salmeron, Ascherio, et al 1997; Salmeron, Manson, et al 1997), although the Melbourne Collaborative Health Study found that higher carbohydrate intake was associated with lower risk (Hodge et al 2004). A stronger association has been observed between total fat and saturated fat intake and type 2 diabetes (Tsunehara et al 1990; Marshall et al 1991), although not all findings are in agreement (Salmeron, Ascherio, et al 1997). Additionally, while two prospective cohort studies have shown no risk of diabetes from consuming increased amounts of sugar (Colditz et al 1992; Janket et al 2003; Hodge et al 2004), two other studies have observed an inverse association between sucrose intake and diabetes risk (Meyer et al 2000; Hodge et al 2004). Intakes of both whole grains (Meyer et al 2000; Fung et al 2002) and dietary fiber (in particular, cereal fiber) are associated with lower risk of type 2 diabetes (Salmeron, Ascherio, et al 1997; Salmeron, Manson, et al 1997; Meyer et al 2000; Hu et al 2001).

Glycemic index

One of the more contentious findings from recent prospective observational studies is that the glycemic index (GI) of the carbohydrate is an independent dietary determinant of risk of type 2 diabetes. In four large cohort studies (Salmeron, Ascherio, et al 1997; Salmeron, Manson, et al 1997; Hodge et al 2004; Schulze et al 2004), diets with a higher GI or higher glycemic load (GL) ($GL = GI \times \text{amount of carbohydrate}$) increased the relative risk of type 2 diabetes by 37%–60% after adjustments for known risk factors including energy and fiber. In the Nurses' Health Study, the combination of a high GL and a low cereal fiber intake further increased the risk of diabetes (relative risk = 2.5) when compared with a low GL and high cereal fiber intake (Salmeron, Manson, et al 1997). Refined starch could be more important in this context than refined sugars because, weight for weight, starch yields twice as much glucose than sucrose, and can be rapidly digested and absorbed. White bread intake may be one of the better single food predictors of type 2 diabetes (Hodge et al 2004).

Not all studies have confirmed the positive relationship between GI/GL and diabetes (Meyer et al 2000; Stevens et al 2002), and there are reservations about the ability of food frequency questionnaires to assess the overall glycemic impact or insulin demand associated with particular diets. However, acarbose, a drug that reduces the rate of carbohydrate absorption from the small intestine (but is not

absorbed itself), reduces the risk of type 2 diabetes and cardiovascular disease by 25%–50% in individuals with IGT (Chiasson et al 2002, 2003), suggesting that lowering postprandial glycemia per se is a worthy goal in diabetes prevention. In practice, both high fiber and low GI diets are associated with improved insulin sensitivity (Pereira et al 2002; Rizkalla et al 2004) and reduced levels of glycated hemoglobin (Giacco et al 2000; Brand-Miller et al 2003) in individuals with diabetes.

Food intake or dietary composition

Because excess body fat is the single most important determinant of type 2 diabetes (Hu et al 2001), the relationship between dietary factors and obesity is also clearly relevant. Recommendations to increase carbohydrate intake at the expense of fat to prevent weight gain may no longer be appropriate when the population is fatter, more insulin resistant, and glucose intolerant. Excessively high carbohydrate intake, specifically of refined grains, has been linked to the current epidemic of obesity (Liu et al 2003; Gross et al 2004). Recent reports indicate that carbohydrate restriction or modification can favorably affect both weight loss and cardiac risk factors in overweight subjects (Bouche et al 2003; Pereira et al 2004; Stern et al 2004).

Whether the composition of ingested calories or energy restriction is more critical to diabetes prevention remains to be seen. Nevertheless, it can be concluded that type 2 diabetes is a largely preventable disease. Intensive lifestyle interventions are not only highly effective but cost-effective too.

Dietary prevention of cancer

Cancer incidence (DePinho 2000) and mortality (Goodwin and Brodwick 1995) rise steeply with age. More than half of all cancers are diagnosed in the over 65 group (Goodwin and Brodwick 1995). Malignant neoplasms are a leading cause of death in the elderly, second to heart disease in the United States (Kochanek and Smith 2004). The link between diet and cancer has been recognized for many years (Doll 1992; Dreosti 1998), with diet second to tobacco smoking as a preventable cause. Raised body weight and physical inactivity also account for about a quarter of common cancers (IARC 2002).

Energy intake

Long-term food restriction increases the survival and lowers the incidence of neoplasms in rats (Thurman et al 1994).

There are no long-term food-restriction studies of cancer incidence in humans, except for comparative studies between countries. The Okinawan population has a lower calorie intake, a reduced incidence of cancer and vascular disease, and lives longer than the rest of Japan (Kagawa 1978; Willcox et al 2001). However, the findings are confounded by genetic and lifestyle differences.

Several studies of overweight adults over periods of 10 or more years show increased incidence of cancer in the higher weight groups (Garfinkel 1985; Bray 1996; Field et al 2001; IARC 2002). There is an increased risk of breast cancer in overweight women (Abu-Abid et al 2002; Mokbel 2003; Key et al 2003; Holmes and Willett 2004). Obesity increases breast cancer risk by 30% in postmenopausal women (Key et al 2003). Strategies for the prevention of cancers in relation to the obesity epidemic and in light of the antiaging effects of caloric restriction have been discussed recently (Hursting et al 2003).

Diet and cancer epidemiology

In the late 1970s, the research focus of diet and cancer shifted from animal experiments (often using potent carcinogens with or without dietary change) to observational studies in humans. Incidence data of human cases started to be collected systematically. It emerged that there were important differences between countries or regions. For some cancers there were 10-fold differences and for a few types, such as esophagus and malignant melanoma there were 100-fold differences between the regions with the highest and lowest incidence rates. Plotting between-country rates for a particular cancer against estimated national consumption of a food or nutrient has given rise to suggestive correlations. Using mostly between-country epidemiology Doll and Peto (1981a) estimated that 38% of the causes of preventable cancers might be related to something in the diet, including alcohol. In the same year, Doll and Peto (1981b) hypothesized that dietary beta-carotene may be protective against cancer, based on observations that beta-carotene is an antioxidant that is present in green leaves and many fruits, and these vegetable foods appear to be inversely associated with some cancers.

Since that time, there has been much epidemiological research on diet and cancer, both case-control studies, where the dietary search is retrospective and prospective cohort studies. There have even been a small number of randomized controlled preventive trials usually with pure nutrients. Mechanisms for any association have been suggested by

basic science research, experimental pathology, or cell culture.

Diet and different types of cancer

There are many different types of cancer. Diet has been suggested and considered as a possible causative factor for at least 18 different types of cancer. Avoiding the dietary causative factors may potentially prevent these cancers. The last 25 years have seen dietary associations with cancer rise and fall. Here are some examples.

Fat intake and breast cancer

When mortality from breast cancer is plotted against national fat consumption the correlations are striking (Armstrong and Doll 1975). However, more dietary fat is eaten by men. Case-control studies then showed weak and inconsistent associations of breast cancer mortality with dietary fat, and most of the large cohort studies found that there was no significant association with total fat consumption (Boyd et al 1993) or the type of fat consumed (Simmons et al 1998).

Fruits and vegetables

At present there is uncertainty about protective effects of fruits and vegetables. Many case-control studies indicate that fruits and vegetables appear to be protective against several types of cancer (Steinmetz and Potter 1996), but the latest results from cohort studies in North America (Smith-Warner et al 2001) and Europe (van Gils et al 2005) have not shown that fruit and vegetables protect against breast cancer. However, they may well protect against cancer elsewhere, for example stomach (De Stefani et al 2004).

Beta carotene

Several randomized controlled prevention trials have not found beta-carotene to be protective against cancer, at least not in large pharmaceutical dosage in older subjects (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994).

Fiber and colorectal cancer

Physiological considerations and case-control studies indicate that dietary fiber protects against cancer of the large bowel (colorectal cancer). Moreover, the definition of dietary fiber is not unified, nor the chemical method used to quantify fiber in food. The largest of the prospective studies by Willett's group in US nurses did not find a significant protective effect (Giovannucci et al 1994). Recently there

was a report of an interesting contradiction of this null finding. The largest prospective study of diet and cancer in the world, the European Prospective Investigation into Cancer and Nutrition (EPIC) is following over 500 000 individuals in 10 European countries and in their early results dietary fibers *were* inversely associated with colorectal cancer (Tjonneland et al 2004). The authors suggest that the clearer result in EPIC may be because of the much greater range of fiber intakes across 10 different countries and different occupations. However, the latest report from the Nurses' Health Study and the Health Professionals' Follow-up Study failed to link fiber intake to colorectal cancer, but revealed considerable confounding by other dietary and lifestyle factors (Michels et al 2005).

Meat and colorectal cancer

Whether there is a positive or potentially causal association of red meat and colorectal cancer is also controversial at present. A minority of the cohort studies, including the large Willett group Nurses' Health Study cohort, show that colorectal cancer is associated with meat consumption (Chan et al 2005). But the majority of other cohort studies do not show this (Truswell 2002). The most recent report of a prospective study of 478 040 men and women from 10 European countries free from cancer at enrollment between 1992 and 1998 and followed for 4.8 years shows a significant association (Norat et al 2005). There appears to be a consistent small association of processed meats and colorectal cancer (Norat et al 2002, 2005). Here, there are other added chemicals, for example, nitrates that may explain the association. In support of the null relationship with meat is evidence that vegetarians do not, on follow-up, have less colorectal cancer than socially matched omnivores (Key et al 1998). A high fish intake was found to be associated with a decreased risk of colorectal cancer (Norat et al 2005).

General conclusions: diet and cancer

The two most recent thorough and authoritative reviews of diet and the causation of cancer were the 670 page review by the World Cancer Research Fund (1997), which is undergoing a necessary review at present; and the report by a committee of the UK Department of Health (1998), which did not include consideration of alcohol units. Evidence of associations of diet with cancer is briefly summarized in a Report of a Joint WHO/FAO Expert Consultation (2003).

Dietary factors are different for different cancers. Avoidance of overweight and immoderate alcohol intake

Table 1 Probable and possible associations of dietary components and major cancers

Cancer	Promote	Delay
Mouth, pharynx, esophagus	Alcohol C Micronutrient deficiency P	
Stomach	Preserved salted foods P	Fruit and vegetables P
Colorectal	Overweight P Inactivity P Alcohol P Red meat P	Dietary fibre P
Breast	Obesity P Alcohol (small) P Inactivity: possible	Breastfeeding: possible
Endometrial	Obesity C	

Abbreviations: C, convincing; P, probable.

NOTE: Dietary factors are different for different cancers. Avoidance of obesity and overweight and of immoderate alcohol intakes can help protect against several different cancers.

helps protect against several types of cancer. Table 1 summarizes the probable and possible associations of dietary components and some major cancers.

Diet to prevent dementia

Increasing age is the strongest epidemiological risk factor for most cases of dementia. As the average lifespan increases beyond 80 years in the 21st century, neurodegenerative diseases like dementia will become more frequent. Primary and secondary prevention of dementia at the individual and population levels could diminish the future increase in the prevalence of dementia. It is estimated that if the median age of onset of Alzheimer disease (AD) could be increased by 6.7 years, then there would be 35.6% fewer cases of AD by 2050 (Sloane et al 2002).

The dementias include AD, vascular dementia, frontotemporal dementia, Lewy body disease, dementia secondary to alcohol and substance abuse, and other uncommon types. The epidemiological study of differences in genetic vulnerability and environmental exposure in populations with different patterns of dementia may contribute to identification of modifiable risk factors for dementia. Researchers are also looking for dietary patterns and specific nutrients that may enhance brain function and so reduce the risk of developing dementia (Solfrizzi et al 2003; Yen 2003; Whalley et al 2004; Luchsinger and Mayeux 2004). Recent work suggests that individuals who consume large amounts of fruits and vegetables may reduce their risk of developing dementia (Joseph et al 2005). Prevention is

particularly important for dementia as there is no disease-modifying treatment available at present.

Dietary factors have been associated with increased and decreased risks of dementia. Higher intake of energy and lower intake of antioxidants may amplify the process of dementia through oxidative stress (Otsuka et al 2002). Increased intake of fatty acids may contribute to dementia through atherosclerosis and thrombosis, inflammation, impaired membrane functioning, or via accumulation of beta-amyloid (Kalmijn 2000).

Dietary antioxidants

Oxidative stress may produce neuronal degeneration through protein oxidation, DNA oxidation, and lipid peroxidation. The antioxidant micronutrients are ascorbate (vitamin C), alphatocopherol (vitamin E), and carotenoids, which are provided in the diet, particularly by fruit and vegetables. In observational studies, a high intake of vitamins E and C is protective against AD (Engelhart et al 2002b; Morris et al 2002). In the Honolulu-Asia Aging Study (HAAS) the use of vitamin E and C supplements was associated with a reduced risk of prevalent cases of vascular dementia, but was neither associated with prevalent cases of AD (Masaki et al 2000), nor with incident cases of dementia (Laurin et al 2002). Vitamin E supplementation is reported neither to prevent the progression from mild cognitive impairment to dementia (Blacker 2005) nor slow the progression of cognitive decline in patients with AD (Sano et al 1997). Dietary supplementation with fruit or vegetable extracts high in antioxidants, such as blueberry or spinach extracts, might improve cognitive performance (Joseph et al 2005).

Flavonoids, which are powerful antioxidants found in wine, tea, fruit, and vegetables may also prevent dementia. A large cohort study (PAQUID) showed that the intake of flavonoids is inversely related to the risk of dementia (Commenges et al 2000; Larrieu et al 2004). A low intake of wine is associated with a reduced incidence of AD (Lindsay et al 2002).

Folate and vitamin B12

Dietary deficiency of folate or vitamin B12 and the associated raised serum homocysteine may contribute to the etiology of AD and vascular dementia. Folate deficiency is one of the commonest forms of vitamin deficiency and is also associated with cerebral cortex atrophy (Snowdon et al 2000). High serum homocysteine levels are associated with vascular disease (Mayer et al 1996; Nygard et al 1997), and

high intraneuronal levels of homocysteine can cause cognitive impairment (La Rue et al 1997). Observational studies show that low serum folate levels are associated with AD and with all types of dementia (Meindok and Dvorsky 1970; Sneath et al 1973; Renvall et al 1989; Clarke et al 1998; Ebly et al 1998; Quadri et al 2004). However, analysis of three major randomized controlled trials (Fioravanti et al 1997; Sommer et al 1998; VITAL 2003) provided no evidence that folic acid with or without vitamin B12 has a beneficial affect on the cognitive function of the older person.

Fat, fatty acids, and caloric intake

A number of studies have suggested that high dietary intake of total fats, saturated fatty acids, trans fatty acids, and cholesterol; and low intake of monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), n-3 PUFA, and n-6 PUFA are associated with increased risk of dementia and its subtypes. The link between a high-fat diet and dementia has been predominantly supported by epidemiological studies (Grant 1997; Kalmijn et al 2000; Luchsinger et al 2002). Luchsinger et al (2002) found that higher intakes of calories and fat were only associated with an increased risk of AD in individuals carrying the ApoE epsilon 4 allele. However, some epidemiological studies have suggested contradictory results. In the Rotterdam Study (Engelhart et al 2002a), high intake of total, saturated, and trans fats and cholesterol, and low intake of MUFA, PUFA, n-6 PUFA, and n-3 PUFA were not associated with increased risk of dementia and subtypes. Furthermore, moderate to severe cognitive impairment is not associated with dietary fatty acids (Manzato et al 2003). Recently, Zhang et al (2005) showed that a high-fat diet induced neural oxidative stress, inflammation, and nuclear transcription factor NF (κ)-B activation in rat cerebral cortex.

The types of fatty acid consumed may affect the risk of dementia. In the PAQUID study, at least weekly consumption of fatty acids from fish or seafood (rich in polyunsaturated fatty acids) was associated with a lower risk of developing dementia including AD (Larrieu et al 2004). However, no significant association was found between consumption of meat (rich in saturated fatty acids) and the risk of dementia (Barberger-Gateau et al 2002). The Zutphen Elderly Study showed that increased fish consumption tended to be inversely associated with cognitive impairment and decline, whereas high linoleic acid intake was associated with cognitive impairment (Kalmijn 2000).

Excessive caloric intake may increase the risk of dementia. Obesity in middle age was found to increase the future risk of dementia in a 27-year longitudinal study of 10276 Californians (Whitmer et al 2005).

Alcohol

Excessive alcohol intake appears to increase the risk of dementia by direct neurotoxic effects, malnutrition, or trauma (French et al 1985). Wernicke's encephalopathy, Korsakoff's psychosis, and alcohol-related dementias are alcohol dementia syndromes in the elderly (Butters 1985). Heavy alcohol use is a contributing factor in 21%–24% of cases of dementia (Smith and Atkinson 1995; Thomas and Rockwood 2001).

Mild to moderate alcohol consumption of 1–3 drinks per day is found to reduce the risk of coronary heart disease, stroke, and dementia. In the Washington Heights Inwood-Columbia Aging project, light to moderate alcohol intake was associated with a lower risk of dementia and AD in persons aged 65 years and older (Luchsinger et al 2004). Similarly in the Rotterdam study, in persons aged 55 years and older, light to moderate alcohol intake (1–3 drinks per day) was associated with a lower risk of dementia (Ruitenberg et al 2002). The Canadian Study of Health and Aging also reported a lower risk of AD with consumption of wine, but not of other alcoholic beverages (Lindsay et al 2002). Other smaller studies have found no association between alcohol intake and a lower risk of cognitive impairment or dementia (Herbert et al 1992; Broe et al 1998; Leibovici et al 1999). Thus, excessive alcohol intake may increase the risk of dementia, whereas mild to moderate intake may diminish the risk.

Conclusions

Further studies are needed to identify the exact role of different nutrients, their interactions and the effect of genetic factors and lifestyle on cerebral aging and dementia (Deschamps et al 2001). There are insufficient data to support supplementation with vitamin C, vitamin E, folate, or vitamin B12 to prevent dementia. Despite some inconsistencies, high caloric and fat intakes are associated with increased risk of dementia, while fish and seafood are associated with a reduced risk of dementia.

Prevention of osteoporosis

Half of all Caucasian women have osteoporosis or osteopenia (low bone mass) by the end of their postmenopausal decade

(Melton et al 1992; Hansen and Vondracek 2004). The incidence in men is lower (Trombetti et al 2002). One in three men aged more than 60 years will suffer an osteoporotic fracture (Diamond 2005). Bone fractures, especially hip fractures, are the most devastating consequence of osteoporosis (Riggs and Melton 1995), leading to significant increases in morbidity and mortality (Cauley et al 2000). A 50-year-old Caucasian woman has a lifetime risk of fractures of 40% (Riggs and Melton 1995) and a 50-year-old man 14% (Eastell and Lambert 2002). In countries with high fracture rates, 20% of symptomatic spine fractures and 30% of hip fractures occur in men (Eastell et al 1998). Low bone mineral density (BMD) is the major determinant of fracture risk (Cummings et al 1993). In the elderly, low BMD can result from low peak bone mass (PBM) or accelerated bone loss (mainly due to loss of estrogen at menopause in women) or a combination (Eastell and Lambert 2002). PBM is the amount of bone acquired at maturity which is 70%–80% genetically determined, with environmental factors such as exercise plus calcium intake contributing 20%–30% (Eastell and Lambert 2002).

Food intake and body weight

Food intake and body weight are important in bone loss and osteoporosis (Macdonald et al 2005). Weight loss reduces bone mass and increases the risk for osteoporosis (von Mach et al 2004). Obesity has a beneficial effect by increasing bone mineral density at the lumbar spine of white American postmenopausal women of mean age 58 years (Castro et al 2005). The risk for osteoporosis among elderly men and women with a BMI of >30 was 33% compared with subjects with a normal BMI (Barrera et al 2004). It is believed that the attainment of maximal peak bone mass by body weight gain in childhood is an important strategy for the prevention of osteoporosis in later life in women (Saito et al 2005). Although protein intake is an important determinant of growth, it is not possible on present evidence to make recommendations about optimal protein intake for either bone growth or the prevention of osteoporosis (Prentice 2004). High protein intake increases urine calcium losses, which may be detrimental to optimum bone health (Heaney and Recker 1982). In older individuals, protein intake may be inadequate, and in a number of studies, though not all, low protein intake has been associated with increased bone loss in elderly men and women. Higher protein intake is generally associated with decreased risk of fracture (Rizzoli and Bonjour 2004) and better outcome after hip

fracture, due, in part, to decreased risk of complications (Delmi et al 1990).

Calcium

Calcium is the main bone-forming mineral. An adequate intake of calcium and vitamin D is essential to maintain skeletal integrity throughout life (Follin and Hansen 2003; Diamond et al 2005). Vitamin D is formed from 7-dehydrocholesterol in the skin during exposure to sunlight and subsequent hydroxylation in the liver to form 25-hydroxyvitamin D, which has a half-life of about 2 months (Eastell and Lambert 2002; Holick 2004). In turn, 25 hydroxyvitamin D is converted mainly in the kidney, to 1,25dihydroxyvitamin D, the active hormone (Holick 2004). The active vitamin D hormone increases calcium absorption from the gastrointestinal tract and thereby protects bone from resorption and facilitates bone mineral deposition (Akesson et al 1997). Calcium absorption in old age is about half that of the adolescent (Follin and Hansen 2003). Osteoporosis is prevented by calcium, which decreases bone turnover and reduces bone loss (Kanis 1999), and which also reduces the rate of degradation of vitamin D (Clements et al 1987). Calcium and vitamin D supplementation have been shown to lower the rates of fracture by 35%–50% (Reid et al 1995; Cumming and Nevitt 1997).

Vitamin D

Skeletal health in the elderly depends largely on the foundations laid in early childhood that are developed and maintained throughout life (Lau 2004). Women with a low milk intake during childhood and adolescence have a lower bone mass in adulthood and a greater risk of fracture (Kalkwarf et al 2003). An active lifestyle plus good nutrition in terms of calcium intake and exposure to sunshine to generate vitamin D are necessary to reduce the risk of osteoporosis (Eastell and Lambert 2002). In Australia, vitamin D deficiency can be prevented in most people by sun exposure of the face, hands, and arms to one third of the minimal erythema dose (the amount that produces a faint redness) on most days (Diamond et al 2005). For fair skin types this can be achieved by exposure to 5–15 minutes of sunlight in summer, depending on latitude, just outside the most damaging period for UVB exposure (10 am–2 pm, standard time), with longer exposures required in winter and in those with more pigmented skin (Diamond et al 2005). However, there is a global vitamin D insufficiency partly due to concern over the risk of melanoma and other skin

cancers caused by overexposure to UVB in sunlight (Calvo et al 2005) and partly due to an indoor lifestyle, even in the normal population (Diamond et al 2005). Reduced skin vitamin D synthesis is particularly a problem in older individuals, who may have reduced mobility and in dark skinned individuals, particularly if they dress modestly for cultural or religious reasons (Nowson et al 2004). This increases the need for dietary vitamin D supplementation in deficiency states. For those with insufficient sun exposure, there are increasing recommendations for much higher doses of supplementation than previously considered: around 1000 IU/day (Vieth 2004).

Homocysteine

Recently, high homocysteine concentrations have been described as a risk factor for osteoporotic fractures (Raisz 2004). Furthermore, supplementation with folate and vitamin B12 in stroke patients, who are at high risk of osteoporotic fracture, reduced hip fractures over a 2-year period to an extent equivalent to that reported for bisphosphonates, which are amongst the most effective pharmacological agents for osteoporotic fractures (Sato et al 2005).

Diet and age-related macular degeneration

Age-related macular degeneration (AMD) is the commonest and most rapidly increasing cause of blindness in the Western world (Bartlett and Eperjesi 2003). In Australia, the prevalence of AMD rises from about 1% in the 65–75-year-old age group to 5% in those aged 75–84 years and approximately 20% in people over the age of 85 (Constable 2004). The major risk factors are having a first degree relative with AMD and smoking (Constable 2004). Overweight and obesity due to excessive food intake is also a significant risk factor for AMD, along with decreased lutein and zeaxanthin status (Johnson 2005). One study showed that high birth weight significantly increased the risk of AMD (Hall et al 2002).

There are currently only limited treatment options for AMD (Bartlett and Eperjesi 2003). The progression of early AMD is accelerated by high-fat intake, whether saturated, monounsaturated, polyunsaturated, or transunsaturated (Seddon et al 2004) and reduced by a low intake of saturated fat (Mitchell et al 2003). Nuts and fish also reduced the risk of progression (Mitchell et al 2003).

Accumulating evidence suggests that low plasma levels of micronutrients, particularly zinc, luteins, and carotenoids

accelerate AMD progression (Mozaffarich et al 2003). Several dietary studies have also shown that increased antioxidant intake protects against AMD progression (reviewed by Hogg and Chakravarthy 2004).

These observations have led to interventional studies to assess the effect of micronutrient supplements on AMD progression. In the USA, the 3640 participant age-related eye diseases study (AREDS) found that supplementation with vitamins C (500 mg), E (400 IU), beta-carotene (15 mg), and zinc (80 mg) slowed AMD progression in patients with underlying AMD (Age-Related Eye Disease Study Research Group 2001).

Healthy aging through dietary therapy

For the primary prevention of the diseases of middle to old age, it appears that it is essential from an early age to adopt a healthy lifestyle of regular physical exercise, not smoking, and a nutrient-rich (wholegrain cereals, legumes, fruits, and vegetables), but low-energy (less fat and sugar) diet to maintain a moderately lean body weight (Paffenberger et al 1993; Fraser and Slavik 2001; Polidori 2003; Report of a Joint WHO/FAO Expert Consultation 2003; Kesteloot 2004; Everitt et al 2005). In young people, the failure to identify and treat overweight, impaired glucose tolerance, hypertension, and hypercholesterolemia may result in the development of type 2 diabetes and coronary artery disease in later life, leading to early morbidity and mortality (Berry et al 2004).

Lifestyle interventions can be beneficial at most ages. Due to the relatively long “lag time” of risk factors for age-related diseases, humans can benefit at all ages from modification of their unhealthy practices of high consumption of saturated fats, salt, and refined carbohydrates, as well as low consumption of fruits and vegetables (Report of a Joint WHO/FAC Expert Consultation 2003). Much of the present mortality is due to behavioral risk factors such as poor nutrition, insufficient physical activity, and tobacco smoking. Sedentary lifestyles are becoming common at all ages. Increased physical activity improves the quality of life and health in the elderly (Drewnowski and Evans 2001). A number of clinical trials in apparently healthy subjects have examined the effects of weight loss achieved by diet or exercise and reported improvements in cardiovascular and diabetes risk factors (Lee et al 2001). Current literature indicates that the risk of many cancers is decreased by reducing lifestyle factors such as smoking, high fat, meat, refined sugar diets, and physical inactivity

Table 2 Dietary approaches that delay age-related diseases

Dietary approach	Age-related disease					
	Cardiovascular disease	Diabetes mellitus	Cancer	Dementia	Osteoporosis	AMD
Caloric restriction	++	+	++			
Reduce obesity	++	++	+	+	Obesity protects	+
Low saturated fat	++	++	+	+		+
Alcohol 10–20 g/day	++		+	+		
Antioxidants	++		+	+		+
– fruits and vegetables	++		+	+		
– isoflavones/flavonoids/polyphenols	+			+		
– vitamins C and E	+			+		+
Plant fibers	+	+	+			
Plant fats	+			+		
Fish (omega-3 fatty acids)	++		+	++		+
B vitamins	+				+	
Low glycemic index		+				
Calcium and vitamin D					++	

Abbreviations: AMD, age-related macular degeneration.

NOTE: ++ = convincing evidence; + = conflicting evidence.

(Barnard 2004). Randomized controlled trials over 3 years have demonstrated that lifestyle changes (weight loss if overweight, increased physical activity, moderate alcohol intake, diet high in fruits and vegetables, low-fat dairy products, and low sodium) have a blood pressure lowering effect similar to that seen with drug therapy (Krousel-Wood et al 2004). The SENECA study of 2600 elderly people in Europe born 1913–1918 and studied over 10 years starting in 1988, reported that a healthy lifestyle at older ages (70+ years) is able to delay the deterioration of health status and reduces mortality (de Groot et al 2004). Dietary modifications that have been shown in clinical trials to delay the onset of cardiovascular disease, type 2 diabetes, certain cancers, osteoporosis, and age-related macular degeneration are summarized in Table 2.

Fruit and vegetable diets

A number of diets have been found to reduce mortality and prolong life. To achieve a degree of calorie restriction without malnutrition the choice is a low-energy diet with high nutrient density. Such a diet could consist of vegetables, fruits, low-fat milk products, whole grain cereals, and legumes (Elmadfa and Freisling 2005). Tubers such as potatoes and cassava should not be included in fruits and vegetables (Report of a Joint WHO/FAO Expert Consultation 2003). The main benefits of the fruit and vegetable diets are the lower intake of saturated fat, cholesterol, and animal proteins, as well as the higher intakes

of complex carbohydrates, dietary fiber, magnesium, folic acid, vitamin C and E, carotenoids, and other phytochemicals (Leitzmann 2005). The long-term benefits of the high fruit and vegetable diet have been studied extensively (Ness and Powles 1997; Kraus et al 2000; Bazzano et al 2002b; Sauvaget et al 2003; Hung et al 2004; Lock et al 2005; Tucker et al 2005). Fruit and vegetable diets contain large amounts of antioxidants, which slow the development of cardiovascular disease (Gaziano 2004). Vegetarians are reported to have reduced mortality from cardiovascular disease (Key et al 1998; Bazzano et al 2002b) and a lower risk of all-cause mortality (Genkinger et al 2004). A high fruit and vegetable intake (5 servings per day) plus low saturated fat diet (<12% energy intake) was found to significantly reduce coronary heart disease and all-cause mortality in a trial of 501 healthy men followed over 18 years in the Baltimore Longitudinal Study of Aging (Tucker et al 2005). In a prospective cohort study of 40 309 Japanese men and women initiated in 1980–1981 and followed until 1998, the daily consumption of green-yellow vegetables and fruit was associated with a lower risk of stroke, intracerebral hemorrhage, and cerebral infarction mortality (Sauvaget et al 2003). The DASH (Dietary Approaches to Stop Hypertension) diet, which is high in fruits and vegetables and low-fat dairy products and reduced in fat and salt, has been shown in large randomized controlled trials to reduce blood pressure, blood cholesterol, and homocysteine, risk factors for cardiovascular disease

(Craddick et al 2003). Data from the Nurses' Health Study on women and the Health Professionals' Follow-up Study in men showed that the benefits of five or more servings of fresh fruits and vegetables per day, especially green leafy vegetables, are mainly due to a lower incidence of cardiovascular disease but not cancer (Hung et al 2004). There was no association between fruit and vegetable intake and incidence of specific cancers (Hung et al 2004). A prospective study of 285 526 women in Europe followed over 5.4 years failed to associate vegetable and fruit intake with the risk for breast cancer (van Gils et al 2005). One study (Montonen et al 2005) has shown that a high fruit and vegetable intake reduced the risk of type 2 diabetes, whereas a diet characterized by butter, potatoes, and whole milk increased the risk. The advantages of the high fruit and vegetable diet may be due to the lower energy intake of that diet, plus the effects of specific dietary constituents, such as antioxidants.

Mediterranean diets

The Mediterranean diet, despite having a high lipid content, protects against the chronic diseases of old age, especially heart disease (Trichopoulou 2001; Barbaste et al 2002; Trichopoulou and Critselis 2004). This diet was developed in the olive growing area of the Mediterranean region in the late 1950s after the Second World War, before the arrival of the fast-food culture (Trichopoulou 2001). Olive oil characterizes the diet and permits the consumption of large quantities of vegetables and legumes in salads. The total lipid content may be high at 40% of total energy intake in Greece or a moderate 30% in Italy (Trichopoulou 2001). Virgin olive oil provides large amounts of stable and not easily oxidizable fatty acids as well as powerful antioxidants (Battino and Ferreiro 2004). A higher intake of mono-unsaturated fatty acids in a typical Mediterranean diet was found to reduce all-cause mortality in an 8.5 year follow-up of the Italian Longitudinal Study on Aging in elderly nondemented subjects aged 65–84 years (Solfrizzi et al 2005). A Mediterranean diet modified so as to apply across Europe was associated with increased survival in 74 607 men and women aged 60 years or more (Trichopoulou et al 2005).

The Okinawan diet

The Okinawan people living on islands south of Tokyo are reported to live longer than any other population on earth. They are smaller in body size, eat 40% fewer calories than

the Americans and live 4 years longer due mainly to their lower mortality from heart disease and cancer (Kagawa 1978; Suzuki et al 2001; Willcox et al 2001). Their diet consists of whole grains, vegetables, fruit, soy, and fish rich in omega-3 fatty acids. When the Okinawans live in the United States, they acquire the diet and the mortality of the Americans. Okinawa has a US naval base, and younger Okinawans are now adopting Western habits, which should reduce their life expectancy. The greater longevity of older Okinawans is only partly due to reduced energy intake and different composition of diet, as there are also differences in the level of exercise and philosophy of life (Willcox et al 2001). In the Uyur region of China there is a population reported to be longer-lived than the Okinawans (Kawamura et al 2003).

Mechanisms for dietary prevention of disease

A number of hypotheses for the overall mechanisms by which diet may modify the development of age-related diseases have been proposed (Meydani 2001; Masoro 2002d; Koubova and Guarente 2003; Polidori 2003). It is widely believed that many age-related diseases result from oxidative damage to DNA, RNA, protein, and lipids by reactive-oxygen species (Harman 1988; Meydani 2001; Head et al 2002; Polidori 2003). A number of studies have shown that CR (Yu 1996; Merry 2004) and dietary antioxidants (Meydani 2001) reduce the oxidative stress in mitochondria and damage in tissues.

Age-associated diseases, such as atherosclerosis, dementia, and cataract may in part be due to glycation caused by the action of high plasma glucose on tissue proteins (Suji and Sivakami 2004) causing accumulation of AGEs (advanced glycation end products). Plasma glucose is of course reduced by CR (Masoro 1996).

Studies in the Ames dwarf mouse with a gene mutation that leads to low pituitary growth hormone production indicate that reduced function of the growth hormone–IGF-1 axis retards aging changes, prevents age-related pathology, and prolongs life in the mouse in a similar manner to CR (Ikeno et al 2003). In humans, raised levels of IGF-1 are seen in many cancers (Hursting et al 2003). However, low levels of IGF-1 may be risk factors for cardiovascular disease (Kaplan et al 2005; Sandhu 2005) and type 2 diabetes (Dunger et al 2004; Sandhu 2005).

Furthermore, many of the intracellular pathways responsible for aging changes have been elucidated (Morris

2005). Interestingly, polyphenols in fruits and vegetables stimulate similar pathways as CR. In each case, activation of sirtuins takes place as an early event. Sirtuins are a class of enzymes that activate various factors inside the cell that increase oxidative stress defenses, suppress insulin receptor signaling, and modulate senescence mechanisms and other processes (Morris 2005). Resveratrol is a particularly powerful polyphenol that can increase lifespan of several species tested to date (Howitz et al 2003; Morris 2005). Thus a diet rich in polyphenols might be able to achieve a similar outcome on health and longevity as CR.

Conclusions

A delayed onset of aging diseases may best be achieved by establishing a healthy lifestyle in early life as in childhood or in the young adult. A healthy lifestyle includes regular physical exercise, not smoking, a happy relaxed mind, and a nutrient-rich low-calorie diet to maintain a moderately lean body weight. Such a diet would include wholegrain cereals, legumes, fruits and vegetables, with a low intake of saturated fat and trans fatty acids. Energy intake, which in excess leads to overweight, appears to be the major dietary factor determining the onset of age-related diseases such as cardiovascular disease, diabetes, cancer, and dementia, and therefore lifespan. The composition of the diet is also important, since there is good evidence that a vegetarian diet (rich in antioxidants), the Mediterranean diet (high in olive oil with monounsaturated fatty acids), and the Okinawan diet (high in fruits and vegetables plus omega-3 fatty acids in fish) are beneficial by delaying age-associated diseases. Lowering fat intake to less than 10% of caloric intake, appears to be important for reducing the risk of cardiovascular disease and diabetes. The development of osteoporotic fractures may be prevented by increasing the intake of calcium, vitamin D, and probably folate.

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References

- Abu-Abid S, Szold A, Klausner J. 2002. Obesity and cancer. *J Med*, 33: 73–86.
- Ackermann RT, Mulrow CD, Ramirez G, et al. 2001. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med*, 161:813–24.
- Age-Related Eye Disease Study Research Group. 2001. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report nr 9. *Arch Ophthalmol*, 119:1439–52.
- Ajani UA, Lotufo PA, Gaziano JM, et al. 2004. Body mass index and mortality among US male physicians. *Ann Epidemiol*, 14:731–9.
- Akesson K, Lau KW, Bayling DJ. 1997. Rationale for active vitamin D analog therapy in senile osteoporosis. *Calcif Tissue Int*, 60:100–5.
- Alberti G, Zimmer P, Shaw J, et al. 2004. Type 2 diabetes in the young: the evolving epidemic. *Diabetes Care*, 27:1798–811.
- Al-Delaimy WK, Rimm EB, Willett WC, et al. 2004. Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr*, 23: 63–70.
- Alpha-tocopherol, Beta Carotene Cancer Prevention Group. 2004. The effect of vitamin E and beta-carotene on the incidence of lung cancers and other cancers in male smokers. *N Engl J Med*, 330:1029–35.
- Anderson DR. 2005. The scientific rationale for health promotion. *Am J Health Promot*, 19:Suppl 3–4.
- Armstrong B, Doll R. 1975. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Br J Cancer*, 68:617–31.
- Ascherio A, Rimm EB, Hernan MA, et al. 1998. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation*, 98:1198–204.
- Barbaste M, Berke B, Dumas M, et al. 2002. Dietary antioxidants, peroxidation and cardiovascular risks. *Nutr Health Aging*, 6:209–23.
- Barberger-Gateau P, Letenneur L, Deschamps V, et al. 2002. Fish, meat, and risk of dementia: cohort study. *BMJ*, 325:932–3.
- Barker DJP. 1995. Fetal origins of coronary heart disease. *BMJ*, 311: 171–4.
- Barnard RJ. 2004. Prevention of cancer through lifestyle changes. *Evid Based Complement Alternat Med*, 1:233–9.
- Barrera G, Bunout D, Gattas V, et al. 2004. A high body mass protects against femoral neck osteoporosis in healthy elderly subjects. *Nutrition*, 20:769–71.
- Bartlett H, Eperjesi F. 2003. Age-related macular degeneration and nutritional supplementation: a review of randomized controlled trials. *Ophthalmic Physiol Opt*, 23:383–99.
- Battino M, Ferreiro MS. 2004. Ageing and the Mediterranean diet: a review of the role of dietary fats. *Public Health Nutr*, 7:953–8.
- Bazzano LA, He J, Ogden LG, et al. 2002a. Dietary intake of folate and risk of stroke in US men and women: NHANES I Epidemiologic Follow-up Study. National Health and Nutrition Examination Survey. *Stroke*, 33:183–8.
- Bazzano LA, He J, Ogden LG, et al. 2002b. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Am J Clin Nutr*, 76:93–9.
- Bazzano LA, He J, Ogden LG, et al. 2003. Dietary fiber intake and reduced risk of coronary heart disease in US men and women. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Intern Med*, 163:1897–904.
- Berg BN, Simms HS. 1960. Nutrition and longevity in the rat. II. Longevity and onset of disease with different levels of food intake. *J Nutr*, 71: 255–63.
- Berg BN, Simms HS. 1965. Nutrition, onset of disease, and longevity in the rat. *Can Med Assoc J*, 93:911–13.
- Berry D, Galasso P, Melkus G, et al. 2004. Obesity in youth: implications for the advanced practice nurse in primary care. *J Am Acad Nurse Pract*, 16:326–34.
- Blacker D. 2005. Mild cognitive impairment – no benefit from vitamin E, little from donepezil. *N Engl J Med*, 352:2439–41.
- Blomhoff R. 2005. Dietary antioxidants and cardiovascular disease. *Curr Opin Lipidol*, 16:47–54.

- Bouche C, Rizkalla S, Luo J, et al. 2003. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. *Diabetes Care*, 26:822–8.
- Boyd NJ, Martin IJ, Noffel M, et al. 1993. A meta analysis of studies of dietary fat and cancer risk. *Br J Cancer*, 68:627–36.
- Brand-Miller JC. 2004. Glycemic index in relation to coronary disease. *Asia Pac J Clin Nutr*, 13(Suppl):S3.
- Brand-Miller J, Hayne S, Petocz P, et al. 2003. Low glycemic index diets in the management of diabetes; a meta-analysis of randomized controlled trials. *Diabetes Care*, 26:2261–7.
- Bray GA. 1996. Health hazards of obesity. *Endocr Metab Clin N Am*, 25:907–19.
- Broe GA, Creasey H, Jorm AF, et al. 1998. Health habits and risk of cognitive impairment and dementia in old age. A prospective study on the effects of exercise, smoking, and alcohol consumption. *Aust N Z J Public Health*, 22:621–3.
- Bronson RT, Lipman RD. 1991. Reduction in rate of occurrence of age related lesions in dietary restricted laboratory mice. *Growth Dev Aging*, 55:169–84.
- Butters N. 1985. Alcoholic Korsakoff's syndrome. Some unresolved issues concerning etiology, neuropathology and cognitive deficits. *J Clin Exp Neuropsychol*, 7:181–210.
- Calle EE, Thun MJ, Petrelli JM, et al. 1999. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*, 341:1097–105.
- Calvo MS, Whiting SJ, Barton CN. 2005. Vitamin D intake: a global perspective of current status. *J Nutr*, 135:310–16.
- Cameron AJ, Welborn TA, Zimmet PZ, et al. 2003. Overweight and obesity in Australia: the 1999–2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Med J Aust*, 178:427–32.
- Castro JP, Joseph LA, Shin JJ. 2005. Differential effect of obesity on bone mineral density in White, Hispanic and African American women: a cross sectional study. *Nutr Metab*, 2:9.
- Cauley JA, Thompson DE, Ensrud KC, et al. 2000. Risk of mortality following clinical fractures. *Osteoporosis Int*, 11:556–61.
- Chahoud G, Aude YW, Mehta JL, et al. 2004. Dietary recommendations in the prevention and treatment of coronary heart disease: do we have the ideal diet yet? *Am J Cardiol*, 94:1260–7.
- Chan AT, Tranah GJ, Giovannucci EL, et al. 2005. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer*, 115:648–52.
- Chiasson J, Josse RG, Gomis R, et al. 2002. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*, 359:2072–7.
- Chiasson J, Josse RG, Gomis R, et al. 2003. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA*, 290:486–94.
- Clarke R, Harrison G, Richards S; VITAL Trial Collaborative Group. 2003. Effect of vitamins and aspirin on markers of platelet activations, oxidative stress and homocysteine in people at high risk of dementia. *J Intern Med*, 264:67–75.
- Clarke R, Smith AD, Jobst KA. 1998. Folate vitamin B12 and total homocysteine levels in confirmed Alzheimer's disease. *Arch Neurol*, 55:1449–55.
- Clements MR, Johnson L, Fraser DR. 1987. A new mechanism for induced vitamin D deficiency in calcium deprivation. *Nature*, 325:62–5.
- Colditz G, Manson J, Stampfer M, et al. 1992. Diet and risk of clinical diabetes in women. *Am J Clin Nutr*, 55:1018–23.
- Commenges D, Scotet V, Renaud S, et al. 2000. Intake of flavonoids and risk of dementia. *Eur J Epidemiol*, 16:357–63.
- Connor SL, Ojeda LS, Sexton G, et al. 2004. Diets lower in folic acid and carotenoids are associated with the coronary disease epidemic in Central and Eastern Europe. *J Am Diet Assoc*, 104:1793–9.
- Constable IJ. 2004. Age-related macular degeneration and its possible prevention. *MJA*, 181:471–2.
- Craddick SR, Elmer PJ, Obarzanek E, et al. 2003. The DASH diet and blood pressure. *Curr Atheroscl Rep*, 5:484–91.
- Cumming RG, Nevitt MC. 1997. Calcium for prevention of osteoporotic fractures in postmenopausal women. *J Bone Miner Res*, 12:1321–9.
- Cummings JH, Edmond LM, Magee EA. 2004. Dietary carbohydrates and health: do we still need the fibre concept? *Clin Nutr Suppl*, 1:5–17.
- Cummings SR, Black DM, Nevitt MC, et al. 1993. Bone density at various sites for prediction of hip fractures. The study of osteoporotic fractures research group. *Lancet*, 341:72–5.
- da Luz PI, Coimbra SR. 2004. Wine, alcohol and atherosclerosis: clinical evidences and mechanisms. *Braz J Med Biol Res*, 37:1275–95.
- Daviglus ML, Stamler J, Greenland P, et al. 1997. Fish consumption and the 30 year risk of fatal myocardial infarction. *N Engl J Med*, 336:1046–53.
- De Caterina R, Zampolli A, Madonna R, et al. 2004. New cardiovascular risk factors: homocysteine and vitamins involved in homocysteine metabolism. *Ital Heart J*, 5 Suppl 6:19S–24S.
- de Groot LCPMG, Verheijden MW, de Henauw S, et al. 2004. Lifestyle, nutritional status, health, and mortality in elderly people across Europe: a review of the longitudinal results of the SENECA study. *J Gerontol A Biol Sci Med Sci*, 59A:1277–84.
- Delmi M, Rapin CH, Bengoa JM, et al. 1990. Dietary supplementation in elderly patients with fractured neck of the femur. *Lancet*, 335:1013–16.
- DePinho RA. 2000. The age of cancer. *Nature*, 408:248–54.
- Deschamps V, Barberger-Gateau P, Peuchant E, et al. 2001. Nutritional factors in cerebral aging and dementia: epidemiological arguments for a role of oxidative stress. *Neuroepidemiology*, 20:7–15.
- De Stefani F, Correa P, Boffetta P, et al. 2004. Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. *Gastric Cancer*, 7:211–20.
- Diabetes Prevention Program Research Group. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*, 346:393–403.
- Diabetes Prevention Program Research Group. 2003. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*, 26:2518–23.
- Diamond TH. 2005. Pharmacotherapy of osteoporosis in men. *Expert Opin Pharmacother*, 6:45–58.
- Diamond TH, Eisman JA, Mason RS, et al. 2005. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *MJA*, 182:281–5.
- Doll R. 1992. The lessons of life: keynote address to the nutrition and aging conference. *Cancer Res*, 52(7 Suppl):2024S–9S.
- Doll R, Peto R. 1981a. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *JNCI*, 66:1191–308.
- Doll R, Peto R. 1981b. Can dietary beta-carotene materially reduce human cancer? *Nature*, 290:201–8.
- Dreosti IE. 1998. Nutrition, cancer, and aging. *Ann N Y Acad Sci*, 854:371–7.
- Drewnowski A, Evans WJ. 2001. Nutrition, physical activity, and quality of life in older adults. *J Gerontol A Biol Sci Med Sci*, 56:89–94.
- Dunger D, Yuen K, Ong K. 2004. Insulin-like growth factor-1 and impaired glucose tolerance. *Horm Res*, 62 Suppl 1:101–7.
- Durrington PN, Bhatnagar D, Mackness MI, et al. 2001. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. *Heart*, 85:544–8.
- Dyerberg J, Eskersen DC, Anderson PW, et al. 2004. Effect of trans- and n-3 unsaturated fatty acids on cardiovascular risk markers in healthy males. An 8 weeks dietary intervention study. *Eur J Clin Nutr*, 58:1062–70.
- Eastell R, Boyle IT, Compton J, et al. 1998. Management of male osteoporosis: report of the UK Consensus Group. *Q J Med*, 91:71–92.
- Eastell R, Lambert H. 2002. Plenary lecture. Strategies for skeletal health in the elderly. *Proc Nutr Soc*, 61:173–80.
- Ebly EM, Schaefer JP, Campbell NRC. 1998. Folate status, vascular disease and cognition in elderly Canadians. *Age Ageing*, 27:485–91.

- Eckel RH, Grundy SM, Zimmet PZ. 2005. The metabolic syndrome. *Lancet*, 365:1415–28.
- Eckel RH, York DA, Rossner S, et al. 2004. Prevention Conference VII: obesity a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation*, 110:2968–75.
- Elmadfa I, Freisling H. 2005. Fat intake, diet variety and health promotion. *Forum Nutr*, 57:1–10.
- Engelhart MJ, Geerling MI, Ruitenberg A, et al. 2002a. Diet and the risk of dementia: does fat matter? The Rotterdam Study. *Neurology*, 59:1915–21.
- Engelhart MJ, Geerling MI, Ruitenberg A, et al. 2002b. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA*, 287:3223–9.
- Everitt AV, Roth GS, Le Couteur DG, et al. 2005. Caloric restriction versus drug therapy to delay the onset of aging diseases and extend life. *Age*, 27:39–48.
- Eyre H, Kahn R, Robertson RM. 2004. Preventing cancer, cardiovascular disease, and diabetes. *Stroke*, 35:1999–2010.
- Fairfield NM, Fletcher RH. 2002. Vitamins for chronic disease prevention in adults. *JAMA*, 287:3116–28.
- Field AE, Coakley EH, Must A, et al. 2002. Impact of overweight on the risk of developing common chronic diseases during a 10 year period. *Arch Intern Med*, 161:1581–6.
- Fioravanti M, Ferrario E, Massaia M, et al. 1997. Low folate levels in the cognitive decline of elderly patients and efficacy of folate as a treatment for improving memory deficits. *Arch Gerontol Geriatr*, 26:1–13.
- Flegal KM, Graubard BI, Williamson DF, et al. 2005. Excess deaths associated with underweight, overweight, and obesity. *JAMA*, 293:1861–7.
- Fobi MA, Lee H, Felahy B, et al. 2005. Choosing an operation for weight control, and the transected banded gastric bypass. *Obes Surg*, 15:114–21.
- Follin SL, Hansen LB. 2003. Current approaches to the prevention and treatment of postmenopausal osteoporosis. *Am J Health Syst Pharm*, 60:883–901.
- Fontana L, Meyer TE, Klein S, et al. 2004. Long-term caloric restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci USA*, 101:6659–63.
- Franco OH, Bonneux L, de Laet C, et al. 2004. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ*, 329:1447–50.
- Fraser GE. 1999. Nut consumption, lipids, and the risk of a coronary event. *Clin Cardiol*, 22(Suppl 7):III 11–15.
- Fraser GE, Shavlik DJ. 2001. Ten years of life: is it a matter of choice? *Arch Intern Med*, 161:1645–52.
- French LR, Schuman LM, Mortimer JA, et al. 1985. A case-control study of dementia of the Alzheimer type. *Am J Epidemiol*, 121:414–21.
- Fulcher GR, Amarena JV, Conner GW, et al. 2004. Prevention of cardiovascular disease: an evidence based clinical aid 2004. *Med J Aust*, 181(6 Suppl) F4–F14.
- Fung T, Hu F, Pereira M, et al. 2002. Whole grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr*, 76:535–40.
- Garfinkel L. 1985. Overweight and cancer. *Ann Intern Med*, 103:1034–6.
- Gaziano JM. 2004. Vitamin E and cardiovascular disease: observational studies. *Ann NY Acad Sci*, 1031:280–91.
- Genkinger JM, Platz EA, Hoffman SC, et al. 2004. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington county, Maryland. *Am J Epidemiol*, 160:1223–33.
- Giacco R, Parillo M, Rivellesse A, et al. 2000. Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in type 1 diabetic patients. *Diabetes Care*, 23:1461–6.
- Giovannucci E, Rimm EB, Stampfer MJ, et al. 1994. Intake of fat, meat and fiber in relation to risk of colon cancer in men. *Cancer Res*, 54:2390–7.
- Goodwin JS, Brodwick M. 1995. Diet, aging and cancer. *Clin Geriatric Med*, 11:577–89.
- Grant WB. 2003. Diet and risk of dementia: does fat matter? The Rotterdam Study. *Neurology*, 60:2020–1.
- Graudal NA, Galloe AM, Garred P. 1998. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta analysis. *JAMA*, 279:1383–91.
- Gross L, Li L, Ford E, et al. 2004. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr*, 79:774–9.
- Grundy SM, Pasternak R, Greenland P, et al. 1999. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*, 100:1481–92.
- Grundy SM, Vega GL. 1988. Plasma cholesterol response to saturated fatty acids. *Am J Clin Nutr*, 47:822–4.
- Hall NF, Gale CR, Syddall H, et al. 2002. Relation between size at birth and risk of age-related macular degeneration. *Invest Ophthalmol Vis Sci*, 43:3641–5.
- Hansen LB, Vondracek SF. 2004. Prevention and treatment of nonpostmenopausal osteoporosis. *Am J Health Syst Pharm*, 61:2637–54.
- Harman D. 1956. Aging: a theory based on free radical and radiation chemistry. *J Gerontol*, 11:298–300.
- Harman D. 1988. Free radicals in aging. *Mol Cell Biochem*, 84:155–61.
- Hassink S. 2003. Problems in childhood obesity. *Prim Care*, 30:357–74.
- Head E, Liu J, Hagen TM, et al. 2002. Oxidative damage increases with age in a canine model of human brain aging. *J Neurochem*, 82:375–81.
- Heaney RP, Recker RR. 1982. Effects of nitrogen, phosphorus and caffeine on calcium balance in women. *J Lab Clin Med*, 99:46–55.
- Heilbronn LK, Ravussin E. 2003. Calorie restriction and aging: review of the literature and implications for studies in humans. *Am J Clin Nutr*, 78:361–9.
- Herbert LE, Scherr PA, Beckett LA, et al. 1992. Relation of smoking and alcohol consumption to incident Alzheimer's disease. *Am J Epidemiol*, 135:347–55.
- Hertog MG, Feskens EJ, Hollman PC, et al. 1993. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*, 342:1007–11.
- Hodge A, English D, O'Dea K, et al. 2004. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diab Care*, 27:2701–6.
- Hogg R, Chakravarthy U. 2004. AMD and micronutrient antioxidants. *Curr Eye Res*, 29:387–401.
- Holick MF. 2004. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*, 80:1678S–1688S.
- Holmes MD, Willett WC. 2004. Does diet affect breast cancer risk? *Breast Cancer Res*, 6:170–8.
- Howitz KT, Bitterman KJ, Cohen HY, et al. 2003. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, 425:191–6.
- Hu F, Manson J, Stampfer M, et al. 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*, 345:790–7.
- Hu F, Willett W, Li T, et al. 2004. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*, 351:2694–703.
- Hung HC, Joshupura KJ, Jiaand R, et al. 2004. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*, 96:1577–84.
- Hursting SD, Lavigne JA, Berrigan D, et al. 2003. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med*, 54:131–52.
- Ikeno Y, Bronson RT, Hubbard GB, et al. 2003. Delayed occurrence of fatal neoplastic diseases in Ames dwarf mice: correlation to extended longevity. *J Gerontol A Biol Sci Med Sci*, 58A:291–6.

- [IARC] International Agency for Research on Cancer. 2002. Weight control and physical activity. IARC Handbooks of Cancer Prevention. Volume 6. Lyon: IARC.
- Janket S, Manson J, Sesso H, et al. 2003. A prospective study of sugar intake and risk of type 2 diabetes in women. *Diabetes Care*, 28: 1008–15.
- Jenkins DJ, Kendall CW, Marchie A, et al. 2002. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein (a), homocysteine, and pulmonary nitric oxide a randomized, controlled, crossover trial. *Circulation*, 106:1327–32.
- Jenkins DJ, Kendall CW, Marchie A, et al. 2003. Effects of dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*, 290:502–10.
- Jenkins DJ, Kendall CW, Marchie A, et al. 2005. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. *Am J Clin Nutr*, 81:380–7.
- Jensen MK, Koh-Banerjee P, Hu FB, et al. 2004. Intake of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr*, 80:1492–9.
- Johnson EJ. 2005. Obesity, lutein metabolism, and age-related macular degeneration: a web of connections. *Nutr Rev*, 63:9–15.
- Johnson IT. 2004. Micronutrients and cancer. *Proc Nutr Soc*, 63:587–95.
- Joseph JA, Shukitt-Hale B, Casadesus G. 2005. Reversing the deleterious effects of aging on neuronal communication and behavior: beneficial properties of fruit polyphenolic compounds. *Am J Clin Nutr*, 81: 313–16.
- Kagawa Y. 1978. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. *Prev Med*, 7:205–17.
- Kalkwarf HJ, Khoury JC, Lanphear BP. 2003. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr*, 77:257–65.
- Kalmijn S. 2000. Fatty acid intake and the risk of dementia and cognitive decline: a review of clinical and epidemiological studies. *J Nutr Health Aging*, 4:202–7.
- Kanis JA. 1999. The use of calcium in the management of osteoporosis. *Bone*, 24:279–90.
- Kaplan RC, Strickler HD, Rohan TE, et al. 2005. Insulin-like growth factors and coronary heart disease. *Cardiol Rev*, 13:35–9.
- Katan MJ, Zock PL, Mensink RP. 1995. Dietary oils, serum lipoproteins and coronary heart disease. *Am J Clin Nutr*, 61(Suppl 6):1368–73.
- Kawamura H, Ozawa Y, Jumabay M, et al. 2003. Time-series analysis of systolic blood pressure variation in thirty-three Uyghur centenarians in China. *Hypertens Res*, 26:597–601.
- Kesteloot H. 2004. Epidemiology: past, present and future. *Ver K Acad Geneesk Belg*, 66:384–405.
- Key TJ, Allen NE, Spencer EA, et al. 2003. Nutrition and breast cancer. *Breast*, 12:412–16.
- Key TJ, Fraser GE, Thorogood M, et al. 1998. Mortality in vegetarians and non-vegetarians: a collaborative analysis of 8300 deaths among 76,000 men and women in five prospective studies. *Publ Health Nutr*, 1:33–41.
- Kirkland JL. 2002. The biology of senescence: potential for prevention of disease. *Clin Geriatr Med*, 18:383–405.
- Kochanek KD, Smith BL. 2004. Deaths: preliminary data for 2002. *Natl Vital Stat Rep*, 52:1–47.
- Koubova J, Guarente L. 2003. Perspective. How does calorie restriction work? *Genes Dev*, 17:313–21.
- Krauss RM, Eckel RH, Howard B, et al. 2000. AHA dietary guidelines, revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*, 102:2284–99.
- Kris-Etherton PM, Lichtenstein AH, Howard BV, et al. 2004. Antioxidant vitamin supplements and cardiovascular disease. *Circulation*, 110: 637–41.
- Kromhout D, Bosschieter EB, de Lezenne Coulander C, et al. 1985. The inverse relation between fish consumption and 20-year mortality from coronary disease. *N Engl J Med*, 312:1205–9.
- Krousel-Wood MA, Muntner P, He J, et al. 2004. Primary prevention of essential hypertension. *Med Clin North Am*, 88:223–38.
- Kulak CA, Bilezikian JP. 1998. Osteoporosis: preventive strategies. *Int J Fertil Womens Med*, 43:56–64.
- Lamarche B, Desroches S, Jenkins DL, et al. 2004. Combined effects of dietary portfolio of plant sterols, vegetable protein, viscous fibre and almonds on LDL particle size. *Br J Nutr*, 92:657–63.
- Lane MA, Ingram DK, Roth GS. 1999. Caloric restriction in nonhuman primates: effects on diabetes and cardiovascular risk. *Toxicol Sci*, 52(Suppl 2):41–8.
- Larrieu S, Letenneur L, Helmer C, et al. 2004. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. *J Nutr Health Aging*, 8:150–4.
- La Rue A, Koehler KM, Wayne SJ, et al. 1997. Nutritional status and cognitive functioning in a normally aging sample, a 6-year reassessment. *Am J Clin Nutr*, 65:20–9.
- Lau EM. 2004. Preventing osteoporosis in every day life. *Clin Calcium*, 14:430–4.
- Launer LJ, Feskens EJ, Kalmijns S, et al. 1996. Smoking, drinking and thinking. The Zutphen Elderly Study. *Am J Epidemiol*, 143:219–27.
- Laurin D, Foley DJ, Masaki KH, et al. 2002. Vitamin E and C supplements and risk of dementia. *JAMA*, 288:2266–8.
- Le Couteur DG, Hilmer SN, Glasgow N, et al. 2004. Prescribing in older people. *Aust Fam Physician*, 33:777–81.
- Lee I-M, Blair SN, Allison SN, et al. 2001. Epidemiologic data on the relationships of caloric intake, energy balance, and weight gain over the lifespan with longevity and morbidity. *J Gerontol A Biol Sci Med Sci*, 56A:7–19.
- Leibovici D, Ritchie K, Ledesert B, et al. 1999. The effects of wine and tobacco consumption on cognitive performance in the elderly. A longitudinal study of relative risk. *Int J Epidemiol*, 28:77–81.
- Leitzmann C. 2005. Vegetarian diets: what are the advantages? *Forum Nutr*, 57:147–56.
- Lichtenstein AH. 1998. Soy protein, isoflavones and cardiovascular disease risk. *J Nutr*, 128:1589–92.
- Lindsay J, Laurin D, Verreault R, et al. 2002. Risk factors for Alzheimer's disease. A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol*, 156:445–53.
- Liu S, Willett W, Manson J, et al. 2003. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr*, 78:920–7.
- Lock K, Pomerleau J, Causser L, et al. 2005. The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Org*, 83:100–8.
- Luchsinger JA, Mayeux R. 2004. Dietary factors and Alzheimer's disease. *Lancet Neurol*, 3:579–87.
- Luchsinger JA, Tang MX, Shea S, et al. 2002. Caloric intake and risk of Alzheimer's disease. *Arch Neurol*, 59:1258–63.
- Luchsinger JA, Tang MX, Siddiqui M, et al. 2004. Alcohol intake and risk of dementia. *J Am Geriatr Soc*, 52:540–6.
- Ludwig DS. 2002. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*, 287:2414–23.
- Lundgren H, Bengtsson C, Blohme G, et al. 1989. Dietary habits and incidence of noninsulin-dependent diabetes mellitus in population study of women in Gothenburg, Sweden. *Am J Clin Nutr*, 49:708–12.
- Lupton JR, Turner ND. 2003. Dietary fiber and coronary disease: does the evidence support the association? *Curr Atheroscl Rep*, 5:500–5.
- Macdonald HM, New SA, Campbell MK, et al. 2005. Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. *Osteoporosis Int*, 16:163–71.
- Manach C, Mazur A, Scalbert A. 2005. Polyphenols and prevention of cardiovascular diseases. *Curr Opin Lipidol*, 16:77–84.

- Manzato E, Roselli della Rovere G, Zambon S, et al. 2003. Cognitive functions are not affected by dietary fatty acids in elderly subjects in the Pro.VA study population. *Aging Clin Exp Res*, 15:83–6.
- Marshall J, Hamman R, Baxter J, et al. 1991. High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study. *Am J Epidemiol*, 134:590–603.
- Masaki KH, Losonczy KG, Izmirlian G, et al. 2000. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology*, 54:1265–72.
- Masoro EJ. 1996. Possible mechanisms underlying the antiaging actions of caloric restriction. *Toxicol Path*, 24:738–41.
- Masoro EJ. 2002a. Caloric restriction: a key to understanding and modulating aging. Amsterdam: Elsevier.
- Masoro EJ. 2002b. Overview. In Masoro EJ (ed). Caloric restriction: a key to understanding and modulating aging. Amsterdam: Elsevier. p 1–10.
- Masoro EJ. 2002c. Age-associated diseases. In Masoro EJ (ed). Caloric restriction: a key to understanding and modulating aging. Amsterdam: Elsevier. p 93–113.
- Masoro EJ. 2002d. Mechanisms of the anti-aging action of caloric restriction. In Masoro EJ (ed). Caloric restriction: a key to understanding and modulating aging. Amsterdam: Elsevier. p 115–47.
- Masoro EJ, Iwasaki K, Gleiser CA, et al. 1989. Dietary modulation of the progression of nephropathy in aging rats: an evaluation of the importance of protein. *Am J Clin Nutr*, 49:1217–27.
- Mattson DI, Meister CJ, Marcelle ML. 2005. Dietary protein source determines the degree of hypertension and renal disease in the Dahl salt-sensitive rat. *Hypertension*, 45:736–51.
- Mattson MP, Wan R. 2005. Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems. *J Nutr Biochem*, 16:129–37.
- Mayer EL, Jacobsen DW, Robinson K. 1996. Homocysteine and coronary atherosclerosis. *J Am Coll Cardiol*, 29:517–27.
- McCay CM, Crowell MF, Maynard LA. 1935. The effect of retarded growth upon the length of the lifespan and ultimate body size. *J Nutr*, 10: 63–79.
- McGuire HL, Svetkey LP, Harsha DW, et al. 2004. Comprehensive lifestyle modification and blood pressure control: a review of the PREMIER trial. *J Clin Hypertens*, 6:383–90.
- Mehr DR, Tatum PE 3rd. 2002. Primary prevention of disease in old age. *Clin Geriatr Med*, 8:407–30.
- Meindok H, Dvorsky R. 1970. Serum folate and vitamin B12 in the elderly. *J Am Geriatr Soc*, 18:317–26.
- Melton LJ, Chrishilles EA, Cooper C, et al. 1992. How many women have osteoporosis? *J Bone Miner Res*, 7:1005–10.
- Mensink RP, Katan MB. 1992. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta analysis of 27 trials. *Arterioscler Thromb*, 12:911–19.
- Merry BJ. 2004. Oxidative stress and mitochondrial function with aging—the effects of caloric restriction. *Aging Cell*, 3:7–12.
- Meydani M. 2001. Nutrition interventions in aging and age-associated disease. *Ann NY Acad Sci*, 928:226–35.
- Meyer K, Kushi L, Jacobs D, et al. 2000. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr*, 71: 921–30.
- Michels KB, Fuchs CS, Giovannucci E, et al. 2005. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. *Cancer Epidemiol Biomarkers Prev*, 14:842–9.
- Miquel J, Bernd A, Sempere JM, et al. 2002. The curcuma antioxidants: pharmacological effects and prospects for future clinical use: a review. *Arch Gerontol Geriatr*, 34:37–46.
- Mitchell P, Smith W, Cumming RG, et al. 2003. Nutritional factors in the development of age-related eye disease. *Asia Pac J Clin Nutr*, 12: Suppl S5.
- Mitka M. 2004. Dash of dissent on salt intake advice. *JAMA*, 291:1686–9.
- Mokbel K. 2003. Risk-reducing strategies for breast cancer- a review of recent literature. *Int J Fertil Womens Med*, 48:274–7.
- Montonen J, Knekt P, Harkanen T, et al. 2005. Dietary patterns and the incidence of type 2 diabetes. *Am J Epidemiol*, 181:219–27.
- Moore TH, Conlin PR, Ard J, et al. 2001. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension*, 38:155–8.
- Morris BJ. 2005. A forkhead in the road to longevity: the molecular basis of lifespan becomes clearer. *J Hypertens*, 23:1285–309.
- Morris MC, Evans DA, Bienias H, et al. 2002. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer's disease in a biracial community study. *JAMA*, 287:3230–3.
- Mozaffarieh M, Sacu S, Wedrich A. 2003. The role of carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: a review based on controversial evidence. *Nutr J*, 2:20.
- Mukamal KJ, Conugrave KM, Mittleman MA, et al. 2003. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med*, 348:109–18.
- Must A, Spadano J, Coakley EH, et al. 1999. The disease burden associated with overweight and obesity. *JAMA*, 282:1523–9.
- Nakamura Y, Ueshima H, Okamura T, et al. 2005. Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA 80, 1980-99. *Am J Med*, 118:239–45.
- Nesbitt SD, Ashaye MO, Stettler N, et al. 2004. Overweight as a risk factor in children: a focus on ethnicity. *Ethn Dis*, 14:94–110.
- Ness AR, Powles JW. 1997. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol*, 26:1–13.
- Nicholls D, Viner R. 2005. Eating disorders and weight problems. *BMJ*, 330:950–3.
- Nicolosi RJ, Wilson TA, Lawton C, et al. 2001. Dietary effects on cardiovascular disease risk factors, beyond saturated fatty acids and cholesterol. *J Am Coll Nutr*, 20(Suppl 5):421S–427S.
- Norat T, Bingham S, Ferrari P, et al. 2005. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst*, 97:906–16.
- Norat T, Lukanova A, Ferrari P, et al. 2002. Meat consumption and colorectal cancer risk: a dose-response meta-analysis of epidemiological studies. *Intern J Cancer*, 98:241–56.
- Nowson CA, Diamond TH, Pasco JA, et al. 2004. Vitamin D in Australia. Issues and recommendations. *Aust Fam Physician*, 33:133–8.
- Nygard O, Nordrehaug JE, Refsum H. 1997. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med*, 337:230–6.
- Olshansky SJ, Passoro DJ, Hershow RC, et al. 2005. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*, 352:1138–45.
- Otsuka M, Yamaguchi K, Ueki A. 2002. Similarities and differences between Alzheimer's disease and vascular dementia from the viewpoint of nutrition. *Ann NY Acad Sci*, 977:155–61.
- Paffenberger RS, Hyde RT, Wing AL, et al. 1993. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med*, 328:538–45.
- Pan XR, Hu YH, Wang JX. 1997. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The DaQing IGT and Diabetes Study. *Diabetes Care*, 20:537–44.
- Peeters A, Barendregt JJ, Willekens F, et al. 2003. NEDCOM. The Netherlands Epidemiology and Demography Comparison of Morbidity Research Group. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med*, 138:24–32.
- Pereira M, Jacobs D, Pins J, et al. 2002. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr*, 75:848–55.
- Pereira MA, O'Reilly E, Augustsson K, et al. 2004. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. *Arch Intern Med*, 164:370–6.

- Pereira M, Swain J, Goldfine A, et al. 2004. Effects of low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA*, 292:2482–90.
- Polidori MC. 2003. Antioxidant micronutrients in the prevention of age-related diseases. *J Postgrad Med*, 49:229–35.
- Prentice A. 2004. Diet, nutrition and the prevention of osteoporosis. *Public Health Nutr*, 7:227–43.
- Quadri P, Fragiaco C, Pezzati R, et al. 2004. Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. *Am J Clin Nutr*, 80:114–22.
- Raisz LG. 2004. Homocysteine and osteoporotic fractures – culprit or bystander? *N Engl J Med*, 350:2089–90.
- Reid IR, Ames RW, Evans MC, et al. 1995. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med*, 98:331–5.
- Remsberg KE, Siervogel RM. 2003. A life span approach to cardiovascular disease risk and aging: The Fels Longitudinal Study. *Mech Ageing Dev*, 124:249–57.
- Renvall MJ, Spindler AA, Ramsdell JW. 1989. Nutritional status of free living Alzheimer's patients. *Am J Med Sci*, 298:20–7.
- Report of a Joint WHO/FAO Expert Consultation. 2003. Diet, nutrition and the prevention of chronic diseases. Geneva: World Health Organization.
- Riggs BL, Melton LJ. 1995. The world wide problem of osteoporosis: insights afforded by epidemiology. *Bone*, 17:5055–155.
- Rizkalla S, Taghrid L, Laromiguiere M, et al. 2004. Improved plasma glucose control: whole body glucose utilization, and lipid profile on a low glycemic index diet in type 2 diabetic men: a randomized controlled trial. *Diabetes Care*, 27:1866–72.
- Rizzoli R, Bonjour JP. 2004. Dietary protein and bone health. *J Bone Miner Res*, 19:527–31.
- Robinson R. 2001. The fetal origins of adult disease. *BMJ*, 322:375–6.
- Roe FJC, Lee PN, Conybeare G, et al. 1995. The Biosure Study: influence of composition of diet and food consumption on longevity, degenerative diseases, and neoplasia in Wistar rats studied for up to 30 months post weaning. *Food Chem Toxicol*, 33:S1–100.
- Ruitenbergh A, Van Swieten JC, Whittleman JCM, et al. 2002. Alcohol consumption and risk of dementia. The Rotterdam Study. *Lancet*, 359:281–6.
- Sacks FM, Svetkey LP, Vollmer WM, et al. 2001. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*, 344:3–10.
- Saito T, Nakamura K, Okuda Y, et al. 2005. Weight gain in childhood and bone mass in female college students. *Bone Miner Metab*, 23:69–75.
- Salmeron J, Ascherio A, Rimm E, et al. 1997. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care*, 20:545–50.
- Salmeron J, Manson J, Stampfer M, et al. 1997. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA*, 277:472–7.
- Sandhu MS. 2005. Insulin-like growth factor-1 and risk of type 2 diabetes and coronary heart disease: molecular epidemiology. *Endocr Dev*, 9:44–54.
- Sano M, Ernesto C, Thomas RG, et al. 1997. A controlled trial of seligiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's disease Cooperative study. *N Engl J Med*, 336:1216–22.
- Sastre J, Pallardo FV, Vina J. 2003. The role of mitochondrial oxidative stress in aging. *Free Rad Biol Med*, 35:1–8.
- Sato Y, Honda Y, Iwamoto J, et al. 2005. Effect of folate and mecobalamin on hip fractures in patients with stroke. *JAMA*, 293:1082–8.
- Sauvaget C, Nagano J, Allen A, et al. 2003. Vegetable and fruit intake and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Stroke*, 34:2355–60.
- Sayer AA, Cooper C, Evans JR, et al. 1998. Are rates of ageing determined in utero? *Age Ageing*, 27:579–83.
- Schulze M, Liu S, Rimm E, et al. 2004. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr*, 80:348–56.
- Seddon JM, Cote J, Rosner B. 2004. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. *Arch Ophthalmol*, 121:1728–37.
- Seidel JC, Verschuren M, van Leer EM, et al. 1996. Overweight, underweight, and mortality. A prospective study of 48 287 men and women. *Arch Intern Med*, 156:958–63.
- Simmons N, van't Veer P, Strain JJ, et al. 1998. Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. *Am J Epidemiol*, 147:342–52.
- Simons LA, McCallum J, Friedlander Y, et al. 2000. Moderate alcohol intake is associated with survival in the elderly: the Dubbo Study. *Med J Aust*, 173:121–4.
- Singh PN, Sabate J, Fraser GE. 2003. Does low meat consumption increase life expectancy in humans? *Am J Clin Nutr*, 78(Suppl 3):526S–532S.
- Sloane PD, Zimmerman S, Suchindran C, et al. 2002. The public health impact of Alzheimer's disease, 2000–2050. Potential implication of treatment advances. *Ann Rev Publ Health*, 23:213–31.
- Smith DM, Atkinson RM. 1995. Alcoholism and dementia. *Int J Addictions*, 30:1843–69.
- Smith-Warner SA, Spiegelman D, Yaun SS, et al. 2001. Intake of fruits and vegetables and risk of breast cancer. A pooled analysis of cohort studies. *JAMA*, 285:769–76.
- Sneath P, Chanarin H, Hodkinson HM, et al. 1973. Folate status in a geriatric population and its relation to dementia. *Age Ageing*, 2:177–82.
- Snowdon DA, Tully CL, Smith DC, et al. 2000. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease finding from the nun study. *Am J Clin Nutr*, 71:993–8.
- Solfrizzi V, D'Introno A, Colacicco AM, et al. 2005. Unsaturated fatty acids intake and all-causes mortality: a 8.5-year follow-up of the Italian Longitudinal Study on Aging. *Exp Gerontol*, 40:335–43.
- Solfrizzi V, Panza F, Capurso A. 2003. The role of diet in cognitive decline. *J Neural Transm*, 110:95–110.
- Sommer BR, Hoff AL, Costa M. 1998. Folic supplementation in dementia, a preliminary report. Proceedings of the 11th Annual Meeting of the American Association for Geriatric Psychiatry; 1998 Mar 8–11; San Diego.
- Srinath Reddy K, Katan MB. 2004. Diet, nutrition and the prevention of hypertension and cardiovascular diseases. *Public Health Nutr*, 7:167–86.
- Steinmetz KA, Potter JD. 1996. Vegetables, fruit, and cancer prevention. *Am Diet Assoc*, 96:1027–39.
- Stern L, Iqbal N, Seshadri P, et al. 2004. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med*, 140:778–85.
- Stevens J, Kyungmi A, Juhaeri, et al. 2002. Dietary fiber intake and glycemic index and the incidence of diabetes in African-American and white adults. *Diabetes Care*, 25:1715–21.
- Strain JJ, Dowe L, Ward M, et al. 2004. B-vitamins, homocysteine metabolism and CVD. *Proc Nutr Soc*, 63:597–603.
- Streppel MT, Arends LR, van't Veer P, et al. 2005. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. *Arch Intern Med*, 165:150–6.
- Strom A, Jensen RA. 1951. Mortality from cardiovascular disease in Norway 1940–1945. *Lancet*, 1:126–9.
- Suji G, Sivakami S. 2004. Glucose, glycation and aging. *Biogerontology*, 5:365–73.
- Suzuki M, Willcox BJ, Willcox DC. 2001. Implications from and for food cultures for cardiovascular disease: longevity. *Asia Pacific J Clin Nutr*, 10:165–71.
- Tang YR, Zhang SQ, Xiong Y, et al. 2003. Studies of five microelement contents in human serum, hair, and fingernails correlated with aged hypertension and coronary heart disease. *Biol Trace Elem Res*, 92:97–104.

- Taubert D, Berkels R, Roesen R, et al. 2003. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA*, 290:1029–30.
- Tavani A, Pelucchi C, Parpinel M, et al. 2004. Folate and vitamin B(6) intake and risk acute myocardial infarction in Italy. *Eur J Clin Nutr*, 58:1266–72.
- Thomas VS, Rockwood KJ. 2001. Alcohol abuse, cognitive impairment, and mortality among older people. *J Am Geriatr Soc*, 49:415–20.
- Tjonneland AM, Overvad K, Bingham SA, et al. 2004. Dietary fibers in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Ugeskr Laeger*, 14:2458–60.
- Topp R, Fahlman M, Boardley D. 2004. Healthy aging: health promotion and disease prevention. *Nurs Clin North Am*, 39:411–22.
- Thurman JD, Bucci TJ, Hart RW, et al. 1994. Survival, body weight, and spontaneous neoplasms in ad libitum-fed and food-restricted Fischer-344 rats. *Toxicol Pathol*, 22:1–9.
- Trichopoulou A. 2001. Mediterranean diet: the past and the present. *Nutr Metab Cardiovasc Dis*, 11(4 Suppl):1–4.
- Trichopoulou A, Critselis E. 2004. Mediterranean diet and longevity. *Int J Cancer Prev*, 13:453–6.
- Trichopoulou A, Orfanos P, Norat T, et al. 2005. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. *BMJ*, 330:991.
- Trombetti A, Herrmann F, Hoffmeyer P, et al. 2002. Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int*, 13:731–7.
- Truswell AS. 2002. Meat consumption and cancer of the large bowel. *Eur J Clin Nutr*, 56(Suppl 1):519–24.
- Tse MMY, Benzie FF. 2004. Practice article. Diet and health: nursing perspective for the health of our aging population. *Nurs Health Sci*, 6:309–16.
- Tsunebara C, Leonetti D, Jujimoto W. 1990. Diet of second-generation Japanese-American men with and without non-insulin-dependent diabetes. *Am J Clin Nutr*, 52:731–8.
- Tucker KL, Hallfrisch J, Qiao N, et al. 2005. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging. *J Nutr*, 135:556–61.
- Tuomilehto J, Lindstrom J, Eriksson JG, et al. 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*, 344:1343–50.
- Turturro A, Blank K, Murasko D, et al. 1994. Mechanism of caloric restriction affecting aging and disease. *Ann N Y Acad Sci*, 719:159–70.
- UK Department of Health. 1998. Report of the Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy. London: The Stationery Office.
- van Gils CH, Peeters PH, Bueno-de-Mesquita HB, et al. 2005. Consumption of vegetables and fruits and risk of breast cancer. *JAMA*, 293:183–93.
- Vieth R. 2004. Why the optimal requirement for vitamin D3 is probably higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol*, 89:575–9.
- von Mach MA, Stoeckli R, Bilz S, et al. 2004. Changes in bone mineral content after surgical treatment of morbid obesity. *Metabolism*, 53:918–21.
- Walford RL, Mock D, Verdery R, et al. 2002. Calorie restriction in Biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2 year period. *J Gerontol A Biol Sci Med Sci*, 57A:B211–24.
- Weindruch R, Sohal RS. 1997. Caloric intake and aging. *N Engl J Med*, 337:986–94.
- Weindruch R, Walford RL. 1988. Retardation of aging and disease by dietary restriction. Springfield: Charles C Thomas.
- Weinstein A, Sesso H, Lee I, et al. 2004. Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA*, 292:1188–94.
- Weir MR. 2004. Dietary salt, blood pressure, and microalbuminuria. *J Clin Hypertens*, 6(Suppl 3):23–6.
- Weisburger JH. 2002. Lifestyle, health and disease prevention: the underlying mechanisms. *Eur J Cancer Prev*, Suppl 2:S1–7.
- Whalley LJ, Starr JM, Deary IJ. 2004. Diet and dementia. *J Br Menopause Soc*, 10:113–17.
- Whelton PK, He J, Cutler JA, et al. 1997. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA*, 277:1624–32.
- Whitmer RA, Gunderson EP, Barrett-Conner B, et al. 2005. Obesity in middle age and future risk of dementia: a 27-year longitudinal population based study. *BMJ*, 330:1360.
- Wiegman A, Rodenburg J, de Jongh S, et al. 2003. Family history and cardiovascular risk in familial hypercholesterolemia: data in more than 1000 children. *Circulation*, 107:1473–8.
- Willcox B, Willcox C, Suzuki M. 2001. The Okinawa Way. How to improve your health and longevity dramatically. London: Michael Joseph.
- Willcox BJ, Yano K, Chen R, et al. 2004. How much should we eat? The association between energy intake and mortality in a 36-year follow-up study of Japanese-American men. *J Gerontol A Biol Sci Med Sci*, 59A:789–95.
- Wojcicki J, Rozewicka L, Barcew-Wiszniewska B, et al. 1991. Effect of selenium and vitamin E on the development of experimental atherosclerosis in rabbits. *Atherosclerosis*, 87:9–16.
- World Cancer Research Fund. 1997. Food, Nutrition and the Prevention of Cancer: a Global Perspective. Washington: American Institute for Cancer Research.
- Yamori Y. 2004. Nutrition and life-style related disease prevention in the future. *Clin Exp Pharmacol Physiol*, 31(Suppl 2):S65.
- Yen PK. 2003. Maintaining cognitive function with diet. *Geriatr Nurs*, 24:62–3.
- Yu BP. 1996. Aging and oxidative stress. Modulation by dietary restriction. *Free Rad, Biol Med*, 21:651–68.
- Zhang X, Dong F, Driscoll MJ, et al. 2005. High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex. *Exp Neur*, 191:318–25.
- Zimmerman JA, Malloy V, Krajcik R, et al. 2003. Nutritional control of aging. *Exp Gerontol*, 38:47–52.

