Nutrition and Fitness

Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle

Editor
A.P. Simopoulos
Nutrition and Fitness: Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle

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Nutrition and Fitness: Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle

Volume Editor

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Dedication

The proceedings of the conference are dedicated to the concept of positive health as enunciated by the Hippocratic physicians (5th century BC).

*Positive health requires a knowledge of man’s primary constitution (which today we call genetics) and of the powers of various foods, both those natural to them and those resulting from human skill (today’s processed food). But eating alone is not enough for health. There must also be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the season of the year, the changes of the winds, the age of the individual and the situation of his home. If there is any deficiency in food or exercise the body will fall sick.*
Olympian Ode 2004

Lee Pinkerson

The Olympic games of Ancient Greece
even more than athletic feats
praise the spirit of life divine
handed down from God through our ancestral line

In body and soul, in heart and mind
the ways of goodness they refined
celebrated and known by all the Greek world
unified in this concept, there’s no place for war

Where the will to live burns bright
they try with all their might
awakening grace to join them and take flight
every four years at the great Olympic games

In the land of the wild olive branch
the walnut and the honey bee
embraced by a sea where the fish run free
is a diet that is high in omega-3

The goats eat their fill
of the plants on the hill
so even the cheese
has omega-3s

The ancients had the nourishment they’d need
to make them strong and make them smart
fill the air with song and excel in the arts
their world did dance in harmony
And the walls would melt away
when together they would play
where race and class no longer separate
every four years at the great Olympic games

A millennium has come again
the Olympics are back where they began
let’s remember all they truly are

More than a game, they’re a way of life
a torch to guide us past painful strife
for possessions will not take us very far

But the food we eat and the work we do
the way we treat each other and the planet too
will show how sweet we greet the daytime star
every four years at the great Olympic games

Lee Pinkerson wrote the lyrics and music for the Olympian song in February 2004 in honor of the 2004 Olympic Summer Games in Athens, and for the Fifth International Conference on Nutrition and Fitness. A CD recording of her singing and guitar performance was given to the conference program participants. She can be reached from her website at http://wwwLEEPINKERSON.COM.
Commemorative 2004 Conference Medal

Medal commemorating the 5th International Conference on Nutrition and Fitness. The medal is etched with the Olympic rings in honor of the 2004 Summer Olympic Games held in Athens, Greece.
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The Fifth International Conference on Nutrition and Fitness was held in Athens, Greece, on June 9–12, 2004. This being the year when the Olympic Games were returned to the country of their origin, the keynote address given by Elizabeth Ferris, MD, a former Olympic medalist and Vice President of the World Olympians Association, was entitled ‘Positive Health – Exploring Relevant Parameters’.

The goals and objectives of the conference were to:

• Review and critique the latest scientific information on nutrition and fitness, taking into consideration genetic endowment, adaptation throughout the life cycle and the nutritional factors that contribute to fitness, specifically, the effect of the various dietary sources of energy on energy expenditure, exercise and performance.

• Determine the relationship of nutrition and fitness to chronic diseases, particularly, the metabolic changes that occur with the type and amount of physical activity for the prevention and management of cardiovascular disease, mental health, obesity, osteoporosis, diabetes and cancer.

• Consider the psychosocial and other determinants of physical activity throughout the life cycle including intervention strategies, and emphasize healthy lifestyles consistent with proper nutrition and fitness.

• Stimulate national governments and the private sector to coordinate and thus maximize their efforts to develop programs that encourage proper nutrition and participation in sports activities by all, throughout the life cycle, to achieve their potential in fitness and thus increase the pool of young athletes, from whom the elite athlete will be forthcoming.

Preface
• Develop strategies for the distribution and implementation worldwide of the 1996 ‘Declaration of Olympia on Nutrition and Fitness’ for the New Millennium, through the establishment of regional committees.

The conference consisted of 10 sessions of oral presentations and 2 poster sessions in which 110 abstracts were presented. Scientists from 46 countries participated representing the continents of Africa, Asia, Australia/New Zealand, Europe, and North and South America. The proceedings of the conference are presented in two volumes in this series. Volume 94 is entitled Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. Volume 95 is entitled Nutrition and Fitness: Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle. Both volumes begin with the Dedication to the concept of ‘Positive Health’, the 2004 Olympian Ode by Lee Pinkerson, the Commemorative Medal, the Conference Organization, the Preface, the 1996 ‘Declaration of Olympia on Nutrition and Fitness’ and the Keynote Address entitled ‘Positive Health – Exploring Relevant Parameters’ by Elizabeth Ferris, MD. The address sets the stage for the importance of physical activity in health and the deleterious effects of inactivity. The Olympic spirit and the Olympic games celebrate achievement and the individual. It is expected that in the 21st Century scientific information will be developed that will deliver individualized genotype-based health care. A conscious effort must be made to develop in all dimensions the environment in which the human genome finds its optimal expression. This, of course, represents a complete circle returning and recognizing the Hippocratic concept of ‘positive health’ of 2500 years ago, based on the individual and in the 21st Century proving it through molecular biology.

Volume 94 entitled Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer presents the papers on obesity, syndrome X, diabetes, cardiovascular disease, and cancer. The papers on obesity emphasize the severe burden of obesity worldwide and the need to have a classification system of obesity that relates to the specific population from whence the data were obtained that relate obesity to morbidity and mortality. Kanazawa and his coworkers in their paper ‘Criteria and Classification of Obesity in Japan and Asia-Oceania Region’ presented by Shuji Inoue, clearly discuss the fact that these populations are at risk for the development of chronic diseases at lower body mass index (BMI) levels than Caucasians.

Cuiqing Chang, in her paper on ‘Exercise and Obesity in China’, discusses the role of physical activity or exercise on the occurrence of obesity, specifically the function and effectiveness of exercise on weight reduction and a prescription for weight loss. China has developed guidelines and recommendations for the classification of obesity. Kafatos et al., in their paper on ‘Obesity in
Childhood: The Greek Experience’, presents the Greek experience, a specific program in which the teacher uses ‘customized’ classroom materials that include a physical activity component and parental involvement. The program is one of the few programs in Europe to have reported positive results in terms of obesity and physical fitness in primary schools in Crete. Educational interventions in schools have great potential needed to tackle the urgent problems of dietary and lifestyle choices contributing to the blight of childhood obesity and its co-morbidities.

Aaron and coworkers, in their paper ‘Epidemiology of Physical Activity from Adolescence to Young Adulthood’, provide a synthesis of the current knowledge about the epidemiology of physical activity during the transition from adolescence to young adulthood. The paper on ‘Adolescent Obesity and Physical Activity’ by Hwalla's group describes the study carried out in Lebanon. The results of this first national population-based study show that adolescent obesity is largely caused by lack of physical activity, and the boys fair worse than the girls. The authors recommend multi-component intervention strategies at the societal and individual levels for weight control that include health professionals, families, schools, businesses, and health care organizations, in order to increase programs and opportunities for physical activity.

Pavlovic and colleagues indicate in their paper titled ‘Nutrition and Physical Activity of the Population in Serbia’ that for both children and adults, inadequate nutrition and physical activity are related to an increase in risk factors and the need for health promotion programs. Drs. Andreoli and De Lorenzo, in their paper on ‘Physical Activity and Body Composition’, emphasize the importance of body composition to evaluate health status in nutritional terms both at the population level and for the individual.

The etiology of the metabolic syndrome is not well understood. The approach to its treatment includes lifestyle modification along with pharmacological therapy, as appropriate. Labadarios, in his paper ‘Syndrome X: Clinical Aspects’ presents an overview of syndrome X and its relationship to obesity, diabetes and cardiovascular disease.

Tataranni’s paper is on ‘Metabolic Syndrome: Is There a Pathophysiological Common Denominator? Lessons Learned from the Pima Indians.’ In addition to clinical physiologic and molecular studies, he carried out a factor analysis designed to statistically test the hypothesis that insulinemia, body size, lipids and blood pressure may result from a single etiologic abnormality. The study failed to identify a single factor underlying the correlation structure of these variables. As a result, Tatarani concluded that molecular and epidemiologic evidence from the studies in Pima Indians suggests that the abnormalities constituting the metabolic syndrome are the result of largely independent physiologic processes. Therefore, clinical treatment and prevention strategies based on the ‘metabolic
syndrome’ hypothesis may prove suboptimal compared with treatment of the individual components.

Storlien et al.’s paper on ‘Lifestyle-Gene-Drug Interactions in Relation to the Metabolic Syndrome’ emphasizes the fact that obesity drives the metabolic syndrome and the polygenic nature of disorders like obesity means that there will be a need for many approaches that will include lifestyle changes along with pharmaceutical support, greatly dependent upon understanding the individual’s genetic make up. Common dietary components, such as fatty acids and simple sugars, are potent gene regulators on many ‘pharmaceutical’ metabolic syndrome targets. Novel drugs are almost certain to interact strongly with dietary and other lifestyle variables. Storlien and coworkers refer to thiazolidinediones, the only really new class of anti-diabetic therapy introduced in the past few years, as a prime example. This class of drugs targets the nuclear hormone receptor PPARγ and the relationship between weight gain and PPARγ2 polymorphism is highly dependent on the dietary polyunsaturated/saturated (P/S) ratio. There are strong indications that modulating muscle metabolism would be of enormous benefit in prevention and treatment of obesity. While exercise training clearly moves muscle morphology and metabolism in a beneficial direction, there is marked genetic heterogeneity in both compliance and response to exercise training in the needy population, i.e. those with the metabolic syndrome. Therefore, it is necessary to understand how drug/diet interactions might act as a multiplier for the beneficial effects of exercise, thus enhancing both the health benefits and the likelihood of compliance.

Donati and Iacoviello’s paper on ‘Coronary Heart Disease, Genetics, Nutrition and Physical Activity’ discusses gene polymorphisms and their interactions with diet and physical activity as they affect lipids, hemostatic and vascular factors. Drs. De Caterina and Madonna in their paper ‘Role of Nutrients and Physical Activity in Gene Expression’ review the subject of how the rapid evolution of vascular and molecular biology in the last 20 years has completely transformed our understanding of the development of coronary heart disease. The authors discuss their studies on the role of omega–3 fatty acids in modulating the immune system and suppressing vascular cell adhesion molecules. Physical activity protects or reduces the risk for the development of cardiovascular disease by indirectly reducing a number of cardiovascular disease risk factors such as high blood pressure, hypercholesterolemia, obesity and diabetes, and also promoting direct anti-atherogenic vascular responses through the action of increased laminar shear on endothelial cells. Recent advances resulting from studies of vascular biology using molecular biology techniques are revealing a previously unsuspected complexity of the vascular responses to nutrients and physical activity, and are providing molecular explanations on how healthy or unhealthy lifestyles interact with our genes, permitting or
inhibiting the expression of the phenotype, even in the presence of unfavorable genes. This has serious implications in providing solid scientific background for preventive strategies that will focus on healthy nutrition, physical activity and life habits. Rontoyannis’ paper ‘Physical Activity and Hypertension: An Overview’ focuses on the benefits of exercise in the control of blood pressure. Rontoyannis emphasizes that walking may be the best and safest aerobic physical activity. The underlying mechanisms responsible for an exercise-induced reduction in blood pressure remain unclear. Possible mechanisms include the lower cardiac output and peripheral vascular resistance at rest; and at any given submaximal levels of work, the reduction in blood catecholamine levels and plasma renin activity, the altered renal function leads to increased elimination of sodium resulting in a reduction of blood volume; and the reduction in insulin levels and insulin resistance, among others. The next paper by Leaf and colleagues, on ‘Omega–3 Fatty Acids and Ventricular Arrhythmias’ presents a thorough review and new information on how omega–3 fatty acids decrease ventricular arrhythmia and sudden death. Leaf showed that the effect of omega–3 fatty acids is to stabilize electrically every contractile cell in the heart. Recent data on the prevention of fatal ventricular arrhythmia in humans indicate that cardiologists should prescribe 1 g of omega–3 fatty acids (EPA + DHA) to their patients, who already had one episode of heart attack, in addition to other medications.

The studies on the beneficial effects of the omega–3 fatty acids in both the primary and secondary prevention of coronary heart disease demand the development of methods to measure circulating fatty acids at the population level. Only a few studies have reported data on the fatty acid composition of circulating lipids in confirmation of dietary intake. Marangoni’s group, in their paper ‘A Method for the Direct Evaluation of the Fatty Acid Status in a Drop of Blood from a Fingertip in Humans: Application to Population Studies and Correlations with Biological Parameters’ discuss their method to determine fatty acids. The method has been validated, is rapid, less expensive than other methods, does not require health personnel, is applicable to population groups, and provides valuable information on the impact of dietary habits, lifestyles and fatty acid supplementation on blood fatty acids.

There has been a lack of consistency in the data relating diet and cancer in cohort studies, most likely due to the way in which dietary intake has been measured. All methods of dietary assessment are associated with measurement error. This fact attenuates estimates of disease risk and reduces statistical power so that a relation between diet and disease may be obscured. In her paper ‘Measurement Error in the Assessment of Interaction between Dietary and Genetic Factors in Cohort Studies of Cancer,’ Bingham points out that the effect of error on regression dilution and estimated sample size is compounded when
attempts are made to assess the interactions between dietary and genetic polymorphisms in assessing risk. Traditionally repeat results from the method used in a cohort, usually a Food Frequency Questionnaire, are compared with those from another assessed more accurate method. However, errors between methods may be correlated so that results from the reference method are not independent of those derived from the test method, thus violating a critical requirement of this procedure. Bingham therefore assessed dietary intake using both a food frequency questionnaire and a detailed seven day diary of food and drink in 13,070 women. The hazard ratio for breast cancer for each quintile increase of energy adjusted fat was strongly associated with saturated fat intake measured using the food diary, but not with saturated fat using the food frequency questionnaire. These results support the view that measurement error might explain the lack of relationship between fat and breast cancer risk in previous prospective studies using data obtained by Food Frequency Questionnaires. Muñoz Rivera and coworkers in their paper ‘Cancer Frequency in Poor Rural Communities Consuming a Very Limited Diet’ conclude that in Mexico, dietary changes do not show a relationship with cancer, whereas they do in other chronic diseases such as obesity and diabetes. This could be due to the age of the indigenous population (the population is young) or to the level of physical activity. In the next paper ‘Omega–6/Omega–3 Polyunsaturated Fatty Acids Ratio and Breast Cancer,’ Bougnoux and colleagues clearly demonstrate the importance of dietary components in the etiology and development of breast cancer. In their studies, they found alpha-linolenic acid and docosahexaenoic acid to be inversely related to the risk of breast cancer, where the trend was opposite for linoleic acid, arachidonic acid, and for the omega–6/omega–3 long chain fatty acids. The higher the omega–6/omega–3 ratio, the higher the estimated relative risk of breast cancer. Similar results were obtained by Tavani et al. In their paper ‘Fish, ω–3 Polyunsaturated Fat Intake and Cancer at Selected Sites’ they investigated the relation between fish consumption and omega–3 polyunsaturated fatty acids, and the risk of selected neoplasms. Their data show that consumption of even small amounts of fish decreases the risk of several cancers, especially of the gastrointestinal tract. Physical activity is an important component of healthy lifestyles. Willer, in his paper ‘Cancer Risk Reduction by Physical Exercise’ reviews the evidence of the effect of physical activity on cancer development and concludes that there is enough evidence to recommend physical activity for life (long-term) for the prevention of certain cancers.

Volume 95 is part 2 of the proceedings, Nutrition and Fitness: Mental Health, Aging, and the Implementation of a Healthy Diet and Physical Activity Lifestyle. Nutrition and physical activity influence mental health. Among the fatty acids, the omega–6/omega–3 ratio and omega–3 fatty acids have been
studied in patients with depression, schizophrenia, bipolar disorders, attention deficit disorders and dementia. Casper in her paper on ‘Psychiatric Disorders, Mood and Cognitive Function: The Influence of Nutrients and Physical Activity’ reviews studies that have related variations in the amount of protein, amino acids, carbohydrates, and polyunsaturated fatty acids to mood changes. Efficacy data on omega–3 fatty acids used as adjunct or in monotherapy in unipolar and bipolar depressive disorders are critically reviewed. Evidence now exists that prenatal exposure to wartime famine may have had a bearing on the development of psychomorbidity, in particular the schizophreniform disorders. Casper also presents an evaluation of the literature that addresses the relationship between regular physical activity in the form of exercise, in relation to mood and cognitive function. Increasing evidence that psychiatric disorders are not only multifactorial, but also multigenic diseases, suggests that genetic variation could emerge as an important variable mediating the effects between nutrition and mental disorders.

Peet, in his paper ‘Nutrition and Schizophrenia’ presents a critical review and evaluation of the literature on the role of dietary components on schizophrenia. In addition to omega–3 fatty acid intervention studies, Peet reviews the evidence that a low saturated fat and low sugar diet may be beneficial, but this has not been tested in controlled clinical trials.

Dubnov and Berry in their paper ‘Managing Obesity after Menopause: The Role of Physical Activity’ carried out a Medline and manual search for articles on overweight and obesity following menopause, the risks and methods of treatment emphasizing physical activity. Their results show that among postmenopausal women, physical activity is a major mode of treatment and postmenopausal women should engage in physical activity daily, because overweight and obesity occurs in over 50% of that population.

Ferrari, in his paper ‘Osteoporosis: A Complex Disorder of Aging with Multiple Genetic and Environmental Determinants’ reviews the genetic and environmental factors influencing bone turnover and bone density, particularly estrogen-deficient women and those with low calcium intake and genes associated with vertebral bone mass and size in adult men. The usefulness of the gene variants or polymorphisms in predicting fracture risk and response to therapy remains to be demonstrated.

Inflammation is now considered to be at the basis of many chronic diseases and conditions including aging. Okuyama and coworkers, in their paper ‘Changes in Dietary Fatty Acids and Life Style as Major Factors for Rapidly Increasing Inflammatory Diseases and Elderly-Onset Diseases’ indicate that the major elderly-onset diseases in Japan are cancer, atherosclerosis related diseases and pneumonia. Elevation of inflammatory tone is a likely major cause for these diseases, which is brought about by excessive intake of linoleic
acid (LA, omega–6) and enhanced arachidonic acid (AA, omega–6) cascade. Because omega–6 and omega–3 fatty acids and their metabolites (eicosanoids, inflammatory mediators) are competitive at many steps of enzyme reactions and receptors, not only the absolute amounts of omega–6 and omega–3 fatty acids, but their balance, particularly the omega–6/omega–3 ratio, is an important factor in regulating the inflammatory tone and related diseases. Changes in life style, such as decreased physical activity and overnutrition in older populations lead to unfavorable energy balance. Reduced frequency of skin exposure to environmental changes (temperature, sweating conditions) is a likely cause for enhanced skin and mucosal sensitivity to allergens in younger populations. These environmental factors could be modified by changing the life style, besides choosing foods to keep a good omega–6/omega–3 fatty acid balance.

Despite the enormous interest in uncovering longevity genes in humans, the results have been elusive. The effects of physical activity in delaying aging are promising whereas the effects of caloric restriction in humans are now being systematically investigated in three major studies funded by the National Institutes of Health (Bethesda, Md., USA) at the Pennington Biomedical Research Center in Baton Rouge, La., at Tufts University in Boston, Massachusetts, and at Washington University in St. Louis, Mo., USA. Caloric restriction (CR) is the only mechanism known to extend life span and retard age-related chronic diseases. This has been proven repeatedly in a variety of species including rats, mice, fish, flies, worms and yeast. CR reduces metabolic rate and oxidative stress, improves insulin sensitivity and stress response, and alters neuroendocrine and sympathetic nervous system function. Whether any, or all of, these changes provide the mechanism for life-span extension effect is presently unresolved. Furthermore, the effects of prolonged CR on biomarkers of aging in nonobese humans are unknown. In experiments of nature, humans have been subjected to periods of non-volitional partial starvation. However, in almost all of these cases the diets have been of poor quality. The absence of adequate information on the effects of good quality CR diets in non-obese humans reflects the difficulties involved in conducting long-term studies in an environment so conducive to overfeeding.

Diet and physical activity cannot be disassociated from each other, not only because of energy need, but also because of the profile of food components – macronutrients, micronutrients and phytonutrients – which allow, sustain and optimize movement. In his paper ‘Physical Activity for Health: An Overview’ Wahlqvist states that preventive physical activity can address the burden of disease and longevity. Therapeutic physical activity can reduce the problems of sarcopenia and frailty, or the growing burden of nutritional and metabolic disease, and of senescence. We must seek a unifying strategy for
health advancement and for optimal health that is sustainable. In order to accomplish that, we must involve ourselves continuing as our own machines, moving, thinking, socializing, and integrated with the natural world.

There is now enough evidence to consider physical inactivity a disease, because epidemiologic studies provide robust evidence that physical inactivity is strongly associated with an enhanced risk of premature chronic diseases and death. Lees and Booth in their paper ‘Physical Inactivity Is a Disease’ provide a concise review of the evidence of the importance of physical activity in the prevention of many diseases that affect modern humans. There is now enough evidence to define the components of a healthy diet as well as the components of physical activity at the population level. At the same time, there are exciting research data defining the type and frequency of genetic variation and how genetic differences influence dietary response and how diet, nutrients and exercise influence gene expression.

In her paper ‘What Is So Special about the Diet of Greece? The Scientific Evidence,’ Simopoulos provides scientific evidence and emphasizes the importance to follow a diet consistent in composition to the diet upon which humans evolved, and their genes were programmed to respond. In this respect, traditional diets do not differ much or are similar in their composition relative to antioxidants, essential fatty acids and a balanced omega–6/omega–3 ratio. The latter is very important because during evolution, the ratio was balanced 1:1 whereas this ratio is 16.8:1 in the diet of the United States and 15:1 in the diet of Northern Europe, but 4:1 in Japan and 30:1 in India. What makes the diet of Crete different from the other Mediterranean diets is the balanced omega–6/omega–3 ratio of 1–2/1. The Greek diet, balanced in the essential fatty acids and high in antioxidants, is the diet that is the closest to the diet on which humans evolved. In his paper ‘Balance of Omega–6/Omega–3 Essential Fatty Acids Is Important for Health: The Evidence from Gene Transfer Studies’ Kang provides evidence at the molecular level of the importance of the balanced omega–6/omega–3 ratio. Furthermore, de Lorgeril and Salen in their paper ‘Dietary Prevention of Coronary Heart Disease: The Lyon Heart Study and After’ clearly show the fact that a modified diet of Crete with a ratio of 4:1 of linoleic to alphalinolenic acid decreased mortality risk by 70%. Similar results have been observed in studies in India showing that the lower the ratio, the lower the risk for total mortality, coronary heart disease mortality, and sudden death. Fidanza and coworkers in their paper ‘The Nicotera Diet: The Reference Italian Mediterranean Diet’ describe the Nicotera Diet as a model for the Italian population and present a food guide modeled after the Greek Column Food Guide, but in the form of a Greco-Roman Temple rather than the
Pyramid Food Guide developed by the US Department of Agriculture and the US Department of Health and Human Services. Wine is an important component in the diets among the Mediterranean countries as well as in South America. Urquiaga and Leighton’s paper on ‘Wine and Health: Evidence and Mechanisms’ is an excellent review of the status of research on wine. Decreased cardiovascular disease and longevity are epidemiological parameters associated with wine consumption. Recent evidence suggests that longevity could also be the direct consequence of phenolics activating histone deacetylation, a gene expression regulatory mechanism proposed to explain the longevity associated with caloric restriction.

Over the last 15 years, new concepts have evolved about food’s functions. Functional foods are thought to be foods that improve bodily functions, help prevent various non-communicable diseases, or help in the cure of some conditions. There has been a wide range of research into the beneficial effects of foods and food ingredients, beyond essential nutritional requirements for macronutrients and essential vitamins and minerals. Lupien’s paper on ‘Implications of Food Regulations for Novel Foods: Safety and Labeling’ includes a concise description of the regulatory schemes in the European community, the United States, Australia, New Zealand, Japan and China. The paper provides examples of current functional food benefits and claims. The need for adequate data is emphasized in order to substantiate claims and benefits to meet current and possible future regulatory requirements.

Australia is one of the first countries to establish a Centre of Excellence in Functional Foods. Tapsell and coworkers in their paper ‘A New Look at Intersectoral Partnerships Supporting a Healthy Diet and Active Lifestyle: the Centre of Excellence in Functional Foods, Australia. Combining Industry, Science and Practice’ outline the basis for the scientific program at the Centre of Excellence in Functional Foods, indicating how this may support the development of healthy diets and healthy lifestyles. Research at the center takes the form of strategic (government funded) and commercial (industry funded) projects.

The World Health Organization (WHO) has recognized the importance of nutrition and physical activity. In May 2004, at the World Health Assembly, member nations voted on WHO’s Global Strategy on Diet, Physical Activity and Health that appears in the paper by Amalia Waxman. The ‘Nutrition and Fitness Policies in the United States’ are discussed by Lee who reviews the programs and policies in the United States and the reasons for the difficulties in their implementation. It will be necessary to develop a broad-based population approach that includes improving accessibility of nutrition information, education, and services; strengthening and sustaining broad-based community
programs and partnerships, and working with the nation’s public and private elementary and secondary schools. Similarly, a population-based approach to physical activity is needed.

These proceedings should be of interest to physicians, nutritionists, exercise physiologists, geneticists, dietitians, food scientists and policy makers in government, private industry and international organizations.

Artemis P. Simopoulos, MD
Declaration of Olympia on Nutrition and Fitness

Ancient Olympia, Greece, May 28–29, 1996

Background

The International Conferences on Nutrition and Fitness are held in Greece every 4 years in the spring prior to the Olympic Games. Following each conference, a declaration is developed at a special meeting at the International Olympic Academy to update advice on nutrition and fitness for all. The proceedings of the conferences are published in the scientific literature listed on pages XXXI–XXXII.

The Third International Conference on Nutrition and Fitness was held at the Olympic Athletic Center of Athens ‘Spyros Louis’, May 24–27, 1996, in Athens, Greece. Four hundred and eighty participants from 31 countries attended the conference. Following the conference, an international panel composed of members of the conference Executive Committee, along with the session chairs, met at the International Olympic Academy at Ancient Olympia to develop the ‘Declaration of Olympia on Nutrition and Fitness’ for 1996.

This international panel agreed that on the occasion of the 100th anniversary of the Olympic Games, it is important to reaffirm the concepts of positive health postulated by Hippocrates and to reassess their relevance to the Olympic ideal and the health of the world’s population. The concept of Positive Health, as enunciated by Hippocrates, is based on the interaction of genetics, diet and physical activity.

‘Positive health requires a knowledge of man’s primary constitution (which today we call genetics) and of the powers of various foods, both those natural to them and those resulting from human skill (today’s processed food). But eating alone is not enough for health. There must also be exercise, of which the effects must likewise be known. The combination of these two things makes regimen, when proper attention is given to the season of the year, the changes of the winds, the age of the individual and the situation of his home. If there is any deficiency in food or exercise the body will fall sick’ (480 BC).
Among the Greeks, the concept of positive health was important and occupied much of their thinking. Those who had the means and the leisure applied themselves to maintaining positive health, which they often conceived esthetically, and to this end put themselves into the hands of trainers who subjected them to a regimen. Training for war and athletic competition was of course well known among them. Health was an excellence in its own right, the physical counterpart and condition of mental activation. The details of the regimen practiced for health were an important part of Greek medicine. The Concept of Positive Health may be represented by a triangle involving genetics, nutrition and physical activity that influence the spiritual, mental and physical aspects of health (fig. 1).

**Genetic Variation, Nutrition, Physical Activity, and Health**

The interaction between genetic and environmental factors influences human development and is the foundation for health and disease. Genetic factors define susceptibility to disease and environmental factors determine which genetically susceptible individuals will be affected. Nutrition and physical activity (exercise) are two of the most important environmental factors in maintaining health and well being.

Each human being, in being unique, is exceptional in some way. Individuality is determined by genes, constitutional factors (age, sex, developmental socio-economic status, occupation, education, time, geography, and climate). Genetic variation is due to variants at a single locus, or polymorphisms, that form the basis of human diversity, including the ability to handle environmental challenges. How extensively variable the human species is depends on the methods used for the determination of variability. At the DNA level, there is a
great deal of variation, whereas at the level of protein diversity, there is much less. In all animals, including humans and practically all other organisms examined, 30% of loci have polymorphic variants in the population. An average individual is heterozygous at about 10% of the loci. Alleles that confer selective advantage in the heterozygous state are likely to have increased in prevalence because of positive selection acting on variants. Changes in the nutritional environment and the type and degree of physical activity affect heritability of the variant phenotypes that are dependent, to a lesser or greater degree, on these environmental variables for their expression.

Genetic variation influences the response to diet. Nutrients and physical activity influence gene expression. In many conditions, proper diet and exercise have similar beneficial effects, and their effects may be additive. Because of differences in gene frequency, dietary habits, and activity levels, universal dietary and physical activity recommendations are not appropriate. Instead, knowledge of specific genes and response to exercise and diet should guide advice for health in the prevention and management of chronic diseases.

**Diet**

The purpose of diet is to supply energy and nutrients required for optimal health. Energy intake must be balanced against physical activity. Over 800 million humans are chronically energy deficient, but obesity is rampant in many industrialized societies.

**Macronutrients**

Fat is a concentrated energy source, but in affluent populations, excess fat promotes chronic degenerative diseases. In such circumstances, total fat intake should be reduced, mainly by decreases in saturated and trans fatty acids. In energy-deficient populations, an increased fat intake may be necessary to enhance energy availability and to insure absorption of fat soluble vitamins, but such increases should avoid adding saturated fats where practicable. All populations need essential polyunsaturated fatty acids for mental and cardiovascular health. An omega–6:omega–3 fatty acid ratio of 4:1 or less appears desirable.

**Carbohydrate** containing foods and soluble and insoluble fiber are needed for energy intake and normal bodily function.

**Protein** intake should be adequate for normal growth and development and in adults for maintenance of body structures.

**Micronutrients**

Adequate balanced micronutrient intake should be provided commensurate with emerging understanding of their need. Since the most extensive nutritional...
influences throughout the world are related to inadequacies of micronutrients, special attention should be directed to correcting these deficiencies: 2 thousand million persons are anemic and 1 thousand million are at risk of iodine deficiency. 40 million children suffer vitamin A deficiency. Understanding of micronutrient functions is currently increasing, and health workers should keep up-to-date with this new knowledge regarding both deficiencies and optimal requirements, e.g. the need for unitary ratios of calcium and magnesium in the diet. The variety of foods in the diets helps to maintain adequate micronutrient intake. Most populations would benefit from an increased intake of fruits and vegetables.

**Physical Activity**

A wealth of scientific reports points to the inescapable conclusion that human fitness and health improve when sedentary individuals begin to exercise. Although low physical activity levels most frequently occur in more industrialized, affluent nations, this behavior is becoming increasingly common in developing countries as well. Because mechanization and industrialization have reduced occupational physical activity levels, a need exists to supplement with additional daily physical activities designed to improve health and fitness.

A wide variety of fitness parameters, including aerobic capacity, muscular strength and endurance, coordination, flexibility and body composition improve with increases in activity levels. Perhaps more importantly, indices of human health also improve. Three of the most common chronic degenerative diseases of westernized nations (hypertension, coronary heart disease, and non-insulin-dependent diabetes mellitus) are increasingly being recognized as diseases of insulin resistance. In all three cases, physical activity clearly has been shown to reduce the severity, and outcome of these diseases. Physical activity also has a well-known role in preventing and reducing obesity and also exerts a beneficial influence upon insulin metabolism. Furthermore, increased levels of physical activity positively impact virtually all chronic diseases, including, but not limited to stroke, peripheral artery disease, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, and some forms of cancer. For previously sedentary individuals, even nontaxing physical activities such as walking, gardening, bicycling, and swimming can elicit improved health, and reduce all causes of morbidity and mortality. Table 1 lists the types of physical activity. Sports training physical activities should include daily training programs in preparation for competition. Health-promoting physical activities aim at promoting growth, improving body functions and protecting from illness. Exercise prescription (regimen) as a means of treating or reversing various diseases should be considered as an essential therapeutic component.
Education about nutrition and physical activity needs to be adapted to each country and to different populations and cultures. Education about the beneficial physical and psychological effects of proper nutrition and physical activity in health and disease needs to be directed at all age groups – children, adults, and the elderly – since research has shown that awareness of the benefits of physical activity is correlated with actual physical activity. Education needs to address the detrimental effects of sedentary life-styles, undernutrition and malnutrition, in particular for children. Education about opportunities to obtain proper nutrition and to carry out physical activity is important in view of findings that actual increases in elective physical activity depend on accessibility.

Education should reach people through various channels – the mass media, print, television, and radio – at worksites, and in the community in order to reach everybody in the population. Another means to achieve education would be through role models in the family, schools, sports, and entertainment. Institutions such as schools can set examples for proper nutrition and physical activity. The food and sports foods industry needs to be cognizant of the scientific evidence regarding optimal nutrition and physical activity levels. Another means of education would be the labelling of the nutritional composition of all foods sold.

There is a particular need for education of health professionals and health workers, nutrition and sport scientists, and educators.

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Table 1. Defining physical activity

<table>
<thead>
<tr>
<th>1</th>
<th>Nonlabor daily physical activities</th>
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<tbody>
<tr>
<td></td>
<td>Feeding</td>
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<tr>
<td></td>
<td>Bodily functions (e.g. temperature regulation, heart rate, breathing rate)</td>
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<tr>
<td></td>
<td>All daily nonlabor minimum physical activities necessary for life maintenance</td>
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<tr>
<td>2</td>
<td>Labor physical activities</td>
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<td></td>
<td>Industrial</td>
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<td></td>
<td>Agriculture</td>
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<td>Carpentry</td>
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<tr>
<td></td>
<td>Homecare, etc.</td>
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<tr>
<td>3</td>
<td>Leisure-recreational (exercise), low-to-moderate intensity of physical activities</td>
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<tr>
<td></td>
<td>Walking</td>
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<td></td>
<td>Dancing</td>
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<td>Hiking</td>
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<td>Bowling</td>
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<td></td>
<td>Cycling</td>
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<tr>
<td></td>
<td>Golf, etc.</td>
</tr>
</tbody>
</table>
(1) Nutrition and physical activity interact in harmony and are the two most important positive factors that contribute to metabolic fitness and health interacting with the genetic endowment of the individual. Genes define opportunities for health and susceptibility to disease, while environmental factors determine which susceptible individuals will develop illness. Therefore, individual variation may need to be considered to achieve optimal health and to correct disorders associated with micronutrient deficiency, dietary imbalance and a sedentary lifestyle.

(2) Every child and adult needs sufficient food and physical activity to express their genetic potential for growth, development, and health. Insufficient consumption of energy, protein, essential fatty acids, vitamins (particularly vitamins A, C, D, E and the B complex) and minerals (particularly calcium, iron, iodine, potassium and zinc), and inadequate opportunities for physical activity impair the attainment of overall health and musculoskeletal function.

(3) Balancing physical activity and good nutrition for fitness is best illustrated by the concept of energy intake and output. For sedentary populations, physical activity must be increased; for populations engaging in intense occupational and/or recreational physical activities, food consumption may need to be increased to meet their energy needs.

(4) Nutrient intakes should match more closely human evolutionary heritage. The choice of foods should lead to a diverse diet high in fruits and vegetables and rich in essential nutrients, particularly protective antioxidants and essential fatty acids.

(5) The current level of physical activity should match more closely our genetic endowment. Reestablishment of regular physical activity into everyday life on a daily basis is essential for physical, mental and spiritual well-being. For all ages and both genders the physical activity should be appropriately vigorous and of sufficient duration, frequency, and intensity, using large muscle groups rhythmically and repetitively. Special attention to adequate nutrition should be given to competitive athletes.

(6) The attainment of metabolic fitness through energy balance, good nutrition and physical activity reduces the risk of and forms the treatment framework for many modern lifestyle diseases such as diabetes mellitus, hypertension, osteoporosis, some cancers, obesity, and cardiovascular disorders. Metabolic fitness maintains and improves musculoskeletal function, mobility, and the activities of daily living into old age.

(7) Education regarding healthy nutrition and physical activity must begin early and continue throughout life. Nutrition and physical activity must be interwoven into the curriculum of school age children and of educators, nutritionists...
and other health professionals. Positive role models must be developed and
prompted by society and the media.

(8) Major personal behavioral changes supported by the family, the com-

munity, and societal resources are necessary to reject unhealthy lifestyles and to

embrace an active lifestyle and good nutrition.

(9) National governments and the private sector must coordinate their
efforts to encourage good nutrition and physical activity throughout the life
cycle and thus increase the pool of physically fit individuals who emulate the

Olympic ideal.

(10) The ancient Greeks (Hellenes) attained a high level of civilization
based on good nutrition, regular physical activity, and intellectual development.
They strove for excellence in mind and body. Modern men, women, and chil-
dren can emulate this Olympic ideal and become swifter, stronger and fitter
through regular physical activity and good nutrition.

**Distribution of the Declaration**

The declaration has been published worldwide in newsletters, magazines
and journals. It has been translated into the Olympic languages of Chinese,
French, Greek, Russian and Spanish. The ten points of the declaration have
been printed in these languages. The Executive Committee wishes to encourage
the translation and distribution of the declaration worldwide. The copyright is
held by the Executive Committee of the Conference.

The declaration was developed at Ancient Olympia, May 28–29, 1996 by
the following persons:

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**References**

Keynote Address

Positive Health: Exploring Relevant Parameters

Elizabeth Ferris
Department of Nutrition and Dietetics, King’s College London, London, UK

This year we are celebrating not only the Fifth International Conference on Nutrition and Fitness with its strong connections with Greece but also the return of the Olympic Games to the city where the modern Olympics was born over a century ago in 1896. To me as an Olympian this conjunction of the Conference with the Athens 2004 Olympics is of special importance and augments the honour of being invited to open the conference.

There is a saying, ‘Once an Olympian, always an Olympian’, – it was coined because of the unique experience competing in the Olympic Games has come to mean. There are 100,000 Olympians from over 200 countries around the world. They form a unique resource, a valuable asset to sport and to the Olympic Movement. It is by Olympians’ efforts and talents that the Olympic Games come alive in the stadium, the pool and the sports arenas. Without them there would be no Games. So it was in 1995, to recognise the contribution Olympians make and provide opportunities for former athletes to continue to play a part in the Olympic Movement, that, with the support of the International Olympic Committee, the World Olympians Association was created of which I am a co-founder and Vice President.

My involvement in sport influenced the choices I made as a doctor. As a medical student at the Middlesex Hospital Medical School at London University, I realised that I was more interested in health than disease and my professional career has followed a path of seeking out ways in which we can explore our capacities to create and maintain our own physical and mental health.
My participation at this conference in a way brings together my several identities – on the one hand as a former elite sportswoman and on the other as a doctor interested in preventive medicine and holistic health, especially nutrition and physical fitness.

The positive value to health of physical activity and nutrition is as old as civilization itself. The case for good food as a means of enjoying a long and healthy life is in no doubt. It was part and parcel of life for the ancient Greeks and when Hippocrates said, ‘Let food be thy medicine and medicine be thy food’, he was expressing something that instinctively people through the ages have sensed must be true. Food is far more than simply a means of staying alive. The song, ‘Food, glorious, food, there’s nothing quite like it’, from the musical, ‘Oliver’, based on Charles Dickens’ book, Oliver Twist, says it all.

The health benefits of physical exercise too have been widely proclaimed over the centuries. The 18th century English poet, John Dryden, pre-empted modern self-help devotees when he advised, ‘The wise for cure on exercise depend; God never made his work for man to mend.’ So much for his faith in the healing powers of doctors.

The ancient Greeks had a thorough knowledge of high-level physical training and knew that you can have too much of a good thing. We may think over-training is a modern phenomenon considering the enormous pressures professional athletes are under to perform well. But two and half millennia ago, Hippocrates expressed his concern about its detrimental effects when he wrote: ‘Physical conditioning is at risk when exercise is at very high levels.’

Aristotle agreed. He warned of the dangers of exposing young children to excessive training, pointing out that it undermined their powers of endurance and scuppered young athletes’ ambitions of Olympic victory later on as adults1.

The ancient Greeks lived in a Mediterranean paradise awash with highly nutritious green, yellow and red vegetables and fruit, nuts, olives, fish, and, of course, wine. With the warm climate and their love of sport it is little wonder that the concept of positive health through nutrition and physical fitness originated in Greece.

In my address today I’d like to explore the parameters of positive health, starting with a little of the history of the Olympic Games to draw a connection between the aspirations of the ancient Greeks and the aims of the creators of the modern Olympics in 1896 that revived those aspirations and that, right up to the present day, remain an important objective of the Olympic Movement. Using

1’TThe disadvantages of excessive training in early years are amply proved by the list of Olympic victors; not more than two or three of whom won a prize both as boys and as men. The discipline to which they were subjected in childhood undermined their powers of endurance.’ [Aristotle, Politics, Book VIII]
this connection as a stepping stone, I will dip into recent scientific research that provides evidence in support of Hippocrates’ analysis of positive health. I will touch on public health issues surrounding the global pandemic of obesity and its related serious health risks. Finally, looking to the future, I will suggest how our growing knowledge of the human genome is likely to impact on how we could maximize our potential for a healthy life.

More than fourteen hundred years after the last ancient Olympic Games were held in the 4th century AD, the idea that physical activity was essential to live a healthy life re-emerged, in particular in Victorian England on the playing fields of boy’s public schools. The concept that to be sound of mind you needed to take care of your physical health formed the basis for the physical education movement that grew up in the 19th century. But the movement did not focus only on physical health. In tune with the ancient Greek approach, it embodied moral, social and cultural principles as well. The physical education movement provides a link between the ancient Greek cultural commitment to sport on the one hand and the creation of the modern Olympic Games here in Athens in 1896 on the other.

Accepted wisdom has it that the modern Olympics was the brain-child of a French aristocrat, Baron Pierre de Coubertin. But, as with so much in history, the story was rather more complex and interesting. Before Coubertin was born, a wealthy Greek called Zappas had made unsuccessful attempts to resurrect the ancient Games in Greece. Meanwhile, in a tiny town in England called Much Wenlock, an English country surgeon, Dr. William Penny Brookes, from 1850 onwards, organised annual Olympic-style sporting festivals. He called them the Wenlock Olympian Games. Why would a rural doctor spend his time and effort, and no doubt his own cash, in creating a re-enactment of the ancient Olympic Games in a field in rural Shropshire – and who competed in them? Dr. Brookes was a philanthropist who believed that everyone in the community, not only the moneyed classes, was entitled to education and access to healthy leisure pursuits. He campaigned for physical education for children and petitioned Parliament to make it compulsory in all elementary schools. Like the ancient Greeks, he believed that sporting participation produced moral and intellectual benefits as well as contributing to physical health.

Dr. Brookes was also a Hellenist, a lover of all things from ancient Greece, and he organised his Olympian Games as nearly as possible to the ancient Olympics. The medals awarded to the winners bore the portrait of Nike, the Greek Goddess of victory, with a quotation from Pindar, the classical poet of the Olympic Games.

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2 The concept of a sound mind in a healthy body, mens sana in corpore sano, originated from the Roman satirist, Juvenal AD c.60–c.130.
Dr. Brookes’ Olympian Games had been in full swing for 40 years before Pierre de Coubertin, who was a young educationalist on a mission for the French government to research foreign systems of physical education, went to Much Wenlock in 1890 to meet Dr. Brookes and see his Games in action. Coubertin was deeply impressed and immediately recognised a kindred spirit in the country doctor. The two men shared a passionate commitment to physical recreation, not only for its health benefits but also for its moral and social value, values that today characterise what is called Olympism. After his meeting with Brookes, Coubertin wrote: ‘…if the Olympic Games that modern Greece has not yet been able to revive still survive today, it is not due to a Greek but to Dr. W.P. Brookes. It is he who inaugurated them 40 years ago and it is still he, now 82 years old but still alert and vigorous, who continues to organise and inspire them’ [2, 3].

The two men shared a vision of recreating the Olympic Games in modern times. As history reveals, Coubertin succeeded in this ambitious venture but sadly Brookes did not live to see the dream become a reality; he died in 1895 aged 87 having given his blessing to Coubertin’s international vision.

The important thing to recognise is that for Brookes and Coubertin the Olympic Games were a means by which universal physical education for all could be attained. I maintain that this is just as true today as it was in 1896. Notwithstanding the ways in which elite sport has changed of late, due in part to professionalism and commercialism, and drug-taking, the Olympic Games have the capacity to inspire young people at the grass roots level to participate in sport and physical activities. I remember the overwhelming rush of young girls wanting to practice gymnastics after Olga Korbut entranced the world with her performance in Montreal in 1976. The power to awaken such interest on a global scale is unique to the Olympic Games because of the extra dimension that the Olympics possesses compared with other international sporting events embodied in the philosophy of Olympism3. Their contribution to positive health lies in the potential to encourage people, especially children, to become more physically active4. And, there are added bonuses in being involved in sport that I will come to a little later.

3The International Olympic Committee, in the Olympic Charter (in force as from 4 July 2003) under Fundamental Principles on p 9 defines Olympism as follows: ‘Olympism is a philosophy of life, exalting and combining in a balanced whole the qualities of body, will and mind. Blending sport with culture and education, Olympism seeks to create a way of life based on the joy found in effort, the educational value of good example and respect for universal fundamental ethical principles.’

4The story of the rise of women in the Olympic Games further illustrates my point. At the first modern Olympics in 1896, there were no women because Baron De Coubertin thought the Games should remain ‘the exaltation of male sport’. The traditional attitude was that women
I’d like to turn now to the immense contribution the scientific community has made to the issue of positive health. Let’s fast forward to Britain in 1953, the year when, as the nation watched the coronation of Queen Elizabeth II in Westminster Abbey, news of the successful conquering of Mount Everest by the British expedition lead by Sir Edmund Hilary was celebrated, and just a few months later, arguably the most important sporting event of the 20th century was held when Roger Bannister conquered the four-minute mile.

On the health front, Fleming’s discovery of penicillin and its development as an antibiotic by Lord Florey, plus a mass vaccination programme saw the gradual demise of infectious diseases as a principal cause of death. Fifty years ago, medical concerns turned to focus on non-communicable diseases, in particular coronary heart disease (CHD), the major cause of premature death in the world. Morris’ seminal study [4] showed that conductors on the famous London red double-decker buses had significantly less coronary artery disease than the drivers of the buses. The health benefits of being a conductor were attributed not unreasonably to the fact that they were much more physically active than sedentary drivers. Incidentally, anyone hoping to take up this healthy job in future will be disappointed – these wonderful Red Routemasters, recognised worldwide as icons of London, are being phased out in favour of buses with just a driver whose only exercise is to press a button to open and close the doors automatically. Alas, for us passengers, no more running and jumping on the platform at the back of moving buses – a game Londoners love to play. An opportunity for a little bit of exercise in the normal course of life itself will be

were biologically unsuited to taking part in sport and, anyway, it was a male domain – a view that prevailed well into the 20th Century.

It didn’t take long for women to overturn the IOC’s entrenched view. Women golfers, tennis players and sailors took part in the second Games in 1900 and women have participated in every Olympic Games since. Throughout the past 100 years, more and more women have competed in the Olympics; in Athens 2004 the proportion of women to men will for the first time approach parity. Of the 10,000 athletes women will make up approximately 41% and will compete in all but boxing and baseball.

A positive by-product of more women athletes in the Olympics is the growth of women’s sport around the world, especially in developing countries. The challenges women face in many countries relating to religion, culture, education, poverty, and health take precedence over concerns about sport. And yet, notwithstanding these social barriers and inequality, women and girls are increasingly playing sport. There is still a long way to go but you have to admit that progress is being made when you see that in Afghanistan, where until recently women were hardly allowed to leave their homes, women are playing mixed table tennis matches in public, and in Morocco, hundreds of women and girls turn up annually for a round-the-houses run in Casablanca. From a public health point of view, perhaps the most important fact is that physically active mothers are most likely to produce physically active children and physically active children are most likely to maintain the habit into their adult years.
lost. No matter – perhaps we can make up for it by climbing the stairs in our office buildings – if we can find them! This remark may sound flippant, but it is relevant to my theme because it highlights the fact that opportunities for activity in our everyday lives, that we used to take for granted, are becoming less and less common for reasons over which we have little or no control.

The benefits of an active lifestyle were further confirmed in the 1980s by Paffenbarger and colleagues. Harvard alumni who took regular exercise, outputting 2,000 kcal or more per week, had a 39% lower risk of developing coronary heart disease and of death from the disease than their less active classmates [5]. We also now know, where a healthy heart is concerned, it is the intensity of the exercise that matters [6].

Coronary heart disease is clearly a lifestyle disease with smoking and physical inactivity top of the list of risk factors, and we know that exercise is beneficial. What about the effects of diet? Recent research has revealed that a nutritional substance – folic acid, one of the B vitamins – gives considerable protection in heart disease by lowering homocysteine levels in the blood. In addition, folate protects against a wide array of other serious diseases including cancer, dementia and birth defects [7]. It has many diverse biological properties expressed through a number of crucial gene pathways and has even been cited as the panacea of the 21st century. The effect of folic acid research has been to open up new avenues of intervention with vitamins and other nutrients in disease prevention, and a new area of research has been identified – nutrigenomics, the study of the links between nutrition and gene function. Nutrigenomics fits very well with what Hippocrates knew instinctively when he spoke of the powerful effects of various foods and physical exercise on man’s primary constitution.

In addition to the protective effect of exercise in coronary heart disease, physical activity has been shown to be significant in other serious diseases that are major causes of death in the modern world – diabetes, osteoporosis, obesity related conditions and cancer. The amount and type of exercise recommended varies. In obesity, where weight loss is the goal, any increase in energy output is desirable. The Chief Medical Officer in the UK just a few weeks ago, in an extraordinary story of bravery and endurance that raises important questions about the relationship of exercise to cancer is that of Jane Tomlinson, a young British mother who, in 2000, was diagnosed with terminal bone cancer and told she had just 6 months to live. Since then, Jane has run three marathons, completed an ‘Iron Man’ event and recently cycled 2,500 miles from Rome to Yorkshire in the North of England where she lives. No-one knows the role vigorous exercise has played in prolonging her life, or that of the professional cycling phenomenon, Lance Armstrong, who had testicular cancer and went on after treatment to win the Tour de France six times.
attempt to arouse the largely sedentary population to ‘get up and go’, produced a report entitled, ‘Physical Activity and Health’ in which he recommended vacuuming and ironing as good examples of moderate exercise. Whilst this may seem like too little too late, it is claimed that 30 min of moderate exercise 5 times a week is enough to prolong life.

We also know that exercise has positive effects on mood and feelings of mental well-being. Fascinating research from the Salk Institute suggests that physical activity has a positive effect on brain plasticity. There are stem cells in the adult brain that produce new nerve cells in the dentate gyrus of the hippocampus, an area associated with memory. Physical activity positively promotes this neurogenesis – in running mice at least [8]. For those of us who have those occasional ‘senior moments’, like when you find yourself in the cupboard under the stairs and cannot for the life of you remember what you’ve gone there for, a little light running on the spot to stimulate a few new brain cells may help you to remember what on earth you’re doing there – if you can remember the original piece of research! In fact, this is a particularly productive line of research in support of physical activity in the aged. We now have evidence that exercise combined with a diet rich in nutrients, in particular folic acid, could help stave off symptoms of dementia and Alzheimer’s disease in increasingly ageing populations.

The effects of nutrition on mental function and behaviour are equally interesting. Young adult prisoners showed a remarkable reduction in antisocial behaviour when their diets were supplemented with vitamins, minerals and essential fatty acids [9]. Poor nutrition, on the other hand, has alarming effects. Young schoolchildren who went without breakfast missed out in more ways than one. Three hours into school, the children had powers of attention as poor as an adult who had had a slug or two of whisky or a tranquiliser. And they did equally badly when they had just a glucose drink. With cereal for breakfast, however, they showed an enormous improvement [10].

With the scientific body of knowledge expanding, the case for physical activity coupled with good food for a long and healthy life is made and is in no doubt. And yet, hardly a day goes by without another report of the growing pandemic of obesity across the globe. Population surveys show that the world is getting fatter and the incidence of Type 2 diabetes is increasing at an alarming rate, in particular, and perhaps most disturbingly, in young children.

In our highly technologically developed modern world in which the need to extend ourselves physically in the normal course of our lives is diminishing day by day, our lifestyles have changed radically during the past 50 or more years. As obesity levels rocket, it seems reasonable to blame the modern diet high in fat, sugar and salt for the increases. This is hardly new: Plato was highly critical of those who were a nuisance to their doctors because of leading an ‘idle life’ and ‘filling our bodies with gases and fluids like a stagnant pool’ [11].
Counter-intuitively, children it appears are actually eating less today, not more, than they used to eat [12, 13]. Children are getting fatter because they are much less active than they used to be and their energy intake in the food they eat is greater than the energy they expend in physical activity. The reasons are largely cultural: more car journeys with less walking, parental concerns about security and safety that restrict where and when children can play, and, in particular, television watching and computer games are all cited as reasons for inactivity in children across the globe [14], even in China where until recently you would never see a fat person let alone an obese child [15]. Along with TV watching goes snacking on high-density junk food and fizzy drinks that further contribute to the greater energy intake/lesser energy output problem [16].

The emphasis, especially in the media, is predominantly on what children eat because it’s obvious to see the outcome and it is easy to make value judgements about children who are fatter than we think they ought to be. In fact, in health terms, it is almost certainly better to be active, fit and a bit fat than lazy and lean.

Perhaps the most alarming information to come to light concerning this growing problem is in a report of the International Council of Sport Science and Physical Education (ICSSPE) that states: ‘school physical education is in a perilous position in all continental regions of the world’ [17]. PE has a low priority in school curricula, and is starved of funding, materials, time and teachers. The future of PE looks bleak. Governments are giving out confusing mixed messages. On the one hand, they are advising children to do more exercise whilst on the other hand making it obvious that physical education is a Cinderella subject on the school curriculum deserving few resources. It doesn’t make any sense.

On a more personal level, good food and good eating initiatives are sprouting as public interest in nutrition grows especially in developed countries. For example, organic farming is expanding in Europe to counter the use of additives and pesticides, alongside a popular anti-GM crops drive that has resulted in Monsanto cancelling its GM crop production programme in Europe. Another initiative is the slow food movement in Italy that has emerged as an antidote to the fast food culture in an attempt to replace it with old values of sitting down to meals with family and friends, and savouring good, wholesome nutritious food and wine. Children too benefit from this style of eating. Children who eat meals with their family consume more fruit and vegetables, fewer fizzy drinks and less fat in food both at and away from home [18].

Again, the ancient Greeks got it right. According to a recently published account of what Olympic winners eat in ancient Greece:

*The main meal was dinner where the presence of family and friends and the consumption of wine were important elements. Dinners were rather prolonged*
during which people were eating, drinking wine with water and discussing current issues. (The term 'symposium' means ‘drinking together with others’)[19].

In the commercial world, if one can believe the stock quotes, the leisure industry is profiting from increasing membership of gym and fitness centres although the percentage of people in the UK who regularly exercise hardly reaches double figures, McDonald’s, under pressure from the media and the public, is changing its image to provide more healthy salad and fruit options, and the vitamin and supplement industry is booming as people self-administer these products in an attempt to bolster their well-being.

In my early school days, I remember that the welcome mid-morning interval between writing and arithmetic was called playtime, and play we did. I suggest that, with respect to children at least, we need to put play back into physical activity. Perhaps, we need to change the terms we use; ‘physical education’ is a rather dry phrase, we could go back to using the word ‘recreation’ – it has a more pleasurable ring about it.

Perhaps a clue to how to appeal to children can be found in what youngsters like to do in their leisure time: they like to play computer games. Sony had a brilliant idea when they called their equipment Play Station. To me the title is an oxymoron. Sony used the word ‘play’ – which according to the Oxford English Dictionary (OED) means to move about swiftly; to fly, to dart to and fro; to frisk, to flit, to flutter, all words that exemplify what children do when they play – juxtaposed with the word ‘station’ which, according to the OED, means standing still, the opposite of motion. But the word ‘play’ is evocative and enticing. Why are computer games so beguiling to children? Is it because they provide positive feedback, enjoyment, accomplishment, the possibility of winning, and even applause for success – all the things an athlete gets, or hopes to get, from sport?

But, not all children are good at sport and many are alienated from participating especially when the emphasis is on competition and performance. Even children who show an aptitude for one sport, gymnastics say, may not show any talent for another, a ball game, like soccer. I started my sporting life as a swimmer but I became bored with the training. It didn’t suit my personality and if the opportunity had not arisen to change to diving, a much more acrobatic sport, I am sure I would have given up. I heard a similar story from an Olympic swimming champion. He was hopeless at school sport – last in cross-country running, no eye-to-ball coordination. One day he fell through a plate glass window and severed a tendon in his calf, couldn’t run and so, fortuitously, took up swimming, loved it and made it to the very top winning 2 Olympic gold medals. The moral of his and my stories is

\[6\] Montaigne said 500 years ago, ‘It should be noted that children at play are not playing about; their games should be seen as their most serious-minded activity.’
that if we had not had the good fortune each to find our own sporting niche neither of us would have won our Olympic medals. Unless options are available to be tried and tested by the individual, a child could be put off sport, and by association, physical activity, for the rest of his or her life – and very possibly to the detriment of their health.

The key question is how people can be enticed into changing their lifestyles to incorporate physical activity and good nutrition into their normal everyday lives. The World Health Organisation recently presented its global strategy to improve public health through healthy eating and physical activity. Governments are considering what public health initiatives they can provide to help solve the problem. In 2004, a British Parliamentary Health Committee published a report [20] in which it recommended 80 measures including a ban on the promotion of sugary drinks and snacks in schools, curbs on advertising junk foods on television in particular during children’s programmes, health warnings and clearer labelling on foods, and new building developments to feature cycle paths, walkways and playing fields. All good ideas – but will they work? And will they work in time to defuse the ticking time bomb of poor health, shortened life spans and premature death in the current generation of physically inactive children for whom obesity and its concomitant problems are becoming the norm.

To date, the health argument has not exactly been able to inflame the public’s imagination. The cosmetic argument only carries weight with those vain enough to care. An alternative approach, it seems, is needed if public attitudes are to change. A possible clue may be gleaned from a fascinating study of the Pima Indians of Arizona [21]. Pima Indians suffer from high levels of obesity and diabetes. The study tested the efficacy of lifestyle interventions. One group of subjects, the Pima action group, had a mix of nutrition and physical activity active interventions. The other group, the Pima pride group, received printed leaflets about activity and nutrition but in addition they engaged in regular discussions on Pima culture and history. At the end of 12 months, the pride group was showing much more favourable results than the action group in terms of their health parameters – they had lost more weight and had more favourable blood glucose and insulin levels. It seemed that by boosting their pride in their Pima identity, almost as a side effect they were able to take more care of their health compared with those in the action group who only focussed on changing their diet and exercise. Did this effect have something to do with building up the pride group’s self-esteem and respect for their Pima identity? I think so. It’s possible to link the concepts of respect and self-esteem with autonomy [22]. Researchers have found that control at work, or the lack of it, i.e. lack of autonomy, is associated with increased health risks [23, 24].

I have touched on some complex issues in an attempt to suggest that the answers to the health problems we face do not lie in governments simply telling
people to eat less and walk more, good as that advice may be. Something has to ignite a person’s interest and that is why I have come back full circle to sport.

Sport for me, before I reached the elite level, was a complete experience. It provided me with a full social life, good friends who, 40 years later, I am still in touch with, travel, teamwork, a sense of achievement and how to deal with failure as well as success. The actual activity, the experience of diving, was completely personal. But it was the context in which I did it that provided the ground in which I grew up and thrived. If, amongst the myriad of choices sport has to offer, a person, in particular a child, can find something to illuminate their curiosity and suit them mentally as well as physically, sport is an activity that, in the broadest terms, can offer a rewarding lifestyle with healthy by-products. Active children are more likely to become active adults, and physically fit and active adults have lower risks of heart disease, diabetes and cancer.

Turning now to the future, scientific studies and public health initiatives I’ve highlighted show that, when reaching for ways of dealing with chronic non-communicable diseases, advice on what lifestyle changes an individual can make has tended to focus on just two variables – dietary habits and patterns of physical activity (with smoking as well in the case of CHD). The underlying assumption has been that these are possibly the most important or even the only parameters in a person’s individual make-up relevant to health (and ill health). I suggest that this is a very restricted view. My own view can be summarised as follows:

1. Genetic factors play at least as important a role as exercise and diet. Moreover, genetic constraints and regulation influence individual potential to respond to exercise and dietary factors. For example, the Finnish Olympic champion cross-country skier, Eero Maentryanta, was a medical mystery. He had 15% more red blood cells than normal and some were convinced he was blood doping although there was no evidence. The mystery was solved by Lodish and colleagues at the MIT when they discovered that Maentryanta and others in his family had a genetic mutation that accounted for the high levels of red blood cells [25].

Another study showed that a single gene – dubbed the ‘performance gene’ – may influence an athlete’s propensity to excel at either sprinting or long distance running. The gene, which encodes for an enzyme – angiotensin-converting enzyme (ACE) –, researchers believe determines whether an individual grows more ‘fast twitch’ or ‘slow twitch’ muscles fibres [26].

With respect to obesity, O’Rahilly’s group at Cambridge together with other researchers have found a genetic connection between proneness to obesity and PPARy genotype [27]. In simple terms, their work shows that some people have a genetic propensity for obesity whilst others don’t. This corresponds to our intuition. We’ve all said at some or other, ‘Lucky old so-and-so – he can eat anything and stay thin’.
We can say something similar regarding the connection between fitness and health. Evidence is all around us of very fit people who succumb to illness and die. Look at Jim Fixx, who started the jogging craze; a very fit man who died suddenly and prematurely from a heart attack. At the other end of the health spectrum is the Australian, Shane Gould, who at 15 years of age was a multiple Olympic champion and the supreme swimmer in the world. This year, 30 years on, at age 47, she returned to swimming and qualified for the Australian Olympic trials. She has to have an extraordinary genetic makeup.

These examples illustrate how an individual’s genotype may determine both potential for protection from developing disease as well as the risk of developing disease. We know, for instance, that smokers vary in their risk of developing lung cancer and coronary heart disease. It is possible that within a few years we may be able to characterise people according to their genotype, and programmes of dietary and exercise interventions could be tailor-made to the individual.

(2) Future research will eventually lead to an awareness of the importance of other variables apart from diet and exercise. This in turn will eventually expand our understanding, not only of the number of variables involved, but also how these variables relate to one another.

In my ideal world, we would eventually end up with a detailed algorithm that would specify all the variables involved and relate them to each other in a quantifiable, indeed, mathematical, way. Statisticians are already grappling with producing such a mathematical equation. How wonderful it would be if a formula such as $2(A+1/2B+2/3C-D...n)/4$ specified the exact relationship of all the relevant variables in a unique equation for each individual, where, say, $A$ is exercise, $B$ is diet, $C$ is genotype, $D$ is hitherto unknown variable and $n$ is all future relevant variables – along the lines that Hippocrates suggested, ‘the season of the year, the changes of the winds, the age of the individual and the situation of his home’...and any number more.

The human genome project has opened wide the potential for the kind of outcomes I am suggesting. The future is exciting. We are very fortunate to have leaders in these fields of research here at our meeting and I wish us to have a wonderful and stimulating conference.

Thank you all for your attention.

Dr. Elizabeth Ferris, 2004

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7To see why diet and exercise cannot be the only variables that are relevant to health see: Campos P: The Obesity Myth: Why America's Obsession with Weight Is Hazardous to Your Health. New york, Gotham Books, 2004.
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Psychiatric Disorders, Mood and Cognitive Function: The Influence of Nutrients and Physical Activity

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Human mental function is genetically based, yet modulated during development and throughout life by environmental factors. Family and twin studies have shown that hereditary factors play an important role in the incidence and clinical expression of affective disorders and schizophrenia [1]. As a result, research has increasingly focused on linking specific psychiatric disorders to specific genetic markers. Hereditary studies, however, have revealed a significant environmental influence on gene expression [1]. Psychological factors are important environmental components which interact with genes or gene products to promote the expression of a phenotype. For instance, Caspi et al. [2] reported that a polymorphism in the 5-HTT gene, in this case one or one or two copies of the short allele of the 5-HTT promoter, increased an individual’s chance to react to stressful life events with depressive symptoms, depressive disorder and suicidal behavior. The heritability for psychiatric disorders [3] suggests that there is a significant environmental component in the pathogenesis of psychiatric disorders. For nutrition which powerfully impacts physical health and disease [4, 5], the mechanisms of the gene-environment interaction are under investigation [6, 7].

In normal populations nutritional factors and physical activity have been shown to have subtle effects on mood and cognitive ability [8]. Studies exploring possible relationships between nutritional factors and the incidence and course of psychiatric diseases are of recent origin.

This chapter will address four questions:

1. Assuming that psychiatric disorders have a genetic basis, is there a role for environmental factors?
2. What are the beneficial effects of the essential \(\omega-3\) polyunsaturated fatty acids (\(\omega-3\)-PUFAS) on human development and what is the evidence that malnutrition during prenatal life affects mental development?

3. In the second part findings from placebo controlled studies and uncontrolled trials will be reviewed with the question in mind: do the data support a role for nutritional compounds, specifically the \(\omega-3\)-PUFAS, in altering the prevalence or the occurrence of psychiatric symptoms?

4. Lastly, are there mental health benefits to physical exercise?

Psychiatric Disorders are the Products of Genetic Regulation and Environmental Influences

The genetic basis of human mental function and dysfunction is complex and due to the interaction of multiple genes. Genes instruct the development of the central nervous system (CNS), at the same time environmental factors promote or in the case of hypoxia, infection or malnutrition may disrupt maturational processes. For schizophrenia, even if 100\% genes are shared as would be the case for an individual with two schizophrenic parents, the risk of developing the condition is estimated to be no more than 46\%, leaving a substantial portion to environmental factors [1]. Furthermore the recent discovery of the neuregulin gene which plays a central role in neural development and contributes to schizophrenia in both Icelandic and Scottish populations suggests the possibility of population based genetic variability [9]. An example of a gene/nutritional environment interaction would be the APOE gene which has been linked to schizophrenia in Chinese and seems to confer vulnerability during times of malnutrition [6]. A hereditary component for affective disorders is well documented [10]. Recently, the South Island Bipolar Study demonstrated an increased prevalence of bipolar and depressive disorders in relatives of bipolar patients [11], which, nevertheless, leaves >60\% to environmental risk factors. Another example of a gene/environment interaction would be the variant of the monoamineoxidase type A (MAOA) gene which has been linked to aggressive, impulsive and even violent behaviors in monkeys and humans. Maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems [12, 13].

Early Development: Prenatal Growth and Diseases in Adult Life

Aside from genetic factors, the maternal environment influences fetal developmental milestones. In the late eighties, epidemiological studies began to point
to the conclusion that adults who had been born with normal, yet low birth weight have an increased susceptibility to diseases in adult life. Barker’s [14] analyses of birth and death certificates of people born in Hertfordshire, UK revealed that 2.3-kg babies had double the rate of death from coronary heart disease, hypertension, stroke and type II diabetes, compared to 4.5-kg babies. These observations which were subsequently confirmed [15] generated the fetal origins hypothesis that proposes that the fetus adapts to a limited supply of nutrients, and in doing so, permanently alters its physiology and metabolism. The new set point appears to increase the risk of disease in later life. There is one report [16] which found a relationship between low weight gain in infancy and suicide in adult life.

Observations that growth restriction during fetal life is associated with increased adrenocortical and adrenomedullary activity [17] and a higher prevalence of autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgSAb) [18] are important in view of the presence of similar endocrine abnormalities in major depressive disorders. Remarkably, an excess of protein may also modulate lifelong changes in the hypothalamic-pituitary-adrenal (HYPAC) axis. Herrick et al. [19] described hypercortisolemia in 28- to 30-year-old subjects whose mothers had been advised to consume 0.45 kg of red meat daily and avoid carbohydrates during pregnancy, an intriguing finding given the popularity of the Atkins diet. Another report [20] that described epigenetic metastability following excess intake of folic acid, vitamin B₁₂, choline, and betaine leading to possible deleterious influences on the establishment of epigenetic gene regulation in humans deserves further study in view of current recommendations for large doses of folic acid in particular for patients taking antiepileptic drugs.

Epidemiological studies of psychiatric disorders [21] have linked severe malnutrition during the first trimester to the risk of schizophrenia by analyzing the incidence of schizophrenia in birth cohorts born between January-February 1944 and November–December 1946 in Holland during the German occupation. Those conceived during the height of the Dutch famine and exposed to very low food rations during the first trimester (from February to April 1945) had an excess of neural tube defects [22] and double the relative risk for schizophrenia [21]. Brain imaging studies [23] have shown decreased intracranial volume and double the rate of brain abnormalities, in particular focal white matter hyperintensities in a subset of these patients compared to controls born during the Dutch hunger winter. As noted previously, Liu et al. [6] suggested that the epsilon-4 genotype of the APOE gene may be associated with the risk of malnutrition for schizophrenia. First trimester exposure to severe malnutrition during the Dutch hunger winter has also been reported to double the risk of schizoid personality disorders [24], schizophrenia spectrum disorders [25], and antisocial personality disorder [26]. Malnutrition during the second trimester appears to double the risk for affective disorders in adulthood [27].
Interaction between Nutrition, Growth and Development

Animal Studies

Bourre et al. [28] have documented during cerebral development in rodents a linear relationship between brain content of (ω–3) acids and the (ω–3) content of the diet up to 200 mg of α-linolenic acid levels per 100 g food intake, however DHA levels remained unaltered following ALA [28]. They observed that a diet low in (ω–3) acids affects learning in rodents. In rhesus monkeys, Connor et al. [29] showed more fatty acid lability when ω–3-deficient monkeys were fed fish oil diets rich in DHA and other ω–3 fatty acids. An earlier study [30] described that rhesus monkeys long term deficient in ω–3 fatty acids displayed bouts of stereotyped behavior typical of monkeys raised in social isolation compared to monkeys fed a matched control diet abundant in ω–3 fatty acids.

Human Studies

Fish oil supplements given from week 30 of the pregnancy extended the pregnancy duration on average 4 days in Danish women compared to women receiving olive oil supplements [31]. Low consumption of seafood has been associated with premature delivery [32]. Cheruku et al. [33] found that higher maternal DHA levels were associated with more mature infant sleep and wake states in newborns. Maternal supplementation with cod liver oil (total 1.2 g DHA +0.8 g EPA) versus corn oil (4.7 g linoleic acid (LA) and 0.09 g α-linolenic acid (ALA) from week 18 of pregnancy until 3 months after delivery increased children’s mental processing composite score significantly at 4 years of age. Intelligence correlated with head circumference at birth, but not with birth weight or gestational length [34]. Maternal supplementation with 2.8 g ALA did not prevent decreases in maternal DHA and AA concentrations, yet did increase EPA and DPA levels, with no difference in birth outcome [35]. Another study found similar visual, cognitive and language scores in breastfed and DHA- and DHA+AA-enriched formula-fed children at 39 months [36]. In a cross-sectional study phospholipid (DHA and AA) status at birth was not associated with cognitive development at 4 years of age [37] or with cognitive performance at 7 years [38].

Nutritional Factors in Affective Disorders

Studies on the effects of amino acids, protein and carbohydrates on mood and the effects of caloric restriction on life span have been reviewed previously [8].
Polyunsaturated Fatty Acids (PUFAS) and Major Depressive Disorders (MDD)

Phospholipids as components of membrane structure play a critical role in signal transduction via receptor mediated phospholipid derived second messengers such as prostaglandins or arachidonic acid. A role for the eicosanoids and immune activation in the pathophysiology of MDD [39, 40] is supported by findings that antidepressants of several classes decrease the production of pro-inflammatory cytokines such as interferon-gamma and tumor necrosis factor-α, and increase that of interleukin-10, an anti-inflammatory cytokine [41]. Significant decreases of plasma polyunsaturated ω–3 fatty acids are inversely associated with major depression [42], whereas increases in the ω-6/ω-3 plasma ratio or red cell membrane phospholipids of patients with major depression correlate directly with the severity of depression.

The comprehensive review by Hibbeln and Salem [43] makes it abundantly clear that testing of the therapeutic efficacy of PUFAS has underdone few double-blind trials, in fact most data derive from case reports, pilot studies, open trials, cross-sectional analyses and unpublished communications.

Omega–3 Fatty Acids in Major Depressive Disorder (table 1)

Placebo-controlled studies typically have included treatment resistant or partially improved patients who may not be representative and who are by definition difficult to treat.

Four placebo-controlled studies have randomly assigned patients on antidepressant medication to receive ω–3 fatty acids. Administration of 2 g EPA daily reduced depressive symptoms by week 3 in a 4-week study of Nemets et al. [44]. Peet and Horrobin [45] found that 1 g EPA daily, but not 2 or 4 g EPA ameliorated depression scores in mostly female medicated patients by week 4 on the Hamilton rating scale (HRS) and the Montgomery Asberg depression rating scale (MDRS) with the greatest improvement occurring at 12 weeks, when patients rated themselves as improved on the BDI. Marangell et al.’s 6-week [46] study failed to show benefit from 2 g DHA daily on the MDRS, even though the placebo group was more depressed at baseline. Su et al. [47] gave EPA/DHA 2:1, a total of 6.6 g daily after a placebo washout in a 12-week study and showed improvement in the HAMD score by 4 weeks with further symptom reduction by 12 weeks. Cross-sectional analyses [48] found elderly patients with MDD and with normal C-reactive protein levels to have lower ω–3 plasma levels and higher ω–6/ω–3 ratios. A population-based study of all males, 50–69 years old residing in southwestern Finland [49] found no evidence
between fish consumption or overall ω–3 dietary intake and depressed mood, MDD or suicide.

### Omega-3 Fatty Acids in Pregnancy and Postpartum Depressive Disorder

Hibbeln [50] analyzed prevalence rates for postpartum depressive disorder (PPD) across countries and found an inverse relationship to seafood consumption. Higher DHA, but not AA or EPA, breast milk concentrations predicted a lower prevalence of PPD. Stronger evidence for a role of ω–3 fatty acid deficiencies in postnatal MDD comes from a study by De Vriese et al. [51] who found lower ω–3 PUFAS and lower ω–3/ω–6 ratio in plasma lipids of women who developed postpartum depression compared to controls. Yet, a placebo-controlled study supplementing breast-feeding women with 200 mg DHA daily for 4 months postdelivery, even if it raised DHA lipid content, failed to influence measures of depression in a study by Llorente et al. [52]. This study was not a valid test, since too few (15%) women with MDD were included. In a small open label trial [53] which administered 2.96 g of fish oil (EPA/DHA ratio 1.3) during the last 4 weeks of pregnancy, 4/7 women experienced postpartum depression, not different from the relapse rate expected in untreated

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**Table 1.** Placebo-controlled treatment studies of ω–3 fatty acids

<table>
<thead>
<tr>
<th>Author</th>
<th>Type, dosage, duration</th>
<th>Subjects, n</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major depressive disorders</strong></td>
<td></td>
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</tr>
<tr>
<td>Nemets et al. [44]</td>
<td>Ethyl-EPA 2 g/day 4 weeks</td>
<td>20</td>
<td>▼ HRSD scores week 2</td>
</tr>
<tr>
<td>Peet and Horrobin [45],</td>
<td>Ethyl-EPA 1.2 or 4 g/day 12 weeks</td>
<td>70</td>
<td>1 g/day ▼ HRSD MADRS week 4</td>
</tr>
<tr>
<td>Marangell et al. [46]</td>
<td>DHA 2 g/day 6 weeks</td>
<td>36</td>
<td>Response rates similar ▼ 24–28% MADRS</td>
</tr>
<tr>
<td>Su et al. [47]</td>
<td>EPA 4.4 g/day 8 weeks + DHA 2.2 g/day</td>
<td>28</td>
<td>▼ HSRD scores week 4 &amp; 8</td>
</tr>
<tr>
<td><strong>Breast-feeding women with postnatal depressive disorder</strong></td>
<td></td>
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</tr>
<tr>
<td>Llorente et al. [52]</td>
<td>DHA 200 mg/day</td>
<td>101</td>
<td>No difference; only 14% of patients had MDD or depressive symptoms</td>
</tr>
</tbody>
</table>

HRSD = Hamilton rating scale for depression; MADRS = Montgomery-Asberg depression rating scale; MDD = major depressive disorder.
women. Considering the high rates of breast-feeding among current mothers and the benefits from nursing, PPD merits further investigation in better designed placebo controlled studies which ought to include an infant assessment. Remarkably, infant monkeys fed a formula containing 1% DHA and 1% AA displayed better visual orienting and motor skills by day 7 and day 14 than breast-fed or standard formula-fed infant monkeys [54].

**Omega–3 Fatty Acids in Bipolar Disorder (table 2)**

Two studies have described either reduced erythrocyte membrane AA or DHA content in bipolar disorder patients [55] or an increased prevalence of bipolar I, bipolar II bipolar spectrum disorder in countries with less than 50 lb seafood consumption per year [56]. These findings notwithstanding, only one report found some benefit from ω–3 fatty acids in bipolar disorders. Stoll et al. [57] who compared time to relapse over 4 months in 14 bipolar patients who received 6.2 g EPA + 3.4 g DHA daily to that in 16 bipolar patients receiving olive oil placebo found more patients in the PUFA supplemented group to remain stable at 4 months than in the placebo group. Two studies by Keck et al. [58] found no benefits from 6 g EPA added for 4 months to the medication regime of bipolar patients.

**Omega–3 Fatty Acids in Schizophrenia (table 3)**

Schizophrenia is currently conceptualized as a neurodevelopmental disorder [1]. Among the nutritional deficiencies low vitamin D has been hypothesized to underlie the relationships to excess of winter births, increased rates of schizophrenia in urban versus rural settings and increased rates in dark-skinned migrants to colder climates [59].

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**Table 2.** Placebo-controlled treatment studies of ω–3 fatty acids in bipolar disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>Type, duration, dosage</th>
<th>Subjects, n</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoll et al. [57]</td>
<td>6.2 g EPA + 3.4 g DHA or placebo; 4 months</td>
<td>30 bipolar I and II, disorder</td>
<td>Longer time to relapse</td>
</tr>
<tr>
<td>Keck et al. [58]</td>
<td>6 g EPA/placebo</td>
<td>59 bipolar depressed pts</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Keck et al. [58]</td>
<td>6 g EPA/placebo</td>
<td>62 bipolar rapid cycling</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>
The rationale to use PUFAS in schizophrenia is based on Horrobin’s theory [60] of abnormal lipid metabolism in schizophrenia and on findings that schizophrenic patients as opposed to normal controls and depressed patients display a deficient flushing response to niacin subdermally suggesting reduced membrane arachidonic acid levels and reduced production of prostaglandin D2 (PGD2) in schizophrenia. Noaghiul and Hibbeln [56] observed no relationship between seafood consumption and lifetime prevalence rates of schizophrenia. Arvindakshan et al. [61] described lower than normal AA and DHA in drug naïve unmedicated compared to medicated schizophrenia patients and controls as well as modestly significant negative correlations between AA. An open trial [62] found symptomatic improvement of negative symptoms in 20 schizophrenia patients following 6 weeks of 10 g EPA/DHA-ratio 1.3. Another uncontrolled study (180/120 mg EPA/DHA, as well as vitamins C and E) found clinical improvement in 33 patients [63].

In four out of five placebo-controlled add-on trials to standard antipsychotic medication EPA, but not DHA, reduced positive symptoms [64]. In a monotherapy trial [64], 12 placebo-treated patients, but only 8/14 EPA treated patient required antipsychotic medication after 3 months. Another analysis [65] in which 2 g EPA, but not 1 or 4 g EPA were found to be better than placebo was based on 9 clozapine-treated patients, only. The strongest evidence for consistent improvement from

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**Table 3.** Polyunsaturated fatty acids in the treatment with schizophrenia: placebo-controlled studies of medicated patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects, n</th>
<th>Type, dosage, duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mellor et al. [62]</td>
<td>20</td>
<td>10 g EPA/DHA ratio: 1.3; 6 weeks</td>
<td>Improvement: AIMS and PANSS</td>
</tr>
<tr>
<td>Arvindaksham et al. [63]</td>
<td>33</td>
<td>EPA 360 mg + DHA 240 mg + vitamins C and E</td>
<td>Sustained 4 months improvement</td>
</tr>
<tr>
<td>Peet et al. [64]</td>
<td>14/12</td>
<td>2 g EPA/placebo</td>
<td>↓PANSS score</td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peet et al. [64]</td>
<td>45</td>
<td>2 g EPA vs. 2 g DHA 3 months</td>
<td>EPA &gt; DHA</td>
</tr>
<tr>
<td>Fenton et al. [67]</td>
<td>87</td>
<td>3 g EPA/placebo 12 weeks</td>
<td>No difference</td>
</tr>
<tr>
<td>Peet and Horrobin [45]</td>
<td>115</td>
<td>1, 2, 4 g EPA/placebo, 12 weeks</td>
<td>2 g improvement in clozapine patients</td>
</tr>
<tr>
<td>Emsley et al. [66]</td>
<td>40</td>
<td>3 g EPA 12 weeks</td>
<td>↓PANSS score, ↓dyskinesia</td>
</tr>
</tbody>
</table>
week 3 to 12 based on total PANSS scores and involuntary movement scores was presented by Emsley et al. [66] who in contrast to Peet and Horrobin [65] found a trend for patients on conventional antipsychotic drugs to fare better. Fenton et al. [67] found no differences over the 12-week period between the placebo- and EPA-treated group in an older chronically ill population.

**Impulsivity and Irritability (table 5)**

Although several uncontrolled studies [68–73] have reported reductions in aggressive behavior or hostility scores after administration of DHA or EPA, no firm conclusions can be drawn without more and better designed double blind controlled studies. DHA supplements for 2 months in a placebo-controlled study [72] did not improve concentration or the behavior of children with attention deficit disorder.

**Mild Cognitive Impairment and Alzheimer’s Disease (table 5)**

Epidemiological studies, summarized in table 4, suggest better cognitive function with long-term use of vitamin C and vitamin E [74, 75]. A decreased risk for Alzheimer’s disease (AD) and mild cognitive impairment (MCI) was found in individuals who used both vitamin C and vitamin E [76, 77]. Plasma

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**Table 4.** Studies examining the relationship between irritability, hostility and/or aggression and ω–3 fatty acids

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Number of subjects (age, years)</th>
<th>Type, dosage</th>
<th>Outcome/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamazaki et al. [68]</td>
<td>22 vs.19 students 3 months</td>
<td>DHA 1.6 g soybean oil</td>
<td>↓aggressive behavior stress-induced</td>
</tr>
<tr>
<td>Gesch et al. [69]</td>
<td>231 male offenders &gt;18 years – 142 days 8 weeks</td>
<td>LA, ALA, DHA 172, EPA 320 mg</td>
<td>26% reduction in disciplinary action</td>
</tr>
<tr>
<td>Zanarini et al. [70]</td>
<td>BPD 20/10 women; 20/10 women; 8 weeks</td>
<td>EPA 1 g mineral 1 g</td>
<td>↓aggression scores</td>
</tr>
<tr>
<td>Iribaren et al. [71]</td>
<td>3,581 youths</td>
<td>DHA levels &gt;1 SD</td>
<td>↓high hostility score</td>
</tr>
<tr>
<td>Hirayam et al. [72]</td>
<td>ADHD 20/20 children</td>
<td>DHA food 3.6 g/week</td>
<td>↑visual memory ↓errors commission</td>
</tr>
<tr>
<td>Raine et al. [90]</td>
<td>83 children; 355 NC 3–5 years</td>
<td>Enrichment</td>
<td>↓schizotypal, criminal behavior</td>
</tr>
</tbody>
</table>
\( \omega-3 \) PUFA and phospholipid levels were found to be reduced in AD and other dementias [78]. Four studies found a relationship between fish and PUFA intake and the incidence of AD [79–81].

### Physical Exercise and Emotional Health

Clinical and experimental evidence from studies in elite athletes and in moderately depressed patient populations suggests that vigorous exercise of 30 min or more of moderate intensity physical activity on most, preferably all days, improves energy levels and reduces anxiety, tension and depressive...
symptoms [82]. Table 6 lists the physiological and psychological mechanisms which have been hypothesized to contribute to the improved wellbeing.

The benefits of daily physical exercise in healthy and depressed populations have been reviewed previously by Casper [82]. The lack of motivation and interest, and the sense of leaden paralysis and lethargy in severe depressive disorders reduce the possibility of exercise in these populations.

**Antenatal Exercise and Birth Weight**

Studies on the impact of exercise on birth outcome are of increasing importance considering that more young women now engage in strenuous exercise daily. In a prospective controlled study [83] that compared pregnant women who exercised >5 times per week with women who exercised 3 times or less per week, no statistically significant difference in the mean birth weight of babies born was found. However, the fact that at randomization 52% of women refused to be assigned to the lower exercise group limits the generalizability. Another study begun at 34 weeks of pregnancy [84] found a bimodal relationship with exercise; women at the higher end, those who exercised > or = 5 times per week and women at the lower end, those who exercised < or = 2 times per week were at increased risk (odds ratios 4.61 and 2.64, respectively) to deliver babies with a low birth weight. A much larger study using data from the National Maternal and
Infant Health Survey [85] found that women who failed to exercise and previously active women who stopped physical activity during pregnancy were more likely to have very low birth weight babies and low birth weight babies. No significant relationship between the duration of gestation and physical activity was observed.

Conclusion

Nutrients, specifically the ω–3 fatty acids, but also vitamins, have a critical role in the structural and functional development and operation of the central nervous system (CNS). Placebo controlled studies in medicated patients suggest that add-on treatment with eicosapentaenoic acid (EPA) in doses varying from 1 to 4 g daily may ameliorate symptoms of major depressive disorders and reduce the abnormal movements and positive and negative symptoms in schizophrenia. There is preliminary evidence from epidemiological studies that high plasma levels of ω–3 fatty acids combined with high intakes of antioxidants, such as vitamins C and E protect against age related cognitive decline. Compared with the well documented cardioprotective effects associated with ω–3 fatty acid rich diets, the antidepressant and antipsychotic effects of ω–3 fatty acids seem to be primarily associated with EPA and not to fit a dose-response curve. The data are conflicting as to whether immune and inflammatory pathways mediate the association between ω–3 fatty acid deficiencies and psychiatric symptoms. Lastly, future need to clarify to what extent improved physical health, higher energy levels, improved sleep and/or reduced abnormal movements may account for the symptomatic improvements in MDD and schizophrenia.

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Schizophrenia is a serious and disabling mental disorder which affects almost one percent of the population worldwide. It is characterised by so-called ‘positive’ symptoms such as delusions (false beliefs) and hallucinations (such as hearing voices), usually together with ‘negative’ symptoms such as lack of drive and initiative, blunted emotions and lack of judgement. Current treatment involves the use of antipsychotic medication and psychosocial interventions. These treatments are palliative but not curative so that most people who suffer from schizophrenia experience lasting disability, mainly due to the negative symptoms.

It is generally accepted that the incidence of schizophrenia is broadly similar throughout the world in all contemporary cultures [1, 2]. This has been taken to imply that the genetic predisposition to schizophrenia appeared at a very early stage of human evolution, and that this genetic makeup may even be inherent to our humanity by promoting such attributes as language acquisition and creativity [3, 4].

Whilst schizophrenia is of comparable incidence across modern cultures, there are marked differences between countries in the long-term outcome of schizophrenia. In particular, it is well established that the 2-year outcome of schizophrenia is substantially better in developing countries such as India and Nigeria, than in developed Western nations in Europe and North America [1, 2, 5]. This distinction holds for a variety of outcome measures, including both social functioning and clinical measures such as relapse rates. This must mean either that the more developed medical services in the West are positively damaging to the long-term outcome of schizophrenia, or alternatively that there is some other powerful force affecting outcome, which is even stronger than all the benefits of modern treatments. Not surprisingly, the latter explanation is preferred by Western commentators, but the nature of that powerful positive
force in developing countries has not been identified. The usual explanation revolves around theories of greater social cohesion, support and acceptance for people with mental health problems in developing countries. However, there is no substantial evidence to support this, and indeed direct personal observation of the management of the mentally ill in developing countries would suggest that this explanation is an example of Western mythology about the nature of society in those countries.

The possible role of nutrition in determining the outcome of schizophrenia has been largely neglected until recently. This neglect appears to stem from the notion of a mind-body duality which somehow regards brain functioning as being separate from the rest of the body. The concept that the brain is an organ which evolved in the same biological environment as the rest of body, and therefore that nutritional patterns which are good for the body as a whole will also be good for the functioning of the brain, appears to be an alien concept to most mental health researchers.

The rest of this article will explore evidence relating nutrition and schizophrenia. Possible mechanisms by which nutrition may contribute to the neuropathology of schizophrenia will be outlined.

Cross-National Ecological Studies

Ecological studies have provided valuable insights into the aetiology of many diseases with a nutritional component such as cancers and diseases of the metabolic syndrome, but this approach has seldom been applied to the investigation of mental health problems. The first such study was carried out more than 15 years ago [6]. The researchers had noted that Scandinavian seamen who consume a diet high in saturated fat, appeared to have a high prevalence of schizophrenia [7]. In order to investigate this further, they used data on the international variations in outcome of schizophrenia which had been collected in a large World Health Organisation study [1]. It was this study that provided the original basis for the well accepted better outcome of schizophrenia in developing countries which is quoted in every standard psychiatric textbook. They correlated schizophrenia outcome data with information on dietary intake of fat from land animals and poultry (primarily saturated fat) relative to fat intake from fish and vegetable sources (primarily polyunsaturated fat). They found that more saturated fat and less polyunsaturated fat in the diet predicted a worse outcome of schizophrenia, and that the ratio of saturated to polyunsaturated fat predicted 99% of the variance in outcome. If this study had shown such a strong relationship with a purely social variable such as a measure of social cohesion, it would have been regarded as a landmark study. However, because the relationship was with nutrition and this went against prevailing thought, the study was almost totally ignored.
Based on this pioneering work we have conducted a further ecological analysis [8].

We used schizophrenia outcome data from two studies: one was the WHO study [1] used by Christensen and Christensen [6], and the other was a follow-up study also sponsored by the WHO, which confirmed the earlier findings about schizophrenia outcome using new patient cohorts [2]. We took nutritional data from the Food and Agriculture Organisation website [9]. Instead of examining dietary constituents, we examined the role of individual foodstuffs. The reason for this was that nutritional intake of foodstuffs intercorrelate, so that diets which are high in saturated fats are also high in sugar, for example. We found strikingly similar predictors of poor two-year outcome of schizophrenia across both of the schizophrenia outcome studies and whether social or clinical variables were used as the primary outcome measure. On the straight correlations, high sugar consumption was shown to relate to a poor schizophrenia outcome whichever outcome measure was used. On several, but not all, measures dairy products meat and eggs were found to be associated with the worse outcome of schizophrenia and the consumption of pulses with a better outcome. The correlation between outcome and sugar consumption is shown in figure 1. On multiple regression analysis, consumption of sugar was the dominant predictor across all social and clinical variables, although consumption of dairy products remained a significant predictor for one clinical variable (hospitalisation rate).

**Fig. 1.** Relationship between national sugar consumption and the 2-year outcome of schizophrenia. Data for sugar consumption are taken from FAOSTAT and data for the relevant year [9]. The 2-year total outcome data for schizophrenia take into account a range of social and clinical variables and are derived from reference 1. A lower score indicates a better outcome. This figure is based on the raw data published in [8].
**Case-Control Studies**

It has been shown repeatedly that cell membrane levels of polyunsaturated fatty acids, particularly docasahexaenoic acid DHA and arachidonic acid (AA), are reduced in cell membranes of patients who suffer from schizophrenia [10–13]. This has normally been measured in erythrocytes. Some of these findings have been called into question on methodological grounds [14]. For example, some studies did not control for the effects of smoking and storage artefact. Nevertheless, such studies formed the basis for investigating nutrition as a possible contributory factor to schizophrenia.

Mellor et al. [15] carried out a nutritional analysis of hospitalised schizophrenic patients. She found a significant correlation between severity of symptoms and dietary intake of ω-3 fatty acids. Those patients who had more ω-3 fatty acids in their normal daily diet with no attempt at intervention, had less severe schizophrenic symptoms.

Stokes and Peet [unpubl.] carried out a further nutritional study on a separate group of schizophrenic patients in a rehabilitation unit. This examined dietary intake of all nutrients with regard to their ability to predict severity of schizophrenia symptoms. It was found that severity of symptoms correlated with both polyunsaturated fatty acids (PUFA) and with sugar intake in the normal daily diet. The correlation with polyunsaturated fatty acids were in the expected direction in that higher dietary intake of PUFA was associated with less severe schizophrenic symptoms. However, the correlation with dietary intake of sugar was, unexpectedly, in the opposite direction. Further analysis showed that this was due to the confounding effect of background medication. Patients taking the antipsychotic drug clozapine were consuming twice as much sugar as those taking other antipsychotic drugs. Clozapine is an antipsychotic drug with potentially life-threatening side effects (agranulocytosis), so it is reserved for the treatment of patients who have not responded to other antipsychotic agents. Therefore, it appears that treatment-resistant schizophrenic patients taking clozapine have an exceptionally high consumption of sugar. Whether this was present before prescription of clozapine and therefore may have contributed to the treatment resistance, or whether it is a consequence of taking clozapine, has yet to be determined. Work in this area is of particular current interest because of concerns about the development of diabetes in patients treated with some of the newer antipsychotic drugs, particularly clozapine [16]. The correlation between PUFA in the diet and severity of schizophrenic symptoms was found to be robust and independent of background medication.

**Historical Association between Diet and Schizophrenia**

At the beginning of the twentieth century it was widely believed that indigenous populations who lived by hunter gathering and substance agriculture,
did not suffer from mental illness. This belief was based on overtly racist concepts that the brains of these ‘primitive’ people were not sufficiently developed for them to experience the complex symptoms of mental illness. After the Second World War concepts of this kind were no longer acceptable. It was recognised that human beings all have the same capacity for brain functioning, with the conclusion that the potential for mental illness is universal. This was reinforced by the WHO studies showing that the incidence (but not the outcome) of schizophrenia was similar across all contemporary cultures.

Unfortunately, this conceptual shift which was primarily driven by ideology may have caused important epidemiological information to be overlooked. There is a substantial body of evidence to suggest that schizophrenia as we know it was relatively uncommon amongst indigenous populations and increased when indigenous peoples came into contact with Western culture, including the shift to a Western diet. This evidence has been summarised elsewhere [17, 18]. By their very nature, these studies were conducted decades ago and they can therefore be criticised because most of them do not conform to modern methodological principles. That said, the number and variety of studies all pointing to low rates of mental illness cannot be ignored.

There is also evidence that the prevalence of mental illness in Western nations increased markedly during the Industrial Revolution [19]. At one time there was vigorous debate as to whether this was due to a true increase in incidence or a worse outcome [20, 21]. Whichever is true, the marked increase in insanity (as it was then called) had to be accommodated by the rapid construction of asylums during this period of time. Sociologists have argued that the reported increase in the rate of insanity was more apparent than real, and was due to increased stigmatisation and lower tolerance of people who behaved unusually, fuelled by the building of institutions to house them [22]. Whilst there is some evidence that mental institutions were abused for the incarceration of people who behaved in a way that was perceived as socially deviant rather than being mentally ill, this explanation cannot possibly account for the massive need for increased provision for the insane which was driven by, rather than being the driver for, the increased prevalence of mental illness in society. At the same time as the mental health of the general population deteriorated, their diet was undergoing enormous change. During this period, population consumption of both saturated fat and sugar showed massive increases [23, 24]. There is a close association between reported cases of insanity and the consumption of sugar by the general population for the period 1800 to 1914 [17]. If this relationship is causal this would imply a fairly immediate harmful effect of sugar on mental state, as there is no evident time-lag.

It therefore appears that indigenous people, who ate a diet with much less saturated fat and sugar than ours, had lower levels of schizophrenia amongst
their population, and that there was a rise in the prevalence and perhaps incidence of schizophrenia during the Industrial Revolution which correlates with increased dietary intake of fat and sugar. This is consistent with the ecological evidence suggesting that a high saturated fat, high sugar diet is associated with a poor two-year outcome of schizophrenia.

**Possible Mechanisms by which Diet Contributes to Neuropathology**

There is no doubt that genetic factors are important in the aetiology of schizophrenia although putative genetic markers have proved difficult to replicate. A polygenic inheritance is likely. The importance of the environmental factors is demonstrated by the fact that concordance for schizophrenia in monozygotic twins is only around 50% [25].

It is generally believed that schizophrenia is a disorder of neurodevelopment. In a large birth cohort [26] it was found that those who became schizophrenic later in life had delayed milestones of motor development, more speech problems, lower educational test scores, solitary play preference, and less social confidence as children. At age 15 both anxiety and lower IQ were independent predictors of future schizophrenia.

Because many of these abnormalities in childhood of people who eventually become schizophrenic, are similar to those of children who are given feeds deficient in DHA as babies and infants, there has been interest in the possible relationship between diet in pregnancy and infancy and subsequent development of schizophrenia. Susser et al. [27] examined the subsequent development of schizophrenia in children of mothers exposed during early pregnancy to the Dutch hunger winter of 1944/1945. Offspring of the mothers who were most exposed to famine during the first trimester of pregnancy showed a double relative risk of schizophrenia. This nutritional deficiency was generalised, and therefore any increased risk of schizophrenia cannot be attributed to any specific nutrient. However, the data do indicate that nutritional factors during pregnancy can be a determinant of future schizophrenia in the offspring. Several studies have attempted to investigate the effect of breast-feeding on subsequent development of schizophrenia. An initial study reporting an excess of formula feeding relative to breast-feeding amongst people who subsequently developed schizophrenia [28] was refuted by a large cohort study which found no difference in rates of schizophrenia between people who had been breast-fed as infants and those who had received formula feeds [29]. More recent evidence suggests that breast-feeding may have a more subtle influence on the presentation of schizophrenia. Avmore et al. [30] found that duration of breast-feeding was positively correlated with the age at onset of illness suggesting that prolonged breast-feeding might delay the onset of schizophrenia.
There is a great deal of evidence that schizophrenia is associated with significant neuropathology. Earlier studies have shown a well replicated increase in the size of the cerebral ventricles which pre-dates the onset of overt schizophrenic symptoms [31, 32]. There is continuing debate as to whether this abnormality is static or progressive, possibly due to apoptosis of neurones [33]. More recently, there is evidence that neuronal cytoarchitecture is abnormal in the cerebral cortex of schizophrenic patients [34]. This has led to an interest in the possible role of neurotrophins in the aetiology of schizophrenia.

Brain-derived neurotrophic factor (BDNF) is required to maintain dendrites [35], and expression in BDNF in the prefrontal cortex shows a significant increase during young adulthood at a time when the frontal cortex matures both structurally and functionally [36]. Schizophrenia typically presents in young adulthood. Lack of brain BDNF has been shown in mice to result in reduced neuronal soma size and dendrite density in the prefrontal cortex [37]. This is similar to the changes in neuronal architecture which have been reported in brains from schizophrenia patients. BDNF is also a modulator of neurotransmitters including gamma-amino butyric acid (GABA), which is regarded as important in the pathogenesis of schizophrenia [38]. BDNF can also protect neurones against apoptosis [39]. Recent molecular genetic studies have shown an association between BDNF gene variants, schizophrenic illness, and the response of schizophrenia to the anti-psychotic drug clozapine [40, 41]. A recent study showed reduced BDNF expression in the prefrontal cortex of patients with schizophrenia [42].

In the light of all the evidence implicating BDNF in the pathogenesis of schizophrenia, it is of considerable interest that BDNF levels in rat brain have been shown to be significantly reduced by a diet which is high in saturated fat and sugar [43]. The possible influence of other dietary constituents including ω-3 fatty acids has not yet been investigated. However, it is striking that the same dietary components which appear to be detrimental to the outcome of schizophrenia, also modulate a neurotrophin which is currently of great interest in schizophrenia research. Evidence from dietary surveys of schizophrenia patients suggests that their diet contains even more saturated fat and sugar than the general population [44, 45].

**Intervention Studies**

There is epidemiological evidence of an association between nutrition and schizophrenia, and plausible biological mechanisms exist by which nutrition could affect the onset and outcome of the schizophrenic process. However, the only way to directly test the validity of a nutritional hypotheses is through intervention studies. The feasibility of carrying out such studies depends upon the time point at which nutritional factors come into play. We have seen evidence to
suggest that malnutrition in pregnancy increases the likelihood of schizophrenia in offspring but breast-feeding may delay the onset of schizophrenia, and that the neuropathology of schizophrenia is well established by the time overt symptoms become manifest. This implies that nutritional interventions for people who have already developed schizophrenia may be of limited impact. Nevertheless, there is evidence that nutritional approaches may be beneficial even after the onset of the schizophrenic illness.

Most formal studies have focused upon treatment with omega-3 fatty acids. This work was stimulated by initial findings, detailed earlier in this article that schizophrenic patients have reduced cell membranes levels of polyunsaturated fatty acids including DHA [10–13], and that dietary intake of ω–3 fatty acids appears to correlate with schizophrenic symptoms, such that more ω–3 fatty acids in the normal daily diet was associated with less severe symptomatology [15]. This led to a pilot study of fish oil which was given in addition to usual medical treatment to a group of schizophrenic patients who were still symptomatic despite being on the most appropriate available antipsychotic medication [15]. These patients showed significant reduction in schizophrenic symptomatology after 6 weeks treatment with 10 g per day of concentrated fish oil which contained around 2 g per day of DHA and 1.5 g of EPA. They also showed a considerable reduction in the severity of a movement disorder known as tardive dyskinesia. This is a neurological abnormality which is found in up to 5% of patients with schizophrenia as part of the illness process, but which increases in frequency after prolonged treatment with the older antipsychotic drugs. There have now been five double-blind placebo controlled trials of ω–3 fatty acids in the treatment of schizophrenia. The first was a pilot study comparing DHA with eicosapentaenoic acid (EPA) added to existing medication for 3 months [46]. The finding from this study was that EPA was significantly more effective than placebo or DHA, and that DHA was no better than placebo. A subsequent UK study comparing 1, 2 and 4 g of ethyl EPA as an adjunct to current medication, found significant improvement in symptoms when 2 g daily of ethyl EPA was added to the antipsychotic drug clozapine, but no significant benefit in the whole patient group [47]. Three further studies have produced contrasting results. An American study in which 3 g daily of ethyl EPA was added to existing medication found no significant benefit [48]. A study carried out in South Africa found significant improvement for both schizophrenic symptoms and tardive dyskinesia when 3 g daily of ethyl EPA was given together with already prescribed antipsychotic drugs [49]. A recent study from Australia in patients with first episode schizophrenia showed that those treated with EPA required significantly lower dosages of antipsychotic medication [50]. Several studies have also investigated EPA as a sole treatment for schizophrenia. In one single case study, it was reported that EPA brought
about complete symptom remission accompanied by reversal of the pre-existing cerebral ventricular enlargement [51]. A placebo-controlled study of EPA as a sole treatment for schizophrenia was conducted in India [46]. The primary efficacy measure was the number of patients who could be maintained without the need to use antipsychotic drugs. All patients given placebo required prescription of antipsychotic with the three months trial period whereas half of the patients treated with EPA did not require antipsychotic medication, with no detriment to their mental state: indeed, the EPA-treated patients had significantly less schizophrenia symptoms than those who were treated with placebo plus conventional antipsychotic drugs.

It is not clear why there is such variability in the results of studies of EPA treatment of schizophrenia. It may be EPA is effective only for certain subtypes of schizophrenia. Importantly, it seems likely that EPA given without reference to the diet as a whole is not an effective strategy. If high levels of saturated fat and sugar in the diet are important to the outcome of schizophrenia then this would need to be addressed in any nutritional approach to the treatment of schizophrenia. It is perhaps significant that the best results with EPA treatment have come from the studies in India and South Africa, where consumption of saturated fat and more particularly of sugar is less than in the UK and the USA [9]. So for there have been no formal studies of a low saturated fat, low sugar diet in the management of schizophrenia. However, some clinicians have adopted this approach and have anecdotally reported success [52]. A period of fasting often followed by a vegetarian diet was frequently used in the USSR to treat mental disorders, and special units were set up for this purpose [53]. Fasting is known to increase brain levels of BDNF in animals [54]. More significantly, some practitioners have urged approaches which involve reduced consumption of saturated fat and sugar, for example by cutting out all processed foods. This follows the principles of ‘orthomolecular’ psychiatry first put forward by Pauling [55]. This was based on the philosophy that the body, and in this case specifically the brain, functions at its best when in the biological environment provided by the nutrition on which we evolved. This has been regarded in the past as fringe medicine and even quackery, but it appears that modern science is now offering support to such concepts.

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Managing Obesity after Menopause: The Role of Physical Activity

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Obesity is an epidemic on a global scale [1], posing a major threat to human health and well-being as well as consuming a large part of health care costs. The health hazards associated with being overweight are numerous; including increased all-cause and cardiovascular mortality, diabetes, hyperlipidemia, hypertension, cancer and more. Post-menopausal women, deprived of the protective effects of endogenous estrogen together with negative environmental factors, have an increased tendency for gaining weight and its associated metabolic syndrome [2]. A major cause for the weight gain is lack of sufficient physical activity (PA). Additionally, PA is paramount in managing obesity and combating weight gain, including in the postmenopausal years [3–5].

Obesity: Prevalence, Causes and Consequences

Almost one fifth of US adults are obese, having a body mass index (BMI) of over 30, and over 19 million American adult women are obese [6]. Almost one half of the women in the western world are overweight, having a BMI of 25 or more [6, 7].

The causes of obesity are genetic and environmental. Yet the high and growing prevalence of obesity is mainly due to environmental effects influencing a genetic susceptibility [8]. In some ways the development of obesity may be considered as a ‘normal’ response to an ‘abnormal’ environment. Food and energy intake are higher than actually needed, while the mechanized surroundings produce a low level of PA. This results in a natural net effect of weight gain
Table 1. The risk for some common disease conditions that are influenced by weight gain, weight loss, and physical activity or physical fitness

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Obesity</th>
<th>Intentional weight loss</th>
<th>Physical activity/physical fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>↑</td>
<td>↓</td>
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</tr>
<tr>
<td>Cardiovascular</td>
<td>↑</td>
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<tr>
<td>CAD events</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Metabolic syndrome</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Gallbladder disease</td>
<td>↑</td>
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<tr>
<td>Cancer</td>
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CAD = Coronary artery disease; HTN = hypertension. The metabolic syndrome includes type 2 diabetes mellitus, hypertension and hyperlipidemia.

throughout the years – both individually and globally. Menopause is associated with weight gain [9], and lack of PA seems a major environmental contributor [10]. This weight gain is accompanied by changes in body composition and fat distribution toward a more android obesity [11], which is associated with the metabolic syndrome [2]. This later results in increased mortality, reflected by a closer association of mortality with the waist-hip ratio or waist circumference (markers of android adiposity) than with BMI (a more general measure of adiposity) [12, 13]. It should be noted that use of hormone replacement therapy has been shown to decrease the shift from gynoid to android fat deposition after menopause [11, 14]. Estrogen has therefore an effect on the site of obesity, and its withdrawal after the menopause assists in bringing about the metabolic syndrome of overweight men.

Some medical complications of obesity are presented in table 1. A more comprehensive list will include increased mortality, several forms of cancer, coronary artery disease, diabetes mellitus, hypertension, stroke, heartburn, gall bladder disease, kidney stones, osteoarthritis, low back pain, arthralgia, pseudotumor cerebri, pulmonary emboli, obstructive sleep apnea, and depression.

Lifestyle Modifications for Intentional Weight Loss

Most obesity complications are reduced with intentional weight loss. The most common methods of weight reduction are lifestyle modification, prescription and non-prescription medications, and gastric surgery for subjects with BMI over 38. Most importantly, whatever the method used for the initial weight
reduction, future lifestyle modification is crucial in order to maintain the newly reduced weight; several methods exist to assist in adherence [15]. Guides for the treatment of adult obesity are and proper food selection are available from the National Institute of Health, the American Obesity Association and the US Department of Agriculture [16–18].

Dieting only is not expected to maintain weight loss in the long term [19]. This is due to the concomitant reduction of muscle mass, which lowers the metabolic rate and reduces energy expenditure. This leads to a lower caloric output along the day. Therefore, current nutritional recommendations for weight loss are simply adherence to the same guidelines that are established for all adults. Food selection aimed for loss should allow a lower energy intake with a large enough bulk of food, such as grains, fruits and vegetables. The weight reduction program should include behavioral changes, as these carry a major role in the maintenance of the newly reduced body weight [20].

**Physical Activity in Postmenopausal Weight Loss**

Among women aged 50–64, only half reported doing any regular PA, while only about one quarter report high intensity exercise [21]. As discussed, insufficient PA is a major factor in postmenopausal weight gain. It is therefore an important tool in weight loss and in the reversal of many obesity related co-morbidities, as shown in table 1: good fitness and engaging in PA lower mortality rates [22, 23], lower the risk of fat and weight gain [24, 25], offer some protection against the medical consequences of obesity and the metabolic syndrome [26, 27], lower the incidence of cancer [23, 28] and improve mood [29].

**Exercise Prescription**

It is recommended for every adult to engage in 30 min of moderate-intensity PA on most, preferably all, days of the week [30–32]. In general, a brisk walk of 3.5 km a day is enough to exert most of the health benefits. The recommended 30 min may be accumulated through shorter bouts of activity along the day. In a follow up after postmenopausal women who participated in a trial which encouraged increasing walking distance, those originally assigned to the walking group were still walking more than the control group –10 years after trial has ended [33]. Thus, lifestyle habits may be effectively changed even in this age: you *can* teach an old dog new tricks.

In meta-analyses assessing weight loss programs, it has been shown that exercise is more of importance in long term weight maintenance [19], while it
offered more fat loss, with less decrease in the energy-utilizing fat free mass [34]. Further, a simple calculation shows that a person has to walk about 100 Km in order to expend the energy equivalent to 1 kg of adipose tissue.

The type of PA should include mainly aerobic exercises, such as walking, jogging, swimming, cycling and aerobic dancing. Resistance training may be added. The intensity can be as low as 40% of maximal heart rate (MHR = 220 minus the age in years) for beginners, corresponding to brisk walking. The frequency of PA is 3–7 times a week, for at least 30 min, split into up to three bouts.

An important issue is that even if a person is unsuccessful at weight loss, the health benefits of exercise alone may be similar to those achieved by weight loss in modulating the metabolic syndrome [35–37]. A suitable summary of this might be that ‘Fat and fit is better than lean and lazy’. Additionally, weight loss by exercise preserves lean body mass [38], a very important factor in weight loss maintenance.

**Conclusion**

Women in the postmenopausal years have an increased risk for weight gain and its associated morbidities. This is mainly due to hormonal changes and an increase in central adiposity, along with insufficient amount of PA. Increasing the amount of PA is expected to attenuate most of the obesity-associated medical situations. Its role in weight management and the prevention of weight gain or regain along the years is fundamental. With the aid of proper nutrition, that is rich in fruit, vegetables and grains, and limited in fat and salt, weight loss and its maintenance is achievable. Behavioral changes aimed at supporting the decreased food intake and increased engagement in physical activities is of sound importance.

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Osteoporosis: A Complex Disorder of Aging with Multiple Genetic and Environmental Determinants

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Determinants of Osteoporosis and Fracture Risk

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1]. This disease represents a major public health concern that will only increase in importance as life expectancy increases and the population ages. Accordingly, osteoporosis has been recognized as a ‘global problem’ by the World Health Organization (WHO) [2]. Specifically, the lifetime risk of suffering an osteoporosis-related fracture approaches 50% in women and 20% in men [3, 4].

Osteoporosis is diagnosed by dual-energy X-ray absorptiometry (DXA) when bone mineral density (BMD, g/cm²) is below $-2.5$ SDs from the mean bone density in young adults (i.e. $< -2.5$ T-score), so-called peak bone mass. However, fracture risk increases continuously as BMD decreases [3], and at least doubles for each SD decrease of BMD relative to peak [5, 6]. Osteoporosis results from a failure to acquire optimal peak bone mass during growth [7], and/or to maintain bone mass in later years. Women experience a more rapid phase of bone loss after the menopause (0.5–2.0%/year), due mainly to estrogen deficiency [8, 9], but bone loss continues in older persons [10, 11]. Osteoporosis is less common in males than females [12] and men have a three times lower risk of fractures compared to women because they reach higher peak bone mass, which reflects a larger bone size rather than a greater bone mineral density within bone [13]. Moreover, hypogonadism affects only about 30% of aging males [14] and men have a shorter life expectancy compared to women.
In addition to bone density, osteoporosis is also determined by ‘bone quality’ traits, which represents the architecture of the skeleton, such as hip geometry, femur cortical thickness and trabecular connectivity in the vertebrae, the properties of the bone material (collagen type 1 and mineral), and its turnover rate [15]. The latter can be evaluated indirectly by a series of serum and urine biochemical markers that reflect bone formation (osteocalcin, bone specific alkaline phosphatase) and resorption (collagen degradation products, such as pyridinoline and C-terminal cross-linking of type I collagen, CTx) [16]. These markers are commonly used to evaluate osteoporosis risk in addition to BMD [17, 18]. Although BMD (by DXA), bone turnover markers and prevalent fractures, alone and in combination, can predict fracture risk at least as well as cardiovascular risk factors can predict the risk of coronary heart disease, they remain relatively insensitive to identify all individuals who will eventually have a fracture [6, 19, 20].

Multiple endogenous, environmental and lifestyle factors concur to the occurrence of osteoporosis and related fractures (table 1). In turn, intervention trials using calcium supplements and/or dairy food products have proven beneficial to improve bone mass gain in children, particularly those with a poor calcium intake [21, 22]. Moreover, calcium, vitamin D and protein supplements all improve bone mass and/or fracture risk in the elderly [23–26]. However, the most important determinant of bone mass remains the genetic constitution.

**Heritability of Bone Mass and Strength**

Both women and men with a family history of osteoporosis have significantly decreased BMD compared other subjects [27–30]. Twins and parent–offspring studies have shown that heritability, i.e. the additive effects of genes,
Osteoporosis explains 60–80% of the population variance for peak bone mass, and the influence of these genetic factors is expressed well before puberty [31, 32]. In contrast, genetic contribution to the rate of bone turnover and bone loss after menopause has been less precisely evaluated, and might actually be smaller (40–60%) [33]. Fracture is a very complex phenotype, which, in addition to bone quantity and quality-related factors (above), also depends on other endogenous factors such as the propensity to fall [34], protective responses, soft tissue padding, etc, and exogenous factors present in the living environment. The latter factors likely explain why additive genetic factors appear to contribute only about 30% to the population-based variance in the liability for fracture [35].

**Genome Screens for Bone Mass in Humans**

Genome-wide screening approaches search for loci flanked by DNA microsatellite markers that co-segregate with the phenotype of interest in a population of related individuals. The pedigrees so far investigated are families with a proband characterized by an extreme skeletal phenotype (high or low bone mass [36–38]), as well as nuclear families and sibships from the population at large [39, 40]. These studies have started to map a large number of QTLs for BMD [41, 42] (fig. 1). In addition, QTLs for bone geometry and size at the spine and femur [41, 43, 44], as well as for bone ultrasound properties [45], have been identified. Although the actual number of genes contributing to bone strength is currently unknown, dozens of genes with relatively small additive effects and a few genes with rather large effects might be involved [46–50].

![Quantitative Trait Loci (QTLs) for bone mineral density (BMD) in Caucasians were identified by genome-wide screening approaches in five separate studies (see text for details). QTLs with suggestive or evidence of linkage are indicated (LOD scores 1.8–3.0 and >3.0, respectively) and those identified in more than one study are shown in bold. Adapted from Ferrari [147].](image)
Population-Based Association Studies

Hundreds of association analyses have been reported with BMD, bone turnover markers, and sometimes fracture, using polymorphic candidate genes coding for bone structural molecules, hormones, growth factors and/or their receptors implicated in bone and mineral metabolism, cytokines involved in bone remodeling, etc. [42, 51]. Among them, association studies with the vitamin D receptor (VDR), estrogen receptor-α (ESR1) and type I collagen A1 chain (Col1A1) have recently been meta-analyzed. The latter studies and those involving interleukin-6 (IL-6) and the recently discovered LDL-receptor-related protein 5 (LRP5) gene polymorphisms are summarized below. It is now clear that genetic variants may influence bone mass at specific skeletal sites, such as the vertebrae or hip, selectively affect males or females, young or old adults, and estrogen-deficient or -replete females, and interact with environmental factors, such as dietary calcium intake.

Vitamin D Receptor Gene (VDR) Polymorphisms

The vitamin D receptor (VDR) mediates the effects of calcitriol [1,25(OH)2 D3] on the intestinal absorption of calcium and phosphate and on bone mineralization. The VDR gene, whose nine exons and multiple promoters span over more than 80kb, carries multiple polymorphisms [52]. Morrison et al. [53] first reported that VDR 3′-UTR Bsm1 alleles (B frequency, 0.4 and 0.1 among Caucasians and Asians, respectively) were associated with BMD in adult women and postmenopausal bone loss. A Fok1 variant in the VDR first start codon (ATG), (f frequency, 0.4 among both Caucasians and Asians) was later reported to be also associated with BMD in postmenopausal women [54]. Subsequently, numerous population-based studies including hundreds to thousands of subjects, mostly pre- and post-menopausal women, looked at the association between VDR alleles, BMD and bone loss, with discordant results [55–67]. In addition, several studies suggested that VDR alleles might be associated with bone mass, bone and/or body size in children [62, 63, 68–72]. However, some investigators failed to find such association [73, 74], and others noted a vanishing influence of VDR genotypes on bone mass with advancing age [63, 75]. Two recent meta-analysis [76, 77] eventually support some significant association of VDR polymorphisms with bone mass in women. In the first analysis, Gong et al. found that 23 of 67 studies reported a significant association between VDR genotypes and BMD at lumbar spine, whereas 22 of 51 studies reported a significant association with femoral neck BMD. Despite an apparent predominance of negative studies, the authors calculated that the number of positive studies in pre- and post-menopausal women far exceeded the number of false positive results expected under the null hypothesis (alpha = 5%) [76].
More recently, a meta-analysis of VDR association studies published between 1994 and 2001 found 13 eligible studies in post-menopausal women, leading to an estimated 2.4% (p = 0.028) lower spine BMD in BB compared to Bb/bb (i.e. a recessive effect of the B allele) [77]. Moreover, in 9 eligible cohort studies, women with the BB and Bb genotypes had a significantly greater bone loss at lumbar spine compared to bb (−0.43%/year, p = 0.011, i.e. a dominant effect of the B allele). In contrast, this analysis did not confirm association in pre-menopausal women nor at the femoral neck [77].

Epidemiological observations and prospective intervention studies suggest an interaction between dietary calcium intake and VDR polymorphisms on their association with bone mass in both children and aging subjects. In a cohort of 144 pre-pubertal girls receiving calcium supplements (850 mg/day) compared to placebo [21], BMD gain in response to calcium was significantly increased at several skeletal sites among BB and Bb, but not in bb girls [63]. In contrast, in 235 pre-pubertal boys, we failed to observe a significant effect of calcium supplements, and either association or interaction with VDR genotypes [unpubl. data]. Others found that VDR 3′-UTR genotypes were similarly distributed among 105 rachitic children from Nigeria (calcium intake, 200 mg/d) and 94 healthy controls, whereas the Fok1 ff genotype was significantly under-represented among cases [78]. A significant interaction between VDR-3′ genotypes and calcium intake on BMD and BMD changes has also been observed in post-menopausal women [65, 79–81]. For instance, a long-term follow-up (6.3 years) study in elderly postmenopausal women (n = 193, mean age, 69 years) reported that among those with low calcium intake (below 456 mg/day), VDR Taq1 TT homozygotes (same as bb) had a significantly lower rate of bone loss at both the femoral neck and lumbar spine compared to tt (same as BB). These differences were no more detectable in those with the highest calcium intake [82]. Two large cohort studies have examined the association between VDR genotypes and fracture risk. In the Nurses Health Study (mean age 60 years), the BB genotype was associated with a more than twofold increased risk of hip (but not forearm) fracture compared with the bb genotype. Risk was greater for women who were older, leaner, or less physically active or who had a calcium intake below 1078 mg/d (odds ratio, 4.3) [83]. In contrast, the Study of Osteoporotic Fractures (SOF), including 9,704 community-dwelling women aged 65 years and older, failed to demonstrate a difference in VDR alleles distribution among 530 cases with a hip, vertebral or other fracture, and controls, both before and after stratification for calcium intake and other variables [84].

In summary, under usual dietary calcium intakes, the VDR allele B could be associated with a modest deficit of bone mass growth in infancy and with an even more modest increase of bone loss after the menopause. However, it remains uncertain whether VDR genotypes contribute significantly to fracture risk.
risk in the elderly. Since it has been suggested that calcium supplementation could be associated with a better bone mass response in carriers of the VDR allele B [31, 85], this possibility needs to be investigated in prospective, calcium-dosing trials stratifying the cohort by VDR genotypes.

**Estrogen Receptors Gene (ESR1 and ESR2) Polymorphisms**

Estradiol plays a major role in the acquisition and maintenance of peak bone mass in both females [86, 87] and males [8, 88, 89]. Genotypes identified by *Pvu*II and *Xba*I restriction enzymes in the first intron of the estrogen receptor (ER) alpha gene (ESR1) were originally found to be significantly associated with BMD in postmenopausal [90] and younger pre-menopausal [91] Asian women. ESR1 gene polymorphisms, including *Pvu*II, *Xba*I and a TA repeat polymorphism in the promoter region, were subsequently analyzed in association with bone mass, bone loss and/or fractures in Caucasian women, with contrasting results [64, 92–100]. Interestingly, some authors reported an interaction between ESR1 polymorphisms and hormone replacement therapy (HRT) [94, 101] as well as a gene-by-gene interaction between ESR1 and VDR alleles [64, 92].

A meta-analysis of the association between ESR1 genotypes and BMD including more than five thousand women from 22 eligible studies (n = 11 in Caucasians and n = 11 in Asians), concluded that homozygotes for the *Xba*I XX genotype have a modestly but significantly higher BMD (+1–2%) at lumbar spine or hip compared to xx [102]. No differences were found between *Pvu*II genotypes, but since the *Xba*I and *Pvu*II sites are in strong linkage disequilibrium, this may explain why some authors found an association with P/p alleles. In this meta-analysis, differences between genotypes tended to be up to five time greater in pre- compared to post-menopausal women, suggesting that ESR1 genotypes might influence peak bone mass acquisition, although only three studies were available before menopause. Most interestingly, differences in fracture risk were disproportionately high compared to the small differences of bone mass observed between genotypes (odds ratio, 0.66 [95% CI, 0.47–0.93] in XX vs. xx) [102], suggesting that ESR1 genotypes might influence bone quality above and beyond BMD.

There is recent evidence that estrogen receptor-β, which is coded by a separate gene (ESR2), plays a distinct role in the regulation of bone mass [103]. Accordingly, associations were recently described between ESR2 CA repeat polymorphisms and BMD in postmenopausal Japanese women [104], as well as in men and women from the Framingham Osteoporosis Study [105]. It will therefore be interesting to investigate potential interactions between ESR1 and ESR2 alleles on bone mass.
Collagen 1α1 Chain Gene (COL1A1) Polymorphisms

Another widely investigated candidate gene for osteoporosis that carries a functional polymorphism in its regulatory region is the collagen type 1α1 gene (COL1A1). Collagen type 1 is a major structural molecule of the bone matrix (and is also found in skin and tendons), where two collagen 1α1 chains associate with one collagen 1α2 chain to form the triple helix of collagen. A G>T polymorphism in the binding site for the transcription factor Sp1 was described, resulting in a rare s variant (frequency, 0.1–0.15 in Caucasians, <0.1 in Asians [106]). The s allele was first associated with lower lumbar spine BMD and a higher prevalence of vertebral fractures in postmenopausal women [107]. A second large population-based study confirmed an allele-dosage effect of the s allele on decreasing BMD, mostly in older subjects, as well as on increasing the incidence of vertebral fractures during a 4-year observation period [108]. Most importantly, the COL1A1 s variant was recently shown to produce too much collagen 1α1 molecules compared to the S allele in vitro, causing bone to be less resistant to mechanical stress [109].

Despite this good evidence for functionality and association with bone fragility, COL1A1 polymorphisms have also sometimes failed to show association with BMD, bone loss, fractures, ultrasound properties of bone, or markers of bone resorption [110–112]. In this case as well, a meta-analysis of published data concluded to a modest effect of the s allele on BMD (equivalent to 0.1–0.2 SD decrease compared to S) but a more prominent association with fracture risk (OR 1.5 and 1.9 in Ss and ss compared to SS genotypes, respectively) [109]. Of note, another large meta-analysis looking at hundreds of genetic association studies across various complex disorders and polymorphic genes confirmed a significant association of COL1A1 Sp1 alleles with fracture risk (OR, 1.6) [113]. Taken together with the functional data mentioned above, these results indeed suggest that COL1A1 Sp1 polymorphisms may affect some ‘bone quality’ component which is poorly reflected by BMD alone.

Interleukin-6 Gene Promoter Polymorphisms

Interleukin-6 (IL-6) is a pleiotropic cytokine playing a central role in the activation of osteoclasts, – the bone resorbing cell –, bone turnover, and bone loss, particularly following estrogen deficiency [114, 115]. A common −174G>C polymorphism (frequency of C, 0.4 among Caucasians) and, to a lesser extent, a rare −572G>C polymorphism (frequency of C, 0.06 among Caucasians) in the IL-6 gene promoter are associated with IL-6 activity in vitro and in vivo [116, 117]. In turn, in 434 healthy white American postmenopausal women (mean age, 72 years), bone resorption was significantly lower among −174CC (and −572GG) compared to the other genotypes, and the age-related decrease in BMD was more prominent among IL-6 −174 GG and GC
genotypes (−9 to −10% over 10 years) compared to CC (−5 to −6.1%) [117, 118].

Several studies have identified the IL-6 gene locus (7p21) to be linked to BMD in postmenopausal women [119, 120] and in families of osteoporotic probands [121, 122], whereas no linkage was found in young, healthy sister pairs [123]. These observations suggested that IL-6 genetic variation might specifically contribute to the population variance in bone mass in the elderly. However, two studies reported an association of IL-6 polymorphisms with peak bone mass, one in young adult males [124] and the other in pre-menopausal females [125]. Moreover, the latter study failed to detect a lower rate of bone resorption or bone loss associated with the −174CC genotype in 234 postmenopausal women (mean age, 64 years). Subsequently, the interaction between IL-6 promoter polymorphisms and factors known to affect bone turnover, namely years since menopause, estrogen status, dietary calcium and vitamin D intake, physical activity, smoking, and alcohol, was examined in the Offspring Cohort of the Framingham Heart Study [126]. This cohort comprises 1,574 unrelated men and women (mean age 60 years) with cross-sectional bone mineral density measurements at the hip. Consistent with the study of Garnero et al. [125], in models that considered only the main effects of IL-6 polymorphisms, no significant association with bone mineral density was observed in either women (n = 819) or men (n = 755). In contrast, significant p values were found for an interaction between IL-6 −174 genotypes and years since menopause, estrogen status, dietary calcium and vitamin D intake in women. Thus, bone mineral density was significantly lower with genotype −174 GG compared to CC, and intermediate with GC, past 15 years since menopause, in case of estrogen-deficiency or insufficient calcium intake (<940 mg/day). In women with both estrogen-deficiency and poor calcium intake, BMD differences at the hip between IL-6 −174 CC and GG were as high as 16.8%.

In summary, these data indicate that the influence of IL-6 gene variants on bone mass may depend on gender, age, estrogen status and dietary calcium. It is currently unknown whether IL-6 polymorphisms directly contribute to fracture risk and it would be particularly interesting to investigate whether they could modulate the skeletal response to selective estrogen receptor modulators (SERMS) [127].

**LDL-Receptor Related Protein 5 Gene (LRP5) Polymorphisms: A Novel Genetic Susceptibility Factor for Male Osteoporosis**

LRP5 is a member of the low-density lipoprotein (LDL) receptor-related family coding for a transmembrane co-receptor for Wnt signaling [128]. Several lines of evidence point to LRP5 as a candidate gene for osteoporosis. Loss-of-function mutations in LRP5 are responsible for osteoporosis pseudoglioma (OPPG), an
Autosomal-recessive disorder characterized by low bone mass, spontaneous fractures and blindness [129], whereas LRP5 gain-of-function mutations result in high bone mass and sclerosing bone dysplasias [130–132]. Moreover, mice with targeted disruption of LRP5 have a deficit in bone formation and sustain fractures [133]. Most importantly, a QTL for bone mineral density in the general population was mapped at 11q12–13, the LRP5 locus (fig. 1) [134–136].

A population-based study of five LRP5 polymorphisms with allele frequencies >2% found that a missense substitution in exon 9 (c.2047G>A, p.V667M) and haplotypes based on exon 9 and exon 18 (c.4037 C>T, p.A1330V) alleles were significantly associated with bone mass and projected area of vertebrae at the lumbar spine in adult males, but not females, accounting for up to 15% of the population variance for these traits in men [137]. Consistent with the presence of a QTL for stature at 11q12–13 [138] [139], the exon 9 variant was also significantly associated with stature in both genders. Moreover, 1-year changes in lumbar spine bone mass and size in pre-pubertal boys were also significantly associated with these LRP5 variants [137], suggesting that LRP5 polymorphisms could contribute to the risk of spine osteoporosis in men by influencing vertebral bone growth during childhood. Accordingly, LRP5 polymorphisms were investigated in 80 European-Caucasian men with idiopathic osteoporosis and 88 controls (mean age: 50.4 years, range 23–70). This rather uncommon form of osteoporosis affects middle-aged men and is characterized by low peak bone mass and an increased incidence of vertebral fractures in absence of secondary causes, and by a clear heritable component [30, 140]. In keeping with the previous association study, exon 9 A and exon 18 T alleles were twice more common in cases than controls, and the odds for idiopathic male osteoporosis and fractures among carriers of the 9A-18T haplotype were greater than 2 [unpubl. data].

Hence, LRP5 polymorphisms could be a first identified genetic factor for gender-related differences in bone size and a specific susceptibility factor for spine osteoporosis in men. Moreover, ongoing analyses of LRP5 polymorphisms in the Framingham Osteoporosis Study suggest an interaction with physical activity in men, in that the favorable effects of physical activity on BMD would be more prominent among carriers of the 18T allele.

**Summary and Perspectives**

Thirty years have elapsed since the first published evidence of a high heritability for bone mineral density (BMD) in twins [141], and 10 years since vitamin D receptor (VDR)-3’UTR alleles were the first described gene variants associated with BMD in humans [53]. Meanwhile, genome-wide screens in humans (and
mice, although not discussed in this review [41]) have taught us where to look for specific genes (fig. 1), and recent developments in molecular technology now allow to identify these genes and their variants [142, 143]. Despite commonly inconsistent results among different studies, population-based association analyses are required to ultimately demonstrate the implication of gene variants to any complex disease [144]. In doing so, we should be aware that the strength of the association may depend on gender, age, ethnicity, and interactions with a number of lifestyle and environmental risk factors for osteoporosis (table 1). Most importantly, we should start to directly evaluate whether candidate gene polymorphisms so far identified in association studies could be translated into clinical practice, i.e. evaluate the positive and negative predictive values of gene markers with respect to osteoporosis and fracture risk, and response to therapy, in the targeted population. Guidelines for population screening as applied to genetic susceptibility to disease have recently been published [145]. Rather than looking disdainfully at the ‘genetic revolution of medicine’ [146], we should do any efforts to bring this increasing knowledge from the bench to the bedside.

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Changes in Dietary Fatty Acids and Life Style as Major Factors for Rapidly Increasing Inflammatory Diseases and Elderly-Onset Diseases

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After World War II (ended in 1945), the mortality from infectious diseases decreased rapidly toward 1960 (fig. 1), and the Japanese are currently enjoying the world’s longest life expectancy among the countries with relatively large populations. However, the disease pattern has changed during this period and the mortality from tuberculosis and pneumonia decreased toward 1970. Thereafter, the mortality from pneumonia, but not tuberculosis, began to increase even when it was age-adjusted. This increase in pneumonia is likely to be allergic in part, which is associated with increasing cancers of the bronchi and lungs. Although the mortality from cardiovascular diseases is currently much lower in Japan than in the USA (~1/4), it is increasing steadily. Allergic hyper-reactivity is not directly associated with mortality, but it is generally accepted that populations suffering from allergic hyper-reactivity have increased several folds during the past 40 years in Japan. Cancer is the leading cause of death after 1981, and the increase in cancers of the US type (colorectum, pancreas, trachea, bronchus, lung, prostate and esophagus) is prominent.

The major elderly-onset diseases in Japan are cancer, atherosclerosis-related diseases and pneumonia. Elevation of inflammatory tone is a likely major cause for these diseases, which is brought about by excessive intake of linoleic acid (LA, ω–6) and enhanced arachidonic acid (AA, ω–6) cascade [1]. Because
ω–6 and ω–3 fatty acids and their metabolites (eicosanoids, inflammatory mediators) are competitive at many steps of enzyme reactions and receptors, not only the absolute amounts of ω–6 and ω–3 fatty acids, but their balance, particularly the ω–6/ω–3 ratio, is an important factor in regulating the inflammatory tone and related diseases [1, 2].

Changes in life style such as decreased physical activity and overnutrition in older populations lead to unfavorable energy balance. Reduced frequency of skin exposure to environmental changes (temperature, sweating conditions) is a likely cause for enhanced skin and mucosal sensitivity to allergens in younger populations. These environmental factors could be modified by changing the life style, besides choosing foods to keep a good ω–6/ω–3 fatty acid balance.

**Competition among Fatty Acids in Three Metabolic Series in Mammals**

Fatty acids are classified into three series depending on their metabolism in mammals: (1) saturated and monounsaturated fatty acid series; (2) ω–6 series (linoleic acid→arachidonic acid), and (3) ω–3 series (α-linolenic acid→eicosapentaenoic acid, EPA→docosahexaenoic acid, DHA). In phospholipids,
saturated fatty acids are incorporated preferentially into the 1-position while polyunsaturated fatty acids are confined to the 2-position, and these ω–6 and ω–3 fatty acids compete with each other at the acyltransferase steps; saturated and monounsaturated fatty acids are not effective as competitors in polyunsaturated fatty acid incorporation. The ω–6 and ω–3 fatty acids at the 2-position of membrane phospholipids are the major precursors and competitors of eicosanoid synthesis. Therefore, the ω–6/ω–3 ratio of phospholipids is a good marker of eicosanoid production and inflammatory tone [2].

Recently, unexpected observations were presented by Broughton et al. [3]; dietary animal fats enriched with saturated and monounsaturated fatty acids also suppressed competitively the production of ω–6 eicosanoids when ω–6/ω–3 ratios were high. Competition among dietary and de novo synthesized fatty acids occurs not only at the steps of incorporation into various lipids but also at the steps of mitochondrial and peroxysomal β-oxidation systems and possibly at the step of excretion to skin/hair [4].

These observations are nutritionally important. Currently, nutritionists tend to advice people to reduce the intake of animal fats first rather than reducing the intake of linoleic acid (ω–6). If the intake of animal fats is reduced without reducing ω–6 fatty acids, eicosanoid tone would be elevated unless the intake of ω–3 fatty acids is increased. Because eicosanoids are not synthesized from saturated and monounsaturated fatty acids, animal fats are relatively safe for the diseases caused by over- and unbalanced productions of ω–6 eicosanoids.

Regulation of Gene Expression by Fatty Acids

Various fatty acids have been shown to exert differential effects on gene expression related to cholesterol and fatty acid metabolism, which is a major topic in the current lipid nutrition research. Here is another world in which the chain length and melting point of fatty acids play major role in the regulatory mechanism.

Dietary long chain polyunsaturated fatty acids up-regulate β-oxidation enzymes, uncoupling protein and anti-oxidative superoxide dismutase, regardless of ω–6 and ω–3 series, while saturated and monounsaturated fatty acids, and linoleic acid to a slightly lesser extent, up-regulate cholesterol synthesis. The prenyl intermediates in cholesterol synthesis play divergent roles, one of which is a role in cell proliferation through prenylation and activation of oncogene products. In this context, the intakes of saturated, monounsaturated and linoleic acids should be restricted particularly in older people requiring to improve energy balance.
Evidence Against Lipid Peroxide Theory of Aging

The original free radical theory of aging came out from comparing the effect of dietary fish oil and several kinds of vegetable oils with different degree of unsaturation in rats [5]. Error in a maze test increased along with increasing the degree of unsaturation of dietary oils while those oils affected the longevity little. Moreover, some inhibitors of free radical reactions prolonged the survival of mice. These observations led to a hypothesis that feeding highly unsaturated fatty acids such as fish oil for a long period leads to accumulation of lipid peroxides in tissues, which, in turn, decompose to form free radicals and injure tissues, thereby accelerating the aging process. In this hypothesis, the ‘free radical injury’ is used synonymously with ‘lipid peroxide injury’ [6]. However, the observed effect of free radical reaction inhibitors on longevity could be interpreted in a different way because weight loss was observed by feeding such inhibitors. These inhibitors are likely to have brought about energy restriction, which is well known to prolong the survival of rodents.

In our studies, a simple maize test was not sufficient to estimate the learning ability of rodents accurately [7]. Using a more sophisticated test (operant-type, brightness-discrimination learning test), we have shown that learning behavior and memory retention are superior in the rats fed ω–3 fatty acid-enriched oil (α-linolenic acid-rich perilla seed oil and DHA-rich fish oil) through 2 generations compared with linoleic acid (ω–6)-rich oils (safflower oil, soybean oil). [8, 9]. The effect of ω–3 fatty acid-deficiency during pregnancy and lactation was reversed by feeding ω–3 fatty acids after weaning but not by feeding ω–6 fatty acid [10] (fig. 2). Furthermore, impaired learning behavior was reversed by DHA (ω–3) only when the diet contained relatively low concentrations of linoleic acid (ω–6). These results indicate that taking ω–3 fatty acids and restricting ω–6 fatty acids are beneficial for the maintenance of brain functions in aged rats [9].

Stroke-prone, spontaneously hypertensive (SHRSP) rats develop hypertension and die of stroke, particularly when salt solution was given as drinking water. Using this animal model, dietary ω-linolenic acid (perilla oil and flaxseed oil) and DHA were shown to prolong the survival [11, 12]. Moreover, DHA was effective in suppressing the stroke-related behavioral changes (loss of circadian rhythm) [13].

Although tissues from fish oil-fed animals are enriched with EPA/DHA and are more susceptible to auto-oxidation in vitro, no signs of elevated lipid peroxide levels and denatured proteins are noted in vivo [14], but fresh tissues tend to contain reduced amounts of lipid peroxides [15]. Oxygen pressure in organs are much lower than in the atmosphere. Cells in tissues are under relatively hypoxic conditions and chain reactions of lipid peroxidation would not
occur when appropriate amounts of endogenous antioxidants (vitamins C and E, glutathione) are present.

Free radicals produced in vivo attack polyunsaturated fatty acids and form lipid peroxides, which decompose to form stable hydroxyl fatty acids by reaction with reduced form of vitamin E, and the oxidized vitamin E is reduced consuming vitamin C or glutathione, and the oxidized vitamin C and glutathione are reduced using energy (NADPH). Thus in living cells, polyunsaturated fatty acids and anti-oxidative vitamins serve as scavengers rather than propagators of free radical reactions [16].

**Hypoxia and Persistent Inflammation Induce Peroxidative Injury**

Free radical injury is recognized as an early event under various pathological conditions. However, elevated levels of free radicals are unlikely to be
brought about by enrichment of membrane lipids with polyunsaturated ω–3 fatty acids. Instead, we interpret that free radicals are produced and injure tissues in vivo when cells are exposed to hypoxic conditions, where inflammatory cells are recruited to clean the damaged cells, and eicosanoids serve as chemoattractants. When cells are enriched with arachidonic acid, ω–6 inflammatory mediators are produced in excess leading to persistent inflammation, and inflammatory cells produce reactive oxygen species. Thus, ischemia and persistent inflammation are the earlier events to increase free radicals. This inflammatory tone is regulated by ω–6/ω–3 balance of membrane lipids. Now, it has been well established that ischemic conditions are induced by high ω–6/ω–3 ratios of dietary and tissue polyunsaturated fatty acids through eicosanoid actions. The major risk factor for atherosclerosis was not dietary cholesterol or hypercholesterolemia but high ω–6/ω–3 ratio of ingested foods as reviewed elsewhere [17, 18].

**Choice of Foods for the Prevention of Cancer**

Cancer research used to focus on detecting environmental carcinogens that initiate DNA damage and carcinogenesis. However, the involvement of persistent inflammation in carcinogenesis has been widely observed. For example, asbestos and glass beads administered to animals do not dissolve easily, hence do not exhibit direct mutagenic activity. However, inflammatory cells are mobilized to surround these substances and tumors are formed. When inflammatory conditions persist, tumors are formed as noted in hepatitis virus infection, chronic hepatitis and hepatic cancer sequences. Subjects suffering from ulcerative colitis develop colon cancer in several times higher frequency. Helicobacter pylori is likely to develop stomach cancer through persistent inflammation. Despite the reducing tendency of the impact of smoking noted, lung cancer, particularly adenocarcinoma type, has been increasing steadily along with the increasing incidence of pneumonia after 1970 in Japan.

Japanese intake of linoleic acid increased 2.5-fold from 1960 to 1975, and the increase in meat intake was associated with a decrease in seafood intake during this period. Consequently, the ω–6/ω–3 ratio of ingested fatty acids increased significantly. Although the intake of animal fats also increased 2.5-fold, the current intake of animal fats in Japan is roughly half that of average Americans.

For the cancers of the US type, persistent inflammation caused by enhanced linoleic acid and arachidonic acid cascade is interpreted to be a major cause. This interpretation is supported by the following observations.
(1) Oils with low ω–6/ω–3 ratios (perilla seed oil, flaxseed oil, fish oil) suppress carcinogenesis compared with high linoleic acid oils.

(2) Inhibitors of arachidonic acid cascade suppress carcinogenesis, e.g. steroidal and non-steroidal anti-inflammatory drugs, 5-lipoxygenase inhibitors.

(3) Knock-out of genes related to arachidonic acid cascade suppresses carcinogenesis, e.g. phospholipase A, cyclooxygenase-2, prostaglandin receptors (EP2, EP4).

Despite the presence of many lines of evidence to support the interpretation that the enhanced linoleic acid cascade is a major risk factor for cancers of the US type, epidemiological studies performed in the US do not necessarily support this interpretation. The failure to reveal the causal relationship between the linoleic acid intake and cancer mortality could be explained as follows.

(1) In the populations without taking competitive amounts of seafood EPA and DHA, membrane phospholipids are enriched with arachidonic acid even in the group with low intake of linoleic acid.

(2) Serum EPA and DHA levels are good markers of seafood intake while serum linoleic and α-linolenic acids are not [19]. High linoleic acid levels in tissues are likely to reflect high seafood intake because EPA and DHA inhibit the elongation and desaturation of linoleic acid to form long chain polyunsaturated fatty acids.

(3) In the nested serum samples, preferential loss of long chain polyunsaturated fatty acids during storage leads to increased proportions of linoleic, saturated and monounsaturated fatty acids.

Another process of fatty acids influencing carcinogenesis is through prenyl intermediates in cholesterol synthesis. Saturated and monounsaturated fatty acids, and linoleic acid to a slightly lesser extent, stimulate cholesterol synthesis and are likely to up-regulate prenyl-intermediates and activate oncogene products. Thus, various fatty acids appear to affect carcinogenesis mainly through both the linoleic acid cascade and prenyl intermediate pathway, and the relative importance of these two pathways is likely to differ depending on the sites (tissues or cells) of carcinogenesis. At present, we interpret that the impact of the linoleic acid cascade (persistent inflammation) is greater than that of elevated prenyl intermediates for the promotion of cancers of the US type or that the impact of animal fats through prenyl intermediates is overcome by ω–3 fatty acids, because their incidence was much lower in the Greenland natives than in the Danes; both populations took large amounts of saturated and monounsaturated fatty acids (~30 energy %) but the former took much greater amounts of ω–3 fatty acids and lesser amounts of ω–6 fatty acids.
Evaluation of Vegetable Oils by Their Fatty Acid Composition and Minor Anti-Nutritional Factors

Vegetable oils are nutritionally classified primarily by their fatty acids; saturated fatty acid-rich oil (palm and coconut oils), oleic acid-rich oil (olive, canola, high-oleic safflower and high-oleic sunflower oils), linoleic acid-rich oil (high-linoleic safflower, corn, soybean, sesame, peanut and rice oils) and α-linolenic acid-rich oil (perilla, flaxseed and chia oils). Obviously, high-linoleic acid oil should be avoided in most of industrialized countries. The Japan Society for Lipid Nutrition adopted a proposal that the direction of nutritional recommendation should be changed so as to reduce the intake of linoleic acid [20]. Saturated and monounsaturated fatty acids are not converted to inflammatory lipid mediators and are relatively safe for the eicosanoid-related diseases. However, the safety of these oils has not been established in animal experiments; the intake of these oils in large quantities should be avoided because the presence of minor anti-nutritional factors is suspected (canola, olive, corn, high-oleic safflower, high-oleic sunflower, evening primrose, partially hydrogenated soybean and partially-hydrogenated canola oils) [11, 12, 21]. α-Linolenic acid is preferentially β-oxidized, excreted to skin and does not accumulate in tissues in large amounts compared with saturated, monounsaturated and linoleic acids. It is converted to EPA and DHA in part to suppress thrombotic and inflammatory tendency. The demerits of α-linolenic acid-rich oils are their instability to heat and easy inflammability under heating conditions although α-linolenic acid is anti-inflammatory in the body. Use of electric frying pan is recommended for α-linolenic acid-rich oils; those stabilized with vitamin E and C ester can be used safely for baking meat, vegetable, egg and seafood at 200°C setting.

Conclusions – Recommended Choice of Foods and Fatty Acids for Healthy Aging

The so-called cholesterol hypothesis lost its bases, and those with high cholesterol levels were found to exhibit lower cancer incidence and longer survival among older people in the Western countries and among the general population over 40 years old in Japan. Nutritional values of foods of animal origin are evaluated by their content of ω–6 and ω–3 fatty acids. Butter and meats from ruminants (cattle and sheep) contain relatively small amounts of linoleic acid because ruminant bacteria convert linoleic acid to saturated and monounsaturated fatty acids, hence these are relatively safe. The ω–6/ω–3 balance of chicken and pork meats depends on that of
their feed, and those with decreased $\omega-6/\omega-3$ ratios are recommended. Increased intake of seafood is recommended for the prevention of cardiovascular diseases, cancer and other inflammatory diseases. Currently, on the average the Japanese ingest the largest amounts of seafood and associated endocrine disturbing substances (e.g. dioxin) among the industrialized countries. The beneficial effects of seafood $\omega-3$ fatty acids have been well established but the relative impact of dioxin on endocrine systems remains to be evaluated in our food environment. Among vegetable oils, perilla oil and flaxseed oil with very low $\omega-6/\omega-3$ ratios are recommended. Oleic acid is not converted to eicosanoids and is safe for the diseases in the elderly, but all the high-oleic oils we have examined so far exhibited anti-nutritional activity in animal experiments, hence the consumption of large amounts of these oils listed above should be avoided even though the impact of the anti-nutritional factor on human health is entirely unknown.

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Physical Activity for Health: An Overview

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The Community Decline in Physical Activity

In general, the trend, with mechanization, computerization, passive leisure, and urbanization, has been for people to reduce their levels of physical activity. However, there are some notable national exceptions, in Finland and Canada, which demonstrate that these trends can be countered [1]. Not only public health strategies, but national leadership and infrastructural programmes are likely to be required from an early age for the reversal of this downward trend in physical activity and associated fitness. It is increasingly clear that, not to do so, invites a major burden of chronic disease and disability and premature death [2, 3].

Until the late 19th and the 20th centuries, there were few examples of regularized athletics and sports in society, with the notable exception of the Greeks and Romans. This is because physique and performance needed recognition and admiration and because settlement, organisation and facilities were usually required, and so was relative wealth and the time to pursue such activity. As a matter of fact, the physical requirements of work in servitude, employment or in communities with subsistence agriculture were often so great as to view time to oneself or one’s family as time for physical rest. Well into the 20th century, it was a common belief that too much exercise would shorten one’s life. Moreover, recent studies demonstrate that extensive sports and work patterns (e.g. lumberjacks) can outstrip energy intakes in their energy requirements and can lead to immune dysfunction [3]. A SWOT (strength, weaknesses, opportunities and threats) analysis of the overall decline in physical activity takes this issue of the health limits of physical activity into account (table 1).
The optima for physical activity, beyond that which is ‘self-paced’ (what one does without thought – e.g. gesticulation whilst talking, restless movement whilst awake or asleep), are probably much as shown in table 2.

In turn, physical activity goals and targets could be formulated as in tables 3 and 4.

For World Health Day in 2002, when the theme was ‘Move for Health’, the degrees of health achievement through exercise were depicted graphically (fig. 2).

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**Table 1.** Decline in physical activity SWOT analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>• Avoid tissue and system damage through excess</td>
<td>• Detrimental body composition</td>
</tr>
<tr>
<td>• Decreased system reserve (e.g. CV, respiratory, CNS)</td>
<td></td>
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**Opportunities**

• Replace physical activity at work with physical activity as leisure (sport)
• More time for education, social networking

**Threats**

• Eco-nutritional disease (END) or chronic non-communicable diseases (CNCDs)

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**Table 2.** Physical activity – optima

• Walking or other aerobic activities (6 days/week, 1–2 h/day)
• Strength training through multiple repetitions against resistance (3–4 days/week)
• Integrated with goal
  – Personal development
  – Social development

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**Table 3.** Physical activity – goals

• Include physical activity in workaday week and travel (purposeful physical activity)
• Find enjoyable leisure-time physical activity (personal and social fulfillment)
• Overcome seasonal, locality and situational barriers to physical activity
• Improved sense of well-being
• Reduce burden of disease
The most obvious and impressive consequence of physical inactivity is obesity, where prevalence is interesting worldwide, irrespective of the stage of economic development and, often, in the face of protein malnutrition with growth retardation and muscle wasting [4] (fig. 1). This constitutes the so-called ‘Double Burden of Disease’ [5, 6].

**Energy Throughput, Food Intake and Body Composition**

Throughout much of the 20th century, energy intake remained largely unchanged, even with economic development [7]. Yet the prevalence of obesity began to escalate and, whilst the quantity and quality of food intake have become important issues, most of the obesity epidemic could probably have
been avoided if physical activity levels had remained adequate. One of the best
examples of this is Japan, where people have continued to walk a lot, and obesity
(BMI ≥30) prevalences have remained as low as about 3%, compared to the
USA where they now exceed 20%.

Also, sub-groups in the population have not experienced the general trend
towards obesity, where they have been regular exercisers. For example, people
who walk, jog or run regularly are generally leaner, without the need to be pre-
occupied with food intake.

It is energy throughput at higher levels which is more important than
energy intake in determining the risk of positive energy balance (and, therefore,
overfatness). This is seen by reference to the studies of Peter Wood at Stanford
University, where he demonstrated that middle-aged runners actually eat more
and lose body weight (fat) [8]. If this phenomenon could be generalized across
the community, say by making walking, cycling and jogging more attractive,
substantial improvement in individual fitness and body composition would be
achieved.

People need to understand more clearly what weight represents – muscle and
bone mass to be optimized, fat stores to be appropriate and directed away from the
abdomen – and the nature of intra-daily and day-to-day fluctuations in body water
(and sodium). This means education about body composition and not pre-occupa-
tion with weight as the key health end-point in physical activity programmes.

**Fig. 2.** ‘Move for Health’: World Health Day 2002. Agita Mundo – Move for Health,
the slogan for World Health Day 2002, is a call to individuals, communities and countries to
associate action for health with the public health task of prevention. (‘Agita’ in Portuguese
means shake – Agita Mundo means shake the world.)
It is now appreciated that body composition and fat distribution are major determinants of total and disease specific mortality [9–13].

There is increasing evidence that the energy density:

\[
\text{Energy density} = \frac{\text{Energy (cal or kJ)}}{\text{Mass of food (g or kg)}}
\]

is a determinant of energy balance [14, 15]. However, this will be less critical when one is physically active, since the errors in energy intake are more likely to be corrected (through the set of appetite, and the energy cost of carriage of increased body mass).

Again, with greater levels of regular physical activity, food component (essential macro- and micro-nutrients; other biologically active and favourable food components like phytonutrients) density is less critical.

\[
\text{Nutrient Density, phytonutrient density} = \frac{\text{Mass of nutrient or phytonutrient or food component (e.g. Mg or \(\mu\)g)}}{\text{or food component density Energy (e.g. 100 kJ)}}
\]

The inactive, however, must be careful to have most of their food nutritious as judged by their food component density.

The pathways to abdominal obesity, nevertheless, are several, although physical activity is central (fig. 3).
Just as we have to realize with the long-term effects of maternal nutrition and *intra-uterine life* on later life morbidity and mortality, so it is likely that we will find the same for appropriate levels of maternal physical activity pre-conception and during pregnancy, and lactation (table 5). However, more work is required in this area, as there has been much debate about appropriate work patterns and sporting engagement for pregnant women [16].

Nevertheless, we do know that physical activity affects *gene expression* [17], and plays a role in the expression of *gestational diabetes*, with its inter-generational effects on insulin resistance [18].

**Physical Activity, Well-Being and the Domains of Health**

There is little doubt that regular physical activity is a key determinant of well-being and mood [19], functional status [20] and perceived health status [21] (fig. 4).

**Preventive Physical Activity**

The *burden of disease* in contemporary economically advanced societies is located amongst the following health domains:

- Cardiovascular disease
- Metabolic disorders
  - e.g. obesity, diabetes
- Neoplasia
- Bone health

---

**Table 5. Physical activity as a requisite for human species**

- Conception and pregnancy
- Childhood, puberty and adolescence
- The reproductive years
- Later life
- Inter-‘life stage’ considerations
- Inter-generational considerations

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Physical Activity for Life

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Physical Activity for Health
Immune function
Cognitive function
Mood

In Australia, the Burden of Disease and Injury is attributed to selected risk factors as shown in figure 5.

Physical activity features highly in the contribution to Burden of Disease [22, 23] and, therefore, in preventive programmes.

Inter alia, physical activity appears to be protective against disease by
• improving cardio-respiratory function
• improving lipid profiles, blood pressure, abdominal body fatness.

This can be seen in a number of studies of diabetes prevention [24], cancer [25], and osteoporosis [26] (fig. 6).

Resistance or strength training is relevant for quality of sleep and depression [27].

We can expect that regular physical activity will displace the onset of morbidity towards the end of life [28], as well as prolong it [28, 29].

Disease-specific survivals are prolonged with regular physical activity, as evidenced in the Harvard Alumni Study [30, 31] and in Finnish studies by Pekkanen et al. [32].
Therapeutic Physical Activity

The clear preventive health role of physical activity may well be translated into therapeutics. To some extent, there is overlap between secondary and tertiary prevention and therapeutics in any case.

Of great importance, with ageing populations is the reduction in the problems of:
- Sarcopenia and frailty
- The growing burden of nutritional and metabolic diseases
- Senescence

At least some cases of sarcopenia can be expected to be preventable and reversible [33, 34].

Eco-Nutrition and Physical Activity

Healthy habitats and precincts, conducive to regular physical activity are essential for community health. Not to have them is to encourage Eco-nutritional Disease (END).

Favourable eco-nutritional precincts will:
- Link family life, leisure and work
• Be safe and congenial for walking, climbing, cycling, playing, swimming, skipping, dancing, skiing or gardening
• Provide contact with various plant and other animal species.

The term ‘chronic disease’ says nothing about the aetiology or pathogenesis. The logic of describing chronic disease as ‘eco-nutritional disease’ becomes apparent when considering:
• The major importance of food, its variety and the requirement for biodiversity on human health
• Movement, best achieved in safe, pleasurable and sustainable precincts
• The required ‘environmental buffer zones’ to minimize the risk of known and emerging transmissible pathogens [35, 36].

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**Fig. 6.** Nutrition and physical activity in the prevention of cancer.
Conclusion

We seek a unifying strategy for both health advancement and health optimization which is sustainable. This must involve us continuing as our own machines, moving, thinking, socializing and integrated with the natural world.

References


Physical Inactivity Is a Disease

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Physical inactivity annually produces 334,144 deaths in the United States and >2 million deaths worldwide \cite{1, 2}. Physical inactivity is one of the 10 leading global causes of death and disability \cite{2}. In 1986, the expenditure in the US for physical inactivity was USD 77 and USD 150 billion (expressed in 2,000 US dollars) in direct and combined direct and indirect costs, respectively \cite{3}. Epidemiological data indicate that physically inactive humans have an increased prevalence of 25 chronic diseases (table 1). Indeed whereas the chronic diseases are recognized as the medical factor for the deaths and economic costs, physical inactivity is acknowledged by the Centers for Disease Control (CDC) as the actual cause of the deaths \cite{4}. Thus, it seems reasonable to suggest that physical inactivity is a medical problem of great impact. This review will use arguments presented in debates as to whether obesity is a disease \cite{5, 6} to provide a framework for the claim that physical inactivity is a disease. The next sections will answer the question as to whether physical inactivity fits the definition of ‘disease’.

Heshka and Allison \cite{5} present some of the typical definitions of disease:

- ‘Condition of the body, or some part or organ of the body, in which its functions are disturbed or deranged; a morbid physical condition; a departure from the state of health, especially when caused by a structural change’ \cite{7}.
- ‘A condition in which bodily health is seriously attacked, deranged, or impaired. Pathologically, disease is an alteration of state of the human body…or of some of its organs or parts interrupting or disturbing the performance of vital functions; any departure for the state of health presenting marked symptoms…various forms of disease may be caused by parasites, filterable viruses, and nutritional, environmental or inherent deficiencies.’ \cite{8}.
- ‘An interruption, cessation or disorder of body functions, systems or organs.’ \cite{9}.
<table>
<thead>
<tr>
<th>Tissue/physiological characteristic</th>
<th>Dysfunction with physical inactivity</th>
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| Hippocampus                         | Decreased neurogenesis, memory, and learning  
Increased prevalence of dementia and Alzheimer’s disease |
| Myocardial cells of heart           | Lower contractility, maximal stroke volume and maximal cardiac output  
Contributes to decreased aerobic fitness |
| Sympathetic nervous system          | Increased resting sympathetic drive, potentially leading to increased blood pressure |
| Vascular endothelial cells in heart | Less nitric oxide production and lower vasorelaxation in response to vasodilators  
Less protection from ischemia |
| Pro-inflammatory milieu in blood    | Increased blood C-reactive protein and tumor necrosis factor-α, leading to greater prevalence of atherosclerosis |
| Plasma triglycerides                | Increased post-prandial hypertriglyceridemia  
Increased prevalence of coronary artery disease |
| Plasma glucose                      | Increased post-prandial hyperglycemia and hyperinsulinemia  
Increased prevalence of coronary artery disease and type 2 diabetes |
| Deep venous thrombosis              | Increased thrombi when sitting on long-distance airline flights; ‘Economy-class syndrome’, potentially producing a pulmonary embolism |
| Pancreas                            | Increased release of insulin due to insulin resistance |
| Blood HDL                           | Decreased blood HDL  
Increased prevalence of coronary artery disease |
| Immunity                            | Depressed immune response |
| Body fat                            | Increased prevalence of breast, colon, and pancreatic cancers  
Increased amount of body fat  
Increase in all the co-morbidities related to obesity |
| Skeletal muscle, size               | Smaller mass of skeletal muscle  
Premature sarcopenia and physical frailty resulting in premature institutionalization |
| Skeletal muscle, insulin-mediated glucose uptake | Increased resistance to insulin leading to pre-diabetes  
Increased prevalence of type 2 diabetes |
| Work endurance                     | Shorter durations of the ability to perform low level work loads and a greater incidence of muscle fatigue-related work injuries |
| Bones                               | Less calcification and strength  
Increased prevalence of osteoporosis and broken hips |
| Aging                               | Acceleration in many of the signs and symptoms associated with aging, such as premature osteoporosis and physical frailty |
The characteristics of physical inactivity are presented in table 1, as documented in Chakravarthy and Booth [1]. Using the above definitions as a guide, eight examples (brain, heart, peripheral nervous system, blood, immune cells, adipose tissue, skeletal muscle, and bones) of ‘some part or organ of the body’ or ‘of some of its organs or parts’ are given with ten examples (decreased brain, heart, lipid oxidation, carbohydrate oxidation, fibrinolysis, immune, muscle strength, bone strength, aerobic fitness, and work endurance) ‘in which its functions are disturbed or deranged’, ‘or of some of its organs or parts interrupting or disturbing the performance of vital functions’, ‘or an interruption, cessation or disorder of body functions, systems or organs’ and seven examples (increased Alzheimer’s disease, coronary heart disease, type 2 diabetes, cancer, obesity, physical frailty, and osteoporosis) of ‘a departure from the state of health’, or ‘a condition in which bodily health is seriously attacked, deranged, or impaired’. Thus, physical inactivity fits the presented definitions of disease.

Another rationale for categorizing physical inactivity as a disease is that the level of voluntary physical activity can be manipulated by various chemical changes. A well known example that implies a neurochemical drive for physical inactivity is the spontaneous decrease in physical activity with aging in both rats [10] and humans [11]. Morley et al. [11] state that decreased physical activity with aging appears to be the key factor involved in producing sarcopenia. Thus, it is likely that a change in a biological drive could be responsible for decreased physical activity with age, providing evidence for the supposition that the putative neurochemical basis of a drive for physical activity becomes deranged or impaired with aging. Other evidence for neurochemical changes regulating voluntary physical activity follows.

Leptin plays a central role in regulating body weight. However, treatment of obesity using recombinant leptin seems to be only effective in individuals with a rare homozygous mutation in the gene for leptin or its receptor, or who exhibit subnormal secretion of the hormone. In most cases, obese humans have paradoxically elevated leptin levels, indicative of leptin resistance [12]. Thus, leptin’s function is deranged or disturbed in most obese individuals and, according to Bray [13] fits the definition for the neurochemical basis of disease. Bray’s argument can be extended to positive feedback loops where physical inactivity alters a molecule whose directional change is associated with a further decrease in physical activity. Three examples are given: (1) Physical inactivity begets obesity, which is associated with increased serum leptin and leptin resistance, causing more physical inactivity. The data supporting the aforementioned positive feedback loop is that increased blood leptin results in greater physical activity and energy expenditure in normal mice [14] and in increased physical activity in parallel with a decrease in their obesity in the rare human condition of leptin deficiency [15]. On the other hand, the majority of obese
individuals who have higher than normal blood leptin, are leptin resistant [16] and have decreased voluntary physical activity [17]. (2) Aging is associated with decreased physical activity, which lowers the chemical drive to maintain muscle mass so that with smaller muscle mass even less physical activity is undertaken, further lowering muscle mass [18]. (3) Training raises muscle GLUT4 protein [19]. Mice engineered to overexpress GLUT4 in skeletal muscle ran four times further in voluntary running wheels [20]. Thus physical activity enhances muscle GLUT4 and higher muscle GLUT4 levels are associated with more voluntary running. These examples suggest potential positive chemical feedbacks by which physical inactivity and activity creates molecular changes associated with less and more, respectively, voluntary physical activity.

One advantage of classifying physical inactivity as a disease will be to challenge the current logic of the majority of studies which employ exercise training and designate the sedentary group as the control group. The proposed revised logic of control group designation would have to emulate the following question and answer. Does sedentary lifestyle ‘cause’ the onset of some chronic diseases? Invariably, the research community would answer this question with a ‘yes’. However, most experiments from the research community are not designed

Fig. 1. Schematic representation outlines the difference between clinical trial and cause and effect research in preventative medicine. In the experimental design of an ‘exercise physiology’ clinical trial, the sedentary disease group subjects are either prescribed an exercise treatment or assigned to the continued physically inactive, disease control group. The goal of such an experimental design is to delineate mechanisms of partial reversal of the disease symptoms by exercise. In order to effectively delineate the mechanisms underlying how physical inactivity causes chronic disease, healthy active subjects must be designated as the control. The latter approach is fundamental in preventative medicine.
to prove this. The vast majority of experiments in exercise research that are related to disease are set up to imitate a clinical trial (fig. 1). In this experimental design, the sedentary group is designated as the control and the exercise group as the treatment. However, the clinical design logic breaks down when extrapolated to a search for cause and effect. A sedentary lifestyle leads to many chronic diseases, as described above, and is the actual cause, with poor nutrition, of 16% of the deaths in the United States [4]. Therefore, the sedentary group in the general population is analogous to the disease group of a clinical trial and the subjects are currently randomly assigned to continued inactivity (placebo) or given the ‘exercise’ treatment. These types of experiments are fine when the goal of the experiment is to determine the effectiveness of exercise as a treatment to restore the healthier condition, unfortunately, this experimental design does not allow for the delineation of mechanisms related to diseases caused by a sedentary lifestyle. It is clear that many mechanisms of physical inactivity that produce maladaptations differ from the mechanisms of exercise that reverse the pathological adaptations. Molecular proof for the aforementioned concept is that while skeletal muscle unloading and overload may share some common regulatory units on the β-myosin heavy chain (βMyHC) promoter, they have separate regulatory regions for unloading and overload, and thus must have different transcriptional activations. For example, a 293-bp promoter region of βMyHC responded to mechanical overload of the mouse soleus muscle, whereas it was not sensitive to unloading [21], proving at the molecular level that, in some cases, increases and decreases in exercise levels do not use the same molecular mechanisms.

A further reason not to designate the sedentary group as the control group is the misinterpretation by the general population and most of the scientific community that a sedentary state is the normal physiological condition. By extension, physical activity is misinterpreted as abnormal with the application of physical activity being a ‘tool’ to cure rather than viewing physical activity as the norm whose deficiency is the actual cause of chronic disease. As a result of the designation of the sedentary group as the control group, the general population and the much of the scientific community devalue physical inactivity research. Further, exercise is considered an inconvenience rather than a required physiological stimulus to maintain normal physiological function as dictated by the acquired human genome.

A tenet of medicine is that understanding the molecular mechanisms of diseases provides the scientific basis for therapy and prevention. Again, the only way to truly decipher the mechanisms of disease prevention is to actually study the process itself as it is evoked by decreased physical activity, poor diet, etc. It is therefore anticipated that future research will investigate the molecular mechanisms of decreasing physical activity from its genetically selected higher level
to the sicker physically inactive population because physical inactivity, not activity, is the actual cause of genes to mis-express proteins, producing the metabolic dysfunctions which, if continued long enough, result in overt clinical disease. This is not a new concept. A statement in the Declaration of Olympia on Nutrition and Fitness [22] that the current level of physical activity should match more closely our genetic endowment introduced the concept that the true normal condition in ‘exercise’ studies is the physically active, not the sedentary, group. As long ago as the 5th century BC, Hippocratic physicians wrote that if there is any deficiency in food or exercise, the body will fail [22]. This old advice holds true today as inadequate opportunities for physical activity impair the attainment of overall health [22] and produce many chronic health conditions.

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References


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The health of the individual and the population in general is the result of interactions between genetics and a number of environmental factors. Nutrition is an environmental factor of major importance [1–4]. Our genetic profile has not changed significantly over the past 10,000 years, whereas major changes have taken place in our food supply and in energy expenditure and physical activity [5–18]. Today, industrialized societies are characterized by the following: (1) an increase in energy intake and decrease in energy expenditure; (2) an increase in saturated fat, omega-6 fatty acids and trans fatty acids and a decrease in omega–3 fatty acid intake; (3) a decrease in complex carbohydrates and fiber intake; (4) an increase in cereal grains and a decrease in fruit and vegetable intake, and (5) a decrease in protein, antioxidant and calcium intake [5–18]. Furthermore, the ratio of omega–6 to omega–3 fatty acids is 16.74:1 in the United States, whereas during evolution it was 2–1:1 (table 1; fig. 1).

Recent investigations of the dietary patterns and health status of the countries surrounding the Mediterranean basin clearly indicate major differences among them in both dietary intake and health status. Therefore, the term ‘Mediterranean diet’ is a misnomer. There is not just one Mediterranean diet but in fact many Mediterranean diets [19], which is not surprising because the countries along the Mediterranean basin have different religions, economic and cultural traditions and diets. Diets are influenced by religious habits, that is, Muslims do not eat pork or drink wine and other alcoholic drinks, whereas Greek Orthodox populations usually do not eat meat on Wednesdays and Fridays, but drink wine.

Although Greece and the Mediterranean countries are usually considered as areas of medium high death rates (14.0–18.0 per 1,000 inhabitants), death rates on the island of Crete have been below this level continuously since before 1930 [cited in 20]. No other area in the Mediterranean basin has had as low a death rate.
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rate as the island of Crete, according to data compiled by the United Nations in their Demographic Yearbook for 1948. It was 11.3–13.7 pre-war and about 10.6 in 1946–1948 [20]. Cancer and heart disease caused almost three times as many deaths proportionally in the US as in Crete [20]. The diet of Crete represents the traditional diet of Greece prior to 1960. The Seven Countries Study was the first to establish credible data on cardiovascular disease prevalence rates in contrasting populations (United States, Finland, The Netherlands, Italy, former Yugoslavia, Japan and Greece), with differences found on the order of 5–to 10-fold in coronary heart disease [21]. In 1958 the field work started in Dalmatia in the former Yugoslavia. From the inception of the research program an important focus was on the diet and its possible relationship to the etiology of coronary heart disease.

Table 1. Omega–6:omega–3 ratios in various populations

<table>
<thead>
<tr>
<th>Population</th>
<th>$\omega-6/\omega-3$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleolithic</td>
<td>0.79</td>
<td>[8]</td>
</tr>
<tr>
<td>Greece prior to 1960</td>
<td>1.00–2.00</td>
<td>[9]</td>
</tr>
<tr>
<td>Current Japan</td>
<td>4.00</td>
<td>[10]</td>
</tr>
<tr>
<td>Current India, rural</td>
<td>5–6.1</td>
<td>[11]</td>
</tr>
<tr>
<td>Current United Kingdom and northern Europe</td>
<td>15.00</td>
<td>[12]</td>
</tr>
<tr>
<td>Current United States</td>
<td>16.74</td>
<td>[9]</td>
</tr>
<tr>
<td>Current India, urban</td>
<td>38–50</td>
<td>[11]</td>
</tr>
</tbody>
</table>

Fig. 1. Hypothetical scheme of fat, fatty acid ($\omega-6$, $\omega-3$, trans and total) intake (as percent of calories from fat) and intake of vitamins E and C (mg/day). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 years [13].
The 5-year follow-up found favorable all-cause death rates in Greece, Japan and Italy compared with the other areas, as well as a lower incidence rate of coronary heart disease [21]. The Seven Countries Study was designed to investigate relations between diet and cardiovascular diseases, primarily described in terms of the fatty acid composition of the diet.

In a recent follow-up study on the relation of chronic diseases to 15-year all-cause mortality risk from the Seven Countries Study, death rates from all causes were very different among the seven countries, with high death rates in Croatia and Finland and low rates in Greece (table 2) [22]. For coronary heart disease, the excess risk of any deaths was greater than 60% in all areas except Greece where it was 45.9%. Similarly, large risks were seen for other diseases from 47.8% in Greece to 72.6% in Serbia. Peripheral arterial disease also carried a high risk of death, ranging from 46.7% in Greece to 80.9% in Italy. The outcome for men with prevalent stroke was 100% mortality in 15 years in the Netherlands and in Greece and 57.1% in Japan. Men diagnosed with chronic obstructive pulmonary disease (COPD) had a high risk of dying, 66.7% or more, except for Greece, 53.3% and Italy, 47.6%. The main purpose of this analysis was to investigate the risk of dying within 15 years related to the presence of specific chronic conditions as found in population-based field studies in different countries.

### Bioprotective Nutrients and Mechanisms in the Greek Diet

In order to precisely define the foods and their components in the diet of Crete, we began a series of studies investigating the components of the traditional

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey participation</th>
<th>15-year all-cause death rate, %</th>
<th>Death rate, %</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croatia</td>
<td>959</td>
<td>83.8</td>
<td>48.3</td>
<td>1.57</td>
</tr>
<tr>
<td>Finland</td>
<td>1,348</td>
<td>97.9</td>
<td>45.5</td>
<td>1.32</td>
</tr>
<tr>
<td>Serbia</td>
<td>1,281</td>
<td>92.1</td>
<td>40.0</td>
<td>1.34</td>
</tr>
<tr>
<td>Japan</td>
<td>867</td>
<td>98.7</td>
<td>39.2</td>
<td>1.57</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>614</td>
<td>80.4</td>
<td>38.8</td>
<td>1.89</td>
</tr>
<tr>
<td>Italy</td>
<td>1,938</td>
<td>89.2</td>
<td>36.1</td>
<td>1.05</td>
</tr>
<tr>
<td>Greece</td>
<td>1,009</td>
<td>89.7</td>
<td>28.4</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Modified from Menotti et al. [22].
diet of Greece prior to 1960, which is represented by the diet of Crete in the Seven Countries Study. Although the investigators of the Seven Countries Study emphasized the low saturated fat intake and the high monounsaturated fat intake from olive oil as the major factors responsible for the biological health effects of the diet of Crete being associated with the lowest rate of coronary heart disease and the longest life expectancy, there is good evidence that foods rich in omega-3 fatty acids and antioxidants could account for the decreased death rate of the people of Crete [23–27]. Omega-3 fatty acids have hypolipidemic, antithrombotic, anti-inflammatory, and antiarrhythmic properties, as shown by a number of papers in these proceedings [28, 29] and influence gene expression [29, 30] as well as being essential for normal growth and development [5] and mental health [31]. Fruits and vegetables have been associated with lower rates of heart disease [45].

Our own studies showed that the Cretans obtained \( \alpha \)-linolenic acid (ALA) by eating wild plants [32–36], snails, nuts [37], fruit (figs), and eggs [38, 39]; and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fresh fish and dry or canned sardines and herring, and from eggs [38, 39], game [40], and snails. Meat from grazing animals contains omega-3 fatty acids whereas meat from grain-fed animals does not [40]. Because sheep, swine, and goats graze, they obtain omega-3 fatty acids from grass, moss, purslane (\textit{Portulaca oleracea}) [32–34], and in general from the leaves and stems of green leafy vegetables. They also feed on dry fruits and nuts. In some areas the swine feed on acorns. The livestock obtain a mixture of omega-6 and omega-3 fatty acids from the foods they eat, and the same mixture is found in their meat and in the milk and the cheese and all other dairy products made from the milk [18, 41]. This balance of omega-6:omega-3 fatty acids is lost in the Western diets (fig. 1) [13, 42]. Because of agribusiness, the grain-fed animals have higher amounts of omega-6 fatty acids in their meat unlike the animals in the wild. The vegetable oils such as corn, sunflower, safflower, and cottonseed oil are all very rich in omega-6 fatty acids and the margarines made from them contain \textit{trans} fatty acids that behave like saturated fats in terms of raising blood cholesterol [43]. Eggs from chickens eating wild greens, worms and insects produce eggs balanced in omega-6 and omega-3 fatty acids whereas the US supermarket egg has a ratio of about 20:1 [38, 39]. Recent studies in the serum cholesteryl esters of the people in Crete showed a threefold increase of ALA versus the population of Zutphen (table 3) [44]. Wine, fruits, vegetables, and olive oil provide high amounts of vitamin C, vitamin E, lycopene, beta-carotene, polyphenols, and other antioxidants [45–49]. The importance of a Cretan-type diet rich in ALA, fish, fruits and vegetables has been demonstrated in the Diet and Reinfarction Trial (DART) [50], the Lyon Heart Study [24–27], the studies by Pella, Singh and coworkers [11, 51, 52], and the most recent Gruppo Italiano
The Omega–6:Omega–3 Ratio in the Greek Diet

Olive oil being high in monounsaturated fatty acids and low in saturated and omega–6 fatty acids does not compete with the elongation and desaturation of ALA nor with the incorporation of omega–3 fatty acids into the red cell membrane phospholipids [5]. Furthermore, the omega–6:omega–3 ratio in the Greek diet is between 2 and 1:1 which is very close to the dietary ratio of the Paleolithic diet [8]. The beneficial effects of such a ratio and their importance in normal growth and development [54–56] and in the prevention and management of cardiovascular disease, hypertension, diabetes, arthritis, and possibly cancer have been extensively reviewed [5, 57–63]. In the secondary prevention of cardiovascular disease, a ratio of 4:1 was associated with a 70% decrease in total mortality [24]. A ratio of 2.5:1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4:1 with the same amount of omega–3 polyunsaturated fatty acids (PUFA) had no effect [64–65]. The lower omega–6: omega–3 ratio in women with breast cancer was associated with decreased risk [66]. A ratio of 2–3:1 suppressed inflammation in patients with rheumatoid arthritis [67], and a ratio of 5:1 had a beneficial effect on patients with asthma, whereas a ratio of 10:1 had adverse consequences [68].

Table 3. Mean fatty acid composition of cholesteryl esters in serum of 92 elderly men from Crete and 97 elderly men from Zutphen

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>% methylesters</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crete</td>
<td>Zutphen</td>
</tr>
<tr>
<td>16:0</td>
<td>11.1±1.0</td>
<td>11.9±1.3</td>
</tr>
<tr>
<td>16:1</td>
<td>3.2±1.1</td>
<td>2.9±1.6</td>
</tr>
<tr>
<td>18:0</td>
<td>0.7±0.3</td>
<td>1.1±0.5</td>
</tr>
<tr>
<td>18:1</td>
<td>31.0±2.7</td>
<td>21.4±3.9</td>
</tr>
<tr>
<td>18:2ω−6</td>
<td>41.9±3.7</td>
<td>53.1±6.5</td>
</tr>
<tr>
<td>18:3ω−3</td>
<td>0.9±0.5</td>
<td>0.3±0.4</td>
</tr>
<tr>
<td>Ratio 18:2/18:1</td>
<td>1.37±0.20</td>
<td>2.60±0.75</td>
</tr>
</tbody>
</table>

Results are expressed as mean % (by weight) methylesters ± SD. From Sandker et al. [44].
Further support for the need to balance the omega–6/omega–3 fatty acid ratio comes from the studies of Ge et al. [69] and Kang et al. [70]. The study by Ge et al. [69] clearly shows the ability of both normal rat cardiomyocytes and human breast cancer cells in culture to form all the omega–3s from omega–6 fatty acids when fed the cDNA encoding omega–3 fatty acid desaturase obtained from the roundworm *Caenorhabditis elegans*. The omega–3 desaturase efficiently and quickly converted the omega–6 fatty acids that were fed to the cardiomyocytes in culture to the corresponding omega–3 fatty acids. Thus, omega–6 linoleic acid (LA) was converted to omega–3 ALA, and arachidonic acid (AA) was converted to EPA, so that at equilibrium, the ratio of omega–6 to omega–3 PUFA was close to 1/1 [70]. Further studies demonstrated that the cancer cells expressing the omega–3 desaturase underwent apoptotic death whereas the control cancer cells with a high omega–6/omega–3 ratio continued to proliferate [69, 71]. Kang et al. [72] in their recent paper showed that transgenic mice expressing the *C. elegans fat-1* gene encoding an omega–3 fatty acid desaturase are capable of producing omega–3 from omega–6 fatty acids, leading to enrichment of omega–3 fatty acids with reduced levels of omega–6 fatty acids in almost all organs and tissues, including muscles and milk, with no need of dietary omega–3 fatty acid supply. This discovery provides a unique tool and new opportunities for omega–3 research, and raises the potential of production of *fat-1* transgenic livestock as a new and ideal source of omega–3 fatty acids to meet the human nutritional needs. In the current volume, Dr. Kang provides additional studies [73].

**Summary of Characteristics of the Greek Diet**

Because Greeks have a cultural dislike for animal fats, the saturated fat intake of the Greek diet is lower than other Western diets [20]. The Greek diet then is characterized by being moderate in fat, about 35%, low in saturated fat (7–8%), high in monounsaturated fat, and balanced in the omega–6:omega–3 essential fatty acids. The antioxidant and phytoestrogen content, and other phytochemicals is much higher than other diets of the people around the Mediterranean basin because Greeks continue to eat wild greens which are rich sources of ALA, vitamin C, vitamin E, glutathione and other phytochemicals with antioxidant properties [32–36]. The beneficial effects of the various compounds found in the vegetables and fruits eaten by Greeks have been shown to have hypoglycemic, hypocholesterolemic, and antitumor properties in animal experiments [45]. Even today the mortality from breast cancer is lower in Greece than in the US, Japan and Europe [74]. Finally, the Lyon Heart Study based on the modified diet of Crete described by de Lorgeril et al. [24] clearly
showed cardioprotective and anticancer effects in a French population indicating that such a diet is not only palatable but can be adapted to other populations. Furthermore, one could consider that the traditional diet of Greece even in its present form is the diet that is closer than the diets of other developed countries, to the diet on which humans evolved (fig. 1).

What appears to be so special about the Greek diet relative to the other Mediterranean diets is the content of bioprotective nutrients, specifically:

1. A more balanced intake of essential fatty acids from vegetable, animal and marine sources, omega–6:omega–3 of about 2:1 instead of 15:1 in Europe and 16.7:1 the US, respectively.

2. Antioxidants: high amounts of vitamin C, vitamin E, β-carotene, glutathione, phytoestrogens, and phytochemicals from green leafy vegetables; phenolic compounds from wine and olive oil; high intakes of tomatoes, onions, garlic and herbs, especially oregano, mint, rosemary, parsley and dill that contain lycopene, allylthiosulfinates, salicylates, carotenoids, indoles, monoterpenes, polyphenols, flavonoids, and other phytochemicals, used in cooking vegetables, meat, and fish.

The Greek Way of Cooking

In addition to the differences in the food composition there are distinct differences in the way Greeks use food ingredients. Traditionally, the Greeks start with olive oil to sauté onions, garlic, parsley, mint, oregano, and either fresh tomatoes, canned tomatoes, or tomato paste is used. This basic recipe contains already 8 different foods that contribute a balance of fatty acids (from olive oil, and additional omega–3 fatty acids and antioxidant vitamins from the green leafy herbs and the tomatoes), potassium, calcium, magnesium, vitamin C, vitamin E, vitamin A, and β-carotene. In other words, this basic recipe is an ‘antioxidant cocktail’ that is also balanced in omega–6 and omega–3 fatty acids. To this, zucchini, potatoes, eggplant, meat, fish or beans may be added. This approach to cooking has the advantage of using a variety of foods all at once that provide vitamins and minerals, is low in saturated fats and omega-6 fatty acids, and very rich in monounsaturates, omega–3 fatty acids, antioxidants and fiber. Compare this with a meal of potato, green beans and meat in which only 3 foods are eaten or a New England Boiled Dinner of corned beef, potatoes, onions and cabbage.

Because honey and cinnamon are used in many of the sweets, the total amount of sugar (sucrose, simple carbohydrates) is less than it would have been otherwise. Another important feature is the use of the juice of grapes to make cookies or puddings known as ‘must’ cookies. The recipe for ‘must’ cookies was developed in classic times. Today we know that red wine or the juice from
red grapes contains resveratrol that raises high-density lipoprotein (HDL) cholesterol, lowers low-density lipoprotein (LDL) cholesterol, and decreases platelet aggregation [75, 76].

Another important aspect of the Greek diet is that the recipes for fish or meat (broiled or baked) always include olive oil, oregano, rosemary and lemon juice added towards the end of cooking so that the olive oil does not oxidize. Furthermore, the vitamin C (from the lemons) and vitamin E (from oregano and rosemary) provide the two important antioxidant vitamins that may prevent the oxidation of LDL and free radical formation. In animal studies and tissue cultures it has been shown that it is the oxidized LDL that is deposited to form atheromas that lead to coronary heart disease [77].

Egg lemon sauce is a frequently used sauce with either egg yolks or whole eggs, olive oil and lemon juice (juice of one lemon per egg yolk). One can see the wisdom of that sauce. Lemon juice provides vitamin C to prevent the oxidation of LDL cholesterol from the egg yolk. This sauce is often served with either fish, meat or over vegetables such as artichokes, asparagus, celery, broccoli, or cauliflower, all of which are high in fiber, which decreases serum cholesterol levels and may also protect against colon cancer.

In summary, the Greek diet is low in saturated fat, is balanced in omega–6 and omega–3 fatty acids, and is rich in antioxidant vitamins and minerals. Olive oil is the most prominent oil in the Greek diet. The black olives are high in vitamin E. Olives contain 2-(3,4-dehydroxyphenyl)ethanol, a phenolic compound which inhibits arachidonate lipooxygenase activity, thus decreasing the formation of proinflammatory eicosanoids (leukotriene B4) [78]. The Greek diet is based on great variety and moderation. About 14–20 different foods are consumed at a meal by Greeks versus about 6–8 consumed by western Europeans and Americans.

**Conclusions**

Since World War II, the Mediterranean diet, as a model of a healthful diet, has been the subject of many studies. It is now clear that there is not one ‘Mediterranean diet’. In fact, the only diet that is consistent with the Paleolithic diet on which humans evolved is the traditional Greek diet as shown by the surveys on the population of Crete and clinical intervention studies using a modification of the diet of Crete [20, 24, 79]. What is then so special or what are the characteristics of such a diet? First and foremost, the traditional Greek diet has the following characteristics. The diet is:

1. Low in saturated fat, high in monounsaturated fat, balanced in omega–6 and omega–3 fatty acids that are present in every meal since both essential fatty acids are found in vegetable, animal, and marine sources.
2 High in fruits, vegetables, and legumes since Greeks continue to eat 0.5 kg (1 lb) of fruit a day. In long-term (25 years) follow-up studies on cohorts of the Seven Countries Study, high intake of fruit and fish were associated with a lower risk of cardiovascular diseases.

3 Rich in antioxidants as a result of using several herbs in cooking legumes, vegetables, meat and fish. The traditional Greek diet is very rich in many antioxidant compounds from high fruit and vegetable intake and wine.

4 Moderate in the amounts of cereals in the form of bread, usually sourdough bread which has a lower glycemic index than the quick breads used in other Western countries.

The Lyon Heart Study based on a modified diet of Crete indicated that the diet was responsible for a reduction in total death by 70% and that the traditional Greek diet can be adapted to other Western countries and cultures [24]. The most likely components that account for the difference in death rate from cardiovascular disease in the Lyon Heart Study and in the Seven Countries Study is the balance of omega–6 and omega–3 essential fatty acids being 4:1 or less and the high amounts of compounds with antioxidant properties. Figure 2 illustrates the traditional Greek diet in the form of a Greek column which takes into consideration genetic individuality, the principles of moderation, variety, proportionality, and balancing energy intake with energy expenditure [80].
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Balance of Omega–6/Omega–3 Essential Fatty Acids Is Important for Health

The Evidence from Gene Transfer Studies

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The ratio of omega–6 to omega–3 essential fatty acids in today’s Western diets is around 15–20:1, indicating that modern diets are deficient in omega-3 fatty acids but too high in omega–6 fatty acids compared with the diet on which humans evolved and their genetic patterns were established (omega–6/omega–3 = 1:1) [1, 2]. This is the consequence of modern agriculture, agribusiness and aquaculture with excessive production of vegetable oils, the emphasis on grain feeds, and processed foods [1–3]. The lipid pattern of our diets renders our tissues very high in omega–6 fatty acids. Since this change in dietary omega–6/omega–3 ratio occurred within too short a time to affect genetic adaptation significantly, we do not have the gene capable of converting omega–6 to omega–3 fatty acids. As a result, a high omega–6/omega–3 ratio exists in our body tissues. The high omega–6/omega–3 ratio may contribute to the high prevalence of many modern diseases (heart disease, cancer, etc.) [4], and appears to be a major problem of modern nutrition.

Although it is generally recognized that a lower ratio of omega–6/omega–3 fatty acids is more desirable in reducing the risk of many chronic diseases, the optimal ratio has not been well defined. In order to examine the potential beneficial effects of a balanced ratio of omega–6/omega–3 fatty acids (~1:1), we have recently used a gene transfer approach to create such a ratio in mammalian cells and studied its impact on cell function and physiology [5–6]. The fat-1 gene, encoding the converting enzyme omega–3 fatty acid desaturase that catalyzes conversion of omega–6 to omega–3 fatty acids, is found in the roundworm Caenorhabditis elegans but missing in mammals [5]. We transferred the fat-1 gene from C. elegans into cultured human cells and whole animals (mice) to render them capable of converting omega–6 to omega–3 fatty acids. The resulting transgenic cells and mice can produce omega–3 from omega–6 fatty acids and
have a balanced omega–6/omega–3 ratio (~1:1) without the need of exogenous
omega–3 supplementation. Use of these cells and animals for study of omega–3
fatty acids can eliminate the potential confounding factors of diet or supplement.
Thus, the transgenic cells and mice can serve as a unique model for elucidating
the importance of the ratio of omega–6/omega–3 fatty acids. The data obtained so
far from these studies (in vitro and in vivo) are summarized as follows.

**Cellular Studies**

In order to introduce the *fat-l* gene into mammalian cells efficiently, we
used a virus-mediated gene transfer strategy. We constructed a recombinant ade-
novirus (Ad.GFP,*fat-l*) carrying both the *fat-l* gene and the green fluorescent
protein (GFP) gene and another adenovirus (Ad.GFP) carrying the GFP gene
alone (as control) and used them to infect various mammalian cells, including
heart cells, neurons, endothelial cells and human breast cancer cells [5, 7–9].

Following the virus-mediated gene transfer, cellular lipids were extracted
and fatty acid composition was analyzed by gas chromatography to determine if
the expression of the *fat-l* gene in mammalian cells could change their lipid
profile. Our results showed that the fatty acid profiles were remarkably differ-
ent between cells expressing the *fat-l* gene and control cells [5, 7–9]. In cells
expressing the *fat-l* gene (omega–3 fatty acid desaturase), all types of omega–6
fatty acids were largely converted to corresponding omega–3 fatty acids,
namely, 18:2ω–6 to 18:3ω–3, 20:2ω–6 to 20:3ω–3, 20:3ω–6 to 20:4ω–3,
20:4ω–6 to 20:5ω–3, 22:4ω–6 to 22:5ω–3 and 22:5ω–6 to 22:6ω–3. As a result,
the contents of omega–3 fatty acids significantly increased whereas the levels
of omega–6 fatty acids decreased in the *fat-l* transgenic cells, leading to a dra-
matic reduction of the omega–6/omega–3 ratio from 9–15:1 in the control cells
to about 1:1 (table 1). Similar effects were observed in all cell types that we
have tested [7–9]. We also measured the production of prostaglandin E₂ (PGE₂),
one of the major eicosanoids derived from 20:4ω–6 (AA), in the fat-l and con-
trol cells by using an enzyme immunoassay [5, 7–9]. We found that the amount
of prostaglandin E₂ produced by the cells expressing the *fat-l* gene was signifi-
cantly lower than that produced by the control cells (30–50% reduction) [5, 7,
8]. These results indicate that gene transfer of the omega–3 fatty acid desaturase
can effectively modify cellular fatty acid composition (the omega–6/omega–3
ratio) and the generation of eicosanoids.

Next, we determined if the gene transfer-induced change in the omega–6/
omega–3 ratio would provide the beneficial effects of omega–3 fatty acids as
observed with fatty acid supplementation. Our previous studies have demon-
strated an antiarrhythmic effect for omega–3 fatty acids when supplemented to
cardiac myocytes [10]. To see whether the gene transfer can provide a similar protective effect, neonatal rat cardiac myocytes expressing the fat-1 gene were tested for their susceptibility to arrhythmias induced by arrhythmogenic agents, such as high concentrations of extracellular calcium. As shown in figure 1, when challenged with a high [Ca$^{2+}$] (7.5 mM), the control cells promptly exhibited arrhythmia characterized by spasmodic contractures and fibrillation, whereas the cells expressing the fat-1 gene could sustain regular beating (resistant to the arrhythmogenic stimulus), similar to the effect of omega–3 fatty acid supplementation [10]. This suggests that gene transfer of the omega–3 desaturase into heart cells can provide the antiarrhythmic effect of omega–3 fatty acids.

In human breast cancer cells (MCF-7), gene transfer of the omega–3 desaturase reduced both cellular omega–6/omega–3 fatty acid ratio from 12.0 to 0.8 and the level of PGE$_2$ by about 40%, leading to an increase in apoptotic cell death and a decrease in cell proliferation [7]. As shown in figure 2, a large number of the cells expressing fat-1 gene underwent apoptosis, as indicated by morphological

### Table 1. Polyunsaturated fatty acid composition of total cellular lipids from the control heart cells and the transgenic cells expressing a C. elegans fat-1 cDNA

<table>
<thead>
<tr>
<th>Mol% of total fatty acids</th>
<th>Control</th>
<th>fat-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ω–6 polyunsaturates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:2ω–6</td>
<td>14.2$^a$</td>
<td>9.2$^b$</td>
</tr>
<tr>
<td>20:2ω–6</td>
<td>1.2$^a$</td>
<td>0.3$^b$</td>
</tr>
<tr>
<td>20:3ω–6</td>
<td>1.6$^a$</td>
<td>0.4$^b$</td>
</tr>
<tr>
<td>20:4ω–6</td>
<td>15.2$^a$</td>
<td>4.1$^b$</td>
</tr>
<tr>
<td>22:4ω–6</td>
<td>4.4$^a$</td>
<td>1.0$^b$</td>
</tr>
<tr>
<td>22:5ω–6</td>
<td>0.2$^a$</td>
<td>0.0$^b$</td>
</tr>
<tr>
<td>Total</td>
<td>36.8$^a$</td>
<td>15.0$^b$</td>
</tr>
<tr>
<td><strong>ω–3 polyunsaturates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:3ω–3</td>
<td>0.2$^b$</td>
<td>3.6$^a$</td>
</tr>
<tr>
<td>20:4ω–3</td>
<td>0.0$^b$</td>
<td>0.6$^a$</td>
</tr>
<tr>
<td>20:5ω–3</td>
<td>0.1$^b$</td>
<td>6.1$^a$</td>
</tr>
<tr>
<td>22:5ω–3</td>
<td>1.2$^b$</td>
<td>5.8$^a$</td>
</tr>
<tr>
<td>22:6ω–3</td>
<td>1.0$^a$</td>
<td>1.3$^a$</td>
</tr>
<tr>
<td>Total</td>
<td>2.5$^b$</td>
<td>17.4$^a$</td>
</tr>
<tr>
<td>ω–6/ω–3 ratio</td>
<td>14.7$^a$</td>
<td>0.9$^b$</td>
</tr>
</tbody>
</table>

Values are means of four measurements. Values for each fatty acid with the same superscript letter do not differ significantly (p < 0.01) between control and fat-1.
**Fig. 1.** Effect of expression of the *C. elegans* ω–3 fatty acid desaturase in cardiac myocytes on their susceptibility to arrhythmia. Cultured (spontaneously beating) neonatal rat cardiac myocytes infected with Ad.GFP (control) or Ad.GFP, *fat-1* were challenged with 7.5 mM extracellular calcium. The control cells promptly exhibited arrhythmia (spasmodic contractures and fibrillation), whereas the *fat-1* cells could sustain regular beating.

**Fig. 2.** The gene transfer induces apoptosis of MCF-7 cells. MCF-7 cells were infected with Ad.GFP (left; control) or Ad.GFP, *fat-1* (right). Three days after infection, cell death was examined using a fluorescence microscope. Upper panels: Infected cells were directly visualized at 510 nm of blue light. Lower panels: Cells were stained with Hoechst dye for nuclei and observed under 480 nm fluorescent light. The brighter looking spots are the nuclei of apoptotic cells.
changes (small size with round shape or fragmentation) and nuclear staining (bright blue). Statistical analysis of apoptotic cell counts showed that 30–50% of cells infected with Ad.GFP.fat-1 were apoptotic whereas only 10% dead cells found in the control cells (infected with Ad.GFP). MTT analysis indicated that proliferative activity of cells infected with Ad.GFP.fat-1 was significantly lower than that of cells infected with Ad.GFP. Accordingly, the total number of viable cells in the cells infected with Ad.GFP.fat-1 was about 30% less than that in the control cells. In addition, DNA microarray assays showed that the gene transfer-induced change in omega–6/omega–3 fatty acid ratio could result in a down-regulation of a number of genes involved in cell proliferation, adhesion, angiogenesis and invasion, and an up-regulation of apoptosis-inducing genes in MDA-MB-231 cells [unpubl. data]. These results are consistent with the reported anti-cancer effects of omega–3 fatty acid supplementation [11–13].

In primary culture of human umbilical vein endothelial cells (HUVEC), expression of fat-1 significantly reduced omega–6/omega–3 fatty acid ratio from about 9 to 1 [9]. This change in cellular omega–6/omega–3 ratio led to a decrease in the surface expression of adhesion molecules (markers of inflammation). The quantity of the adhesion molecules (as determined by immunoassay), E-Selectin, ICAM-1, and VCAM-1 was reduced by 42, 43, and 57%, respectively, in response to cytokine exposure (TNF-α 5 U/ml, 4 h) [9]. We then examined whether changes in the adhesion molecule profile were sufficient to alter endothelial interactions with monocytes, the most prevalent white blood cell type found in atherosclerotic lesions. Under laminar flow and a defined shear stress of ~2 dyn/cm², fat-1 compared to control vector infected HUVEC supported ~50% less firm adhesion with almost no effect on the rolling interactions of THP-1 cells [9]. These results indicate that expression of the fat-1 gene in HUVEC inhibit cytokine induction of the endothelial inflammatory response and firm adhesion of monocytes, suggesting that a balanced omega–6/omega–3 fatty acid ratio may have an antiatherosclerotic effect.

We have also determined the effect of fat-1 expression on neuronal apoptosis. We found that the expression of the fat-1 gene, which could significantly reduce the neuronal omega–6/omega–3 fatty acid ratio from 6 to 1.5 and the production of prostaglandin E₂ by 20%, resulted in protection from growth factor-withdrawal-induced apoptotic cell death of rat cortical neurons [8]. Following gene transfer, apoptosis was induced by 24 h of growth factor withdrawal and detected by Hoechst staining. As shown in figure 3, cortical cultures infected with the Ad.GFP.fat-1 underwent (~60%) less apoptosis than those infected with Ad.GFP [8]. Accordingly, MTT analysis indicated that the viability of Ad.GFP.fat-1 cells was significantly (~50%) higher than that of cells infected with Ad.GFP. These observations confirm the protective effects of omega–3 fatty acid supplementation on neuron death [14, 15] and
highlight the importance of omega–6/omega–3 ratio in this neuroprotective effect.

Animal Studies

To heterologously express the *C. elegans* omega–3 fatty acid desaturase in mice, we modified the *fat-1* gene encoding this protein by optimization of codon usage for mammalian cells and coupled it to a chicken β-actin promoter. We then microinjected the expression vector into fertilized eggs to produce transgenic mouse lines. We have now successfully generated mice expressing the *fat-1* gene [6].

Both transgenic and wild-type mice are maintained at a diet high in omega–6 fatty acids (mainly linoleic acid) with very little omega–3 fatty acids.
Under this dietary regime, wild-type mice have little or no omega–3 fatty acid in their tissues because the animals naturally cannot produce omega–3 from omega–6 fatty acids, whereas the fat–1 transgenic mice have significant amounts of omega–3 fatty acids (derived from omega–6 fatty acids) in their tissues [6]. Figure 4 shows the differential fatty acid profiles of total lipids extracted from skeletal muscles of age and sex-matched wild-type and transgenic mice. In the wild-type animals, the polyunsaturated fatty acids found in the tissues are mainly (98%) the omega–6 linoleic acid (LA, 18:2ω–6) and arachidonic acid (AA, 20:4ω–6) with trace (or undetectable) amount of omega-3 fatty acids. In contrast, there are large amounts of

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Fig. 4. Partial gas chromatograph traces showing the polyunsaturated fatty acid profiles of total lipids extracted from skeletal muscles of a wild-type mouse (WT, upper panel) and a fat-1 transgenic mouse (TM, lower panel). Both the wild-type and transgenic mice were 8 weeks old female and fed with the same diet. Note, the levels of ω–6 polyunsaturated acids (18:2ω–6, 20:4ω–6, 22:4ω–6 and 22:5ω–6) are remarkably lower whereas ω–3 fatty acids (marked with *) are abundant in the transgenic muscle (lower panel) compared with the wild-type muscle in which there is very little ω–3 fatty acid (upper panel).
omega–3 polyunsaturated fatty acids, including linolenic acid (ALA, 18:3ω–3), eicosapentaenoic acid (EPA, 20:5ω–3), docosapentaenoic acid (DPA, 22:5ω–3) and docosahexaenoic acid (DHA, 22:6ω–3), in the tissues of transgenic mice. Accordingly, the levels of the ω–6 fatty acids LA and AA in the transgenic tissues are significantly reduced, indicating a conversion of omega–6 to omega–3 fatty acids. The resulting ratio of omega–6 to omega–3 fatty acids in the tissues of transgenic animals is close to 1. This omega–3 rich profile of lipid with a balanced ratio of omega–6 to omega–3 and an even more balanced AA/(EPA+DPA+DHA) can be observed in all of the organs/tissues, including muscle and milk (table 2). Our data clearly show that the transgenic mice expressing the fat-1 gene are capable of producing omega–3 fatty acids from omega–6 fatty acids, resulting in enrichment of omega–3 fatty acids in their organs/tissues without the need of dietary omega–3 supply, which is impossible in wild-type mammals.

The transgenic mice appear to be normal and healthy. Availability of these animals allows us to produce two different fatty acid profiles in experimental animals by feeding them just a single diet. Therefore, this novel mouse model is desirable for us to address the authentic biological effects of omega–3 fatty

<table>
<thead>
<tr>
<th></th>
<th>Omega–6/omega–3</th>
<th>AA/(EPA+DPA+DHA)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>WT</td>
<td>TG</td>
</tr>
<tr>
<td>Muscle</td>
<td>49.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Milk</td>
<td>32.7</td>
<td>5.7</td>
</tr>
<tr>
<td>RBC</td>
<td>46.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Heart</td>
<td>22.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Brain</td>
<td>3.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Liver</td>
<td>26.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Kidney</td>
<td>16.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Lung</td>
<td>32.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>23.8</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Both the wild-type and transgenic mice were 8-week-old females and fed with the same diet.

The omega–6/omega–3 fatty acid ratio is \((18:2\omega–6 + 20:4\omega–6 + 22:4\omega–6 + 22:5\omega–6)/(18:3\omega–3 + 20:5\omega–3 + 22:5\omega–3 + 22:6\omega–3)\).
acids and omega-6/omega-3 ratio in the body, without confounding factors of diet. Most recently, we have just begun to examine the potential differences in physiology and pathophysiology between the transgenic and wild-type mice, and have obtained some exciting preliminary data. For example, when maintained on a high omega-6/omega-3 diet, the transgenic mice have a much lower tumorigenicity of melanoma than wild-type animals; challenging lungs with LPS or bleomycin produces less severity of pulmonary inflammation and fibrosis in the transgenic mice than wild-type animals; the fat-1 transgenic mice have lower levels of blood triglyceride and appear to be less susceptible to atherosclerosis. In addition, the wild-type mice behaviorally exhibit hyperactivity whereas the fat-1 mice do not [unpublished data, these studies are underway]. Although more studies are needed, our observations in vivo obtained so far are consistent with the in vitro data and support the notion that a balanced ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many diseases.

Conclusions

Our findings as presented here clearly indicate that gene transfer of the C. elegans omega-3 fatty acid desaturase to mammalian cells can dramatically balance cellular omega-6/omega-3 fatty acid ratio and provide beneficial effects of omega-3 fatty acids, without the need for supplementation with exogenous omega-3 fatty acids. Thus, our studies have demonstrated a novel and effective approach to modifying fatty acid composition of mammalian cells. This genetic approach in modifying omega-6/omega-3 ratio is helpful for studying the importance of omega-6/omega-3 fatty acid ratio in a biological system. Indeed, our data derived from these gene transfer studies clearly show that a low or balanced omega-6/omega-3 fatty acid ratio exerts many beneficial effects either in vitro or in vivo. These results support the notion that excessive amounts of omega-6 fatty acids and a very high omega-6/omega-3 ratio promote the pathogenesis of many modern diseases (heart disease, cancer, etc.), while balancing or reducing the ratio of omega-6/omega-3 fatty acids may decrease the risk of these diseases. I expect that our ongoing studies using fat-1 transgenic mice will provide more meaningful and definite information in the near future.

In addition, our discovery in transgenic mice provides a new strategy for producing omega-3 fatty acid-rich foodstuff (e.g. meat, milk and eggs) by generating large fat-1 transgenic animals/livestock (e.g. cow, pig, sheep and chicken) with this technology. This genetic approach may be a cost-effective and sustainable way of producing omega-3 essential fatty acids for the increasing demand in the future.
Acknowledgements

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References


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Sudden cardiac death (SCD) is usually defined as death from a cardiac cause occurring within one hour from the onset of symptoms [1]. In many studies, however, investigators used quite different definitions with a time frame of 3 h or even 24 h in the old World Health Organization definition. The magnitude of the problem is considerable as SCD is a very common, and often the first, manifestation of coronary heart disease (CHD), and it accounts for about 50% of cardiovascular mortality in developed countries [1]. In most cases, SCD occurs without prodromal symptoms and out of hospital. As a matter of fact, this mode of death is a major public health issue. Since up to 80% of SCD patients had CHD [2], the epidemiology and potential preventive approaches of SCD should, in theory, parallel those of CHD. In other words, any treatment aimed at reducing CHD should reduce the incidence of SCD.

The hypothesis that eating fish may protect against SCD is derived from the results of a secondary prevention trial, the Diet And Reinfarction Trial (DART), which showed a significant reduction in total and cardiovascular mortality (both by about 30%) in patients who had at least 2 servings of fatty fish per week [3]. The authors suggested that the protective effect of fish might be explained by a preventive action on ventricular fibrillation (VF), since no benefit was observed on the incidence of nonfatal AMI. This hypothesis was consistent with experimental evidence suggesting that ω–3 polyunsaturated fatty acids (PUFA), the dominant fatty acids in fish oil and fatty fish, have an important effect on the occurrence of VF in the setting of myocardial ischemia and reperfusion in various animal models, both in vivo and in vitro [4, 5]. In the
same studies, it was also apparent that saturated fatty acids are proarrhythmic as compared to unsaturated fatty acids. Using an elegant in vivo model of SCD in dogs, Billman and colleagues recently demonstrated a striking reduction of VF after intravenous administration of pure ω–3 PUFA, including both the long chain fatty acids present in fish oil and α-linolenic acid, their parent ω–3 PUFA occurring in some vegetable oils [6]. These authors have found the mechanism of this protection to result from the electrophysiological effects of free ω–3 PUFA when these are simply partitioned into the phospholipids of the sarcolemma without covalently bonding to any constituents of the cell membrane. After dietary intake, these fatty acids are preferentially incorporated into membrane phospholipids [7]. Nair and colleagues have also shown that a very important pool of free (non-esterified) fatty acids exists in the normal myocardium and that the amount of ω–3 PUFA in this pool is increased by supplementing the diet in ω–3 PUFA [7]. This illustrates the potential of diet to modify the structure and biochemical composition of cardiac cells. In case of ischemia, phospholipases and lipases quickly release new fatty acids from phospholipids, including ω–3 fatty acids in higher amounts than the other fatty acids [7], thus further increasing the pool of free ω–3 fatty acids that can exert an antiarrhythmic effect. It is important to remember that the lipoprotein lipase is particularly active following the consumption of ω–3 PUFA [8]. One hypothesis is that the presence of the free form of the ω–3 PUFA in the membrane of every cardiac muscle cell renders the myocardium more resistant to arrhythmias, probably by modulating the conduction of several membrane ion channels [9]. So far, it seems that the very potent inhibitory effects of ω–3 PUFA on the fast sodium current, INa [10, 11], and the L-type calcium current, ICaL [12], are the major contributors to the antiarrhythmic actions of these fatty acids in ischemia. Briefly, ω–3 PUFA act by shifting the steady-state inactivation potential to more negative values, as was also observed in other excitable tissues such as neurons.

Another important aspect of the implication of ω–3 PUFA in SCD is their role in the metabolism of eicosanoids. In competition with ω–6 PUFA, they are the precursors to a broad array of structurally diverse and potent bioactive lipids (including eicosanoids, prostaglandins and thromboxanes), which are thought to play a role in the occurrence of VF during myocardial ischemia and reperfusion [13, 14].

Other clinical data show suppression (by more than 70%) of ventricular premature complexes in middle-aged patients with frequent ventricular extrasystoles randomly assigned to take either fish oil or placebo [15]. Also, survivors of AMI [16] and healthy men [17] receiving fish oil were shown to improve their measurements of heart rate variability, suggesting other mechanisms by which ω–3 PUFA may be antiarrhythmic.
Support for the hypothesis of a clinically significant antiarrhythmic effect of ω–3 PUFA in the secondary prevention of CHD, as put forward in DART [3], came from two randomized trials testing the effect of ethnic dietary patterns (instead of that a single food or nutrient), i.e. a Mediterranean type of diet (consistent with a modified diet of Crete) and an Asian vegetarian diet, in the secondary prevention of CHD [18, 19]. The two experimental diets included a high intake of essential α-linolenic acid, the main vegetable ω–3 PUFA. Whereas the incidence of SCD was markedly reduced in both trials, the number of cases was very small and the antiarrhythmic effect cannot be entirely attributed to α-linolenic acid as these experimental diets were also high in other nutrients with potential antiarrhythmic properties, including various antioxidants. These findings were extended by the population-based case-control study conducted by Siscovick and colleagues on the intake of ω–3 PUFA among patients with primary cardiac arrest, compared to that of age- and sex-matched controls [20]. Their data indicated that the intake of about 5–6 g of ω–3 PUFA per month (an amount provided by consuming fatty fish once or twice a week) was associated with a 50% reduction in the risk of cardiac arrest. In that study, the use of a biomarker, the red blood cell membrane level of ω–3 PUFA, considerably enhanced the validity of the findings, which also were consistent with the results of many (but not all) cohort studies suggesting that consumption of one to two servings of fish per week is associated with a marked reduction in CHD mortality as compared to no fish intake [21, 22]. In most studies, however, the SCD endpoint is not reported.

In a large prospective study (more than 20,000 participants with a follow-up of 11 years), Albert et al examined the specific point that fish has antiarrhythmic properties and may prevent SCD [23]. They found that the risk of SCD was 50% lower for men who consumed fish at least once a week than for those who had fish less than once a month. Interestingly, the consumption of fish was not related to non-sudden cardiac death suggesting that the main protective effect of fish (or ω–3 PUFA) is related to an effect on arrhythmia. These results are consistent with those of DART [3] but differ from those of the Chicago Western Electric Study, in which there was a significant inverse association between fish consumption and non-sudden cardiac death, but not with SCD [24]. Several methodological factors may explain the discrepancy between the two studies, especially the way of classifying deaths in the Western Electric Study [24]. This again illustrates the limitations of observational studies and the obvious fact that only randomized trials can definitely provide a clear demonstration of causal relationships.

The GISSI-Prevenzione trial was aimed at helping in addressing the question of the health benefits of foods rich in ω–3 PUFA (and also in vitamin E) and their pharmacological substitutes [25]. Patients (n = 11,324) surviving a
recent AMI (<3 months) and having received the prior advice to come back to a Mediterranean type of diet (consistent with a modified diet of Crete) were randomly assigned supplements of ω–3 PUFA (0.85 g daily), vitamin E (300 mg daily), both or none (control) for 3.5 years. The primary efficacy endpoint was the combination of death and non-fatal AMI and stroke. Secondary analyses included overall mortality, cardiovascular (CV) mortality and SCD. The exact definition of SCD was not given in the paper. However, the clinical events were validated by an ad-hoc committee of expert cardiologists [25], who presumably used the current definition of SCD. Treatment with ω–3 PUFA significantly lowered the risk of the primary endpoint (the relative risk decreased by 15%). Secondary analyses provided a clearer profile of the clinical effects of ω–3 PUFA (table 1). Overall mortality was reduced by 20% and CV mortality by 30%. However, it was the effect on SCD (45% lower) that accounted for most of the benefits seen in the primary combined endpoint and both overall and CV mortality. There was no difference across the treatment groups for nonfatal CV events, a result comparable to that of DART [3]. Thus, the results obtained in this randomized trial are consistent with previous controlled trials [3, 18, 19], large-scale observational studies [21–24] and experimental studies [4–7], which together strongly support an effect of ω–3 PUFA in relation with SCD.

An important point is that the protective effect of ω–3 PUFA on SCD was greater in the groups of patients who complied more strictly with the Mediterranean diet (consistent with a modified diet of Crete). This suggests a positive interaction between ω–3 PUFA and some components of the Mediterranean diet which is, by definition, not high in ω–6 PUFA and low in saturated fats, but rich in oleic acid, various antioxidants and fiber, and associated with a moderate consumption of alcohol (see below for further comments).

Regarding the other dietary fatty acids, animal experiments have clearly indicated that a diet rich in saturated fatty acids is associated with a high

<table>
<thead>
<tr>
<th>Relative risk (95% CI)</th>
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<tbody>
<tr>
<td>Death, nonfatal AMI and stroke</td>
</tr>
<tr>
<td>Overall mortality</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
</tr>
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</table>
incidence of ischemia- and reperfusion-induced ventricular arrhythmia, whereas PUFA of either the ω−6 or ω−3 family reduce that risk [4–6]. Large (but not all) epidemiological studies have shown consistent associations between the intake of saturated fatty acids and CHD mortality [26]. However, the SCD endpoint is usually not analyzed in these studies. In addition, a clear demonstration of a causal relationship between dietary saturated fatty acids and SCD would require the organization of a randomized trial, which is not ethically acceptable. Thus, besides the effect of saturated fatty acids on blood cholesterol levels, the exact mechanism(s) by which saturated fats increase CHD mortality remain unclear. If animal data, demonstrating a proarrhythmic effect of saturated fatty acids, are confirmed in humans, the first thing to do in order to prevent SCD in humans would be to drastically reduce the intake of saturated fats. In fact, this has been done in randomized dietary trials and, as expected, the rate of SCD decreased in the experimental groups [18, 19]. However, as written above about the same trials [22, 23], the beneficial effect cannot be entirely attributed to the reduction of saturated fats, because other potentially antiarrhythmic dietary factors, including ω−3 PUFA, were also modified in these trials.

In contrast with ω−3 PUFA, few data have been published so far in humans regarding the effect of ω−6 PUFA on the risk of SCD. Roberts et al have reported that the percentage content of linoleic acid (the dominant ω−6 PUFA in the diet) in adipose tissue (an indicator of long-term dietary intake) was inversely related to the risk of SCD, which was defined in that study as instantaneous death or death within 24 h of the onset of symptoms [27]. This is in line with most animal data and may suggest that patients at risk of SCD may benefit from increasing their dietary intake of ω−6 PUFA, in particular linoleic acid, in the same way as for ω−3 PUFA. Let it be mentioned, however, that ω−3 PUFA were more effective on SCD than ω−6 PUFA in most animal experiments [4–6].

In addition, diets high in ω−6 PUFA increase the linoleic acid content of lipoproteins and render them more susceptible to oxidation [28], which would be an argument against such diets because lipoprotein oxidation is a major step in the inflammatory process that renders atherosclerotic lesions unstable and prone to rupture [29–31].

Erosion and rupture of atherosclerotic lesions were shown to trigger CHD complications (see below, the section on plaque inflammation and rupture) and myocardial ischemia and to considerably enhance the risk of SCD [32–35]. As a matter of fact, in the secondary prevention of CHD, diets high in ω−6 PUFA failed to improve the overall prognosis of the patients [36]. Also, in the Dayton study, a mixed primary and secondary prevention trial, in which the chief characteristic of the experimental diet was the substitution of ω−6 PUFA for saturated fat, the number of SCD was apparently lower in the experimental group.
than in the control group (18 vs. 27) but the number of deaths from other causes, in particular cancers, was higher in the experimental group (85 vs. 71), thus offsetting the potential protective effect of ω–6 PUFA on SCD and resulting in no effect at all on mortality [37]. Such negative effects were not reported with ω–3 PUFA. Thus, despite the beneficial effect of ω–6 PUFA on lipoprotein levels, which could, in theory, reduce SCD in the long term by reducing the development of atherosclerosis, it seems preferable not to increase the consumption of ω–6 PUFA beyond the amounts required to prevent deficiencies in the essential ω–6 fatty acid, linoleic acid (approximately 4–6% of the total energy intake), which are found in the current average Western diet. As a substitute for saturated fat, the best choice is obviously to increase the intake of vegetable monounsaturated fat (oleic acid) in accordance with the Mediterranean diet pattern. If oleic acid has apparently no effect on the risk of SCD (at least by comparison with ω–3 and ω–6 PUFA), its effects on blood lipoprotein levels are similar to those of ω–6 PUFA and it has the great advantage of protecting lipoproteins against oxidation [38].

Thus, the best fatty acid combination to prevent SCD (and the other complications of CHD) and, in other words, to cumulate antiarrhythmic, antioxidant and hypolipidemic effects, would result from the adoption of a diet close to the Mediterranean diet pattern (consistent with a modified diet of Crete) [38, 39].

Finally, Roberts et al. [40] reported no significant relationship between trans isomers of oleic and linoleic acids in adipose tissue and the risk of SCD whereas Lemaitre et al. [41] found that cell membrane trans isomers of linoleic acid (but not of oleic acid) are associated with a large increase in the risk of primary cardiac arrest. As for the role of trans fatty acids on ventricular arrhythmias, it has not been investigated in experimental models.

Thus, although specific human data on the effect of saturated fatty acids on SCD are lacking, results of several trials suggest that it is important to reduce their intake in the secondary prevention of CHD. Despite a possible beneficial effect on the risk of SCD, increasing consumption of ω–6 PUFA should not be recommended in clinical practice for patients with established CHD. Diets including low intakes in saturated fatty acid (as well as trans isomers of linoleic acid) and ω–6 PUFA (but enough to provide the essential linoleic acid) and high intakes in ω–3 PUFA and oleic acid (Mediterranean diet pattern consistent with a modified diet of Crete) appear to be the best option to prevent both SCD and nonfatal AMI recurrence [19, 38].

For several decades, the prevention of CHD (including the prevention of ischemic recurrence after a prior AMI) has focused on the reduction of the traditional risk factors: smoking, HBP, hypercholesterolemia. Priority was given to the prevention (or reversion) of vascular atherosclerotic stenosis. As discussed above, it has become clear in secondary prevention that clinical efficiency
needs to primarily prevent the fatal complications of CHD such as SCD. This does not mean, however, that we should not try slowing down the atherosclerotic process, and in particular plaque inflammation and rupture. Indeed, it is critical to prevent the occurrence of new episodes of myocardial ischemia whose repetition in a recently injured heart can precipitate SCD or CHF. Myocardial ischemia is usually the consequence of coronary occlusion caused by plaque rupture and subsequent thrombotic obstruction of the artery. Recent progress in the understanding of the cellular and biochemical pathogenesis of atherosclerosis suggests that, in addition of the traditional risk factors of CHD, there are other very important targets of therapy to prevent plaque inflammation and rupture. In this regard, the most important question is: How and why does plaque rupture occur?

Most investigators agree that atherosclerosis is a chronic low grade inflammation disease [29]. Pro-inflammatory factors (free radicals produced by cigarette smoking, hyperhomocysteinemia, diabetes, peroxidized lipids, hypertension, elevated and modified blood lipids) contribute to injure the vascular endothelium, which results in alterations of its antiatherosclerotic and antithrombotic properties. This is thought to be a major step in the initiation and formation of arterial fibrostenotic lesions [29]. From a clinical point of view, however, an essential distinction should be made between unstable, lipid-rich and leukocyte-rich lesions and stable, acellular fibrotic lesions poor in lipids, as the propensity of these two types of lesion to rupture into the lumen of the artery, whatever the degree of stenosis and lumen obstruction, is totally different.

In 1987, we proposed that inflammation and leukocytes play a role in the onset of acute CHD events [42]. This has recently been confirmed [32–35]. It is now accepted that one of the main mechanisms underlying the sudden onset of acute CHD syndromes, including unstable angina, myocardial infarction and SCD, is the erosion or rupture of an atherosclerotic lesion [32, 33], which triggers thrombotic complications and considerably enhances the risk of malignant ventricular arrhythmias [34, 35]. Leukocytes have been also implicated in the occurrence of ventricular arrhythmias in clinical and experimental settings [43, 44], and they contribute to myocardial damage during both ischemia and reperfusion [45]. Clinical and pathological studies showed the importance of inflammatory cells and immune mediators in the occurrence of acute CHD events and prospective epidemiological studies showed a strong and consistent association between acute CHD and systemic inflammation markers [46]. A major question is to know why there are macrophages and activated lymphocytes [29] in atherosclerotic lesions and how they get there. Issues such as local inflammation, plaque rupture and attendant acute CHD complications follow.

Steinberg et al. [47] proposed in 1989 that oxidation of lipoproteins causes accelerated atherogenesis. Elevated plasma levels of low-density lipoproteins
LDL are a major factor of CHD, and reduction of blood LDL levels (for instance by drugs) results in less CHD. However, the mechanism(s) behind the effect of high LDL levels is not fully understood. The concept that LDL oxidation is a key characteristic of unstable lesions is supported by many reports [29]. Two processes have been proposed. First, when LDL particles become trapped in the artery wall, they undergo progressive oxidation and are internalized by macrophages, leading to the formation of typical atherosclerotic foam cells. Oxidized LDL is chemotactic for other immune and inflammatory cells and up-regulates the expression of monocyte and endothelial cell genes involved in the inflammatory reaction [29, 48]. The inflammatory response itself can have a profound effect on LDL [29], creating a vicious circle of LDL oxidation, inflammation and further LDL oxidation. Second, oxidized LDL circulates in the plasma for a period sufficiently long to enter and accumulate in the arterial intima, suggesting that the entry of oxidized lipoproteins within the intima may be another mechanism of lesion inflammation, in particular in patients without hyperlipidemia [30, 31, 48]. Elevated plasma levels of oxidized LDL are associated with CHD, and the plasma level of malondialdehyde-modified LDL is higher in patients with unstable CHD syndromes (usually associated with plaque rupture) than in patients with clinically stable CHD [30]. In the accelerated form of CHD typical of post-transplantation patients, higher levels of lipid peroxidation [49–51] and of oxidized LDL [52] were found as compared to the stable form of CHD in non-transplanted patients. Reactive oxygen metabolites and oxidants influence thrombus formation [see 53 for review], and platelet reactivity is significantly higher in transplanted patients than in non-transplanted CHD patients [54].

The oxidized LDL theory is not inconsistent with the well-established lipid-lowering treatment of CHD, as there is a positive correlation between plasma levels of LDL and markers of lipid peroxidation [52, 55] and low absolute LDL level results in reduced amounts of LDL available for oxidative modification. LDL levels can be lowered by drugs or by reducing saturated fats in the diet. Reduction of the oxidative susceptibility of LDL was reported when replacing dietary fat with carbohydrates. Pharmacological/quantitative (lowering of cholesterol) and nutritional/qualitative (high antioxidant intake) approaches of the prevention of CHD are not mutually exclusive but additive and complementary. An alternative way to reduce LDL concentrations is to replace saturated fats with polyunsaturated fats in the diet. However, diets high in polyunsaturated fatty acids increase the polyunsaturated fatty acid content of LDL particles and render them more susceptible to oxidation (which would argue against use of such diets. As a matter of fact, in the secondary prevention of CHD, such diets failed to improve the prognosis of the patients [for a review, see 36]. In that context, the traditional Mediterranean diet, with low saturated
fat and polyunsaturated fat intakes, appears to be the best option. Diets rich in oleic acid increase the resistance of LDL to oxidation independent of the content in antioxidants [56, 57] and results in leukocyte inhibition [58]. Thus, oleic acid-rich diets decrease the pro-inflammatory properties of oxidized LDL. Constituents of olive oil other than oleic acid may also inhibit LDL oxidation [59]. Various components of the Mediterranean diet may also affect LDL oxidation. For instance, α-tocopherol or vitamin C, or a diet combining reduced fat, low-fat dairy products and a high intake of fruits and vegetables were shown to favorably affect either LDL oxidation itself or/and the cellular consequences of LDL oxidation [60, 61].

Finally, significant correlation was found between certain dietary fatty acids and the fatty acid composition of human atherosclerotic plaques [62, 63], which suggests that dietary fatty acids are rapidly incorporated into the plaques. This implies a direct influence of dietary fatty acids on plaque formation and the process of plaque rupture. It is conceivable that fatty acids that stimulate oxidation of LDL (ω–6 fatty acids) induce plaque rupture whereas those that inhibit LDL oxidation (oleic acid), inhibit leukocyte function (ω–3 fatty acids) [64] or prevent ‘endothelial activation’ and the expression of proinflammatory proteins (oleic acid and ω–3 fatty acids) [65, 66] contribute to pacify and stabilize the dangerous lesions. In that regard, it is noteworthy that moderate alcohol consumption, a well known cardioprotective factor, was recently shown to be associated with low blood levels of systemic markers of inflammation [67], suggesting a new protective mechanism to explain the inverse relationship between alcohol and CHD rate. As both dietary ω–3 fatty acids and moderate alcohol consumption are major characteristics of the Mediterranean diet, it is not surprising to observe that this diet was associated with lower rate of new episodes of CHF in the Lyon Diet Heart Study.

Thus, any dietary pattern combining a high intake of natural antioxidants, a low intake of saturated fatty acids, a high intake of oleic acid, a low intake of omega-6 fatty acids and a high intake of omega-3 fatty acids would logically produce a highly cardioprotective effect. This is consistent with what we know about the Mediterranean diet pattern (consistent with a modified diet of Crete) [38, 39] and with the results of the Lyon Diet Heart Study.

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The Lyon Diet Heart Study


Nicotera, a small town in the Calabria Region in Southern Italy, was the third Italian rural area of the Seven Countries Study (SCS) examined in the fall of 1957 as a pilot study. Because both due to shortage of funds and similarity with the two rural areas of Greece, this study was not followed longitudinally.

Nicotera, selected for the quite high olive oil and legumes consumption, is perched on a spot of the Poro Mountain overlooking the Tyrrhenian Sea about 60 km north of Reggio Calabria near the toe of Italy. The main farm products were olives, grapes, figs, oranges, tomatoes, pulses, wheat, bergamot for the perfume trade, and for local use, a little meat and poultry. In the hamlet of Nicotera Marina few families were engaged in fishing. There was no manufacturing industry. The population was relatively poor in comparison to the two rural areas of Italy in the SCS, but there was a migration of persons under the age of 40. Besides the main center of Nicotera and the hamlet of Nicotera Marina there were three more detached hamlets: Comerconi, Badia, and Preitoni. The total population of the entire survey area was 9,043 inhabitants at the time of the survey. About 80% of the people lived in the centers and went out daily to work in their small fields often as far as several kilometers away. Both men and women were engaged in moderate physical activity and only men in some cases in rather heavy physical work. Because of its geography (altitude 0–641 m) and road conditions, transportation was mainly by mule. The prevalence of myocardial infarction in men aged 45–64 years was very low (4 cases out of 598 examined in 1957), and hypertension, overweight and obesity were uncommon. Similar findings were observed in the cohort of men from Corfu (Greece) examined in 1960.
The Dietary Habits of Subjects from Nicotera

The weighed record method for 7 days in three different seasons of 1960 was used for the dietary survey of the Nicotera families. Because this type of dietary survey is time consuming and very expensive, this procedure was followed in a sample of 32 families. From the roster of all men examined in 1957, sixteen names were chosen at random. Then for each head of family so selected, the family living closest to him was picked. In this way one dietitian could at the same time carry out the survey on two families.

The procedure of the dietary survey with this method is fully described in previous papers [1, 2]. Some difficulties occurred with the Nicotera family dietary surveys. For the first survey in January one dietitian became ill and it was impossible to find a replacement, so the total number of subjects had to be reduced from 32 to 24. In the second survey in May–June, six of the families refused to continue to cooperate, six substitute families were then statistically selected from the roster. The final result was that 17 families were surveyed for all three seasons, 11 families for two seasons and seven families for one season, with a total of 35 families. Because of no significant seasonal difference in energy nutrient, all the families were considered together [3].

The percentage distribution occupation of 35 Nicotera heads of families is as follow: farmers 37, craftsmen 26, clerks 17, salesmen 11, construction workers 6 and mule drivers 3.

Table 1 shows the three-season mean of food intake expressed in g/day of 328 components of 35 Nicotera families examined in 1960. Cereals were well represented and also were vegetables, legumes and fish. Virgin olive oil was the most common edible fat. Meat, eggs, cheese and milk were consumed sparingly. Wine, mostly red wine, was used moderately by men.

Meal Patterns and Way of Cooking in Nicotera

We report here only the meal patterns of 35 Nicotera heads of families. For the other components of the family the differences in food consumption at meal was quantitative more than qualitative. Then, because of the differences in food selection, the meal patterns of 35 heads of families examined in different seasons, are subdivided in two homogeneous groups: one for craftsmen, clerks and salesmen (n = 19) and one for farmers and construction workers (n = 16). The prevalent foods consumed at each of three main meals are presented in a decreasing order of three season mean frequency. Obviously, there are marked differences related to home food production according to the season.
The craftsmen group meal pattern was the following. At breakfast, bread, coffee, or more often roasted barley hot drink and milk were consumed. At lunch, for the first course pasta with tomato sauce, soup with vegetables or legumes and pasta, or vegetable soup were preferred. The second course was composed of fish or meat and as side dishes cooked or green vegetables and cured olives. Home-produced goat’s milk cheese or salami were consumed occasionally. Homemade bread, garden fruit and homemade wine were consumed in reasonable amounts. The dinner was composed of either olive oil or tomato sauce pasta and sometimes vegetable soup. Fish or meat was followed by side dishes as at lunch. Cheese was preferred to salami occasionally. The consumption of bread, fruit and wine was similar to that at lunch.

The farmer group meal pattern was the following. At breakfast, coffee or more often roasted barley hot drink with less bread and much less milk than the other group was consumed. For lunch, the vegetables or legumes and pasta soup was preferred to pasta with tomato sauce. As second course, fish was preferred to meat; the selection of side dishes was similar to that of the craftsmen group. Both cheese and salami were consumed occasionally. The consumption of bread was similar to that of the craftsmen group, while the intakes of fruit and wine were lower. At dinner, the vegetable or legume and pasta soup was always

Table 1. Mean daily intake of foods (g) of subjects from Nicotera (Italy) in 1960: mean of three seasons

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13–19</td>
<td>20–39</td>
</tr>
<tr>
<td></td>
<td>13–19</td>
<td>20–39</td>
</tr>
<tr>
<td>n</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Cereals</td>
<td>531</td>
<td>519</td>
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<tr>
<td>Legumes</td>
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<td>57</td>
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<tr>
<td>Potatoes</td>
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<tr>
<td>Vegetables</td>
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<td>280</td>
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<tr>
<td>Fruit</td>
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<td>96</td>
</tr>
<tr>
<td>Fish</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>Oils</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Fats</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Meat</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>Eggs</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Cheese</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Milk, ml</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Sugar products</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Wine, ml</td>
<td>93</td>
<td>291</td>
</tr>
</tbody>
</table>

The Nicotera Diet 117
preferred to pasta with tomato sauce. Also, fish was preferred to meat as a second course, and cooked vegetables as side dishes were preferred to raw ones. Cured olives were regularly consumed while cheese was preferred to salami as an occasional dish. For bread, fruit, and wine, the consumption was similar to that at lunch. Few people drank some milk in the evening. When farmers went to their farms far away, they consumed as snacks bread with fruit or raw vegetables from their garden or farm.

The home preparation of some foods is interesting as is the way of cooking of some dishes. Bread was made with high extraction flour from home-produced wheat, milled using stone mills. The barley hot drink was prepared at home from barley produced on the farm. It was roasted over charcoal in special iron containers with continuous rotation until the barley became dark brown. The roasted barley was grounded in a coffee-mill and then boiled in water and passed through a strainer.

The majority of recipes were prepared using a great variety of ingredients with important nutritional characteristics: various vegetables from the home garden, cured olives, green leafy herbs, spices (oregano, parsley, basil, rosemary, red pepper). For example, the sauce for pasta was prepared with olive oil, tomatoes, onions, garlic, basil, parsley, red pepper, wild herbs all from the garden, and little meat or fish. For vegetable soup the variety of vegetables was great so there was a high probability that the recipes included either many different nutrients or an elevated concentration of certain nutrients. In the first case, different nutritional properties of ingredients were combined. In the second case, a synergy among the properties of the same nutrients was obtained.

The most common fish consumed was: stock fish (air-dried cod), dried salted cod and blue fish. The fish recipes included olive oil, vegetables, parsley, onion, garlic, cured olives, tomatoes, and red pepper. Regarding meat beef, pork, and kid, they were consumed in decreasing order using the same ingredients as in the fish recipes.

**The Nicotera Diet as the Reference Italian Mediterranean Diet**

To objectively assess how close a diet is to its Reference Mediterranean Diet we have set up the Mediterranean Adequacy Index (MAI). The MAI is simply obtained by dividing the sum of total energy percentage from those food groups mostly consumed in a healthy Mediterranean Diet (bread, cereals, legumes, potatoes, vegetables, fresh fruit, nuts, fish, wine, vegetable oils – especially virgin olive oil) by the sum of total energy percentage from those food groups consumed less in a healthy Mediterranean Diet (milk, cheese, meat, eggs, animal fat and margarines, sweet beverages, cakes/pies/cookies, sugar).
Each Mediterranean country should have its own Reference Mediterranean Diet and accordingly for Italy we have proposed the diet of Nicotera subjects examined in 1960 [4].

Table 2 shows the median values of MAI computed from energy percentage of food groups consumed by Nicotera subjects examined for three seasons in 1960. The mean value of MAI can be, in general, higher because of non-normal distribution of dietary data. Also different may be the mean values of MAI computed from food groups values expressed as g/day or g/4.2 MJ because of differences in energy density of some foods.

As an example, we report here the MAI values of diets consumed by the two rural SCS Italian cohorts followed longitudinally from 1965 to 1991. In Crevalcore (Northern Italy) the MAI value, computed from energy percentage of food groups, changed from 2.9 in 1965 to 2.2 in 1991. The corresponding values in Montegiorgio (Central Italy) were 5.6 and 3.9. In both areas, the MAI values were lower than those of the Nicotera subject diet and deteriorated over time, thus indicating a progressive abandoning of the traditional Mediterranean diet particularly in Montegiorgio.

Recently, we have also computed the MAI of diets consumed by random samples of men from 16 SCS cohorts examined around 1960. The MAI is negatively correlated ($R = -0.72$) with 25-year death rate from coronary heart disease [5].

**The Healthy Italian Mediterranean Diet Temple Food Guide**

On the occasion of the International Conference on European Mediterranean Diets held in Rome at the Medical School at the University of Rome Tor Vergata on January 20, 2003, we presented the Healthy Italian Mediterranean Diet Temple

<table>
<thead>
<tr>
<th>Age class</th>
<th>Males</th>
<th>Females</th>
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<tr>
<td></td>
<td>n subjects</td>
<td>MAI</td>
</tr>
<tr>
<td>13–19 years</td>
<td>35</td>
<td>8.0</td>
</tr>
<tr>
<td>20–39 years</td>
<td>43</td>
<td>6.3</td>
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<tr>
<td>40–59 years</td>
<td>64</td>
<td>7.2</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>18</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Food Guide (HIMDFG), to clearly provide the message of the healthy Mediterranean diet essence. The idea of the Temple came from the Simopoulos paper on ‘The Mediterranean Food Guide’ [6].

The development of the Greek-Roman Temple was based on the Nicotera diet of heads of families examined in 1960, which was set up as the Reference Italian Mediterranean Diet for adults. In the three wide steps at the base of the Temple there are written in upward order the following sentences: most healthy lifestyle, energy intake = energy expenditure, virgin olive oil and wine. On the big left lateral column it is written: brown bread, cereals and in smaller characters, potatoes. While on the big right column it is written: vegetables, fresh fruit and in smaller characters, nuts. In the two smaller central columns the words legumes and fish are written. All the above food groups are prevalently consumed in a healthy Mediterranean diet. On the metopes in a progressive order, the words of food groups less prevalently consumed in a healthy Mediterranean diet (milk and dairy products, meats, eggs, fats, cakes, sugar) are written. On the tympanum the word ‘Moderation’ which is a basic characteristic of a healthy Mediterranean diet dominates. On the Temple, we preferred to indicate food groups using words instead of misleading figures or drawings as in the overly used and misleading Pyramid.

The HIMDFG, after appropriate modifications related to food availability, life habits and cultural traditions can be adapted to other populations.

Conclusions

The Nicotera diet of heads of families is a well balanced diet. All nutrients meet, in general, the national reference values. Very high are the intakes of antioxidant vitamins and food components, and folate. The ratios of various classes of fatty acids are more than satisfactory. The very low prevalence of myocardial infarction, hypertension and obesity observed in Nicotera men can be considered the biological answer to their diet; for this reason it was chosen as the Reference Italian Mediterranean Diet. Consequently, the MAI of the Nicotera diet can be considered an advisable value.

Then, as we have already said, the Nicotera diet is practically similar to the diet of SCS cohort of men examined in Corfu (Greece) in 1960. The MAI value of the Corfu diet computed from food groups expressed as g/day is 10.7. The MAI of men examined in Nicotera computed in the same way is 8.2. In Corfu as in Nicotera the prevalence of myocardial infarction in 1960 was low (3 cases out of 529 men) as also hypertension, overweight and obesity. In Corfu the coronary heart disease death rate per 1,000 in 25 years was in the same range of cohorts from Japan, Crete, and Dalmatia, with the following MAI values:
4.4 (Crete cohort), 5.2 (Dalmatia cohort), 8.3 (Ushibuka-Japan cohort), 11.6 (Tanushimaru-Japan cohort).

However, the Mediterranean diets followed by the SCS cohorts and retained healthy from epidemiological confirmation have not to be considered as food suppliers only, but they should be set into the life style context of those populations at that time.

In the above populations the sociocultural meanings related to foods have changed considerably over the past generation. Accordingly, appropriate adaptations taking into account these new socioeconomic realities are needed.

References


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Wine and Health: Evidence and Mechanisms

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Epidemiological observations provide us valuable insights in the role played by the environment on human health. The observations lead to hypotheses which necessarily have to be confronted in the laboratory. This sequence is apparent in the development of our present ideas related to wine and health. The epidemiological work is not finished and much remains to be evaluated experimentally.

Epidemiological Evidence

Epidemiological studies show that moderate alcohol consumption, particularly wine, is associated with decreased risk in all-cause mortality, especially ischemic heart disease death as well as other chronic diseases, and a longer life [1, 2]. The shape of the correlation is generally described as a J-shaped curve in which moderate drinkers (two drinks per day) of any kind of alcohol have a decreased risk of coronary heart disease relative to non-drinkers, whereas heavy drinkers have an increased risk of infarction and stroke.

Moderate drinkers, male or female, show a 30–40% decrease in risk of coronary heart disease mortality, and 10–20% decrease in mortality from all causes. On cardiovascular disease a reduction which might reach 60% in morbidity and mortality has been reported [3–8].

The studies and discussions held on the so called ‘French Paradox’ give wine a special position. It is a characteristic component of the Mediterranean diet and might account for the lower incidence of coronary heart disease among Mediterranean populations [9–10]. Renaud and Ruf [10] show that the correlation
among coronary deaths and various foods, in 21 countries, is stronger for wine 
\((-0.87, p < 0.001)\) than for other components like vegetables or vegetable fats; 
at the same time they found a positive correlation with milk-fat products \((0.66, 
p < 0.001)\). Thus, wine would exert a more marked effect than that of fruits and 
vegetables, also rich in antioxidants. The same general conclusions were 
reached for alcohol, most particularly wine, in a study which involved countries 
with similar economic development [11].

Gronbaek and collaborators in the Copenhagen City Heart Study on 6,051 
men and 7,234 women, 30–79 years old, found that wine, but not beer or spirits, 
was associated with a decrease in cardiovascular, cerebrovascular, and all 
causes mortality [12]. In this study, 3 to 5 drinks per day led to reduction in car-
diovascular mortality by 47% in the wine drinkers, and also mortality by other 
causes was 50% lower. This work is in contrast to others in which not only wine, 
but also other alcoholic beverages are considered to be responsible for the ben-
eficial effects [13]. A more recent work by Renaud and collaborators on 34,014 
middle-aged men from eastern France, 77% of them wine drinkers, led to the 
conclusion that moderate consumers \((2–5 \text{ glasses per day})\) have a 24–31% 
reduction in all-cause mortality, attributed to cardiovascular disease and cancer 
[6, 14]. The results also showed that the protective effect of a moderate intake of 
wine on all-cause mortality is observed at all levels of blood pressure and serum 
cholesterol.

The specificity of wine for lowering the risk of all-cause mortality and 
cancer has been confirmed by Gronbaek and collaborators [15]. It was only in 
wine drinkers that the all-cause mortality was lowered by more than 20% for an 
intake of up to 3 drinks per day. They also found that it was only wine but not 
spirits or beer that reduced cancer mortality by up to 20% \((3 \text{ glasses of 
wine/day})\). As for cancer, the subsequent question was to evaluate on what types 
of cancer wine may have protective effects. Gronbaek and collaborators have 
already shown that wine drinking does not increase the risk of upper digestive 
tract cancer as compared to beer or spirits [16].

Moderate wine or alcohol consumption is also beneficial for conditions 
associated with aging, and a better cognitive performance and lower risk of 
dementia have been described [17, 18]. However, some studies showed a differ-
ence according to the type of alcohol. In the Canadian Study of Health and 
Aging, the follow up of 4,088 persons for 5 years showed a 31% reduction in 
the risk of developing dementia in alcohol drinkers compared to non drinkers 
[19]. In addition, the risk was lower in wine drinkers \((\text{odds ratio (OD) } 0.49;
95\% \text{ confidence interval (CI) } 0.28–0.88)\) than in beer or spirit drinkers \((\text{OR }
0.84; 95\% \text{ CI } 0.51–1.41 \text{ and OR } 0.78; 95\% \text{ CI } 0.52–1.19), \text{ respectively.} \)

In another cohort study (the Copenhagen City Heart Study), the alcohol con-
sumption recorded in 1976 in a cohort initially designed to study cardiovascular
diseases has been linked to the risk of getting dementia in the period 1990–1994 [20]. Compared to non drinkers, the risk of developing dementia was significantly lower among occasional wine drinkers (OR 0.43; 95% CI 0.23–0.82), in weekly drinkers (OR 0.33; 95% CI 0.13–0.86), but nonsignificant in daily drinkers (OR 0.57; 95% CI 0.15–2.11). However, an increased risk was observed for beer (OR 2.28; 95% CI 1.13–4.60 in occasional drinkers, OR 2.15; 95% CI 0.98–4.78 in weekly drinkers and OR 1.73; 95% CI 0.75–3.99 in daily drinkers) or for spirits (OR 0.81; 95% CI 0.42–1.57 in occasional drinkers, OR 1.65; 95% CI 0.74–3.69 in weekly drinkers and OR 1.12; 95% CI 0.43–2.92 in daily drinkers).

In Bordeaux (France), a population-based prospective study found that subjects drinking 3–4 standard glasses of wine per day (>250 and up to 500 ml), categorized as moderate drinkers, the crude OR was 0.18 for the incidence of dementia (p < 0.01) and 0.25 for Alzheimer’s disease (AD)(p < 0.03), as compared with the non-drinkers. After adjusting for age, sex, education, occupation, baseline cognitive performances and other possible confounders, the ORs were, respectively, 0.19 (p < 0.01) and 0.28 (p < 0.05). In the 922 mild drinkers (<1–2 glasses per day) there was a negative association only with AD, after adjustment (OR 0.55; p < 0.05). The inverse relationship between moderate wine drinking and incident dementia was explained neither by known predictors of dementia nor by medical, psychological or sociofamilial factors [21–22].

A recent cohort of elderly persons from New York City included 980 community-dwelling individuals aged 65 and older without dementia at baseline and with data on alcohol intake. The subjects were recruited between 1991 and 1996 and followed annually. After 4 years of follow-up, 260 individuals developed dementia (199 AD, 61 dementia associated with stroke). After adjusting for age, sex, apolipoprotein E (APOE)-epsilon 4 status, education, and other alcoholic beverages, only intake of up to three daily servings of wine was associated with a lower risk of AD (OD 0.55; 95% CI 0.34–0.89). Intake of liquor, beer, and total alcohol was not associated with a lower risk of AD. Stratified analyses by the APOE-epsilon 4 allele revealed that the association between wine consumption and lower risk of AD was confined to individuals without the APOE-epsilon 4 allele [23].

Type II diabetes mellitus (NIDDM) is another condition that correlates with aging and in which oxidative stress plays a pathogenic role. Moderate alcohol consumers have a decreased risk of diabetes [24]. Moderate wine consumption correlates with decreased risk of macular degeneration, an age-related disorder [25].

Moderate wine drinkers appear to be at lower risk of becoming heavy and excessive drinkers as well as developing alcoholic cirrhosis [26, 27]. This study suggests that a person who prefers beer is more likely to become a heavy or an
excessive drinker than a person who prefers wine. Among men, moderate drinkers who included wine in their weekly alcohol intake had significantly lower risks of becoming heavy or excessive drinkers as compared to those who did not drink any wine. Women who included beer in their alcohol intake showed increased risk of heavy and excessive drinking compared to non-beer drinking women. Further they found that the risk of developing cirrhosis in wine drinkers (more than 30% wine in their total alcohol intake) was less than 50% of the risk in non-wine drinkers for any given level of total alcohol intake, while beer and spirits drinking did not modify the relation between total alcohol intake and risk of developing cirrhosis.

Other studies have reported relations between beer drinking and high-risk behaviors such as frequent heavy drinking and other alcohol-related problems, while wine drinking seems to be considered ‘the beverage of moderation’ [28–30].

There is a large variety of other positive phenomena associated with moderate wine consumption. Wine has been described as a healthy beverage for centuries, a property mainly associated with its capacity of killing or stopping the growth of microorganisms. This has been observed for many bacteria and there is an interesting report on the capacity of wine to control oyster-borne hepatitis A [31]. A particularly intriguing property of wine is that in contrast to beer and hard liquor, it does not favor an increase in the waist-to-hip ratio, a parameter strongly associated with cardiovascular risk [32]. The risk of kidney stones also decreases in moderate wine consumers, in studies that simultaneously show that fruit juices, particularly grapefruit juice, increase the risk [33].

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**Fig. 1.** Favorable changes in CV risk factors shown in moderate wine drinkers.
Deleterious Effects of Alcohol Consumption

When dealing with the negative effects of alcoholic beverage consumption it is necessary to establish very clearly the levels of consumption that correspond to a statement such as ‘alcohol consumption leads to cardiovascular morbidity, to cirrhosis, to birth defects, to cancer, to hypertension, and to migraine’. Indeed, the very concept of moderate consumption stems, among others, from studies that identify the consumption levels associated with minimal risk. There have been discussions on the meaning of the increased cardiovascular risk of non-drinkers, yet the meaning of the increased risk for heavy drinkers is straightforward but often forgotten by those who stress cirrhosis as the consequence of excessive drinking. A positive correlation has been observed for hemorrhagic stroke and drinking; however, this effect has to be confronted with the higher frequency of obstructive events that do benefit from moderate consumption [1].

There are a number of cancers that are referred to as alcohol-related; cancers of the mouth, pharynx, larynx, esophagus, and sometimes stomach and liver. They are associated with very heavy drinking, with alcohol abuse; generally, they correlate with heavy smoking and heavy drinking, and do not show increased frequency in light-to-moderate drinkers. Gronbaek and collaborators in a population cohort study observed the association between alcohol intake and cancer of the upper digestive tract [16]. Their conclusion was that a moderate intake of wine probably does not increase the risk, whereas moderate intake of beer or spirits increases the risk considerably. In an editorial commentary, the possible role of nitrosamines is emphasized. For lung cancer, in three prospective Danish studies, it was found that a high consumption of beer and spirits is associated to an increased risk of lung cancer, whereas wine intake apparently protects [34]. For mammary cancer no clear demonstration of alcohol beverages as a risk factor was found [35]. Yet, a significant correlation for women drinking 3 or more glasses per day has been described [4] and in Mediterranean populations, with a much lower breast cancer incidence than in USA, a doubling in the frequency of women drinking two to three glasses per day has been found [36]. The conclusion is that with the possible exception of breast cancer, moderate drinkers are not at increased risk of any type of cancer [37].

Wine should be considered as a healthy component of the diet in many cultures. On the whole, with the evidence available, moderate wine consumption should be considered as safe, with the sole exception of activities requiring a maximum degree of alertness. Further research is required to examine the hypothesis that genetically predisposed people might become addicted to alcohol through moderate consumption [38].
**Epidemiological Conclusions**

Today the main concern for most epidemiologists is not the benefits, which are not contested, but the potential negative consequences associated with moderate drinking. Additionally, some epidemiologists reject a difference among wine and other alcoholic beverages. The differences are attributed to lifestyle differences among those who prefer one type of alcoholic beverage over another thus making it exceedingly difficult to determine whether the differences in apparent health effects are actually related to the beverage itself. Drinkers of any type of wine have a lower mortality risk than do beer or liquor drinkers, yet it remains unclear whether this reduced risk is due to nonalcoholic wine ingredients, drinking patterns or associated traits [39].

**Mechanisms**

*Biology of Wine Constituents: Effects of Alcohol and Polyphenols*

After the epidemiologists recognized the potential beneficial role of wine, the challenge was to find the biological basis of the phenomena. So far the research has focused on alcohol and on phenolics as constituents of wine, and on several biological targets, recognized as cardiovascular risk factors, that would be modified in the alcohol consumers.

**Alcohol**

Alcohol intake modifies plasma lipids and hemostatics factors. The health related biological effects observed in response to ethanol consumption are: increased high density lipoprotein (HDL) cholesterol levels, decreased fibrinogen, increased plasminogen and tissue-type plasminogen activator (t-PA), endothelial nitric oxide synthase (eNOS) stimulation, and a direct cardioprotective effect on the heart.

**Lipid Factors**

A high concentration of serum cholesterol is a major risk factor for coronary heart disease (CHD). This risk is mediated through the major cholesterol-carrying lipoprotein of serum, low-density lipoprotein (LDL). Additionally, decreased HDL cholesterol levels constitute a central risk factor for CHD [40].
At present there is consensus on the positive association between alcohol intake and plasma HDL cholesterol level. From some studies it is estimated that half of the beneficial effects of moderate alcohol intake are due to an increased HDL cholesterol concentration. Rimm et al. [41] in a meta-analysis reported that an experimental dose of 30 of ethanol a day increased HDL cholesterol by 3.99 g/dl (95% CI 3.25–4.73). There is also evidence that alcohol dehydrogenase genotype and alcohol metabolic rate do not modify the effects of alcohol on plasma HDL concentration [42].

One of the main antiatherogenic functions of HDL is reverse cholesterol transport. HDL removes unesterified, or ‘free’ cholesterol from peripheral tissues, after which much of the cholesterol is esterified by the plasma enzyme lecithin:cholesterol acyltransferase. Subsequently, HDL cholesterol is efficiently delivered directly to the liver and steroidogenic tissues via a selective uptake pathway [43]. Moderate alcohol intake increases serum HDL cholesterol level and stimulates cellular cholesterol efflux [44]. Exercise also increases serum HDL cholesterol level as improves reverse cholesterol transport [45].

Human serum paraoxonase, an esterase, is associated with HDL and has been shown to reduce the susceptibility of LDL to lipid peroxidation [46]. As the oxidative modification of LDL plays a central role in the initiation and acceleration of atherosclerosis, increased serum levels of paraoxonase in HDL diminish the atherogenic effect of LDL [47]. There is evidence that light drinking upregulates, whereas heavy drinking downregulates paraoxonase activity and its expression, irrespective of its genetic polymorphism in rats and humans [48].

The HDL receptor SR-BI (scavenger receptor class B type I) mediates the selective uptake of plasma HDL cholesterol by the liver and steroidogenic tissues. As a consequence, SR-BI can influence plasma HDL cholesterol levels, HDL structure, biliary cholesterol concentrations, and the uptake, storage, and utilization of cholesterol by steroid hormone-producing cells [49]. This receptor also facilitates efficient transfer of vitamin E (α-tocopherol) from HDL to cultured cells. In SR-BI-deficient mutant mice, relative to wild-type control animals, there was a significant increase in plasma α-tocopherol levels. This increase in plasma α-tocopherol was accompanied by a significant decrease (65–80%) in the α-tocopherol concentrations in bile and several tissues including ovary, testis, lung and brain but not in the liver, spleen, kidney or white fat. These data show that SR-BI plays an important role in transferring α-tocopherol from plasma lipoproteins to specific tissues. Defective tissue uptake of lipoprotein α-tocopherol in SR-BI-deficient mice may contribute to the reproductive and cardiovascular pathologies exhibited by these animals [50]. Oxidative stress regulates the expression of SR-BI receptor, oxidized LDL (oxLDL) decreased SR-BI expression in a dose- and time-dependent manner and the ability of oxLDL to decrease SR-BI expression was dependent on the degree of
LDL oxidation. OxLDL decreased both $[^{14}\text{C}]$cholestereryl oleate/HDL uptake and efflux of $[^{14}\text{C}]$cholesterol to HDL in a time-dependent manner [51].

Sex is another factor associated with decreased risk of developing cardiovascular disease. Decreased risk is found in premenopausal women, together with elevated HDL levels. HDL and estrogen stimulate eNOS and the production of nitric oxide (NO) which has numerous protective effects in the vascular system, including vasodilation, reduced leukocyte adhesion, and anti-inflammatory effects [52]. HDL isolated from premenopausal women, or postmenopausal women receiving estradiol replacement therapy, stimulated eNOS; whereas HDL isolated from postmenopausal women or men had minimal activity. HDL-associated estradiol is capable of stimulating eNOS in an SR-BI-dependent manner [53] leading to a new paradigm that involves eNOS, for the explanation of the cardiovascular effects of HDL and estrogens.

**Hemostasis Factors**

The effects of alcohol on the coagulation and thrombolytic processes are not sufficiently studied. In general, haemostatic factors in moderate alcohol drinkers show a more thrombolytic profile. Consistent evidence has been provided linking moderate alcohol intake with lower fibrinogen levels. Rimm and collaborators, in a meta-analysis, reported that 30 g of alcohol a day was associated with a 7.5-mg/dl decrease in fibrinogen concentration [41].

Numerous studies have investigated the effect of alcohol on platelet aggregation. All tend to demonstrate that alcohol added in vitro leads to a significant decrease of platelet aggregation induced by thrombin, collagen, epinephrine and ADP [54]. Some human studies have shown that physiological concentrations of ethanol inhibit platelet aggregation in humans as well as in animals in response to several agonists, like collagen, thrombin, ADP and platelet-activating factor, in others this inhibition was not found [55–57]. Therefore, aggregation studies are not consistent, a finding attributed to the difference on assay methods used in vitro or ex vivo to measure platelet aggregation [41].

A rebound phenomenon of hyperaggregability is observed after acute alcohol consumption but not after wine consumption. The apparent protection afforded by wine has been replicated in animals with grape phenolics added to alcohol. This rebound phenomenon could explain the ischemic strokes or sudden deaths known to occur after episodes of drunkenness [58].

Fibrinolysis is increased in alcohol drinkers. Rimm and collaborators reported that 30 g of alcohol a day was associated with a 1.25-ng/dl increase in t-PA antigen concentration, and a 1.47% increase in plasminogen concentration [41].
Preincubation of human monocytes with low alcohol followed by incubation in the absence of alcohol resulted in an increase in t-PA and urokinase-type plasminogen activator (u-PA) expression [59]. And in mice, ethanol induces a significative increase in clot lysis, increases expression for t-PA and u-PA and decreases expression for PAI-1 (plasminogen activator inhibitor) [60].

We carried out an intervention study in humans to evaluate the effect of a Mediterranean diet (MD), an Occidental diet (OD) and their supplementation with red wine, on biochemical, physiological and clinical parameters related to atherosclerosis and other chronic diseases. For 3 months, two groups of 21 male volunteers each received either a MD or an OD; during the second month, red wine was added isocalorically, 240 ml/day. At 0, 30, 60 and 90 days, clinical, physiological and biochemical evaluations were made. We found that MD, compared with OD, was associated with an improvement in hemostatic cardiovascular risk factors: lower plasma fibrinogen and factors VIIc and VIIIc, higher levels of protein S and longer bleeding time. Red wine supplementation of both diets resulted in further decrease in plasma fibrinogen and factor VIIc, and in increases in PAI-1 and t-PA antigen. Red wine was also associated with an increase in antithrombin III (ATIII) but only in individuals on MD. Overall, these findings provide evidence that both MD and red wine have independent but complementary benefits with regard to cardiovascular risk. They decrease thrombosis [57, 61].

The antithrombotic effect of red wine is attributed in part to alcohol, but mainly to wine phenols [62]. Alcohol and polyphenols are both involved, as discussed below.

**Other Alcohol Effects**

In rats, moderate alcohol consumption induced significant oxidative stress in the heart which was then reflected into induction of the expression of several cardioprotective oxidative stress-inducible proteins including heat-shock protein (HSP) 70. So alcohol by itself imparts cardioprotection by adapting the heart to oxidative stress, with a reduction of myocardial ischemic reperfusion injury, myocardial infarct size and cardiomyocyte apoptosis [63–64].

**Polyphenols**

*Polyphenol Bioavailability*

The total amount of phenols found in a glass of red wine is on the order of 200 mg versus about 40 mg in a glass of white wine. Wine contains many
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phenolic substances, most of which originate in the grape berry. Wine phenolics include the non-flavonoids: hydroxycinnamates, hydroxybenzoates and the stilbenes; plus the flavonoids: flavan-3-ols, the flavonols, and the anthocyanins [65]. These phenols are partly absorbed from the gastrointestinal tract in animals and humans, metabolized in the intestinal cells and in the liver and excreted by the urine [66, 67]. Metabolites are glucuronide or sulfate conjugates and methylated conjugates [68]. While polymeric condensed tannins and pigmented tannins constitute the majority of wine phenolics, their large size precludes absorption so their health effects are likely restricted to the gut [69]. The health effects of dietary polyphenols might be explained by both intact compounds and their metabolites formed either in the tissues or in the colon by the microflora [70–73].

**Polyphenol Effects**

Polyphenols and their metabolites have many biological activities. They present antioxidant, antithrombotic, anti-inflammatory and anticarcinogenic properties. Their mechanism of action can be explained by a direct antioxidant effect and by modification of some protein properties than produce changes in enzymes activities (inhibition or activation) and gene expression. Some of these effects are the following:

**Antioxidant**

Polyphenols are recognized as strong antioxidant and oxygen free radical scavengers [74, 75]. Red wine and red wine phenols increase in vitro the resistance of human LDL against oxidative modification [76]. Several studies report an increased resistance to oxidative modification of human LDL after long-term consumption of red wine and red wine polyphenols [77, 78]. In contrast, other studies report that red wine and a phenolic extract from red wine do not affect LDL oxidizability [79, 80]. In an acute ingestion study in humans, post-prandial LDL obtained after a meal consumed with ethanol was more susceptible to metal-catalyzed oxidation than the homologous baseline LDL. On the contrary, postprandial LDL obtained after a meal consumed with wine, was as resistant as or more resistant to lipid peroxidation than fasting LDL [81]. Also the experimental meal taken with wine provoked a significant increase in the total plasma antioxidant capacity and in the plasma concentration of α-tocopherol and SH groups. In another study, the supplementation of a meal with grape seed
extract reduced the postprandial oxidative stress by decreasing the oxidants and increasing the antioxidant levels in plasma and, as a consequence, enhancing the resistance to oxidative modification of LDL [82].

In our intervention study in humans described earlier, to evaluate the effect of a MD, an OD and their supplementation with red wine, we found that the total antioxidant reactivity (TAR) was significantly higher in volunteers on MD compared to those on OD and wine intake increased TAR significantly in both groups. The OD group showed higher levels of oxidative DNA damage, measured as 8-hydroxydeoxyguanosine (8-OHdG) levels in blood leukocyte DNA and elevated protein damage markers, when compared with the MD group. Wine intake significantly decreased 8-OHdG in both diets, particularly in the OD, where the 8-OHdG levels decreased to values similar to those in the MD plus wine group. Wine intake induced an increase in plasma and urinary polyphenols. The results presented support the following conclusions: an OD induces oxidative stress; a diet rich in fruits and vegetables enhances antioxidant defenses; wine supplementation to an OD or a MD improved antioxidant defenses in both groups and counteracted the oxidative damage produced by the OD [83, 84].

Antithrombosis

In in vitro and ex vivo experiments, polyphenols enhance the generation of NO, a platelet inhibitor and vasodilator [85, 86]. Some studies were also performed to investigate the effect of wine polyphenols on experimental thrombosis in rats. In these studies, NO was evaluated as a possible mediator of the effects [87]. Supplementation for 10 days with red wine or alcohol-free red wine, but not white wine or alcohol, induced a marked prolongation of bleeding time (BT) (258 ± 13 vs. 132 ± 13 s in controls; p < 0.001) a decrease in platelet adhesion to fibrillar collagen (11.6 ± 1.0 vs. 32.2 ± 1.3%; p < 0.01) and a reduction in thrombus weight (1.45 ± 0.33 vs. 3.27 ± 0.39 mg; p < 0.01). The effects of red wine were prevented by the NO inhibitor, L-NAME. In rats with diet-induced hyperlipidemia, alcohol-free red wine supplementation for one month reversed the prothrombotic effect of the diet, measured as delay in the thrombotic occlusion of an artificial prosthesis inserted into the abdominal aorta, without affecting the increased cholesterol and triglyceride levels [62]. Plasma antioxidant capacity measure as TRAP values, were significantly higher in animals receiving alcohol-free wine. These studies provide evidence that red wine modulates primary hemostasis and prevents experimental thrombosis in rats, independent of its alcohol content, by a NO-mediated mechanism.
Anti-Inflammation

Chemotaxis and accumulation of leukocytes in the arterial wall are considered to be critical events in the inflammation associated with atherosclerosis. Flavonoids were reported to inhibit adhesion of immune cells to endothelial cells. They downregulate gene expression of inflammatory mediators [88, 89].

Anticarcinogenesis

It has been reported that dehydrated-dealcoholized red wine (wine solids) when consumed as part of a precisely defined complete diet, delays tumor onset in transgenic mice that spontaneously develop externally visible tumors without carcinogen pretreatment [90]. Particular phenol components of wine such as resveratrol and quercetin have shown an inhibitory effect on carcinoma cell proliferation [91, 92]. Other studies have shown that red wine contains phytochemicals that inhibit aromatase activity in vitro and suppress aromatase-mediated breast tumor formation in vivo [93, 94].

Some Protein Polyphenol Interactions

Polyphenols, especially flavonoids, have numerous effects caused by their interaction with different proteins. Middleton and collaborators reviewed the mammalian enzyme systems that are target of flavonoids [89]. Recent examples of these are the inhibition of aromatase activity [94] and angiotensin-converting enzyme (ACE) [95] and activation of sirtuin, an enzyme associated with longevity [96].

Flavonoids and their in vivo metabolites may exert modulatory actions in cells through actions at protein kinase and lipid kinase signalling pathways. They have been reported to act on phosphoinositide 3-kinase (PI 3-kinase), Akt/protein kinase B (Akt/PKB), tyrosine kinases, protein kinase C (PKC), and mitogen-activated protein kinase (MAP kinase) signaling cascades. Inhibitory or stimulatory actions at these pathways are likely to affect cellular function by altering the phosphorylation state of target molecules and by modulating gene expression [97].

Endothelial Function

Normal endothelium-dependent vasomotor function or endothelial function (EF) is a physiological response, mediated by NO, which appears to play a key role in the prevention or reduction of the risk of atherosclerosis. Endothelial
dysfunction is associated with risk factors for coronary heart disease such as hypercholesterolemia, hypertension, cigarette smoking, hyperhomocysteinemia and diabetes mellitus. Red wine polyphenols activate tyrosine kinases, increase cytosolic free calcium and stimulate a $\text{Ca}^{2+}$-dependent release of NO in bovine aortic endothelial cells [98].

Moderate red wine intake improves endothelial function evaluated as flow-mediated dilation of the brachial artery [99]. Recalling our study on diets and wine supplementation we showed that in the absence of wine, there is a reduction of endothelial function with OD when compared to the MD ($p = 0.014$). This loss of endothelial function is not seen when both diets are supplemented with wine ($p = 0.001$). These effects are attributed to oxidative stress associated with an OD, and to the elevated plasma antioxidant capacity associated with wine consumption and the MD. Wine polyphenols protect NO from oxidation.

Acute red wine consumption produces an increase in coronary flow-velocity reserve in human volunteers. This finding suggests that some polyphenols may have potent vasorelaxing effects on coronary microvessels during hyperemia [100].

Red wine polyphenol extract enhances eNOS expression and increases NO production in human umbilical vein endothelial cells (HUVECs) [101, 102].

Red wines strongly inhibit the synthesis of endothelin-1 (ET-1), a vasoconstrictor peptide that decreases endothelial function. Wine polyphenols decreased ET-1 release and transcription in bovine aortic endothelial cells [103]. ET-1 release induced by oxLDL is inhibited by quercetin [104].

**Conclusion**

The experimental results presented in this review do not support the frequently held conclusion that ethanol is the main active component, independent of antioxidants, when considering the biological consequences of moderate alcoholic beverage consumption. Quite clearly, effects such as those shown for hemostasis, or those to be expected when HDL levels increase, are related to polyphenols or to an efficient antioxidant system, respectively, which wine could provide. For example, if the new paradigm to explain the protective role of elevated HDL levels requires the participation of eNOS, it is obvious that antioxidants will be necessary to protect the NO generated, a well-known requirement for NO-mediated effects. This consideration could also lead to the idea that ethanol, consumed together with antioxidant-rich foods, would be biologically safer than drinking alone. Equally, the different results obtained in epidemiological studies that consider alcohol consumption could well be related to the dietary habits of those populations, in particular the type, quantity and opportunity of antioxidant-rich food consumption, as well as pro-oxidant food consumption.
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Implications of Food Regulations for Novel Foods

Safety and Labeling

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Novel Foods, What Are They?

Novel or functional foods have been difficult to define in a legal sense. The European Union has published regulations for novel foods, but the main thrust of these rules is to control newer foods derived from present biotechnology developments. Despite the difficulty of precise definitions, there appears to be a common public understanding of the concept that many foods may contain beneficial (or harmful) substances in addition to the common nutrients of digestible carbohydrates, proteins, fats, ethanol, and essential vitamins and minerals. Both from the public point of view, and as a result of science-based experimental test systems, the concept of novel or functional foods or components is that such foods or components can have a beneficial effect on bodily functions and structures. In some countries well-founded claims for such effects have been allowed, while in other countries no claims have been permitted.

There is no current legal definition for ‘functional food’ in most countries and foods of this type are regulated under existing food or related legislation in countries where functional claims are made. In many countries regulations exist for conventional foods, foods for special dietary use, dietary supplements, and medical foods for use under the supervision of a physician for management of specific diseases. In the European Union there are regulations for ‘novel foods’ which in some cases could also be considered as functional foods. Each of these categories have regulations which govern which claims can be made, and either specific rules or guidelines for the types of data which are needed to establish...
the validity of any claims on the labels of foods, or in advertising. In most countries there are also clear legislative provisions for drugs, and certain claims for disease treatment can make a food product a drug in the legal sense and lead to severe regulatory consequences, even if that was not intended by the promoter making the claim for a food.

At the international level there has been discussion about functional foods, novel foods, and labeling and claims for these types of foods and foods for special dietary use. The FAO/WHO Codex Alimentarius Commission has adopted a General Standard for the Labeling and Claims for Prepackaged Foods for Special Dietary Use, and General Guidelines on Claims, Nutrition Labeling, and Nutrition Claims, and all of these should be taken into consideration in determining if a claim can be made, and the nature of the claim [26–28].

As discussed below, there are rules in the European Union, Australia and New Zealand that cover novel foods and foods derived from recombinant DNA techniques that are somewhat overlapping in the EU, while they are separate in Australia and New Zealand. At the Codex international level foods derived from biotechnology are being actively discussed, and a number of FAO/WHO Expert Consultations have been held to better define basic concepts, examine the quality and safety aspects of these foods, including possible problems of allergenicity, and related topics. The FAO/WHO Expert Consultations have endorsed the approach used in the USA of ‘substantial equivalence’ for foods derived from biotechnology. This has meant up to now that if the nutritional and other quality and safety aspects were substantially equivalent to similar foods that were not produced using recombinant DNA techniques that specific labeling was not required. The Codex Committee on Food Labeling and the Codex Task Force on Foods Derived from Biotechnology are actively discussing international aspects of labeling and a general standard for foods derived from biotechnology, but no final recommendations have been made for adoption by the 165 member country members that comprise the Codex Alimentarius Commission.

Novel or Functional Food Claims

Foods are usually defined as articles for food and drink, while drugs are usually defined as articles intended for use in the diagnosis, cure, treatment, or prevention of disease. In the past there was no middle ground between foods and drugs, and health-related claims were not permitted on foods. However, developments in several countries and at the international level have tended to take into account newer features of foods and how they are produced and processed, research into the possible beneficial or protective effects of foods
and their ingredients. Because of this, regulatory authorities and new legislation in some countries have opened up the possibility of properly substantiated health-related claims for foods and their ingredients.

This is an evolving area, in particular with the concept of ‘novel foods’ and ‘functional foods’, and it has been a difficult task to substantiate claims, and to maintain a good and constantly stronger scientific database to support claims. In the United States, one of the first claims on a food product was on an all bran cereal product stating that increased intake of wheat fiber could reduce the risk of colon cancer, and citing the US National Cancer Institute as the authority for this claim. Subsequent nutritional and dietary research has not fully supported this claim. Claims about increased intake of Vitamin A and cancer protection have also been put in doubt due to a trial of smokers in Finland where results showed that higher intakes of vitamin A actually increased the incidence of lung cancer. Therefore, in making claims about the functionality of foods or their ingredients, it is necessary to use caution, since a disproved or doubtful claim can lead to regulatory problems or loss of market share for the product in question, and other products of the same company.

Research into phytochemicals, probiotics and prebiotic substances that do not have traditional nutritive value has shown a wide range of possible functions for foods. Phytochemicals such as indoles, thiocyanates, sulfur containing compounds, allium compounds, isoflavones and phenols have been shown to have some possible beneficial or protective effects. Probiotics are microorganisms such as lactobacilli and bifidobacteria, which can modify the bacterial flora in the intestine and enhance certain immune functions, possible promote absorption of certain essential minerals, and protect against some diseases of the intestine and colon. Prebiotics are oligosaccharides, which may be instrumental in modifying the risks on intestinal disorders, osteoporosis, cancer and heart disease. In each of these areas, considerable additional research is under- way, and firmly establishing the beneficial effects of any of these substances has been shown to be difficult. Table 1 includes a list of some examples of foods or food ingredients that have shown possible benefits.

**Other Product Classifications and Their Regulation**

As mentioned above, in addition to foods sold as such, there are also foods for special dietary use for the general public, novel foods, dietary supplements, and medical foods, also called neutraceuticals. Each of these product classes has a more specific definition than do ‘functional foods’, and the regulation of their marketing is more structured in many countries.
### Table 1. Examples of functional components* [taken from ref. 21]

<table>
<thead>
<tr>
<th>Class/components</th>
<th>Source*</th>
<th>Potential benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotenoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-carotene</td>
<td>Carrots</td>
<td>• Neutralizes free radicals which may cause damage to cells</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>Various fruits, vegetables green vegetables</td>
<td>• Neutralizes free radicals</td>
</tr>
<tr>
<td>Lutein</td>
<td></td>
<td>• Contributes to maintenance of health vision</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Tomatoes and tomato products (ketchup, sauces, etc.)</td>
<td>• May reduce risk of prostate cancer</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>Eggs, citrus, corn</td>
<td>• Contributes to maintenance of health vision</td>
</tr>
<tr>
<td>Collagen hydrolysate</td>
<td>Gelatin</td>
<td>• May help improve some symptoms associated with osteoarthritis</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insoluble fiber</td>
<td>Wheat bran</td>
<td>• May reduce risk of breast and/or colon cancer</td>
</tr>
<tr>
<td>Beta-glucan**</td>
<td>Oats</td>
<td>• Resuces risk of cardiovascular disease (CVD)</td>
</tr>
<tr>
<td>Soluble fiber**</td>
<td>Psyllium</td>
<td>• Reduces risk of CVD</td>
</tr>
<tr>
<td>Whole grains**</td>
<td>Cereal grains</td>
<td>• Reduces risk of CVD</td>
</tr>
<tr>
<td>Fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega–3 fatty acids – DHA/EPA</td>
<td>Tuna; fish and marine oils</td>
<td>• May reduce risk of CVD and improve mental, visual functions</td>
</tr>
<tr>
<td>Conjugated linoleic acid (CLA)</td>
<td>Cheese, meat products</td>
<td>• May improve body composition, may decrease risk of certain cancers</td>
</tr>
<tr>
<td>Flavonoids</td>
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</tr>
<tr>
<td>Anthocyanidins</td>
<td>Fruits</td>
<td>• Neutralizes free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Catechins</td>
<td>Tea</td>
<td>• Neutralize free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Flavanones</td>
<td>Citrus</td>
<td>• Neutralize free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Flavones</td>
<td>Fruits/vegetables</td>
<td>• Neutralizes free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Glucosinolates, Indoles, Isothiocyanates</td>
<td></td>
<td>• Neutralizes free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Sulphoraphane</td>
<td>Cruciferous vegetables (broccoli, kale), horseradish</td>
<td>• Neutralizes free radicals, may reduce risk of cancer</td>
</tr>
<tr>
<td>Phenols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>Fruits, vegetables, citrus</td>
<td>• Antioxidant-like activities, may reduce risk of degenerative diseases; heart disease, eye disease</td>
</tr>
<tr>
<td>Ferulic acid</td>
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</tbody>
</table>
The Codex describes foods for special dietary uses as ‘foods which are specially processed or formulated to satisfy particular dietary requirements which exist because of a particular physical or physiological condition and/or specific diseases and disorders and which are presented as such. The composition of these foodstuffs must differ significantly from the composition of ordinary foods of comparable nature, if such ordinary foods exist’. While foods of this nature are obviously intended to be ‘functional’, the specific nature of such products

<table>
<thead>
<tr>
<th>Class/components</th>
<th>Source*</th>
<th>Potential benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plant sterols</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanol ester</td>
<td>Corn, soy, wheat, wood oils</td>
<td>• Lowers blood cholesterol levels by inhibiting cholesterol absorption</td>
</tr>
<tr>
<td><strong>Prebiotic/probiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructo-oligosaccharides (FOS)</td>
<td>Jerusalem artichokes, shallots, onion powder</td>
<td>• May improve gastrointestinal health</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>Yogurt, other dairy</td>
<td>• May improve gastrointestinal health</td>
</tr>
<tr>
<td><strong>Saponins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saponins</td>
<td>Soybeans, soy foods, soy protein-containing foods</td>
<td>• May lower LDL cholesterol; contains anti-cancer enzymes</td>
</tr>
<tr>
<td><strong>Soy protein</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy protein**</td>
<td>Soybeans and soy-based foods</td>
<td>• 25 g per day may reduce risk of heart disease</td>
</tr>
<tr>
<td><strong>Phytoestrogens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoflavones – daidzein, genistein</td>
<td>Soybeans and soy-based foods</td>
<td>• May reduce menopause symptoms, such as hot flashes</td>
</tr>
<tr>
<td>Lignans</td>
<td>Flax, rye, vegetables</td>
<td>• May protect against heart disease and some cancers; lowers LDL cholesterol, total cholesterol and triglycerides</td>
</tr>
<tr>
<td><strong>Sulfides/thiols</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialyl sulfide</td>
<td>Onions, garlic, olives, leeks, scallions</td>
<td>• Lowers LDL cholesterol, maintains health immune system</td>
</tr>
<tr>
<td>Allyl methyl trisulfide, Dithiolthiones</td>
<td>Cruciferous vegetables</td>
<td>• Lowers LDL cholesterol, maintains healthy immune system</td>
</tr>
<tr>
<td><strong>Tannins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proanthocyanidins</td>
<td>Cranberries, cranberry products, cocoa, chocolate</td>
<td>• May improve urinary tract health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May reduce risk of CVD</td>
</tr>
</tbody>
</table>

*Examples are not an all-inclusive list.
**FDA-approved health claim established for component. December 1999.
and the restriction on their uses appear to clearly separate them from other types of possible ‘novel foods’ or ‘functional foods’. The Codex description also implies that newly discovered beneficial effects of traditional foods would not be covered by the Codex description of foods for special dietary uses [26–28].

The European Union regulation on novel foods and novel food ingredients (Regulation EC No. 258/97) applies to genetically modified products, foods and food ingredients isolated from microorganisms, fungi, algae, and plants or animals, except for foods and food ingredients obtained from plants or animals by traditional propagating or breeding practices and having a history of safe food use [4]. Food additives, flavorings, and extraction solvents are exempted from the EU novel food regulation since they are regulated under other EU rules. The EU novel foods regulations are mainly concerned with food safety, are not specific about label claims, and have the thrust of having been prepared to regulate foods and food ingredients derived from biotechnology. Many of the novel foods regulated by EU rules have been developed to fit into the concept of functional foods, and are regulated under the EU novel food regulation at present. However, a lively level of discussion on the concept of functional foods is also underway in Europe and elsewhere and could lead to additional regulation, particularly with regard to health claims.

Dietary supplements such as vitamin and mineral capsules or tablets, and a wide array of other products such as herbal remedies, and even foods that are labeled as dietary supplements have become increasingly popular. In the United States, there is specific legislation that exempts these products from many of the restrictions for foods or drugs contained in the US Food, Drug and Cosmetics Act [1]. Many of these dietary supplement products, and equivalent products sold over the counter in pharmacies in Europe, and perhaps elsewhere, have label claims that are considered by many food regulators as somewhat exuberant, and possibly false or misleading. In the USA, products of this type must bear a label statement that these products have not been approved by the US Food and Drug Administration (FDA) and that the product is not intended for use as a drug [9–11].

Medical foods or neutriceuticals are specially formulated products intended for use under the supervision of a physician for the specific dietary management of a disease or condition. These foods meet distinctive nutritional requirements that are based on recognized scientific principles and are established by medical evaluation. As with foods for special dietary use, medical foods are also intended to be functional and have a direct and beneficial influence on a specific medical condition. In the USA, medical foods do not require pre-market clearance by FDA and there have been some concerns about the quality and efficacy of some of the products that are being marketed as medical foods [12–14].
National Regulatory Systems and Requirements and International Considerations

Since ‘novel foods’ and ‘functional foods’ are not defined or set aside as a specific class of product in most countries, they are regulated under existing law as foods, novel foods, special dietary foods, medical foods, or as drugs, depending on how they are marketed, and the claims that are made for the products in their labeling, or in advertising.

In the United States many products that are being sold as traditional foods have label claims about their beneficial effects when consumed as a part of a varied and balance diet. The 1990 Nutrition Labeling and Education Act (NLEA) [2] required additional labeling about the nutritional content of foods beyond that previously required or recommended under the Food, Drug and Cosmetic Act. The NLEA also allowed for properly substantiated nutrition and health claim on the labels of foods. With regard to health claims, FDA tended to require that marketers of foods with health claims obtain prior approval of the claim and present evidence of ‘significant scientific agreement’ among qualified experts showing that any claims were justified. In practice, this process has not been very effective, but FDA regulation of claims under NLEA was restrictive enough to lead to new legislation called the Dietary Supplement Health and Education Act (DSHEA) [3, 15, 16, 18, 21].

The DSHEA further loosened control on products that are ingested and allowed claims for pills, capsules, tablets, or even food-like products that were labeled as dietary supplements and included a label statement declaring that the products and claims were not approved by FDA, and that these products were not intended for use as a drug. While no pre-marketing approval is required from FDA, marketers of such products are required to notify of FDA of such products and label claims, and to have evidence that any information provided is truthful and not misleading.

The FDA can regulate materials that advertise foods and dietary supplements if the advertising is used in association with the sale of a product and is considered ‘labeling’, while other advertising is regulated by the US Federal Trade Commission. In either case false or misleading claims are not allowed, but the enforcement of these regulations has not been particularly vigorous and products with questionable claims and possible safety problems continue to be marketed in the USA [20, 22].

In the European Union countries foods are regulated under national food laws, and under EU regulations. In general, the control of claims is more strict that in the USA, but differences exist between various EU member countries with regard to claims allowed under national law. These differences can lead to EU wide marketing of products with hard to substantiate claims, since approval
of a product in one or two countries can lead to EU wide distribution of these products under existing EU rules [5, 23].

As an example of European control of claims, local level Trading Standards Officers in the UK have taken Nestle and other food marketers to court over certain label claims. In June 2000, the Shropshire County Council successfully sued Nestle for marketing a shredded wheat product with label claims that eating this cereal would reduce the risk of coronary heart disease. Nestle was fined GBP 7,500 for making an illegal medical claim, and also had to pay GBP 13,600 costs involved in holding the court proceedings [6]. In the UK, this court decision is considered as a test case, and will have significance to all food marketers about making future claims unless they have adequate scientific data to back up claims. In many cases it would appear necessary to liaise with regulatory authorities prior to marketing products, but this had practical difficulties when central government is not fully involved in regulating products, and at the same time allows local authorities to take legal action which has nationwide or EU-wide significance [7, 8, 17].

In the EU novel food regulation, companies wishing to market a product which is considered a novel food must present information to authorities in a Member State where a product will first be marketed to demonstrate product safety, and also present information on proposed labeling. Information provided should include product specifications, effects of production processes, history of any organism used as a source of the novel food, anticipated intake or extent of use, information of previous human exposure to the product, and nutrition, toxicological and microbiological information. As noted above, the main concern is the safety of the novel food, but some consideration of labeling is also possible [4, 25, 28].

Food and related rules which govern claims for functional foods also are in effect in Japan, other European countries, Australia and New Zealand, and there are differences between procedures and products allowed in each of these countries. Developing countries also have some legislation in place. Marketers of functional food products in these markets must carefully assess existing rules that apply because of the differences that exist in each of these markets.

In Japan regulations for Foods for Special Health Uses (FOSHU) have been in force for over two years. The Japanese rules require that a manufacturer or marketer of a FOSHU product present a dossier to the Japanese government with pertinent information on the ingredients, processing, labeling, quality, safety, and health effects of each FOSHU product. If the government authorities are satisfied that the dossier supports quality and safety requirements, and substantiates the health effects to be put on the label or used in advertising, approval of the FOSHU product can be given. Over 200 FOSHU-approved products are currently on the
market in Japan, and appear to be freely accepted by Japanese consumers. Similar procedures are also in place in China.

In Australia and New Zealand, the Australia New Zealand Food Authority (ANZFA) has published rules under Part 1.5 for Foods Requiring Pre-market Clearance. Food Standard 1.5.1 covers Novel Foods, while Food Standard 1.5.2 covers Foods Produced using Gene Technology [29].

ANZFA Standard 1.5.1 describes non-traditional foods as foods with no history of significant human consumption in Australia or New Zealand, and ‘novel foods’ as non-traditional foods with safety concerns. It requires pre-market approval of novel foods on the basis of a dossier that includes information on the composition of a product, on any undesirable substances that may be present, on any known adverse effects from consumption of the product, on traditional preparation or cooking, and on patterns and levels of consumption.

ANZFA Standard 1.5.2 covers food produced using gene technology and limits the technology to foods where recombinant DNA techniques have been used. For such foods specific labeling in required which states that the food or certain ingredients have been genetically modified. It can be seen from the above paragraphs on current ANZFA rules that the concepts defined in the EU rules on ‘novel foods’ have been divided into two separate ANZFA Standards, with somewhat different procedures and results.

At the international level, the Codex Alimentarius Commission has not held extensive discussions on functional foods. Work has been done on basic labeling rules, on nutrition claims and nutrition labeling, and claims for foods for special dietary use. In general these Codex standards and guidelines state that packaged food should not be described or presented on any label or labeling in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character in any respect.

Supporting Data for Novel Food or Functional Food Claims and Future Perspectives

Based on the discussion above, it is clear that marketers of foods which fit the profile of novel foods or functional foods must be prepared to have in their possession adequate scientific data to substantiate any claims that they wish to make on products [24]. This will involve several steps in building an adequate level of data, and must be done with the realization that data to establish the safety and efficacy of foods and food ingredients is considerably more difficult than is the case with food additives, pesticide residues, or chemical contaminants which are used in or can occur in food production and processing. In previous discussions on functional foods three sequential steps have been suggested:
1 Basic research and experimentation: identification and understanding of the mechanisms of interaction between the food or ingredient and modification of gene expression or cellular biochemical function in order to demonstrate potential functional effects.

2 Development of models and methodologies including possible biomarkers to demonstrate through studies on human nutrition possible functional effects and the consequences thereof to justify specific functional or physiological claims.

3 Design and carrying out of appropriate human nutrition studies, which may have to be done on a large scale, to demonstrate functional effects and benefits to health including reduction to disease where pertinent to justify structure/function or health claims.

Consumer studies in the USA have shown that 95% of consumers believe that certain foods can provide health promotion of disease prevention benefits beyond basic nutritional benefits [19]. Consumers are willing to accept the concept of functional foods and want to know more about them. It is likely that consumers in Europe and other parts of the world have similar attitudes and desires. Therefore, the future for novel foods or functional foods appears to be very positive. However, marketers of novel or functional foods or ingredients that can increase the functionality of foods must conduct careful and adequate basic studies and human trials to justify the claims that may be made for functional food products.

Given the differences in regulation of foods, special dietary foods, novel foods, foods for special dietary use, and medical foods in different countries and regions, potential marketers of these foods must be prepared to fully understand the regulatory requirements which apply in each marketing area, and be ready to meet these requirements both before marketing a product, and after a product has been placed on the market through adequate post marketing surveillance. The potential for novel or functional foods is great. Those meeting the challenges of successful development of scientific data so that products can be marketed should meet with great success.

References


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A New Look at Intersectoral Partnerships Supporting a Healthy Diet and Active Lifestyle: The Centre of Excellence in Functional Foods, Australia, Combining Industry, Science and Practice

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Reviews on healthy lifestyles normally begin with a picture of health problems, with nutrition and/or food positioned along the way as an element of concern. This review starts with food, and with reference to the Centre of Excellence in Functional Foods, argues that to establish effective health-promoting partnerships we must be prepared to genuinely address competing imperatives and find a space for co-operative activity.

Food can be described from so many perspectives. It is part of our social, economic and population health fabric. In Australia, food has special significance in all these domains. The food industry employs 17% of the total manufacturing workforce and Australia’s food exports account for around 22% of overseas trade [1]. The National Food Industry Strategy, an initiative of the Department of Agriculture, Fisheries and Forestry, underpins the significance of food to Australia’s economic health, with business, innovation and environmental platforms. The National Centre of Excellence in Functional Foods (NCEFF) was funded through the innovation platform to provide leadership for functional foods in Australia, with an emphasis on integrating science and business interests.

Food is also referred to in Australia’s research priorities, with the development of new health-promoting foods, a part of the Preventive Healthcare priority goal [2]. The food supply is noted as a key ‘settings strategy’ in the framework for
the national obesity prevention strategy, Healthy Weight 2008 [3]. In this section, outcomes sought include increased choices and local availability of lower energy density and healthy foods and drinks, increased proportions of manufactured foods and meals with reduced energy density and increased proportions of meals with reduced portion size, including meals consumed outside the home. Thus, the scene is set for intersectoral activity that can use any number of starting points or organising principles to make it happen. The path, however, must navigate through a number of ambiguities underpinning the need for an effective knowledge management strategy. These issues will now be explored, positioning the National Centre of Excellence in Functional Foods within the analysis.

**Functional Food: An Intersectoral View**

One of the essential attributes in developing effective intersectoral partnerships is adequate communication. There are many different ways in which information on food is communicated and positioned. The concept of functional foods, for example, may well have different meaning or weight depending on the context in which it is being discussed. From the Centre of Excellence perspective, these were seen as the nutrition (science), marketing, and regulatory perspectives.

**Nutrition Perspective**

There is no universal definition of functional foods, but there is a common reference to foods that provide benefits beyond basic nutrition [4]. This implies an understanding of foods and food components and the link between their consumption and specific health outcomes. The identification of whole dietary patterns and their potential relationship to improved health outcomes [5], however, would also fit this way of thinking. The concept of functional foods has a number of origins, but there are clear links with advances in nutrition science and in particular food science and technology. A recent edition of the journal of the Australian Institute of Food Science and Technology provides information (under the heading of functional foods) on pecan nuts, lutein-enriched eggs, citrus fruits, anti-oxidants obtained from grapes and apples, and alternative sweeteners [6]. These represent different categories in which the functional food concept may be examined, in particular whole foods and bioactive components of foods. The American Dietetic Association position statement on Functional Foods [7] lists foods and components in terms of potential health benefits and associated scientific evidence, displaying the disparity that often lies between the food category and the science to support its position. There is a wide range of studies that can address certain health outcomes, but the amount and type of
research required to justify a health claim is open to debate. This then creates another perspective for functional foods, that of regulation.

**Regulatory Perspective**

Around the globe, the way in which information on food can be legally presented to consumers is an interesting line of investigation in its own right. There are clear differences in the American, European and Japanese frameworks, but also there are efforts to gain some synergy [8], bearing in mind the implications for regional and world trade.

Australia has a long-standing history of food regulation, including food standards legislation that dates back into the early part of the last century. In the last decade, Australia and New Zealand formed a joint Food Standards Code, which currently includes a description of health claims (Standard 1.1A.2), but prohibits them on food. The only authorised health claim is the link between folate and a reduced risk of neural tube defects [9].

Standard 1.1A2 describes health claims as those that relate to
- intrinsic weight-reducing properties
- a therapeutic or prophylactic action or equivalent
- the word ‘health’ or equivalents with the name of the food
- any expression or implication of advice of a medical nature
- the name or reference to a disease or physiological condition.

In December 2003, a policy guideline on health claims was announced by the Australia New Zealand Food Regulation Ministerial Council [10] to guide the development of a system of health claims. The policy includes 26 broad principles and refers to criteria for general and high level claims. General level claims will require the industry to provide evidence on request for conditions that do not refer to serious diseases. High level claims, referring to serious diseases, will require pre-approval by Food Standards Australia New Zealand (FSANZ). The development of a model for substantiation will underpin the system for approval of health claims. This will necessitate effective problem solving between the scientific and regulatory sectors, bearing in mind that the output from this exercise concerns communication between the food industry and consumers, and this brings us to the market place.

**Market Perspective**

The literature on functional foods in the marketing domain is widespread, and takes many forms. Like the nutrition and regulatory sectors, the term has a defined space in this context, where it appears relatively unconstrained to describe market trends. Data in this literature refer to sales and consumer surveys. Functional foods are constructed as responding to a consumer demand for more ‘hands on’ responsibility for their own health, resulting in substantial
growth in sales of this food category, particularly in the US, Japan and Europe [11]. The language describing functional foods is in contrast to that of the nutrition and regulatory contexts (Table 1).

The nutrition perspective refers to foods and food components, while the regulatory descriptors identify broad domains of action or implications of actions, including reference to a role of giving medical advice. The marketing language has an appearance of confabulation, a less formal approach, drawing on any number of concepts and disciplines. Here, the language used in reference to functional foods alone can be seen to display the disparity between groups and the challenges facing intersectoral partnerships in which food has a primary position. There are many other examples, and indeed there are sectors other than the three mentioned here, which all add to the complexity of the task. Understanding the differences between groups, and developing frameworks that enable genuine sharing of the central issues, however, warrants consideration.

**Intersectoral Partnerships in Food**

If there is one issue in the world today that is linking food with a vast range of intersectoral components it is obesity. While the issue is identified and
prioritised by the health sector, the need for intersectoral approaches to addressing the problem is well recognised [12].

In Australia, over 60% of the adult population (25 years and over) are overweight and 20% obese. The rate of childhood obesity is one of the worst on record, resulting from a decline in physical activity and rise in energy intake [13]. The situation is causing concern, not least because there have been obesity prevention strategies in place for some time and they seem to have had little impact [14].

In New South Wales a school canteen policy has been put in place through an intersectoral partnership between Health and Education which outlines a number of resolutions including a statement that foods regarded as ‘extras’ in the Australian Guide to Healthy Eating can only be sold on two occasions per term [15]. A recent study of food consumption patterns of Australian children 5–15 years of age found on average 37% of energy was consumed at school. Fourteen percent of the children purchased food from the canteen, but overall, energy dense foods and beverages were over-represented in foods consumed at school whether brought from home or purchased at school [16]. The authors recommended that biscuits, snack bars, and cordials/drinks brought from home, and fast food, packaged snacks and confectionery bought at the canteen be replaced by fruit and water. This simple solution lies in stark contrast to the information provided on consumer food purchasing trends in the marketing literature [11]. It seems that if we could combine this latter knowledge with the nutrition concerns, a more innovative solution may be developed that addresses the need for less energy-dense foods and which will be adopted by children and their parents.

This leads to the issue of the technological know-how to produce new products. A recent review of research trends indicates the extent of this knowledge and the capacity it brings to improve the food supply [17]. This knowledge base is substantially greater than many areas referred to in the traditional domains of nutrition and health, drawing on aspects of the chemical, physical and structural analyses of foods to links between biology and engineering [17]. Technological advances from this domain are closely aligned to new product development and lie behind the emergence of the functional food market. It will be important for those working in the nutrition and health field to appreciate this sector if new solutions to well-described problems such as obesity are to be found.

The missing element in the discussion is of course the consumer. While the marketing literature would suggest that consumers are adopting functional foods, their sustained acceptance of this range is a complex matter, and one that has implications for all forms of food and nutrition communications. One review of this area suggests that risk perceptions and concerns relating to technology, scientific innovation and personal health issues should form the basis of these communications [18]. A study of Finnish consumers found that functional foods were not seen as a separate category, but rather as a secondary category within a food
In summary, obesity is well recognised as a serious health problem requiring an intersectoral approach. Food is implicated in the problem by virtue of its contribution to energy intake. The food and nutrition sector itself, however, has many parts, but if the capacity of this sector is to be maximally enhanced in helping to solve the problem, then developing frameworks to enable full participation needs to be on the agenda. There are limitations, for example in comparing tobacco control to food control, when unlike tobacco, food is an essential part of life [20]. It is likely, however, that we need some paradigm shifts in our relationships with food, where the strategic uptake of nutrition knowledge becomes an imperative in food product development, marketing and distribution addresses the question of energy delivered to the target population, and consumers become much more conscious of their management of energy intake and energy expenditure.

**The National Centre of Excellence in Functional Foods, Australia**

The Australian National Centre of Excellence in Functional Foods (NCEFF) was established in July 2003 to support the Australian food industry in the development of a functional foods market. The Centre itself is based on intersectoral collaboration, a joint venture between the Commonwealth Scientific and Industrial Organisation (CSIRO) – Division of Health Sciences and Nutrition, the Department of Primary Industries, Victoria, Food Science Australia and the Australian Research Council Key Centre for Smart Foods at the University of Wollongong. The task of the Centre is to provide leadership in the functional food area, bringing together science, technology, industry and related stakeholders. The collaboration between the four partner organisations creates additionality by combining capacities in food technology, nutrition and consumer sciences (from basic sciences through to human trials), and disciplines in public health, food regulation, marketing and innovation management.

The Centre has two main streams of operation, a generic stream funded by the National Food Industry Strategy and the four partner organisations, and a separate industry-funded stream. The generic stream funds independent pre-competitive research and activities, while the industry-specific stream works closer to the market on projects sponsored by industry. This enables the generation of new knowledge available to all and a framework for building concepts for a functional food market generally.

Projects are organised under clusters of substantiation research and development (nutrition perspective), regulation, and market intelligence/innovation
management. Thus, research undertaken is considered in the light of the types of nutrition communications that might lead from the research, as well as the likely market for any emerging products. In keeping with the direction Australian legislation is taking on health claims, a whole of diet approach lies at the centre of the research strategy. The first stage of the strategic (generic) research program focuses on the impact of types and amounts of macronutrients and of anti-oxidants on energy balance, energy expenditure and oxidative capacity. This set of studies, currently underway, will produce knowledge that is relevant to new food formulations that support optimal metabolic responses under various conditions, including physical activity. In marketing terms this would relate to foods for healthy aging, weight control, healthy lifestyle and child and adolescent health. Projects in the regulatory and market intelligence clusters relates to the strategic research program, identifying business opportunities, keeping up with developments in the regulatory environment, and facilitating communication between stakeholders on nutrition related issues.

As the Centre develops new linkages will be formed with other research providers and organisations as part of the consolidation of effort. The functional foods platform is aimed toward improved nutrition and carries with it a view to a healthy lifestyle. The achievement of this aim, however, has many dimensions, but starting with food, it is possible to see how these dimensions can be systematically and productively linked. To finish, the example that follows is based on research conducted at the Smart Foods Centre prior to the formation of NCEFF. It demonstrates how whole foods can have a functional label, why dietary methodology is relevant in substantiating effects and what consumers think of the consequences of the area under research.

A Case Study of Functional Food Research: Walnuts in the Dietary Management of Type 2 Diabetes mellitus

The role of dietary fat in insulin resistance has been well researched at a number of levels [21]. However, while there is strong evidence implicating dietary saturated fat (SFA) in the development of type 2 diabetes mellitus (T2DM) [22], the potentially protective role of dietary polyunsaturated fats (PUFA), first observed many years ago, appears to have been forgotten, and is relatively under-researched in diabetes management [22]. There are a number of ways in which PUFA may protect against insulin resistance and T2DM, but one interesting mechanism is the effect on body fatness. In animal model studies Huang and colleagues have demonstrated the effect of type of fat on obesity via an impact on body fatness and various measures of hormonal systems regulating food intake and energy balance (leptin, Arc receptor, NPY and
AgRPmRNA expression). In obesity prone mice, a high SFA diet induces obesity without hyperphagia, but the effect could be reversed by changing the SFA for PUFA (notably – n−3) with a much less effective response by changing to a low-fat diet [23, 24]. A higher PUFA diet (and with attention to the type of PUFA) resulted in a lower energy intake and a low food efficiency ratio (weight gain/intake) [25], something that could be assessed in human studies.

Nutrition principles for the management of type 2 diabetes mellitus are based on a systematic review of the scientific evidence [22]. The nature of this evidence relates to the effects of macronutrients on metabolic control and other health variables. In particular, the evidence in support of the inclusion of polyunsaturated fats is quite strong [26], such that foods that deliver these fatty acids could be seen as having a functional role in the diet. This functionality could be defined in terms of delivering the essential fatty acids, or through the impact of these fatty acids (or foods) on health indicators such as body fat. If this were the case, it would also be helpful to know if patients were able to consume these foods regularly and whether they perceived the foods to have a functional role. Because walnuts have a unique composition providing high amounts of n−6 and n−3 fatty acids, their functionality in this regard was of interest.

In this study, 55 adult men and women with type 2 diabetes mellitus were randomly allocated to three dietary advice strategies (low fat, LF, LF inclusive of PUFA-rich foods, LFP, and LFP with the inclusion of 30 g walnut supplied). Dietary intakes were assessed by validated diet history interview at baseline, 3 and 6 months and nutrient intake analysis was done using Foodworks (v.3.01, Xyris, Brisbane). There was no significant difference in nutrient intakes between groups at baseline, but after 6 months the walnut group was the only group to achieve all dietary targets (table 2).

This study demonstrated the significance of including 30 g walnuts per day in the diet [27] to deliver the required amounts of essential fatty acids [see 28]. In this sense the walnuts provided a functional role in meeting target intakes of nutrients that stands to be limiting if high fat foods are excluded from the diet. In this study walnuts could be seen as n−3 enriched functional foods. To gain insights into consumer perceptions here and with another group of patients in a similar trial (n = 126) [29], we applied a questionnaire derived from focus group interviews to elucidate the three determinants of intention to consume these foods in the Theory of Planned Behaviour [30] attitude, normative and control factors. Using regression analysis we were able to show that the TPB provided a significant explanation of intention ($R^2 = 0.54$, $p < 0.01$) and was able to predict intention 55% of the time. Attitude was a significant determinant of intention whereas subjective normative beliefs and control beliefs were not related. Overall the odds of intending to use n−3 enriched functional foods doubled for each one-unit increase in attitude score. There were significant correlations
between age ($r = 0.21, p < 0.05$) and income ($r = -0.19, p < 0.05$) with intention; however, these were not determinants of intention. With attitude having the greatest influence on intentions, immediate prospects for modifying behaviour come through a change in attitude. Thus, if functional foods are to be adopted by consumers, then their attitudes towards functional foods warrants attention. This has implications for the communication of science, another important string to the bow of intersectoral collaboration.

The above case study outlines how animal model research can inform food based research with humans, and how this in turn may provide evidence of the functionality of specific foods in the diet. On top of this, consumer research provides information on how nutrition knowledge needs to be communicated and the potential acceptance of related products in the marketplace. These are some of the aspects of the research program of the National Centre of Excellence in Functional Foods.

### Conclusions

Where food is seen as the starting point for developing healthier lifestyles, a number of stakeholders may be identified, and clearly the food industry is a major one. The concept of functional foods unites health, industry and regulatory groups in a move towards providing healthy food products, but effective communication of this concept and of approaches to its development is central to its successful adoption by consumers. The National Centre of Excellence in Functional Foods.
Functional Foods, Australia, has taken all these aspects on board in developing an infrastructure to support this process.

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Why a Global Strategy on Diet, Physical Activity and Health?

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The Growing Burden of Noncommunicable Diseases

In January of 2004, the World Health Organization’s (WHO) Executive Board agreed to forward the WHO Global Strategy on Diet, Physical Activity and Health to its World Health Assembly, after allowing countries an extended period, until 29 February, for comments. The strategy was endorsed by the WHO member states at the 56th World Health Assembly in May 2004. The strategy is an important global public health initiative, which was prompted by Member States’ concern at the explosion in noncommunicable diseases (NCDs), for which unhealthy diet and physical inactivity are, together with tobacco use, among the key risk factors.

Noncommunicable diseases are increasing at alarming rates globally. The burden of NCDs in developing countries already outweighs that of communicable diseases, both in high- and low-income countries. In 2002, NCDs accounted for 60% of total mortality worldwide and 46% of the global burden of disease [1]. Low- and middle-income countries account for the increase in burden of disease from NCDs. One example comes from China. In China’s rural areas – and that’s still more than 800 million people – NCDs account for more than 80% of deaths; communicable diseases, less than 3% [2, 3]. Only in Africa do deaths from communicable diseases outweigh those from noncommunicable diseases. For example, in South-East Asia 5,730,000 deaths were attributed in 2002 to communicable diseases and 7,423,000 to noncommunicable diseases. In the Eastern Mediterranean 1,746,000 deaths were attributed to communicable diseases and 2,030,000 to noncommunicable diseases and, in this region, the Western Pacific, 9,000,000 deaths were attributed to NCDs with 1,701,000 to communicable diseases [1].
This disease burden is expected to increase to 60% by the year 2020. Countries have not yet been able to successfully defeat the burden of infectious diseases and they are already faced with a double burden of noncommunicable diseases. Heart diseases, stroke, cancer and mental disorders are expected to be the largest contributors. Of the estimated 57 million deaths which occur each year, 33.4 million are attributed to NCDs. Of these, 16.7 million are attributed to cardiovascular diseases (CVDs), especially ischemic heart disease and cerebrovascular diseases. Twice as many die from CVDs in developing countries than in developed countries.

Obesity is now also a global epidemic [4]. There are globally more than 1 billion overweight people and at least 300 million of them are clinically obese. Close to 800 million people are suffering from malnutrition, a slow decline over the past decade.

In some Pacific Island states as much as 70% of women and about 60% of men in urban areas are obese (BMI >30).

The number of people with type two diabetes is expected to increase threefold by 2020, and most of this growth is projected to occur in Asia.

The Causes of Noncommunicable Diseases

Noncommunicable diseases are increasing for several key reasons. Throughout the world, birth rates are declining, life expectancy is increasing and populations are aging. One consequence of this change in world demographics is increased rates of chronic diseases. These demographic changes can be explained by significant improvements in both medical science, technology, and successful public health and other development efforts over the last 100 years.

The world population exposure to the modifiable risk factors for cardiovascular diseases, cancer, diabetes and other NCDs is also increasing at a very rapid pace. Lifestyle and consumption patterns are key determinants of such diseases and include changes in diets, physical activity and tobacco use. These risk factors are indicators of future health status [4]. Five of the top 10 global disease burden risk factors identified by the World Health Report 2002 – high blood pressure, high cholesterol, low intake of fruit and vegetables, high body mass index and physical inactivity – independently, and often in combination, are the major causes of these diseases. Food is clearly a major factor in all this. This report reflects the impact of risk factors over the last decade or so. But current risk levels predict major increases in chronic diseases.

The increased prevalence of modifiable risk factors is closely linked to economic development. Urbanization is key to understanding lifestyle changes [5]. Rapid growth of urban centers results, in most parts of the world,
in deficiencies in housing, infrastructure, and basic services. This trend is accompanied by influences of global trade, industrialization and expansion of food markets. Populations are exposed to increased availability and aggressive promotion of processed cheap food – generally high in fat, sugar and salt – but reduced access and affordability of fruits and vegetables. An increase of 82% of caloric sweetener has been recorded due to higher income levels and urbanization. In addition, lifestyles become sedentary with a rapid shift from energy-expenditure-intensive to automated occupations, changes in transportation and the increased use of motorized vehicles [6, 7]. All lead to a decrease in energy expenditure.

**Need for a New Approach**

This is, therefore, a global epidemic and requires a global response. Countries need to act now to ensure that developing countries do not experience the high peak in NCD prevalence that has occurred in the developed world.

The evidence for the disease burden is strong. The science behind the role of the two risk factors, diet and physical activity, in the etiology of NCDs is robust, and experience from countries taught us that we know enough to act and change the current trends.

Upon request by its Member States, WHO has over the past 2 years developed the Global Strategy on Diet, Physical Activity and Health. Consistent with an approach in which countries participated from the outset, six regional consultations with Member States were completed between March and June 2003. These involved more than 80 countries in formal meetings. The strategy also reflects the expertise and advice of several United Nations organizations, in particular the Food and Agriculture Organization (FAO). WHO has also received significant input from representatives of civil society and nongovernmental organizations, and from the private sector, in particular the food and non-alcoholic drinks industry, as well as sport manufacturing organizations. WHO has been supported in this process by a reference group of prominent experts from all over the world, representing several fields and disciplines. This group provided scientific and policy input and advice for the development of the strategy throughout the process.

The strategy builds upon the vast evidence, best practices and experience in countries in tackling and preventing NCDs. It also draws on the experience and knowledge of health, nutrition and physical activity experts from a wide range of disciplines and countries, both developed and developing. One of the strategy’s most important conclusions is that reducing the burden of NCDs requires a multi-sectoral, multi-stakeholder approach.
The strategy is not prescriptive but, like a toolbox, provides WHO Member States with a comprehensive range of policy options from which to choose. Many countries are already developing their own national strategies.

What are the policy options the strategy is recommending? The strategy suggests recommendations for action by all stakeholders: WHO, Member States, NGOs, the private sector and UN agencies. Key principles are set to guide the development of strategies to address unhealthy diets and physical inactivity: best available scientific evidence, comprehensiveness, multisectoral and multidisciplinary approaches, a life course perspective, addressing poverty, gender and culture sensitivities, and the accountability of all stakeholders to achieving success. The strategy sees governments assuming a steering role in changing the environment to support their populations and individuals improve their lifestyle. It stresses the importance of building on existing structures and national mechanisms rather than creating new ones. It suggests that national effective legislation and appropriate infrastructure are critical for introducing effective policies. The main policy recommendations of the strategy are: for countries to develop national dietary and physical activity guidelines, provide accurate and balanced information to consumers, in particular with regard to nutrition labelling, nutrition and health claims, addressing issues related to marketing of foods, especially to children. The strategy recommends that countries review and evaluate their food and agriculture policies to be consistent with healthy diet. In particular, it suggests that countries provide incentives to promote a healthy diet. Price policies are important as prices determine food choices, especially among the poor. Food programmes need to take note of the growing burden of NCDs and their risk factors, and agriculture policies can have a great effect on national diets. The strategy advocates for policies to change social norms to increase physical activity and incorporate it into daily life. Many public policies such as transport and urban planning play a huge role in levels of physical activity. Further, the strategy reiterates the importance of providing clear messages about the benefits and amounts of physical activity levels needed to reduce risks for NCDs. School policies and supportive school environments for healthy diet and physical activity are also recommended.

The strategy pays much attention to the role of health services and health professionals in primary prevention and urges that diet and physical activity recommendations and follow up are built into health services. The document also elaborates on the role of surveillance and the importance of continued research and evaluation at a national, as well as a global, level to monitoring progress and trends.

For the private sector the strategy highlights the importance of improving the nutrition profiles of products, to reduce salt, fat (and type of fat) and sugar. It also advocates for a review of current marketing practices.
Civil society has a major role to play. The strategy acknowledges its role and describes how NGOs can assist governments in disseminating information, influencing consumers, promoting availability of healthy foods and advocating and supporting health promoting programmes.

Finally the strategy appreciates the important role of the United Nations and other intergovernmental organizations in assisting WHO and its Member States in addressing issues which are crucial for implementing the strategy but which are often outside the health sector, such as: economic analysis, development programmes, agriculture policies.

National action can be effective – it has provided much of our evidence base for effective interventions. But independent action is not enough in an increasingly globalized and interdependent world. The WHO’s goals to advance public health worldwide – and perhaps as importantly, to set new public health priorities – can only be met through decisive and coherent action by countries, sustained political commitment, and broader, multi-level involvement with all relevant stakeholders worldwide.

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Nutrition and Fitness Policies in the United States

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Nutrition and fitness policies in the United States must be considered a failure from a public health perspective. Obesity in the United States has been increasing steadily over the past several decades, particularly in the past decade. It is now considered to be an epidemic. Reports from the US Department of Health and Human Services [1–4], RAND [5–7] and a growing number of scholars attest to this fact [8–11]. In fact, eight million children ages 6–19 years are overweight, a number that has tripled in the past 20 years. Moreover, obesity can play a major role in the disability, particularly among adults from 30 to 70 years of age. It is now linked to higher health care costs than cigarette smoking or problem drinking.

The picture with respect to physical activity and fitness is hardly any better. According to the Healthy People 2000 review in 1999, only 15% of adults aged 18 years and older engaged in 30 min of moderate physical activity 5 days per week, down from 22% in 1985 [12].

The costs in terms of the health of the population are enormous. It has been estimated that the poor diets of Americans, their sedentary lifestyle and their excess alcohol consumption contributes to about 400,000 of the 2,000,000 or so annual deaths in the United States. This amount is the same as the toll from cigarette smoking [11, p 7].

How did this happen? How did the United States become an overweight, sedentary, unfit population?

In order to provide some perspective on these developments and what is described as the ‘obesity epidemic’ in the United States, I will review the evolution of public policies related to nutrition, fitness, physical activity, and the health of the population, particularly during the past 40 years. In this review, I will draw on various federal government documents, including those of the
Department of Health and Human Services (DHHS), prior to 1980, the Department of Health, Education and Welfare (DHEW), the Department of Agriculture (USDA), and the US Congress; on my service as Assistant Secretary for Health and Scientific Affairs in DHEW during the Johnson Administration (1965–1969) and the Assistant Secretary for Health in DHHS during the first Clinton Administration (1993–1997); scholarly work with colleagues at UCSF, as well as contributions by the Institute of Medicine and Professor Marion Nestle of New York University. After my historical review, I will examine some of the forces that have influenced and continue to influence the public policy process, particularly at the federal level. Commercial interests have had a far greater influence on nutrition policies than the public interest [11]. Federal policies on physical fitness during the past 40 years have had little effect. Finally, I will discuss some recent policy developments that may affect current trends. Throughout I will stress the tensions between a population health perspective and a focus on individual behavior or lifestyle.

**Historical Perspective**

**Physical Fitness and Physical Activity**

Physical fitness was of little interest to federal policymakers, except those in the armed forces until President Eisenhower created the President’s Council on Youth Fitness and Sports by Executive Order in 1956 after the President learned that American children were less fit than European children. Over the decades, Presidents have expanded the Council’s mandate to include all Americans and changed its name to the President’s Council on Physical Fitness and Sports.

Over the years, the President’s Council devoted relatively little attention to health-related fitness activities for the whole population and concentrated primarily on working with private industry, insurance companies, and schools. President Clinton transferred the support for the Council to DHHS to achieve greater integration with the work of the Office of Disease Prevention and Health Promotion in the Office of the Assistant Secretary for Health. President Bush has continued the emphasis on linking the Council’s activities to health promotion efforts at the national, state, and local level [13].

It was not until the 1970s, particularly after the publication in 1974 of the report A New Perspective on the Health of Canadians [14] that health behaviors, such as eat habits and physical activity, began to attract the attention of policymakers. A great deal of attention was paid to health promotion, particularly the behavior of the individual, as an important factor in health. Many of America’s health problems were labeled ‘behavioral’ or ‘lifestyle’ problems. The bad habits
were said to contribute to the growing burden of chronic illness, increasing demand for health care and contributing to the rising costs of health care.

This point of view was expressed succinctly in 1977 by the late Dr. John Knowles, who was then President of the Rockefeller Foundation in an essay entitled, ‘The Responsibility of the Individual’: ‘Prevention of disease means forsaking the bad habits which many people enjoy – overeating, too much drinking, taking pills, staying up at night, engaging in promiscuous sex, driving too fast, and smoking cigarettes’[15].

Beginning in the 1960s, population-based studies in Alameda County, California demonstrated the importance of seven health-related behaviors (e.g. maintaining normal body weight, engaging in regular physical activity) in increasing life expectancy among those who maintained these behaviors compared to those who did not engage in at least four of these healthy behaviors [16–18].

While legislation enacted in the mid-1970s included an emphasis on health promotion and disease prevention, the legislation had little impact on health promotion and disease prevention policies at the state or local levels [19, 20].

In 1978, the DHEW Task Force on Disease Prevention and Health Promotion identified strategy targets in 12 categories of health-related goals (e.g. chronic disease, communicable disease). In the goal, ‘Enhance General Physical and Emotional Well Being,’ three key variables were stressed: nutrition, unwanted fertility/family planning, and exercise. The potential role of employee health programs and school physical education programs in promoting exercise were noted. The Task Force stated a theme that was to be repeated over the years: ‘A strong national commitment to disease prevention and health promotion is needed to ensure that Americans will be a truly healthy population’[21].

Twenty-five years and eight Secretaries of DHEW and DHHS later, the Secretary of DHHS, Tommy Thompson, convened a national health summit in 2003 ‘to call on Americans to take the steps that will lead to a healthier nation’ [22]. The 25 years between these two clear statements has seen more words than effective action.

In the late 1970s, there were a number of important developments in the DHEW, under the leadership of Dr. Julius Richmond, the Assistant Secretary for Health/Surgeon General. He began to shift the focus of federal health policy from health services and financing medical care to health promotion and disease prevention. He also initiated what has become known as the Healthy People process.

Healthy People 2000: National Health Promotion and Disease Prevention Objectives, released in 1990, listed Physical Activity and Fitness as the first priority and nutrition as second [23]. At the Healthy People 2000 Review in 1998–1999, the percentage of overweight adults (age 20–74 years) had risen from 26% in 1976–1980 to 35% in 1994; the figures for black females had risen from 44 to 52%, for Hispanic females from 33% in 1990 to 35% in 1995 and for
low-income females aged 20–74 from 37% in 1976–1980 to 47% in 1991. Vigorous physical activity for children and adolescents (age 10–17 years) was stable at 64 percent. However, only 27% of students in grades 9–12 were engaged daily in physical education at school; for adults (18 years and older), the figure was only 16% engaged in vigorous physical activity [12].

The importance of health-related behavior, or lifestyle, was stressed by McGinnis and Foege in their famous paper, ‘Actual Causes of Death in the United States,’ published in 1993. In this paper, the method of calculating the cause of death differed sharply from the usual listing of the most common causes of death, headed by diseases of the heart (29.5%), all cancers (22.9%), and stroke (6.9%). The actual causes of death identified by McGinnis and Foege [24] are headed by tobacco (19%) and poor diet/lack of exercise (14%).

The 1996 Surgeon General’s Report on Physical Activity and Health reflected a major change in thinking about physical activity at the federal level [25]. The focus shifted from an emphasis on intensive, regular aerobic physical exercise to a wide range of health enhancing physical activities. The report noted low levels of physical activity among the majority of adults including 25% who are not active at all. The population reporting no leisure time physical activity was higher among women, African Americans and Hispanics, among older adults and among the less affluent.

Healthy People 2010, released in January 2000, represented a significant shift from past Healthy People publications in the goal to ‘eliminate health disparities’ and its greater consideration of the relationship of education and household income to health status. This broader perspective was evident in the breadth of actions needed to achieve equity: ‘Healthy People 2010 recognizes that communities, states, and national organizations will need to take a multidisciplinary approach to achieving health equity – an approach that involves improving health, education, housing, labor, justice, transportation, agriculture and the environment, as well as data collection itself’ [26].

Physical activity is now considered a leading health indicator and, as I noted at the outset of this paper, the picture is not a good one. During recent decades overweight prevalence has increased significantly and levels of light to moderate physical activity and vigorous activity have changed little.

It is important to note that the barriers most adults face when trying to increase physical activity are lack of time, lack of access to convenient facilities and lack of a safe environment in which to be active. For example, many suburbs lack sidewalks and in many inner city areas the sidewalks are not safe for the elderly walking alone or for children walking to school.

We do not seem to have made much progress since 1979 when Dr. Richmond issued his first health objectives for the nation.
Nutrition Policy

A sound nutrition policy is fundamental to any effort to improve our nation’s health. From its foundation in 1862, the US Department of Agriculture (USDA) had two functions: (1) to assure a reliable and adequate food supply, and (2) to provide information to the public on ‘subjects connected to agriculture in the most general way,’ which has been interpreted as giving dietary advice [11, p 33].

In 1917, the USDA issued its first set of dietary recommendations in a 14-page pamphlet, How to Select Food. While establishing precedents with respect to food groups and dietary advice, permitting all foods to be recommended, it ignored the analysis of the USDAs first director of research, W.O. Atwater, related to the harm done to our health by the excessive consumption of sugar and large quantities of fat meats.

The establishment of the Food and Nutrition Board, National Research Council, National Academy of Sciences in 1941 and the enactment of the School Lunch Program by Congress in 1946 were early developments in nutrition policy. In the mid-1960s, there were two modest expansions of nutrition policies: the Food Stamp Program in 1965 and the Child Nutrition Act of 1966. The Child Nutrition Act established the School Breakfast Program. In addition, President Johnson outlined the Food for Freedom Program, also called the ‘war on hunger’.

The DHEW began nutrition surveys after the report, Hunger USA [27], by the Citizen’s Board of Inquiry, revealed serious problems of malnutrition among the poor. Based on the survey results, a number of food assistance programs were expanded in the 1970s – including the Food Stamp Program, the School Lunch Program, and the Child Nutrition Program. In addition, a nutrition program for the elderly was launched. Most of these programs were administered by the USDA, but the nutrition program for the elderly was administered by the Administration on Aging/DHHS. The period from the turn of the century to the 1960s has been described by Professor Marion Nestle as ‘Eat More – Preventing Dietary Deficiencies 1890 to 1960s’ [11].

The Senate Select Committee on Nutrition and Human Needs, chaired by Senator McGovern, became a key player in the development of federal policies for food assistance for the poor in the late 1960s and early 1970s. By the mid-1970s, the Select Committee began to address broader nutrition policies [28].

While domestic issues initially attracted the Select Committee’s attention, it was the grain shortage in the Soviet Union and the inflation produced by the Arab oil embargo in the early 1970s that led Congress to take broader measures to ensure adequate food supply that have continued to this day: (1) income support for farmers to assure adequate food production, and (2) expansion of the Food Stamp Program in order to protect the poor from food price inflation.
Regulation of food labeling was stepped up by the Food and Drug Administration (FDA), and Congress gave added nutrition responsibilities to the USDA to be shared with DHEW, including dietary advice to the public, in the Food and Agriculture Act of 1977 [11].

Although many areas of agriculture policy that are germane to the consideration of this conference remain controversial, I will focus on dietary recommendations and nutrition policy – an area of continuing conflict.

Just as the advances in research related to exercise and other determinants of health began to shift health policies in the DHEW toward health promotion and disease prevention, nutrition policymakers began to pay attention to the research that elucidated the relationship between diet and chronic illness, particularly coronary heart disease. In 1977, the Senate Select Committee on Nutrition and Human Needs issued its report, Dietary Goals for the United States [29], which generated a great deal of controversy because of its recommendations to eat less fat, cholesterol, saturated fat, sugar, and calories. The Dietary Goals represented a fundamental shift in federal dietary advice from ‘eat more’ to ‘eat less’ [11]. The controversy and intense pressure by the food industry interest groups led the Select Committee to modify its recommendations regarding salt, cholesterol and meat consumption.

The shift in policies from eat more to eat less was also reflected in the DHEW Task Force Report on Disease Prevention and Health Promotion [21] and in the Surgeon General’s Report Healthy People [30] in 1979. The Task Force recommended, ‘total fat intake, especially animal fats, refined carbohydrates, and salt should be reduced as part of a prudent diet’ [21].

The Dietary Guidelines for Americans were first issued jointly by the USDA and DHHS in February 1980 as the consensus about the relationship of diet to a variety of chronic diseases grew. In the mid-1980s, the National Heart, Lung, and Blood Institute/National Institutes of Health launched a major nationwide campaign to lower blood cholesterol across the entire population. The campaign included specific advice regarding the intake of fat, especially saturated fat. In 1988, after years in preparation, the DHHS issued the Surgeon General’s Report on Nutrition and Health [31]. The report described the magnitude of the problem as follows: ‘As the diseases of nutritional deficiency have diminished, they have been replaced by diseases of dietary excess and imbalance – problems that now rank among the leading causes of illness and death in the United States, touch the lives of most Americans, and generate substantial health care costs’ [31].

While providing support for the Dietary Guidelines for Americans, the Surgeon General’s Report on Nutrition and Health gave special emphasis to the importance of obesity as a public health problem and on the need to reduce the intake of total fats, especially saturated fats [31].
In the section on Implications for Public Health Policy, the report noted: ‘Americans, in general, would benefit from a lifestyle that includes more physical activity and a diet containing fewer calories’ [31].

The Policy Process

Why, when the research related to diet and exercise was so consistent, was it so difficult during the past 25 years to reach agreement on dietary advice and to implement programs that dealt more effectively with the increasingly obese population? In part, the answer is politics and the policy process.

During this period, food companies exerted significant influence on dietary guidelines and nutrition policy. They effectively lobbied Congress and members of the executive branch as well as co-opted nutrition experts as allies. The practice of the food companies and the response of government are not unique, but reflect the public policy process more broadly. Professor John Kingdon has been a longtime student of Congress and how an issue becomes a priority for policymakers and is enacted into law. Some policies, such as Food Stamps and agricultural subsidies, were initiated when there was agreement on the problem, when policy options had been developed and when the political stream was aligned with the problem and the policy streams. This has been described by Kingdon as a ‘window of opportunity’ [32].

Other analysts have focused on the reasons why certain policies are so resistant to change. According to Paul Sabatier and Hank Jenkins-Smith, long-term policy change depends on the competition among two or more ‘advocacy coalitions’ whose members monitor and actively try to influence specific policy issues. In their view, most policy change is the product of shifts in large-scale social, economic, or political conditions. However, even with a major shift in political power or other external circumstances, it is often difficult for government to respond to even serious problems because an effective response would violate the core values of an advocacy coalition. Altering dietary advice to advise people to eat less red meat would not only violate the core values of some about the proper role of government, it would also have a negative economic impact on all those who raise, slaughter, process, and market beef.

In the absence of changes in broader, contextual conditions, Sabatier and Jenkins-Smith observe that policy can still change if partisan positions are modified through a process of ‘policy learning.’ Policy learning is a fairly subtle and gradual process. The members of an advocacy coalition almost never change their deep-core values and beliefs, which dictate their basic orientation to an issue and the role of government. They may, however, change their ‘near-core’ policy-oriented beliefs and a variety of ‘secondary’ beliefs when new information successfully challenges their claims about the nature of a problem.
or the effectiveness of a solution. Given a new understanding of the problem and potential remedies, current policies may become indefensible and a coalition may accept new methods of governmental intervention [33].

Professor Nestle astutely summarized the issue when she wrote: ‘Diet is a political issue. Because dietary advice affects food sales, and because companies demand a favorable regulatory environment for their products, dietary practices raise political issues that cut to the heart of democratic institutions’ [11, p 28].

The struggle in terms of policy and politics is over the way the government balances corporate interests and the public interest. To date, the balance has favored the corporate interests. However, we have seen in the case of cigarette smoking and the tobacco companies that a combination of grass roots organizations and legal challenges can dramatically change the landscape. The process is, however, more complex. Twenty-three years ago, Thomas and coworkers wrote: ‘The health prospects of Americans during the last two decades of the twentieth century will depend on the quality of decisions made by federal, state, and local governments, by business and industry, by community organizations, by voluntary and professional health associations, by health professionals themselves, and by families and individuals acting on their own behalf. In short, if the health of Americans is to improve, both individual and collective actions will be necessary’ [34, p 146].

The record of the past 23 years has not been a good one in achieving national health objectives related to physical activity and nutrition. Will the next 20 years be any different?

Will the growing efforts to stimulate action at the grassroots with respect to obesity, overweight, and physical activity now be successful when they have had so little impact in the past? The evidence about physical activity and diet in relation to health status, chronic disease and disability is growing. Efforts by the Surgeon General of the US Public Health Service in collaboration with non-profit and professional organizations and several major foundations have initiated national efforts to increase physical activity among adults. Some of these efforts seem to be bearing fruit. Time will tell whether a broad-based movement can be initiated and sustained.

The New York Times has reported changes in the landscape of food politics in a recent article, ‘Lawyers Shift Focus From Big Tobacco to Big Food’ [35]. To date, lawyers have settled five cases out of court, three with major food companies, one with McDonalds, and one with the New York City school system. In tobacco suits, the lawyers became successful when they focused on deceptive marketing rather than personal injury. This appears to be the focus in the current food cases.
**Conclusion**

The United States faces an epidemic of obesity with grave consequences for the health of the population and the costs of health care. During the past century, and particularly during the past 40 years in the United States, health and nutrition policies have not been effective in improving the diets of Americans or increasing their levels of physical activity. It is suggested that the struggle with tobacco companies and the recent declines in cigarette smoking may have lessons for diet and physical activity. In the meantime, do as we say, not as we do.

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