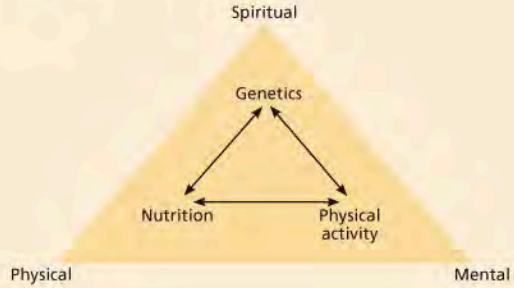
World Review of
Nutrition and Dietetics
Editor: A.P. Simopoulos
Vol. 94

Nutrition and Fitness

Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer

1

Editor
A.P. Simopoulos



KARGER

Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer

Acknowledgement
The publication of these proceedings is made possible by
a grant from the Stavros S. Niarchos Foundation

World Review of Nutrition and Dietetics

Vol. 94

KARGER

5th International Conference on Nutrition and Fitness
Athens, June 9–12, 2004

Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer

Volume Editor

Artemis P. Simopoulos
The Center for Genetics, Nutrition and Health, Washington, D.C., USA

37 figures, 1 in color, and 28 tables, 2005

KARGER

Basel · Freiburg · Paris · London · New York ·
Bangalore · Bangkok · Singapore · Tokyo · Sydney

Additional proceedings from the conference are published in volume 95 of this series

Artemis P. Simopoulos
The Center for Genetics,
Nutrition and Health
Washington, D.C., USA

Library of Congress Cataloging-in-Publication Data

International Conference on Nutrition and Fitness (5th : 2005 : Athens, Greece)
Nutrition and fitness : obesity, the metabolic syndrome, cardiovascular disease, and cancer / 5th International Conference on Nutrition and Fitness, Athens, June 9–12, 2004 ; volume editor, Artemis P. Simopoulos.
p. ; cm. – (World review of nutrition and dietetics, ISSN 0084–2230 ; v. 94)
Includes bibliographical references and index.
ISBN 3-8055-7944-6 (hard cover : alk. paper)
1. Nutritionally induced diseases–Congresses. 2. Obesity–Congresses. 3. Diabetes –Congresses. 4. Coronary heart disease–Congresses. I. Simopoulos, Artemis P., 1933- . II. Title. III. Series.
[DNLM: 1. Nutrition–Congresses. 2. Cardiovascular Diseases–Congresses. 3. Metabolic Sydrome X–Congresses. 4. Neoplasms–Congresses. 5. Obesity–Congresses. 6. Physical Fitness–Congresses. W1 WO898 v.94 2005 / QU 145 I60153nb 2005]
QP141.A1W59 vol. 94
[RA645.N87]
612′.3′08 s–dc22
[614.5′939]

2005012462

Bibliographic Indices. This publication is listed in bibliographic services.

www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISSN 0084–2230
ISBN 3–8055–7944–6

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://www.leepinkerson.com.

Commemorative 2004 Conference Medal

Front Back

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.

Contents

Conference Organization

Conference Chair

Artemis P. Simopoulos, MD (USA)

Conference Co-Chairs

George P. Chrousos, MD (USA/Greece)
Konstantinos N. Pavlou, DSc (Greece)

Executive Committee

Frank W. Booth, PhD (USA)
Peter Bourne, MD (USA/UK)
Regina C. Casper, MD (USA)
Cuiqing Chang, MD, PhD (China)
Nicholas T. Christakos, Esq (USA)
George P. Chrousos, MD (USA/Greece)
Raffaele De Caterina, MD, PhD (Italy)
Nikos Filaretos (Greece)
C. Gopalan, MD, PhD, DSc (India)
Sotiris Kitrilakis (Greece)
Demetre Labadarios, MD, PhD (South Africa)
Alexander Leaf, MD (USA)
Philip R. Lee, MD (USA)
Federico Leighton, MD (Chile)
Harumi Okuyama, PhD (Japan)
José Ordovas, PhD (USA)
Costas Parisis, MD, PhD (Greece)
Konstantinos N. Pavlou, DSc (Greece)
Artemis P. Simopoulos, MD (USA)
Eliot Sorel, MD (USA)
Panos G. Stamatopoulos, MD (Greece)
Leonard Storlien, PhD (Sweden)
Bill Toomey (USA)
A. Stewart Truswell, MD, DSs (Australia)
Mark L. Wahlqvist, MD, PhD (Australia)
Clyde Williams, PhD (UK)

Local Committees in Greece

A. Organizing Committee

Chair: Panos G. Stamatopoulos
Co-chair: Leonidas N. Seitanidis
Secretaries: Evagelia Maglara
Kalliopi – Anna Poulia
Treasurer: Kostantinos N. Pavlou
Members: Elena Averoff
Antonia Georgiopoulou

Nikos Groumas
Maria Hassapidou
Stavros Kavouras
Sotiris Kitrilakis
Saki Kypreou
Konstantinos Natsis
George P. Rontoyannis
Nikos Terzidis
Nikos Yiannakouris

B. Scientific Committee

Christos Aravanis
Eleni Avlonitou
Panos Behrakis
Athina Bei
Garifalia Emmanouil
Dimitrios Hassiotis
Nikos Katsilambros
Denis Kokkinos
Manousos Konstantoulakis
Maria Liparaki
Antonis Maillis
Pantelis Nikolaou
George P. Rontoyannis
Yiannis Steriotis
Pavlos Toutouzas
Alexandros Tsopanakis

Conference Organized by

The Center for Genetics, Nutrition and Health
2001 S Street, N.W., Suite 530
Washington, DC 20009 (USA)
Tel. +1 202 462 5062
Fax +1 202 462 5241
E-Mail cgnh@bellatlantic.net

Major Sponsors

The Center for Genetics, Nutrition and Health
Stavros S. Niarchos Foundation

Under the Patronage of

Food and Agriculture Organization of the United Nations
International Union of Nutritional Sciences
International Olympic Academy
Committee for Athens 2004 Olympics
Hellenic Ministry of Education
Hellenic Ministry of Sports

Conference Sponsors

AstraZeneca
Belovo
California Walnut Commission/Walnut Marketing Board
Harokopio University
Hellenic American Union
Hellenic Football Federation
Mars, Inc.
Minami Nutrition/MorEPA/Barleans
National Dairy Council (USA)
Nutrilite Health Institute
World Cancer Research Fund International/American Institute for Cancer Research
Unilever

In Co-Operation with

Hellenic Association of Sports Medicine
Hellenic Institute of Sports Research, Athens
Hellenic Heart Foundation
National Institute on Alcohol Abuse and Alcoholism, NIH, USA
Onassis Cardiosurgery Center, Athens
University of Thessaly

Preface

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.

- 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 alpha-linolenic 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).

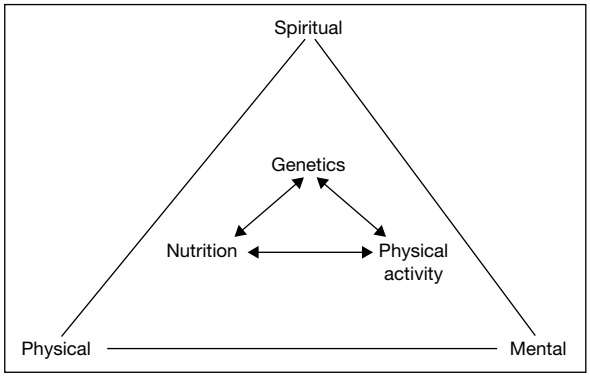


Fig. 1. The interaction of genetics, nutrition and physical activity influences the spiritual, mental and physical aspects of health.

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.

Table 1. Defining physical activity

1	Nonlabor daily physical activities
	Feeding
	Bodily functions (e.g. temperature regulation, heart rate, breathing rate)
	All daily nonlabor minimum physical activities necessary for life maintenance
2	Labor physical activities
	Industrial
	Agriculture
	Carpentary
	Homecare, etc.
3	Leisure-recreational (exercise), low-to-moderate intensity of physical activities
	Walking
	Dancing
	Hiking
	Bowling
	Cycling
	Golf, etc.

Education

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.

Declaration

(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 community, 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 children 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:

Alexander Leaf, MD (Cochairman), USA
Peter G. Bourne, MD (Cochairman), USA, UK
Richard B. Birrer, MD (Secretary), USA
Regina Casper, MD, USA
Ji Di Chen, MD, China
William Clay, FAO, United Nations
Loren Cordain, PhD, USA
S. Boyd Eaton, MD, USA
Gilman Grave, MD, USA
Philip R. Lee, MD, USA
Konstantinos N. Pavlou, ScD, Greece
Catherine Siandwazi, Tanzania, UK
Artemis P. Simopoulos, MD, USA

References

1 Simopoulos AP (ed): Proceedings of the First International Conference on Nutrition and Fitness. Am J Clin Nutr 1989;49(suppl):909–1124.

2 Simopoulos AP, Pavlou KN (eds): Volume I. Nutrition and Fitness for Athletes. Proceedings of the Second International Conference on Nutrition and Fitness. World Rev Nutr Diet. Basel, Karger, 1993, vol 71.

3 Simopoulos AP (ed): Volume II. Nutrition and Fitness in Health and Disease. Proceedings of the Second International Conference on Nutrition and Fitness. World Rev Nutr Diet. Basel, Karger, 1993, vol 72.
4 Simopoulos AP (ed): Volume I. Nutrition and Fitness: Evolutionary Aspects, Children, Health,Policies and Programs. Proceedings of the Third International Conference on Nutrition and Fit ness. World Rev Nutr Diet. Basel, Karger, 1997, vol 81.
5 Simopoulos AP, Pavlou KN (eds): Volume II. Nutrition and Fitness: Metabolic and Behavioral Aspects in Health and Disease. Proceedings of the Third International Conference on Nutrition and Fitness. World Rev Nutr Diet. Basel, Karger, 1997, vol 82.
6 Simopoulos AP, Pavlou KN (eds): Volume 1. Nutrition and Fitness: Diet, Genes, Physical Activity and Health. World Rev Nutr Diet. Basel, Karger, 2001, vol 89.
7 Simopoulos AP, Pavlou KN (eds): Volume 2. Nutrition and Fitness: Metabolic Studies in Health and Disease. World Rev Nutr Diet. Basel, Karger, 2001, vol 90.

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 overtraining 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 adults[1].

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] 'The 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.[2] 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 [1]. 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.

[2]The concept of a sound mind in a healthy body, mens sana in corpore sano, originated from the Roman satirist, Juvenal AD c.160–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 Olympism.[3] Their contribution to positive health lies in the potential to encourage people, especially children, to become more physically active.[4] And, there are added bonuses in being involved in sport that I will come to a little later.

[3]The 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.'

[4]The 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 folate 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.[5] 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

[5]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.[6] 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

[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.'

his and my stories is 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.[7] 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

[7]To 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.

References

1 Anthony D: Minds, Bodies and Souls: A Trilogy of the British Olympic Heritage Network. London, British Olympic Association, 1994.
2 de Coubertin P: Les Jeux Olympiques à Much Wenclock; In: La Revue Athlétique, 1, No.12 (December 1890). WOS 2nd MB, p 182.
3 Mullins S: British Olympians: William Penny Brookes and the Wenlock Games. London, British Olympic Association, 1986.
4 Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JW: Coronary heart disease and physical activity at work. Lancet 1953;ii:1053–1057, 1111–1120.
5 Paffenbarger RS, Hyde RT, Wing AL, Steinmetz CH: A natural history of athleticism and cardiovascular health. JAMA 1984;252:491–495.
6 Tanasescu M, Leitzmann MF, Rimm EB, et al: Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994–2000.
7 Lucock MD, Yates Z: A differential role for folate in developmental disorders, vascular disease and other clinical conditions: The importance of folate status and genotype; in Massaro EJ (ed): Folate and Human Development. Totawa, Humana Press, 2001, pp 263–298.
8 van Praag H, Christie BR, Sejnowski TJ, Gage FH: Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA 1999;96:13427–13431.
9 Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ: Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Brit. J Psychiatry 2002;181:22–28.
10 Wesnes KA, Pincock C, Richardson D, Helm G, Hails S: Breakfast reduces declines in attention and memory over the morning in schoolchildren. Appetite 2003;41:329–331.
11 Plato: The Republic. Part 111: Education, Book 111, Physical Education. London, Penguin Classics, 1987, p 109.
12 National Diet and Nutrition Survey: Young People aged 4–18 Years. London, Stationery Office, 2000.
13 Durnin JGVA: Physical activity levels – past and present; in Norgan N (ed): Physical Activity and Health. Cambridge, Cambridge University Press, 1992, pp 20–27.
14 Dietz WH: The obesity epidemic in young children. BMJ 2001;322:313–314.
15 Cheng TO: Obesity in Chinese children. JRSM 2004;97:254.
16 Giammatei J, Blix G, Marshak HH, Wollitzer AO, Pettitt DJ: Television watching and soft drink consumption. Arch Pediatr Adolesc Med 2003;157:882–886.
17 Hardman K, Marshall I: World-wide Survey of the State and Status of School Physical Education. ICSSPE Report, 2002.
18 Gilman MW, Rifas-Shiman SL, Frazier AL, Rockett HRH, Camargo CA Jr, Field AE, et al: Family dinner and diet quality among older children and adolescents. Arch Fam Med 2000;9:235–240.
19 Terkesidou L: The Golden Diet of the Ancient Olympic Winners. Athens, Kastaniotis Publishers, 2004.
20 House of Commons Health Committee: Obesity: Third Report of Session 2003–2004. Publication Parliament UK.
21 Venkat Narayan KM, Hoskin M, Kozak D, Kriska AM, Hanson AM, Pettitt DJ, et al: Randomized clinical trial of lifestyle interventions in Pima Indians: A pilot study. Diabet Med 1998;15:66F–72F.
22 Sennett R: Respect in a World of Inequality. New York, Norton, 2003.
23 Marmot MG, Bosma H, Hemingway H, Brunner E, Stansfield S: Contribution of job control and other risk factors to social variations in coronary hear disease. Lancet 1997;350:235–240.
24 Kuper H, Marmot M: Job strain, job demands, decision latitude, and the risk of coronary heart disease within the Whitehall II study. J Epidemiol Commun Health 2003;57:147–153.
25 'Whitehead finds answer to old puzzle' – article from MIT Tech Talk, May 17 1995. The work was reported in Cell.

26 Montgomery H: Renin-angiotensin systems and human performance. Genes in Sport Conference, 30 November 2001, UCL School of Human Health and Performance.
27 Luan J, Browne PS, Harding DJ, O'Rahilly S, Chatterjee KVK, Wareham NJ: Evidence for gene-nutrient interaction at the PPARy locus. Diabetes 2001;50:686–689.

Elizabeth Ferris, MBBS
Department of Nutrition and Dietetics
King's College London, Franklin Wilkins Building
150 Stamford Street, London SE1 9NH (UK)
Tel +44 1367 860313, E-Mail elizabeth.ferris@kcl.ac.uk

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 1–12

Criteria and Classification of Obesity in Japan and Asia-Oceania

Masao Kanazawa[a], *Nobuo Yoshiike*[b], *Toshimasa Osaka*[c], *Yoshio Numba*[d], *Paul Zimmet*[e], *Shuji Inoue*[f]

[a]The Third Department of International Medicine, Tokyo Medical University, [b]Division of Health and Nutrition Monitoring, and [c]Division of Human Nutrition, National Institute of Health and Nutrition, [d]Department of Geriatric Disease Medicine, University of Tokyo, Tokyo, Japan; [e]International Diabetes Institute, Caulfield, Vic. Australia; and [f]Department of Nutrition and Physiology, Kyoritsu Women's University, Tokyo, Japan

In developed and developing countries, morbidity and mortality rates are increasing in individuals classified as being obese [1–6]. The higher morbidity and mortality rates of obese people are due to the increased incidence of obesity-related (lifestyle-related) diseases. It is now recognized that different criteria of obesity by BMI are necessary in different ethnic groups and populations [7, 8]. In addition to the degree of obesity, other factors which increase the morbidity rate of obese people include abnormal fat distribution such as upper body obesity and visceral obesity [9, 10]. Recently, the definition of 'pathological obesity' has been made in Japan [11].

Definition of Obesity and Previous Criteria of Obesity

Obesity is defined as excessive fat accumulation but not over-weightedness. The average human body usually consists of 82% lean body mass, which is essential for sustaining daily life and physical activities, and 18% body fat which, in essence, is energy store for emergency situations [12]. Thus, obesity can be defined as 'overstorage of body fat beyond 18%'. Usually, body fat above 25% in men and 30% in women is considered to be obese. According to this definition, obesity should be determined by measuring body fat. Although there are presently many methods for measuring body fat, no methods can be conducted easily, accurately and inexpensively.

Obesity is, therefore, determined by three methods: (1) standard body weight; (2) physique index, or (3) skinfold thickness. Standard body weight was the most popular method applied throughout the world; however, standard body weight was determined differently in each country. Even in Japan, there were several scales of standard body weight [13–16]. However, these scales were not necessarily determined based on scientific evidence.

Under these circumstances, in 1992, the Japan Society for the Study of Obesity (JASSO) decided to unify and propose a standard body weight based on scientific evidence and an easily calculated method. At that time in Japan, Tokunaga et al. [17] reported that the incidence of obesity-related diseases was observed least frequently when the body mass index (BMI), one of the physique indices applied as an obesity marker, was about 22.

JASSO applied the results and determined standard body weight as 'a weight equivalent to BMI 22'. BMI is calculated by dividing body weight in kg by the square of the height in meters. Thus, standard body weight was determined as multiplying the square of height by 22 (height $(m)^2 \times 22$) [18].

Since we did not have enough data to determine obesity in those days, JASSO proposed the criteria for obesity as 20% overweight against standard body weight based on medical commonsense but not on medical evidence in 1992. The value of BMI 26.4 is equivalent to 20% above the standard body weight. According to that criteria, the prevalence of obesity in Japan was 13.69% in men and 15.58% in women [19]. In those days, Western countries already utilized the criteria of obesity as BMI $\geq$30. When we applied it, the prevalence of obesity was only 1.79% in men and 3% in women [19] (fig. 1).

New Criteria and Classification of Obesity in Japan

In 1997, the World Health Organization (WHO) initiated the International Obesity Task Force (IOTF) and assessed that obesity is a serious health hazard in developed and even in developing countries. With the assistance of the International Association for the Study of Obesity (IASO), they proposed the criteria of overweight as BMI between 25 and 30 and obesity as BMI above 30, respectively, based on Caucasian data proposed by Garrow [20].

In 1998, JASSO studied the relationship between degree of obesity (BMI) and hypertension, diabetes and hyperlipidemia (triglycerides, HDL-cholesterol and total cholesterol) with the assistance of the Japanese Ministry of Health and Welfare [21]. A total of 150,000 men and women above 30 years age were recruited from 15 cohorts in Japan. As shown in table 1, the incidences of hypertension, hyperlipidemia (hypertriglyceridemia, hypo-HDL cholesterolemia and total hypercholesterolemia) and hyperglycemia were increased in

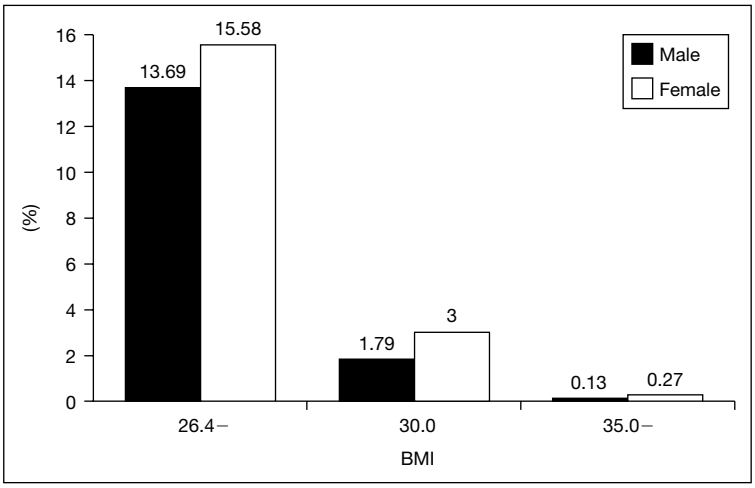


Fig. 1. Prevalence of obesity (BMI ≥26.49) in Japan. With permission, Int J Obes.

parallel with the increased degree of BMI. When we calculated the odds ratio for evaluating risks for suffering from these diseases, BMI 22 (BMI 20–23.9) was estimated as 1, and odds ratios around 2 times higher BMI were 25 in hypertension, hypertriglyceridemia and hypo-HDL-cholesterolemia, 29 in total hypercholesterolemia, and 27 in diabetes. All these values fell into the category of overweight or pre-obese by the WHO classification [20]. If we consider BMI ≥30 as obesity according to the WHO criteria, we cannot explain the rapidly increased incidences of closely obesity-associated diseases in Japan since the prevalence of obesity in this criteria is less than 3%, as described above.

As shown in figure 2, the prevalence of subjects with BMI ≥25 in these cohorts was 21.43% in males and 18.85% in females, which implies that about 20% (one fifth) were obese in Japan. It has turned out that this figure can explain the rapidly increased incidences of obesity-associated chronic diseases (lifestyle-related diseases) like diabetes, hypertension and hyperlipidemia. Taken together, JASSO decided to determine BMI ≥25 as obesity [11]. The proposed JASSO criteria for obesity in comparison with the WHO criteria is shown in table 2. JASSO replaced overweight in the WHO classification by obesity grade 1 in the JASSO classification, and divides obesity into four grades instead of the three grades used by the WHO divides. Recent results based on a Japan Nutritional Survey showed that the prevalence of obesity (BMI ≥25) reached almost 30% in males aged 30–60 years and females aged 50–70 years (fig. 3) [22]. The situation seems to be continuously worsening.

Table 1. BMI and comorbidities

EMI division		n	Incidence, %								
			~15.9	16~17.9	18~19.9	20~23.9	24~25.9	26~27.9	28~29.9	30~	total
Hypertension	Male	78,855	13.2	17.7	17.9	22.6	30.6	35.6	42.2	46.9	26.6
	Female	71,431	17.8	10.0	10.4	19.1	32.0	40.7	47.2	50.4	22.6
Hyper-	Male	76,076	10.7	11.3	14.5	23.6	29.4	32.0	36.3	36.8	25.6
cholesterolemia	Female	69,702	31.4	21.7	23.3	32.1	40.0	42.4	44.3	42.4	33.0
Hypo-HDL-	Male	76,066	1.8	3.6	4.2	9.3	15.7	19.7	24.1	28.1	12.3
cholesterolemia	Female	69,699	0.4	0.8	1.5	3.4	6.3	8.3	9.3	10.1	4.2
Hypertriglyceridemia	Male	74,639	6.3	10.6	13.2	28.2	42.7	50.2	55.9	60.3	34.1
	Female	67,417	5.9	5.0	8.7	18.9	31.8	36.9	41.3	44.2	21.3
Hyperglycemia	Male	43,555	6.0	8.1	6.7	8.1	8.5	11.3	15.0	15.4	8.9
	Female	25,101	8.2	3.6	3.3	4.7	8.6	11.8	16.4	19.4	6.0

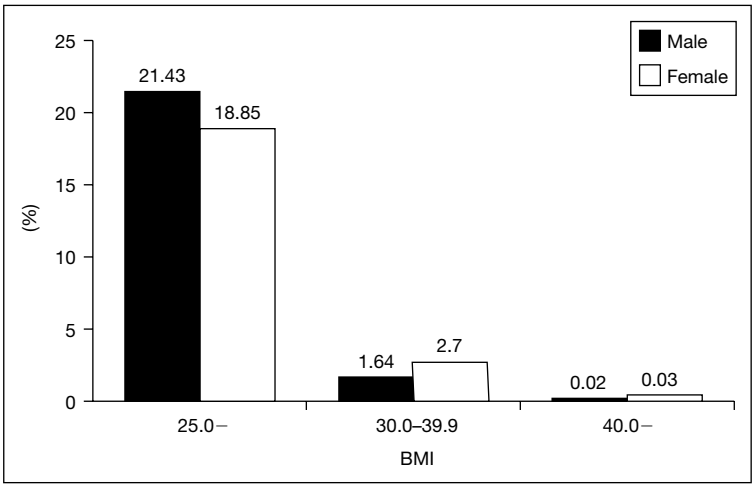


Fig. 2. Prevalence of obesity from a 15-cohort study in Japan according to the criteria of JASSO (BMI ≥25) and WHO (BMI ≥30) classifications.

Table 2. Classification of obesity in JASSO and in WHO

BMI	JASSO	WHO
<18.5	Underweight	Underweight
18.5≤～<25	Normal weight	Normal weight
25≤～<30	Obese class 1	Preobese
30≤～<35	Obese class 2	Obese class I
35≤～<40	Obese class 3	Obese class II
40≤	Obese class 4	Obese class III

To examine whether this criteria applies to people from the Asia-Oceania region, the member countries of this IASO region met in Hong Kong twice. We compared the data of seven countries (Japan, Korea, Philippines, Indonesia, Hong Kong, Malaysia and Thailand), and have come to the conclusion that the criteria of BMI ≥25 as obesity is appropriate for people from Asia-Oceania where the main energy intake comes from carbohydrates (about 60%). We installed the criteria of overweight as BMI between 23 and 25 since the data from Hong Kong clearly showed that the incidence of obesity-related diseases significantly increased in subjects with BMI ≥23 (table 3) [23]. Thus, we propose that BMI ≥25 should be the classification for obesity in the peoples of Asia-Oceania as a whole and not only for Japanese.

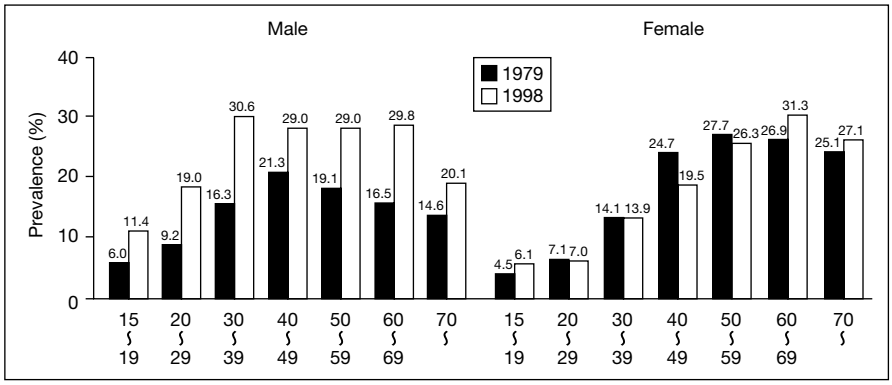


Fig. 3. Prevalence of obesity in Japan according to the Japanese Nutritional Survey in 1999. With permission, Japanese Ministry of Welfare and Labor.

Table 3. Proposed classification of weight by BMI in adult Asians

Classification	BMI	Risk of co-morbidities
Underweight	<18.5	Low (but increased risk of other clinical problems)
Normal range	18.5–22.9	Average
Overweight	≥23	
At risk	23–24.9	Increased
Obese I	25–29.9	Moderate
Obese II	≥30	Severe

The proposed criteria for obesity in Asia-Oceania are supported by the following results: (1) Chang et al. [24] compared values of BMI and body fat measured by dual X-ray absorptiometry (DXA), and found that BMI ≥25 kg/m^2 corresponds to ≥25% of body fat in men and ≥38% in women, implying that the determination of obesity by BMI is supported by body fat determination They also indicated that the level of % body fat for BMI ≥25 in the people of this region is similar to BMI ≥30 kg/m^2 in Caucasians. Recently proposed criteria of obesity based on evidence in this region indicates a BMI value between 25 and 30 (table 4).

In these situations, JASSO delivered the Tokyo Declaration, and the committee of the Asia-Oceania region published an obesity guideline called 'The Asia-Pacific Perspective Defining Obesity and Its Treatment' to appeal that obesity is a serious problem in Japan and Asia-Oceania and should be treated seriously [23].

Table 4. Different criteria of BMI for obesity

	BMI
WHO	≥30
WHO/WPR (WPPRO)	≥25
Japan	≥25
Bin; Chen (China)	≥25
Jia (China)	≥26
Zhang; Zhou (China)	≥28
Jun (China)	≥29
Lee (Hong Kong)	≥25
Ko (Hong Kong)	≥27
Tseng (Taiwan)	≥25
Lin (Taiwan)	≥27
Moon (Korea)	≥26.4
Chang (Korea)	≥25
Sykes (Singapore)	≥25
Vikram (India)	≥24
Mohan (India)	≥25
Misra (India)	≥24 (males), ≥23 (females)
Shiwaku (Japan)	≥25 Japanese ≥30 Mongolian

Differentiation of Pathological Obesity

The next issue to be determined was how to differentiate pathological obesity from simple obesity. In addition to the degree of obesity, fat distribution is an another important risk factor for the incidence of obesity-related diseases. Obesity is classified into two types according to fat distribution: (1) upper body obesity, or abdominal obesity, or male type obesity in which fat mainly accumulates in the upper abdominal area (so-called 'apple type obesity'), and (2) lower body obesity, or female type obesity in which fat mainly accumulates under the gluteal area (so-called 'pear type obesity') (fig. 4) [9]. Upper body obesity is more susceptible to obesity-related diseases [9, 25, 26]. Previously, the waist-hip ratio (W/H) was proposed to differentiate upper body from lower body obesity. However, recent evidence indicates that waist circumference is a more appropriate indicator [7, 28]. In Japan, waist circumference over 85 cm^2 in males and over 90 cm^2 in females is classified as upper body obesity [11].

It has also been reported that upper body obesity can be classified into two types by abdominal computed tomographic (CT) scanning: (1) visceral fat obesity, in which fat mainly accumulates around the visceral organs in the abdominal cavity, and (2) subcutaneous fat obesity in which fat mainly accumulates in

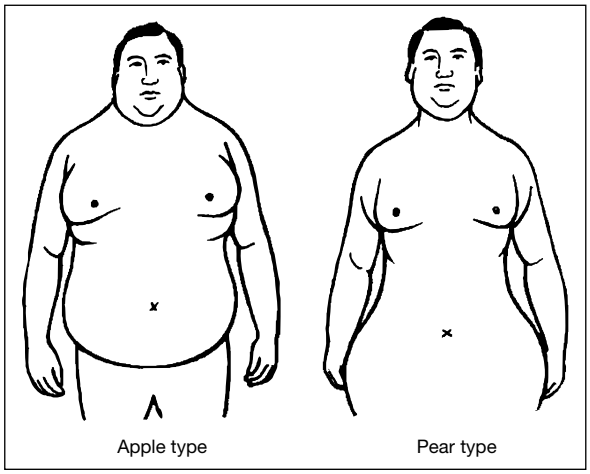


Fig. 4. Illustration of upper body (apple type) obesity and lower body (pear type) obesity.

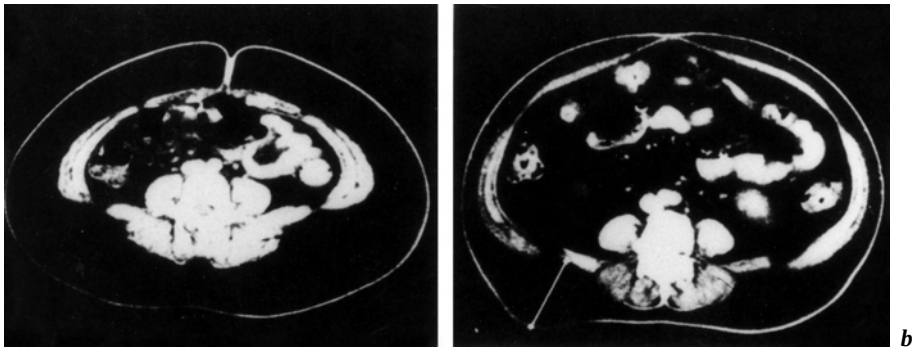


Fig. 5. Illustration of visceral fat obesity and subcutaneous fat obesity by abdominal CT scanning.

the subcutaneous tissue of the abdominal wall (fig. 5) [10]. Visceral fat obesity is more susceptible to obesity-related chronic diseases [10, 28, 29]. Previously, visceral obesity was proposed to be differentiated by the visceral fat area (V) and subcutaneous fat area (S)/(V/S) ratio [10]. It has also turned out that total visceral fat area is more appropriate to differentiate [28]. Total visceral fat area over 100 cm^2 is classified into visceral obesity in Japan [11]. We believe that a similar situation will be found in the peoples of Asia-Oceania where the main energy intake comes from carbohydrates. Under these circumstances, JASSO proposed the criteria for 'pathological obesity' or 'obesity disease' as the

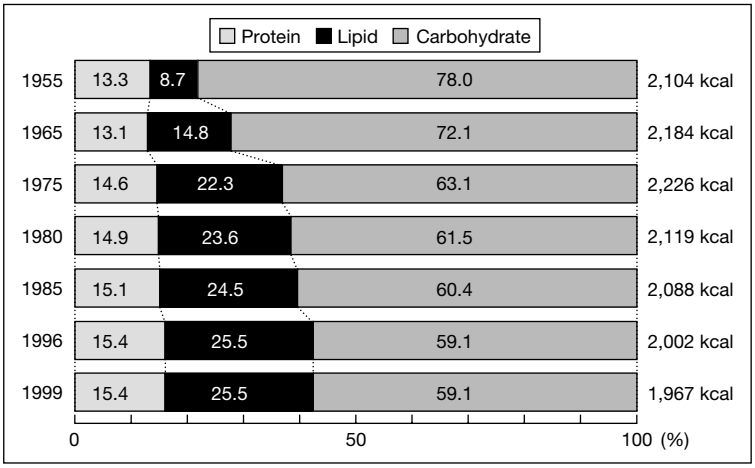


Fig. 6. Average daily energy intake and fat content in Japan between 1955 and 1999 according to a Japanese Nutritional Survey. With the permission, Japanese Ministry of Welfare and Labor.

following: In the case of BMI ≥25, we call either condition 'pathological obesity'. (1) conditions associated with obesity-related diseases such as diabetes, hypertension, hyperlipidemia, etc. – we list up 10 obesity-related chronic diseases in contrast to three diseases where risk factors for coronary heart disease were focused on in Western countries, or (2) visceral fat obesity is confirmed by CT scanning even without obesity-related chronic diseases [11].

Causes of Obesity in Japan

What causes the increased prevalence of obesity in Japan? Several causes have been advanced: (1) overeating; (2) wrong eating pattern; (3) physical inactivity; (4) heredity, and (5) disturbance in thermogenesis. Hyperphagia and inactivity are two major risk factors for obesity. Hyperphagia may be an important factor for the development of severe obesity; however, average energy intake in adult people in Japan has not been increased or rather declined during these 45 years according to the results of a National Nutritional Survey in Japan (fig. 6) [22]. During these periods, however, it is estimated that prevalence of obesity has increased 4 times in males and 3 times in females. This indicates that physical inactivity may be one of the main causes of the increased prevalence of obesity in Japan due to the reduction of energy expenditure. Energy expenditure constitutes 60% of basal metabolism, 30% of activity metabolism and 10% of diet-induced

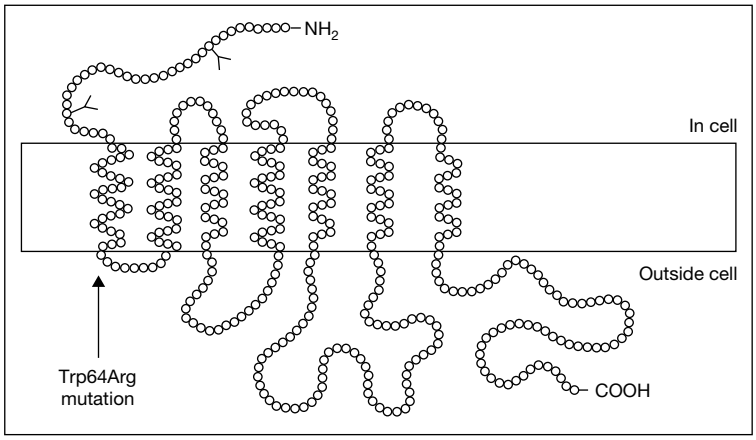


Fig. 7. Illustration of the structure of β_3-adrenergic receptor and its mutation.

thermogenesis. The effects of physical inactivity are as follows: (1) reduction of energy expenditure of physical activity, and (2) alterations in metabolism which includes (a) reduction of basal metabolism, (b) insulin insensitivity which leads to an increase in insulin in secretion, and (c) activation of lipogenic key enzymes, all of which contribute to the increase in fat accumulation. As we recognize, modern Japanese people live in energy-saving societies. They have excellent public transport systems, sophisticated machinery at their workplaces, and good electrical equipment in their homes. Figure 6 also indicates that an increased high fat content in energy intake may also contribute to the increased prevalence of obesity in Japan. During the 1970s, Japan experienced a rapidly increasing economic growth. During the same period, fat intake rose to 20% of the total energy intake, and the prevalence of obesity increased remarkably. Including an increase in fat intake, wrong eating patterns such as irregular meals, not having breakfast, gorging or night eating, which induces an energy-saving metabolism in modern people, also contributed to the increased prevalence of obesity in Japan.

Another contributing factor is genetic disorders. β_3-Adrenergic receptor is the site of thermogenesis in diet-induced or cold-exposure conditions. Figure 7 illustrates the structure of the β_3-adrenergic receptor. Point mutation of tryptophan to arginine at the 64th amino acid sequence reduces the capacity of diet-induced thermogenesis. This single nucleotide polymorphism (SNPs) was first reported in Pima Indians in the USA [30]. The incidence of this polymorphism is reportedly very high in Pima Indians, and around 80% of them become obese diabetics by 40 years of age [30]. Yoshida et al. [31] reported that the incidence of this abnormality was around 20% in the Japanese. This high incidence of the SNP may contribute to the increased prevalence of obesity in Japan.

Conclusion

JASSO decided to determine BMI ≥25 as obesity and classified obesity into 4 grades, whereas WHO determine BMI ≥30 as obesity and classified obesity into 3 grades. We propose that BMI ≥25 is appropriate for the criteria of obesity in the people of Japan and Asia-Oceania, where the main energy intake comes from carbohydrates. If these criteria are accepted by the WHO, we may claim that the degree of obesity is low, but obesity-related problems in Japan and Asia-Oceania are similar to those in Western societies. We also propose that different criteria for obesity should be accepted for different ethnic groups and populations based on medical evidence.

Inactivity including lack of exercise is a main cause for this mild obesity in Japan. Wrong eating patterns in modern life and genetic abnormalities in the Japanese may also contribute to the increased prevalence of obesity in Japan.

References

1 Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G: Influence of obesity on cardiovascular risk: Twenty-three-year follow up of 22 025 men from an urban Swedish population. Int J Obes 2002;26:1046–1053.
2 Kawada T: Body mass index is a good predictor of hypertension and hyperlipidemia in a rural Japanese population. Int J Obes.2002;26:725–729.
3 Huang KC, Lin WY, Lee LT, Chen CY, Lo H, Hsia HH, Liu IL, Shau WY, Lin RS: Four anthropometric indices and cardiovascular risk factors in Taiwan. Int J Obes 2002;26:1060–1068.
4 Oppert JM, Charles MA, Thibult N, Guy-Grand B, Eschwege E, Ducimetiere P: Anthropometric estimates of muscle and fat mass in relation to cardiac and cancer mortality in men: The Paris Prospective Study. Am J Clin Nutr 2002;75:1107–1113.
5 Tsugane S, Sasaki S, Tsubono Y: Under-and overweight impact on mortality among middle-aged Japanese men and women: A 10-y follow-up of JPHC study cohort I. Int J Obes 2002;26:529–537.
6 Meyer HE, Johanne SO, Gaard A, Tverdal A, Selmer RM: Body mass index and mortality: The influence of physical activity and smoking. Med Sci Sports Exerc 2002;34:1065–1070.
7 WHO Expert Consulation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163
8 Anuurad E, Shiwaku K, Nogi A, Kitajima K, Enkhmaa B, Shimono K, Yamane Y: The new BMI criteria for Asians by the Regional office for the western pacific region of WHO are suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers. J Occup Health 2003;45:335–343.
9 Kissebah AH, Vydelingum N, Murray R, Evans DJ, Havtz AJ, Kalkhoff RK, Adams PW: Relation of body fat distribution to metabolic complications of obesity. J Clin Endocr Metab 1982;54:254.
10 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987;36:54–59.
11 Matsuzawa Y, Inoue S, et al: A new criteria of judgment of obesity and diagnosis of pathological obesity (in Japanese). J Jpn Soc Study Obesity 2000;6:18–28.
12 Widdowson EM, McCance RA, Spray CM: The chemical composition of the human body. Clin Sci 1951;110:113–125.
13 Matsuki S: Judgment of obesity (in Japanese). Nihon Ishikai Zashi 1972;68:916–932.
14 Minowa S: Judgment of obesity (in Japanese). Koushueisei 1980;46:520–527.

15 Japan Ministry of Public Welfare: Tables and Figures for Judgement of Obesity and Leanness (in Japanese). Tokyo, Dai-ichi, 1986.
16 Tsukamoto H, Tamura M: Physical constitution from a view of mortality rate. Tables of Meiji Life Insurance Company's Standard Body Weight (in Japanese). Kosei no Shihyou 1986;33:3–14.
17 Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Fujioka S, Tarui S. Ideal body weight estimated from the body mass index with the lowest morbidity. Int J Obes 1991;15:1–5.
18 Japan Society for the Study of Obesity: Obesity – Guideline for Diagnosis, Treatment and Management (in Japanese). Tokyo, Ishiyaku,1993.
19 Yoshiike N, Zaman MM, Matsumura Y, Yamaguchi M: Descriptive epidemiology of body mass index in Japanese adult a representative sample from the national Nutrition Survey 1990–1994. Int J Obes 1998;22:684.
20 Report of a WHO Consultation on Obesity: Obesity – Preventing and Managing the Global Epidemic. Geneva, WHO/NUT/NCD, 1997.
21 Yoshiike N, Inoue S, et al: Relation between body mass index and risk for diabetes, hypertension, hyperlipidemia: An epidemiological study by multicenter cooperative study (in Japanese). J Jpn Soc Study Obes 2000;6:4–17.
22 Japanese Ministry of Health and Welfare: Nutritional Status of Japanese People: The Results of National Nutritional Survey in 1999 (in Japanese). Tokyo, Dai-ichi, 2001.
23 WHO Western Pacific Region, International Association for the Study of Obesity: The Asia-Pacific perspective: Redefining obesity and its treatment. Sydney, Health Communications Australia, 2000.
24 Chang CJ, Wu CH, Chang CS, Yao WJ, Yang YC, Wu JS, Lu FH: Low body mass index but high percent body fat in Taiwanese subjects: Implications of obesity cutoffs. Int J Obes 2003;27:253–259.
25 Pascot A, Lemieux I, Prud'homme D, Tremblay A, Nadeau A, Couillard C, Bergeron J, Lamarche B, Despres JP: Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. J Lipid Res 2001;42:2007–2014.
26 Hunter GR, Giger JN, Weaver M, Strickland OL, Zuckerman P, Taylor H. Fat distribution and cardiovascular disease risk in African-American women. J Natl Black Nurses Assoc 2000;11:7–11.
27 Lean MEJ, Han TS, Seidell JC. Impairment of health and quality of life in people with large waist circumference. Lancet 1998;351:853–856.
28 Pouliot MC, Despres JP, Lemieux S, Moorzani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ: Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–468.
29 Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Waliul I AAHM, Keno Y, Kobatake T, Nagai Y, Fujioka S, Tarui S, Matsuzawa Y: Contribution of visceral fat accumulation to the development of coronary artery disease in nonobese men. Atherosclerosis 1994;107:239–246.
30 Walston, J, Silver K, Bogardus C, Knowler WC, Celi FS, Austin S, Manning B, Strosberg AD, Stern MP, Raben N, et al: Time of onset of non-insulin-dependent diabetes mellitus and genetic variation ion the β_3-adrenergic-receptor gene. N Engl J Med 1995;333:343–347.
31 Yoshida T, Sakane N, Umekwa T, Sakai M, Takahashi T, Kondo M: Mutation of β_3-adrenergic-receptor gene and response to treatment of obesity. Lancet 1995;346:1433–1444.

Shuji Inoue, MD, PhD
Department of Nutrition and Physiology
Kyoritsu Women's University, 2-2-1 Hitotsubashi, Chiyoda-ku
Tokyo 101–8433 (Japan)
Tel. +81 3 3237 2477, Fax +81 3 3237 2688, E-Mail ishuji@s1.kyoritsu-wu.ac.jp

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 13–26

Exercise and Obesity in China

C. Chang

Institute of Sports Medicine, 3rd Hospital, Peking University, Beijing, China

Obesity is a chronic metabolic disease caused by the interaction of genetic and environmental factors, which is defined as a condition in which there is an excess of body fat. According to the etiopathogenesis, over 95% of obese sufferers have simple obesity. The occurrence of simple obesity is closely associated with genetics, unhealthy dietary patterns and inactivity or exercise deficiency. Obesity is related to several chronic conditions such as type 2 diabetes, hypertension, cardiovascular disease and some cancers, as well as itself an independent chronic disease [1].

Although it is not a communicable disease, obesity has been listed as an epidemic by the World Health Organization (WHO) because of its global epidemic proportions, which are increasing rapidly. At present, China is in a stage of social-economic transformation, and the changes in people's life style and dietary patterns have led to the prevalence and incidence of obesity increasing dramatically in China. This has led to an increase in the prevalence such obesity-related conditions as type 2 diabetes, hypertension and cardiovascular disease, and lowered the quality of life of obese people. A series of health, social and psychological problems related to obesity are attributed to obesity. In order to improve the Chinese people's health condition, elevate the quality of life, and prolong an energetic life span, it has become an imminent task to prevent and control obesity.

For prevention of obesity in the Chinese population, the Working Group on Obesity in China (WGOC) of the International Life Sciences Institute Focal Point in China, which was set up in 2000, consisting of epidemiologists, nutritionist, endocrinologist, professionals of angiocardiopathy, sports medicine and child health care, issued the body mass index (BMI) cut-off point for overweight and obesity in Chinese adults in April 2002. In April 2003, the guidelines for prevention and control of overweight and obesity in Chinese adults recommended by WGOC was approved and published by the Ministry of Health of

China. In November 2003, WGOC issued a draft recommendation of BMI classification standard for Chinese children aged 7–18 years for discussion.

An active life style and a healthy diet can effectively improve fat metabolism and reduce fat accumulation in body. Adjusting the dietary pattern and regular physical activity is recognized as an economic, effective and safe approach to prevent and treat obesity, as well as the best program to manage body weight scientifically during one's lifetime. This paper will review the prevalence of obesity in China and the role of physical activity or exercise in the occurrence of obesity, and the exercise prescription on weight reduction.

Assessment and Classification of Overweight and Obesity

Body mass index (BMI), which is defined as weight/height (kg/m^2), and waist circumference (WC) are the most widely used to measure and classify obesity in adults. BMI generally correlates highly with whole body adiposity and WC is a good index to measure visceral or abdominal obesity. In 1997, the WHO clearly defined the various classifications of overweight and obesity [2]. Overweight is defined as BMI equal to and greater than 25; obesity is defined as BMI equal to and greater than 30, WC equal to and greater than 94 cm for men and 80 cm for women. However, these criteria may not be appropriate in Asian or Pacific Island populations. Indeed, Asians such as Indians, Japanese and Chinese are predisposed to visceral or abdominal obesity. The increased risk associated with obesity occurs at lower BMIs in these population [3], because people with abdominal obesity have a higher level of body fat than the adiposis universalis ones at the same value of BMI. In China, the body fat level of women is 30% in BMI 21–22, reaching 31.5% in BMI 23–24; for men, the body fat level is 26% in BMI 25–26 [4]. Compared with the WHO criteria to classify overweight and obesity, the type of obesity in the Chinese population is different from Western ones, so the Chinese should have their own BMI classification standards. WGOC, therefore, under the support of International Life Sciences Institute Focal Point in China, organized a meta-analysis on the relation between BMI, WC and risk factors of related chronic diseases [5–8]. On the basis of the cross-section analysis of 239,972 adults (20–70 years) and perspective analysis of 80,000 adults surveyed in the 1990s, including 21 provinces, municipalities and autonomous regions in mainland China as well as in Taiwan, BMI at 24 or over 24 was recommended as the cut-off point for overweight men and women, 28 for obesity. Waist circumference beyond 85 cm for men and beyond 80 cm for women were recommended as the cut-off points for central obesity. The recommendation of the BMI classification and comorbidities risk associated with different levels of BMI and waist circumference are presented in table 1 for Chinese adults.

Table 1. Risk of comorbidities associated with different levels of BMI and waist circumference in Chinese adults

Classification	BMI, kg/m^2	Risk of comorbidities Waist circumference, cm		
		<85 (men) <80 (women)	85–95 (men) 80–90 (women)	≥95 (men) ≥90 (women)
Underweight	<18.5	–	–	
Normal range	18.5–23.9	–	Increase	Severe
Overweight	24.0–27.9	Increase	Severe	Very severe
Obesity	≥28	Severe	Very severe	Very severe

Adopted from 'Guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults'.

Table 2. Draft recommendations on BMI classification for Chinese children aged 7–18 years

Age, years	Boys		Girls	
	Overweight	Obesity	Overweight	Obesity
7–	17.4	19.2	17.2	18.9
8–	18.1	20.3	18.1	19.9
9–	18.9	21.4	19.0	21.0
10–	19.6	22.5	20.0	22.1
11–	20.1	23.6	21.1	23.3
12–	21.0	24.7	21.9	24.5
13–	21.9	25.7	22.6	25.6
14–	22.6	26.4	23.0	26.0
15–	23.1	26.9	23.4	26.9
16–	23.5	27.4	23.7	27.4
17–	23.8	27.8	23.8	27.7
18–	24.0	28.0	24.0	28.0

As children are still growing, the adult BMI cut-off is not considered appropriate for children. In November, 2003, WGOC issued 'The recommendation of the BMI classification for Chinese children aged 7–18 years' (table 2). The draft recommendation took BMI at the 85th percentile as the cut-off for overweight, the 95th percentile as the cut-off for obesity of the age groups [9], which is based on the meta-analysis with 3 data sets: (1) Data collected by 2000

National Survey on Fitness and Health of School Children, with exclusion of children stunted and wasted, the reference sample population (RSP) consists of 242,575 children aged 7–18 years. (2) Database on BMI and blood lipid profile (TC, TG, HDL-C) of 2,293 children aged 10–18 years collected in Beijing. (3) Database on BMI and blood pressure of 4,982 children aged 7–15 years collected in Beijing in 2001.

Prevalence of Obesity in China

The Prevalence of Obesity Is Lower than in the Developed Countries or Western Societies, but Is Increasing Rapidly

The prevalence of obesity (BMI ≥30) in Europe and America is about 20%. According to data of the National Health and Nutrition Examination Survey III (NHANES III, 1988–1994), 39.4% adult men and 24.7% women were overweight, 19.8% men and 24.9% women were obese in the United States [10]. In 1999, the overweight were 34%, the obese 27% [11].

It is known that the Chinese population has one of the lowest BMI in the world, and the prevalence of obesity was less than 3% (using WHO standard for obesity, the same as follow) until 1992 [12]. However, with rapid development and economic improvement, and the people's elevated living standard, there was a dramatic increase in the prevalence of overweight and obesity in the Chinese [6, 13–16], especially in children and adolescents. In the National Nutrition Survey of 1992 [13], 14.4% of adult aged 20–74 years were overweight, 24.6% in urban regions and 10.4% in rural regions; 1.5% was obese, 2.9% in urban regions and 1.0% in rural regions, far less than the developed countries of Europe and America at the same time. Meta analysis of the data from 240,000 adult aged 20–70 years in 1990s indicated that 22.4% were classified as overweight, 3.0% as obese [6]. If applying the Chinese BMI cut-off point, 26.0% (24≤ BMI ≤27.9) were classified as overweight, 7.6% (BMI ≥28) as obese. On the basis of data from 42,751 subjects aged 20–74 years who had lived in the communities for no less than 5 years in 11 provinces, autonomous regions and municipalities of China from July 1995 to June 1997, Wang et al. [14] reported that the prevalence rate of overweight and obesity were 21.51 and 2.92%, respectively. The age-standardized prevalence rates of overweight and obesity were 18.28 and 2.48%, respectively. Compared with 1992, the prevalence rate of obesity increased 2.48 and 2.19 times in urban men and women, 1.26 and 3.69 times in rural men and women, respectively. In 5 years, the annual incremental rate of obesity in urban and rural adult men and women reached 25.49, 21.71, 11.76 and 38.56%, respectively. Other available data from representative population samples suggested that the prevalence of

Table 3. Prevalence of overweight and obesity for boys and girls aged 7–22 years in China, 1985–2000

Area		Overweight		Obesity	
		Boys	Girls	Boys	Girls
Urban	1985	1.42	2.02	0.27	0.22
	1995	6.79	5.12	2.65	1.59
	2000	11.07	7.36	5.72	2.94
Rural	1985	0.65	2.23	0.06	0.10
	1995	2.50	3.56	0.69	0.48
	2000	4.85	4.71	1.90	1.15

The Chinese children BMI classification standard was applied.

overweight and obesity increased at a surprising speed in China, which started to show significant increases from the early 1990s, but more prominently in the late 1990s [15–16]. The authors investigated 15,389 middle-aged men and women from 15 natural populations all over China with different geographical, economical (urban and rural) and occupational status in 1998, and compared with the matching data of 1980–1984 and 1992–1994. The results showed that the average prevalence rate of overweight rose 137% in adult men, 95% in adult women during the 16 years between 1980s and 1990s. In some of the population, such as Beijing dwellers aged 35–59 years, 50–60% were overweight in 1998 [15]. The National Survey on Fitness and Health of Citizens in 2000 found that 10% of boys and 5% of girls aged 7–18 years were obese, being 1.7 and 1.6 times of 1995, respectively [16].

In China, the ratio of overweight to obesity is now 7.39 to 1, much higher than that in Europe and America (2 to 1, or 1 to 1), which indicates that most of Chinese overweight are pre-obese. On the other hand, China has a higher prevalence of overweight and obesity in children and adolescents. The prevalence of overweight and obesity across the three National Survey of Fitness and Health of School Children is presented in table 3 for boys and girls aged 7–22 years [9]. All of these data suggest that there is a great potential risk for obesity to further increase in China.

District Differences: Higher in the North than the South, and Higher in Urban than in Rural Areas

The National Sampling Survey on Hypertension in 1991 was carried out in 950,356 men and women aged 15–75 years from 30 provinces, autonomous

regions and municipalities of China (not including Taiwan). The results showed that the average BMI of the Chinese population was 21.4 kg/m^2, the northern had a higher BMI (>22.0) than the southern (<21.0) [17]. The same conclusion was obtained from Wang et al. [14] and Wu et al. [15] reports in 1998. The population standardized prevalence of obesity was 2.5% for men and 4.4% for women in the north, higher than that in the south (1.25% of men and 1.90% of women). In urban regions, the standardized prevalence of obesity was 2.48% for men and 3.73% for women, comparable figures for rural regions were 0.78 and 2.58% [14]. In the 31 Province and Municipalities Nutrition Survey on 72,800 Young Men aged 17–21 years of 2001, the Chinese BMI cut-off point was applied and 8.7% were classified as overweight and 2.2% as obese in the urban regions compared to 4.7 and 0.8% in the rural regions Northern China had the highest level of overweight and obesity, which was 11.0 and 3.1%; Middle and Southern China had the lowest level, which was 3.4 and 0.6% [18].

In addition, the prevalence of obesity in the economically developed region of the south increased quickly with the rapid economic progress of the southeast and along the coast. In 2001, there were 26.6% of men and women in Shenzhen city and 29.6% of men and women in Beijing city classified as overweight (BMI ≥25) [19–20]. These figures show that the gap in prevalence of obesity caused by different diets, and economic and cultural differences, have been getting less and less between the northern and the southern regions.

Gender-Related Variation

A gender-related difference in prevalence of overweight and obesity was evident. In the early 1990s, Chinese women had a higher level of overweight and obesity [13, 17]. In 1991, the average BMI of women was generally 0.1–0.7 higher than men. There were 56.9% of men and 51.4% of women with a BMI between 19.0 and 22.9, but 10.2% of men and 14% of women with a BMI greater than 25 [17]. The same results were observed in the data of 1992, the women's BMI was higher than for men of the same age. The BMI of men and women increased with aging, but the increasing speed was faster in women than in men. The prevalence of overweight and obesity was 14.99 and 1.89% for women, both higher than for men (10.51 and 1.07%) [13].

In the late 1990s, a new feature of prevalence of overweight and obesity appeared between men and women [14, 21]. In 1997, the prevalence of obesity in women was 1.7 times higher than in men, but the prevalence of overweight in men was equal to or even higher than for women. The ratio of overweight to obesity in men was higher than that for women during every age, but also in the

south (men 13.59:1, women 8.18:1) or the north (men 8.78:1, women 5.08:1), in urban regions (men 9.50:1, women 5.75:1) or rural regions (men 13.81:1, women 6.02:1) [14]. During the 5 years of 1992–1997, the annual incremental rate of prevalence of obesity was 25.49% of men and 21.71% of women in the urban region [14], which meant that the increasing speed of obesity in men had exceeded that of the women. Zhang et al. [21] also reported that the adult men had a higher level of overweight and class I obesity than the women, the average age of men was lower than women in the same BMI group. All of the above figures suggested that the increasing situation of obesity in men may be more serious than in women.

Trend to Lower Age in Obesity Prevalence

The prevalence of overweight and obesity increased with aging and reached the peak at the age of 45–55 years [13, 14, 19, 22]. China is about to become an aging society, and it is inevitable that the obese population will increase. The recent surveys found that the risk of overweight and obesity in the 30-year-old group had increased significantly [14, 22], indicating that overweight and obesity in Chinese adults begins at an earlier age.

Physical Activity and Weight Control

The principles of thermodynamics dictate that increases in caloric intake, decreases in energy expenditure, or both can lead to obesity. The increased prevalence of obesity in China was closely related to both of the above. The change of dietary patterns and deficiency of physical activity can make contributions to obesity in China. Traditional Chinese dietary patterns were characterized by with low-fat, low-energy density, high carbohydrate and high fiber. Since 1985, the traditional dietary pattern has changed deeply, showing a decrease of cereal and vegetables, and a rapid increase of meat and oil and fat [23]. Du et al. [23] investigated the implications of dietary transitions in China during the past 50 years. Data were collected from the representative national surveys, China Health and Nutrition Survey (1989–1997), China National Nutrition Survey (1982–1992), Annual Household Consumption Surveys of the State Statistic Bureau and the Annual Death Report of China. The results showed that in the early part of the major economic transformation, cereal intake increased before 1985 and decreased thereafter. There was also a long-term reduction of vegetable consumption, which has now stabilized. Intakes of animal products increased slowly before 1979 but more quickly after the

economic reforms. The total energy intake is reduced, as energy expenditure has, and large changes in the composition of energy have occurred. The percentage of energy from dietary carbohydrates declined from 70–80 to 53–60%, while the percentage of energy from fat increased from 19.3 to 27.3% on average and 32.2% in urban residents in 1997. More than one third of all Chinese adults and 58.7% of adults in urban areas consumed over 30% of their energy from fat. These changes resulted in rapid increases of the prevalence of overweight and obesity and death related to chronic diseases in urban residents. Meanwhile, unhealthy eating behavior contributed to the prevalence of obesity in China as more and more people go out for dinner, which means a lot of food eaten, not eating breakfast, eating fast food, and often eating high fat and caloric dense food and snacks [24].

The decrease in energy expenditure from lack of physical activity was also an important cause leading to the increases of obesity in the Chinese population. Although there are not direct data on population levels of energy expenditure, physical activity levels in the population appeared to decline during the past decades. It seemed likely that the decline in energy expenditure was due to the great changes of gradually engineering out of daily life the need to expend energy. Some more prominent examples of this trend included the increasing mechanization in the workplace, modern vehicles, labor-saving devices for the house, and the ubiquitous use of computers at work and at home. According to the China Health and Nutrition Survey of 1997, the proportion of both men and women engaging in heavy physical labor decreased, but increased in light physical labor in urban areas. In rural areas, the proportion of people engaging in light physical labor did not change, but increased relatively in heavy physical activity for both men and women [23]. A survey on the correlation between physical activity and other risk factors of cardiovascular disease in the middle-aged population reported that the average time for physical activity of heavy and medium intensity in a day was 20.7% in rural dwellers, significantly higher than that in urban dwellers (7.2%); no time or less time for physical activity in rural dwellers was less than in urban dwellers [25]. The physical inactivity trended to increase the risk of cardiovascular diseases related to obesity. These differences of physical activity level between city and countryside were consistent with the prevalence seen in overweight and obesity in China, being higher in the city than the countryside.

Besides the decline of occupational physical activity, leisure physical exercise and fitness-related activities were not sufficient either. Investigation on the physical activity of 1,112 civil servants from 9 provinces of Eastern China showed that 92.1% of women and 78.8% of men performed exercise or physical activity less than 3 times per week, 77.3% of women and 22.7% men less than 30 min per day [26]. Another investigation on adult women reported that

60.06% took part in physical exercise, the average exercise time was 3.82 h per week (0.55 h/day), but only 20% often did it [27].

An additional problem is that many overweight or obese individuals are sedentary and unfit. These persons simply cannot perform large amounts of exercise, at least over the short-term. A sedentary lifestyle may have been the major factor that led to obesity. Bell et al. [28] studied motorized transportation and obesity in China based on the cross-sectional data (1997) of 4,741 Chinese adults aged 20–55 years from eight provinces and the Cohort data (1989–1997) of 2,485 adults aged 20–45 years in 1989 (59% follow-up). The results showed that the odds of being obese were 80% higher for men and women in households who owned a motorized vehicle compared with those who did not own a vehicle. Compared with those whose vehicle ownership did not change, men who acquired a vehicle experienced a 1.8-kg greater weight gain and had 2 to 1 odds of becoming obese. On the other hand, the sedentary persons enjoy spending most of their leisure time on indoor recreation such as watching television and playing electronic games instead of exercising or being active outdoors. The other factors of limiting outdoor activity are crowded living conditions caused by population increases, relatively and absolutely insufficient exercise facilities, and severe air pollution.

Exercise Prescription for Weight Reduction

Prevention and treatment of obesity have not short circuited. Weight reduction needs a measure combined with dietary restriction, regular moderate exercise, improving unhealthy life styles, and pharmacotherapy. As it is not likely to control or manage weight lifelong by depending on medicines, a combination of appropriate caloric restriction and regular moderate exercise is the major approach to weight loss [29].

It is clear that regular moderate physical activity is helpful for weight control and maintenance of weight loss, as well as overweight or obese individuals obtaining important health benefits from activity. Adherence to formal exercise programs is typically poor, particularly among obese individuals. According to the present basal theory study and applying research achievement, the exercise prescription for weight reduction should be as follows [30].

1. Exercise mode: Aerobic exercise recommended, a kind of rhythmic low resistance dynamic exercise, such as walking, jogging, bicycling, rope skipping, dancing, swimming, mountain clamping and activities using various kinds of balls, etc. These dynamic rhythmic exercises of multiple muscles are known as the effective exercises for weight loss. When selecting an exercise, It should be treated according to personal interest and

health condition. It is better to select the exercise or activity you enjoy and you can perform throughout all your life.

2. Exercise intensity: Moderate or low intensity, equivalent of 50–70% VO_2max, 3–6 mets, 60–70% of the greatest predicted heart rate, Borg score 9–11, a little tired or slightly tired of perceived exertion. Exercise at moderate or low intensity can burn the body fat effectively [31]. For overweight individuals, vigorous exercise may be uncomfortable or even painful, only medium or low intensity exercise can be accepted and performed continuously. A study of Weyer et al. [32] indicated that the exercise scheme, 3–6 mets, 30 min per day, all days of the week, recommended by American Center of Disease Control and American College of Sports Medicine, have reached good effects on weight loss.
3. Exercise duration: 30–60 min per day recommended, but 60–120 min per day better [33–34]. The total exercise times can be accumulated throughout a day, but 10–20 min or more per session is encouraged for effective body fat loss.
4. Exercise frequency: 3–5 days per week, preferably all days of the week. Exercise does not produce any efficiency until it is accumulated to the extent.
5. Appropriate resistance and stretch exercise: 2–3 days per week, 10–15 min each day, so as to train the body. It is not easy to get obese when you are increasing the skeletal muscle weight of the body.
6. Abdominal exercise: Such as sit ups, abdomen massage, 1–2 times each day, 3–5 days of the week. To aim at the central obesity, it is necessary to perform abdominal muscle exercise for increasing abdominal muscle strength.

Exercise Strategy for Weight Reduction

Weight reduction requires a long-term approach. The process of weight reduction requires time to establish a healthy lifestyle and good living habits. There should be no sense of hunger or being uncomfortable with exercise during the whole phase of weight reduction. Although regular physical activity is beneficial for the prevention of weight gain and weight maintenance, regular participation in physical activity does not make all people thin. For weight loss, no matter what exercise you do, the key point is to exercise at low and moderate intensity for a long time. Weight reduction is not merely weight loss, body fat loss is more important. The exercise prescription should keep to the individual's ability and present activity levels, trying to meet individual need. The individualized prescription should be practicable and convenient, avoiding over exercise and

preventing injury. The speed of weight reduction should not be too quick, generally recommended at 2–4 kg/month. In addition, the diet should be restricted and adjusted appropriately according to the exercise amount at anytime.

For the overweight or obese individual with a low level of physical activity, exercise should be performed on their current level of activity to establish a baseline, then gradually increase the activity to meet the goal, step by step from small to a large amount of exercise, from endurance to resistance exercise, from easy to a more strenuous activity. Activity can be accumulated throughout the day. As individuals become more physically fit, they are able to exercise comfortably at a higher intensity and are able to achieve any given amount of exercise in a shorter period of time.

For the obese person who says there is no time to exercise, it is recommended to increase routine daily physical activity and try to be more active every day, such as riding a bicycle or walking to work instead of going by bus, taking the stairs instead of the elevator, standing instead of sitting if possible, walking after meals, watching less TV, etc. There is much evidence that behavioral interventions to increase lifestyle physical activity are effective in promoting weight loss and healthy outcomes [35–37]. A major benefit of regular physical activity is in the preservation of weight loss once it has been achieved. Help the person with changing their opinion on exercise, thinking of activity as a chance to improve health instead of wasting time, exercise is a kind of enjoyment and improvement of health without side effects; strengthening the opinion of exercise throughout life. Encourage the persons to become and stay physically active.

According to the above principle, a weight reduction strategy should include three phases: an adaptive phase, a weight reduction phase, and a maintaining or solidifying phase.

1. Adaptive phase: Weight loss by physical activity requires a long-term view and can be enhanced by helping overweight or obese individuals first become physically fit so that they are capable of sustaining larger increases in energy expenditure. During this phase, the aim is to cultivate a good habit of exercise or physical activity, and enhance muscle and joint range of motion, making the body adapt to exercise; the set goal is 300 kcal to be consumed by exercise. It generally takes 1–2 weeks or 1 month, based on the present activity level.
2. Weight loss phase: The aim is to reduce body fat and increase fitness. The set goals are to decrease 5–10% of current weight at a rate of 2–4 kg per month, 500–600 kcal lost through exercise. It generally takes 3–6 months or more to accomplish this.
3. Maintaining and solidifying phase: The aim is to keep on and maintain a fit and active lifestyle, establishing a new energy balance at a lower energy

level. The set goals are to consume 300 kcal or more by exercise. It generally takes 6–12 months or more. Diet restriction appears to be a more successful avenue to achieve short-term weight loss. Adding 30–60 min of physical activity three times a week to a caloric restriction program increases the amount of weight lost by approximately 2 kg. Physical activity appears to be crucial for maintaining weight loss once it has occurred. Most lost weight is regained over 1 or 2 years, unless the individual becomes and stays physically active.

Conclusions

Overweight and obesity have reached epidemic proportions in China with the characteristics of a rapid increase (evident district differences, gender-related variation, and trend to an earlier age) in the prevalence and incidence. With the economic reform comes the change of diet patterns and reduction of physical activity, which make a major contribution to the rapid increase of obesity in the Chinese population. In order to prevent and control the prevalence of obesity in China, the WGOC issued the classification standard of weight by BMI in adult Chinese and a draft recommendation of BMI classification standard for Chinese children aged 7–18 years. Meanwhile, the Ministry of Health of China published the guidelines for prevention and control of overweight and obesity in Chinese adults. Regular physical activity is helpful for weight loss, prevention of weight gain and maintenance of weight loss. Weight reduction is only achieved in the long term. An exercise prescription for weight reduction should keep to the individual's ability and their present physical activity level. Three stages, i.e. adaptive phase, weight loss phase, maintenance and solidification phase, were recommended in the exercise strategy for weight reduction.

References

1 World Health Organization: Obesity Preventing and Managing. The Global Epidemic. Report of a WHO Consultation on Obesity. Geneva, WHO, 1997, pp 3–5.
2 World Health Organization: Obesity: Preventing and Managing the Global Epidemic. Geneva, WHO, 1998.
3 Kissebah AH, Krakower GR: Regional adiposity and mortality. Physiol Rev 1994;74:761–811.
4 Bray GA: Contemporary Diagnosis and Management of Obesity. Newtown, Handbood in Health Care, 1998, p 13.
5 Coorperative Meta-analysis Group of China Obesity Task Force of International Life Sciences Institute Focal Point in China. Recommendation on BMI classification for Chinese adults (in brief). Chin J Prev Med 2001;35:349–350.
6 Cooperative Meta-analysis Group of China Obesity Task Force: Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. Chin J Epidemiol 2002;23:5–10.

7 Zhou BF: Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults – study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci 2002;15:83–96.
8 Zhou BF: Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases – report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. Biomed Environ Sci 2002;15:245–252.
9 Ji CY: Recommendations on BMI Classification for Chinese Children and Adolescents. Conference on Obesity of Children and Adolescents, Beijing, 2003, pp 1–26.
10 Flegal KM, Carroll MD, Kuczmarski RJ, et al: Overweight and obesity in the United States: Prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord 1998;22:39–47.
11 NCHS, CDC: Prevalence of overweight and obesity among adults: United States, 1999 [Internet]. NCHS [Cited 2001, Oct. 31].
12 National Nutrition Survey: The dietary and nutritional status of Chinese population. 1992 National Nutrition Survey: Summary Results of the Survey. Beijing, People's Medical Publishing House, 1996, pp 94–101.
13 Du SF, Zhai FY, Ge KY, Chen FN: Distributions of body mass index of Chinese adults. J Hyg Res 2001;30:339–342.
14 Wang WJ, Wang KA, Li TL, Xiang HD, Ma LM, Fu ZY, Chen JS, Liu ZY, Bai J, Feng JG, Jin SX, Li YQ, Qin Rl, Chen H: A study on the epidemiological characteristics of obesity in Chinese adults. Chin J Epidemiol 2001;22:129–132.
15 Wu YF, Zhou BF, Tao QS, Wu XG, Yang J, Li Y, Zhao LC, Xie GQ. Prevalence of overweight and obesity in Chinese middle-aged populations: Current status and trend of development. Chin J Epidemiol 2002;23:11–15.
16 Wu YF: Obesity: An epidemic must be paid attention by Chinese. Chin J Epidemiol 2002;23:3–4.
17 PRC National Blood Pressure Survey Cooperative Group: The study of sampled study of body weight and its relation to blood pressure in China. 1995;3(suppl):31–35.
18 Shang L, Xu YY, Du XH: Geographic difference of nutrition status in Chinese male youth. Chin J Publ Hlth 2003;19:1163–1165.
19 Xie J, Jiao Sf, Yi XJ, Wang Y, Guo B, Wu LJ: Epidemiological investigation on overweight and obesity in Beijing city community. Chin J Epidemiol 2003;24:749.
20 Shao GX, Huang ZP, Zhang XG, Zhu QY, Li XL, Tang H: Body mass index distribution of men and women in Shenzhen region. Chin J Prev Contr Chron Non-commun Dis 2003;11:86.
21 Zhang RX, Xue CY, Zheng ZX, Ou YH, Wang WQ, Lu XC. Relationship between BMI, percentage of body fat and body fat distribution in health adults. Acta Nutr Sin 2002;24:144–148.
22 Epidemiological Investigation Cooperative Group on Diabetes of Guangdong Province: Cross-sectional investigation and analysis of obesity in Guangdong province. Guangdong Med 2003;24:877–880.
23 Du SF, Lu B, Wang ZH, Zhai FY, Popkin BM: Transition of dietary pattern in China. J Hyg Res 2001;30:221–225.
24 Cheng TO: Fast food and obesity in China. J Am Coll Cardiol 2003;42:773.
25 Deng ML, Mai JZ, Liu XQ, Guo CY, Shi ML, Gao XM, Wu Y, Lian ZB, Li H, Li YH, Rao XX: Study on the correlation between physical activity and other risk factors of cardiovascular disease in middle-aged group of Guangzhou city. South China J Prev Med 2002;28:12–15.
26 Liu ZM, Wang JH, Yang WD, Lu AM: Investigation and analysis on ideal physical activity of public servants in China. J Shanghai Phys Educ Inst 2001;25:12–16.
27 Wu MQ, Huang W, Feng CZ, Huang J, Liang CM: Investigation on health and physical activity of adult women in Jiangmen city. Chin Prev Med 2002;3:314–315.
28 Bell AC, Ge K, Popkin BM: The road to obesity or the path to prevention: motorized transportation and obesity in China. Obes Res 2002;10:277–283.
29 Live AS: Weight control practices of US adults trying to lose weight. Ann Intern Med 1993;119: 661–666.
30 China Disease Control Bureau of Health Ministry: Guidelines for prevention and control of overweight and obesity in Chinese adults, 2003, pp 18–23.
31 Romijn JA, Coyle EF, Sidossis LS, et al: Relationship between fatty acid delivery and fatty acid oxidation during strenuous exercise. J Appl Physiol 1995;79:1939–1945.

32 Weyer C, Linkeschowa R, Heise T: Implications of the traditional and the new ACSM physical activity recommendations on weight reduction in dietary treated obese subjects. Int J Obesity 1998;22:1071–1078.
33 Saris WH, Blair SN, van Baak MA, Eaton SB, Davies PS, Di Pietro L, Fogelholm M, Rissanen A, Schoeller D, Swinburn B, Tremblay A, Westerterp KR, Wyatt H: How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and Consensus Statement. Obes Rev. 2003;4:101–114.
34 Ai H, Liang HG, Ruan W, Zhao L: Evaluation of the outcome of an organized, semi-closed program for weight reduction in community. Chin J Sports Med 2004;23:116–123.
35 Dunn AL, Marcus BH, Kampert JB, et al: Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: A randomized trial. JAMA 1999;281: 327–334.
36 Andersen RE, Wadden TA, Bartlett SJ, et al: Effects of lifestyle activity vs structured aerobic exercise in obese women: A randomized trial. JAMA 1999;281:335–340.
37 Jakicic JM, Wing RR, Butler BA, et al: Prescribing exercise in multiple short bouts versus one continuous bout: Effects on adherence, cardiorespiratory fitness, and weight loss in overweight women. Int J Obes Relat Metab Disord 1995;19:893–901.

Cuiqing Chang
Institute of Sports Medicine
3rd Hospital, Peking University, 49 North Garden Road
Beijing 100083 (China)
Tel. +86 01 62017691 2505, Fax +86 01 62017700, E-Mail cuiqingchang@yahoo.com.cn

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 27–35

Obesity in Childhood: The Greek Experience

A. Kafatos, C.A. Codrington, M. Linardakis

Preventive Medicine and Nutrition Clinic, Department of Social Medicine, University of Crete School of Medicine, Crete, Greece

Over the last two decades obesity has become the most prevalent nutritional disease of children and adolescents in the United States and in many European countries [1, 2], as well as a growing problem worldwide [3, 4]. The accumulating evidence of multiple surveys, albeit much of it fragmentary, indicates that this rising incidence of overweight and obesity among children parallels the global 'obesity epidemic' among adults [5]. A vast body of evidence is amassing on the short-term health consequences of childhood obesity and the multiple adverse effects tracking through to morbidity and mortality in adulthood [6–9]. The scale of the problem and the attendant rising rates of type 2 diabetes and other co-morbidities characterizing the metabolic syndrome among both children and adults is, therefore, justifiably causing concern, as shown by the recent volume of publications [9] and public health policy initiatives [10, 11].

Prevalence

In Greece, adult obesity rates are among the highest in Europe. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) show the highest prevalence of obesity in adult men and women from Spain, Greece and Italy [12]. Available data for children and adolescents suggests a similar pattern, although there are differences in reported prevalence rates and 'ranking' in comparison with other countries depending on the reference values used to define overweight and obesity; i.e. the BMI cut-off criteria adopted by the IOTF of childhood equivalents of overweight and obesity in adulthood [13], the CDC growth charts (85th and 95th percentiles as the cut-offs for overweight

and obesity, respectively) [14], or population-specific reference values. The reliability, validity and comparability of existing prevalence data is also complicated by differences in survey populations and, critically, on whether the BMI calculations were based on self-reported weight and height data or obtained through direct physical examination.

The only national survey data reported to date in Greece relies on self-reported data-sets [15]. This survey involved 4,299 children and adolescents aged 11–16 years and was carried out in 1997–1998 as part of the WHO Health Behavior in School Aged Children (HBSC) study. According to the IOTF criteria, 9.1% of all girls and 21.7% of all boys were classified as overweight, with corresponding values for obese girls and boys of 1.2 and 2.5%, respectively. Corresponding values using the CDC growth charts were 8.1% of girls and 18.8% of boys classed as overweight, and 1.7% of girls and 5.8% of boys as obese. The authors conclude that the prevalence of obesity is low in Greek adolescents 'compared to most other Western countries'. The claim is, however, misleading given that their data is compared with only 3 surveys, the US NHANES data [16], and regional surveys in Britain [17] and Germany [18], which in turn are based on direct anthropometric measurements. Less optimistically, comparison with other (HBSC Study) national school-based surveys using identical data collection methods indicate that the highest prevalence of overweight in adolescents are to be found in the United States, Ireland, Greece, and Portugal [19].

While providing a useful overview, survey results such as these based on self-reported data, particularly where no validity sub-study has been conducted, are liable to underestimate the problem [20–24]. To date, more reliable data sets based on direct anthropometric measurements are available from two regional school-based studies, in Crete [24, 25], and in Thessaloniki [26]. Comparable data is also available for the ethnic Greek pediatric population of Cyprus [27]. These studies were incorporated in a comparative review of a number of surveys in European countries using similar methodologies and the IOTF-recommended cut-off criteria to estimate prevalences of overweight and obesity [28]. The report showed the highest prevalence (>30%) of combined overweight and obesity among children aged 7–11 years in the Mediterranean South: Italy, Malta, Spain, Greece and Cyprus. Among adolescents (14–17 years) in these Mediterranean countries the incidence of overweight is substantially lower (~20%), comparable to reported rates for adolescents in Britain, but still higher than their counterparts elsewhere in Europe.

Within Greece, available data suggests regional variations in incidence rates: similarly high overall prevalences of overweight are reported for the child and adolescent populations in Crete and in Thessaloniki, but higher incidences of obesity are reported for Crete. The prevalence of combined overweight and

obesity has also been reported as being higher in urban areas compared to semi-urban/rural areas [15]. 'North/south' regional variations (in growth curves) have been documented in Italy [29]. Whether the variations observed between studies in Greece to date are a function of study design or measurement sensitivity or socio-demographic factors impacting on regional susceptibility to obesity has yet to be determined. Similar reservations apply to available data on gender and age-related trends. Given this, Krassas et al. [26] report a pattern of higher prevalences of overweight and obesity among children compared to adolescents for Thessaloniki, an age-related trend which was not found in the Crete study. Similarly, gender difference in prevalences of overweight and obesity were not as marked in children in Crete, although all studies show the prevalence of obesity as being consistently higher in adolescent boys.

Prevention

While the merits and limitations of existing survey data may be discussed ad nauseum, the essence is not disputed: namely, that the prevalence of obesity among children and adolescents in Greece is among the highest in Europe. Specific socio-cultural factors can be implicated in this phenomenon – namely, the 'overfeeding syndrome' observed in Greece following the trauma of hunger and starvation experienced during the occupation in World War II. Influences such as the effects of undernutrition in utero and infancy reported for the Dutch famine cohort [30, 31] may also have been contributory factors. The contemporary situation among the Greek population is witness to the sequel insofar as obesity in childhood frequently tracks into adulthood [9] and parental obesity is a risk factor for childhood obesity [32, 33]: i.e. the obese child is at risk of becoming the obese parent of obese children. More generally, in common with other Mediterranean countries [34], nutritional trends in Greece away from the traditional dietary habits and towards more energy dense diets are considered to play a significant role. Diet, physical activity and sedentary behaviors are the 'universal' risk factors for overweight youth identified in our increasingly 'obesogenic' environments, and interventions for prevention and treatment of childhood obesity typically target these behavioral risk factors, although their relative causal significance is not well understood [35, 36]. Difficulties associated with the effective treatment of obesity [37], and the long-term adverse effects of childhood obesity, makes population-based approaches to the prevention of childhood obesity a public health priority, with primary preventive strategies initiated early in life as arguably one of the most promising ways to face this epidemic.

The Greek experience of primary preventive programs is limited to date. However, one of the few programs in Europe to have reported positive results in

terms of obesity and physical fitness is the 6-year health and nutrition education intervention program in primary schools in Crete [38]. The concept, design, intervention strategies and results of the health and nutrition education intervention program undertaken in Crete have been reported in detail elsewhere [25, 39]. In brief: The program was a school-based health education intervention characterized by teacher-delivery of 'customized' classroom materials, a physical activity component, and parental involvement. The program, initiated in 1992, followed a progressive 6-year course design through grades 1 to 6. For evaluative purposes, intervention took place in 2 counties of Crete with a third county acting as control. A sample of 24 schools (602 children) in the intervention counties and 16 schools (444 children) the control county were randomly selected and baseline measures were taken of all children enrolled in the study (age 5.5–6.5 years). To date there have been 3 follow-up examinations: (1) in 1995, an interim examination of a sub-sample following 3 years of intervention ($n = 471$); (2) in 1998, examination of all available subjects (age 10.5–11.5) at the end of the program ($n = 831$); (3) in 2001–2002, follow-up at grade 10 of the pupils examined in 1998 ($n = 634$).

At baseline and all subsequent evaluations a standard set of measures were obtained. These included anthropometric data (for calculation of BMI, waist-to-hip ratio, and skinfold measurements); biochemical indicators (total cholesterol, HDL, serum triglycerides, serum vitamins, etc.); physical activity record and physical fitness assessment (using the EUROFIT tests protocol); dietary assessment based on 3-day weighed food records; pupils' health knowledge and attitudes. Data was also collated from parents (age, anthropometric measures, occupation and educational level, health knowledge and attitudes).

Results at the end of the program were encouraging with observed changes in biochemical indices of health status (total cholesterol, TC:HDL, LDL:HDL), improvements in health knowledge, and significantly greater physical activity and fitness levels being recorded for the intervention group [25]. Most notably, the age-related increase in BMI was shown to be smaller in the intervention group – a distinctive result for a health education intervention study shared to date only by Kiel Obesity Prevention Study [40]. Preliminary evaluation of the 2001–2002 data 4 years after cessation of the program indicates smaller but persistent differences between the subjects, now adolescents, in terms of nutritional status, cardiorespiratory fitness and certain behaviors [41]. Specifically, as shown in figure 1, the reduction in total cholesterol noted in both groups during adolescence was significantly greater in the intervention group compared to the control group ($p < 0.001$) although, as shown in table 1, positive effects on the lipoprotein profiles observed during the intervention period did not persist. Most interestingly, figure 2 shows that (mean) BMI had increased significantly less ($p < 0.001$) in adolescents who had been in the intervention group

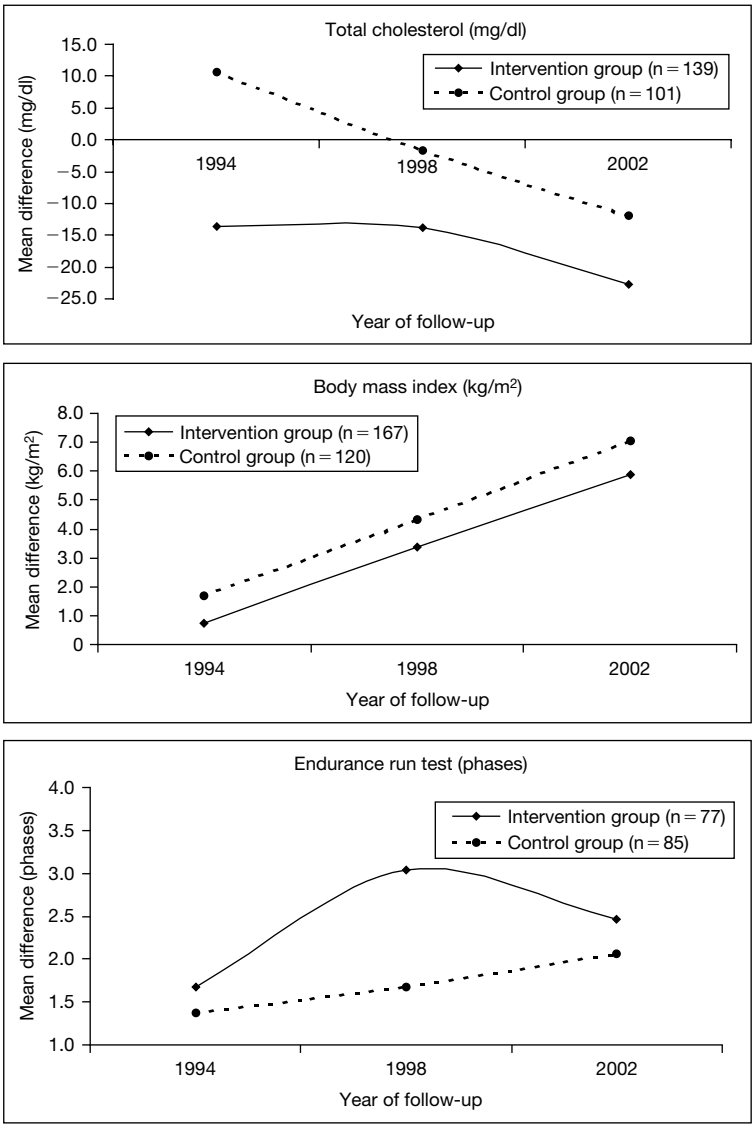


Fig. 1–3. Differences in each follow-up examination from the baseline examination in 1992. Source: Linardakis et al. [41].

compared to those who had been in the control group. This may reflect persistent differences in physical activity and fitness. As shown in figure 3, the previously significant differences in performance in the shuttle run test, indicative of cardiorespiratory fitness, diminished after the program ended. However,

Table 1. Serum lipoprotein levels of children of Crete

		n	Baseline 1992	Evaluation			Total	Changes	p
				1st: 1994–1995	2nd: 1997–1998	3rd: 2001–2002			
Total cholesterol, mg/dl	I	139	186.9 ± 2.6	173.9 ± 2.5	173.8 ± 2.6	164.4 ± 2.4	174.7 ± 2.2	−16.2 ± 1.8	<0.001
	C	101	174.2 ± 3.1	185.1 ± 2.9	172.3 ± 3.1	162.6 ± 2.8	173.6 ± 2.6	−0.9 ± 2.0	
Triglycerides, mg/dl	I	139	51.3 ± 1.7	44.3 ± 1.9	65.6 ± 2.0	64.7 ± 2.2	56.5 ± 1.4	6.9 ± 1.8	NS
	C	101	50.9 ± 1.9	40.1 ± 2.3	67.6 ± 2.4	62.9 ± 2.6	55.3 ± 1.7	6.0 ± 2.1	
HDL-C, mg/dl	I	137	60.6 ± 1.3	54.3 ± 1.3	58.7 ± 1.3	52.7 ± 1.0	56.6 ± 1.0	−5.3 ± 1.0	NS
	C	101	62.8 ± 1.5	58.2 ± 1.5	57.8 ± 1.5	50.9 ± 1.2	57.4 ± 1.2	−7.2 ± 1.1	
LDL-C, mg/dl	I	139	115.9 ± 2.5	110.5 ± 2.2	102.7 ± 2.3	98.6 ± 2.1	106.9 ± 2.0	−12.0 ± 1.6	<0.001
	C	101	101.2 ± 3.0	118.9 ± 2.6	101.0 ± 2.7	99.1 ± 2.4	105.1 ± 2.4	5.1 ± 1.9	
Index of total cholesterol to HDL-C	I	137	3.21 ± 0.07	3.49 ± 0.09	3.12 ± 0.07	3.27 ± 0.07	3.27 ± 0.06	0.08 ± 0.05	0.002
	C	101	2.92 ± 0.09	3.34 ± 0.10	3.15 ± 0.08	3.31 ± 0.08	3.18 ± 0.07	0.34 ± 0.06	

Mean values ± SE.

I = Intervention group; C = control group.

ANCOVA – (GLM: repeated measures analysis): The test was carried out on the differences from baseline. Sex, and mean difference of BMI (of all examinations from baseline) were used as covariates in all examinations. NS = No significant difference.

Source: Linardakis et al. [41].

adolescents from the intervention group continued to spend more time on moderate-to-vigorous activities than their counterparts from the control group, although the statistical significance of this difference observed during the course of the intervention program was not sustained 4 years after termination of the program. Another positive behavioral result was that smoking onset rates were found to be significantly lower among adolescents in the intervention group (7% compared with 13% in the control group, $p < 0.005$). It is possible to speculate that reinforcement of positive behavioral choices, particularly physical activity, through maintenance of such health education programs through high school would be beneficial. Certainly, the long-term effects of these programmes can only be assessed by tracking the study populations through adolescence and adulthood. There is sufficient evidence in the meantime, however, to recommend the development of comprehensive programs beginning as early as possible to tackle the particularly urgent problems of dietary and lifestyle choices contributing to childhood obesity.

In conclusion: rates of childhood obesity in Greece are among the highest in Europe; an alarming trend that is shared by other Mediterranean countries. The significant comorbidities and health problems associated with this pediatric obesity epidemic are now being recognized, but we are lagging in the development of appropriate preventive responses. Public health strategies, which if successful will impact on the increasing adult obesity rate, require political commitment and appropriate funding which to date have not been forthcoming in Greece. The limited experience to date of primary preventive strategies indicate that educational interventions in the school environment have great potential and, in the Greek experience, offer one encouraging element of the multi-faceted strategies needed to tackle the urgent problems of dietary and lifestyle choices contributing to the growing blight of childhood obesity.

References

1 Ogden CL, Flegal KM, Carroll MD, Johnson CL: Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 2002;288:1728–1732.

2 Ebbeling CB, Pawlak DB, Ludwig DS: Childhood obesity: Public-health crisis, common sense cure. Lancet 2002;360:473–482.

3 Wang Y: Cross-national comparison of childhood obesity: The epidemic and the relationship between obesity and socioeconomic status. Int J Epidemiol 2001;30:1129–1136.

4 de Onis M, Blössner M: Prevalence and trends of overweight among preschool children in developing countries. Am J Clin Nutr 2000;72:1032–1039.

5 World Health Organization: Obesity: Preventing and Managing the Global Epidemic. World Health Organization Technical Support Series No. 894. Geneva, WHO, 2000.

6 Reilly JJ, Methven E, McDowell ZC, Hacking B, Alexander D, Stewart L, Kelnar CJH: Health consequences of obesity. Arch Dis Child 2003;88:748–752.

7 Deckelbaum RJ, Williams CL: Childhood obesity: The health issue. Obes Res 2001;9(suppl 4): S239–S243.

8 Engeland A, Bjorge T, Tverdal A, Sogaard AJ: Obesity in adolescence and adulthood and the risk of adult mortality. Epidemiology 2004;15:79–85.
9 Goran MI: Metabolic precursors and effects of obesity in children: A decade of progress, 1990–1999. Am J Clin Nutr 2001;73:158–171.
10 World Health Organization: The First Action Plan for Food and Nutrition Policy, WHO European Region 2000–2005 (http://www.euro.who.int/Document/E72199.pdf). Copenhagen, WHO Regional Office for Europe, 2000.
11 Robertson A, et al (eds): World Health Organization: Food and Health in Europe: A New Basis for Action. Geneva, WHO Regional Publications, European Series, 2004, No 96.
12 Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H, et al: Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Publ Hlth Nutr 2002;5:1147–1162.
13 Cole TJ, et al: Establishing a standard definition for child overweight and obesity worldwide: International survey. BMJ 2000;320:1–6.
14 Flegal KM, Ogden CL, Wei R, Kuczmarksi RL, Johnson CL: Prevalence of overweight in US children: Comparison of US growth charts from the centers for Disease Control and Prevention with other reference values for body mass index. Am J Clin Nutr 2001;73:1086–1093.
15 Karayiannis D, Yannakoulia M, Terzidou M, Sidossis LS, Kokkevi A: Prevalence of overweight and obesity in Greek school-aged children and adolescents. Eur J Clin Nutr 2003;57:1189–1192.
16 Troiano RP, Flegal KM: Overweight children and adolescents: Description, epidemiology and demographics. Pediatrics 1998;101:497–504.
17 Reilly JJ, Dorosty AR: Epidemic of obesity in UK children. Lancet 1999;354:1874–1875.
18 Kromeyer-Hauschild K, Zellner K, Jaeger U, Hoyer H: Prevalence of overweight and obesity among school-children in Jena (Germany). Int J Obes Relat Metab Disord. 1999;23:1143–1150.
19 Lissau I, Overpeck MD, Ruan WJ, Due P, Holstein BE, Hediger ML: Health Behavior in School-Aged Children Obesity Working Group. Body Mass Index and overweight in adolescents in 13 European countries, Israel, and the United States. Arch Pediatr Adolesc Med. 2004;158:27–33.
20 Paccaud F, Wietlisbach V, Rickenbach M: Body mass index: Comparing mean values and prevalence rates from telephone and examination surveys. Rev Epidemiol Sante Publique. 2001;49: 33–40.
21 Spencer EA, Appleby PN, Davey GK, Key TJ: Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Publ Health Nutr 2002;5:561–565.
22 Brener ND, Mcmanus T, Galuska DA, Lowry R, Wechsier H: Reliability and validity of self-reported height and weight among high school students. J Adolesc Health 2003;32:281–287.
23 Himes JH, Faricy A: Validity and reliability of self-reported stature and weight in US adolescents. Am J Human Biol. 2001;13:255–260.
24 Mamalakis G, Kafatos A, Manios Y, Anagnostopoulou T, Apostolaki I: Obesity indices in a cohort of primary school children in Crete: A six year prospective study. Int J Obes Relat Metab Disord. 2000;24:765–771.
25 Manios Y, Moschandreas J, Hatzis C, Kafatos A: Health and nutrition education in primary schools of Crete: Changes in chronic disease risk factors following a 6-year intervention programme. Br J Nutr. 2002;88:315–324.
26 Krassas GE, Tzotzas T, Tsametis C, Konstantinidis T: Prevalence and trends in overweight and obesity among children and adolescents in Thessaloniki, Greece. J Pediatr Endocrinol Metab 2001;14(suppl 5):1319–1326.
27 Savva SC, Kourides Y, Tornaritis M, Epiphaniou-Savva M, Chadjigeorgiou C, Kafatos A: Obesity in children and adolescents in Cyprus. Prevalence and predisposing factors. Int J Obes 2002;26: 1036–1045.
28 Lobstein T, Frelut M-L: Prevalence of overweight among children in Europe. Obes Rev 2003;4: 195–200.
29 Cacciari E, Milani S, Balsamo A, Dammacco F, De Lucca F, Chiarelli F, Pasquino AM, Tonini G, Vanelli M: Italian cross-sectional growth charts for height, weight and BMI (6–20y). Eur J Clin Nutr. 2002;56:171–180.
30 Ravelli GP, Stein ZA, Susser MW: Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295:349–353.

31 Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP: Obesity at the age of 50-y in men and women exposed to famine prenatally. Am J Clin Nutr 1999;70:811–816.
32 Magary AM, Daniels LA, Boulton TJ, Cockington RA: Predicting obesity in early adulthood from childhood and parental obesity. Int J Obes Relat Metab Disord 2003;27:505–513.
33 Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH: Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997;337:869–873.
34 Cruz J: Dietary habits and nutritional status in adolescents over Europe – Southern Europe. Eur J Clin Nutr. 2000;54(suppl 1):S29–S35.
35 Patrick K, Norman GJ, Calfas KJ, Sallis JF, Zabinski MF, Rupp J, Cella J: Diet, physical activity, and sedentary behaviors as risk factors for overweight in adolescence. Arch Pediatr Adolesc Med 2004;158:385–390.
36 Reilly JJ, McDowell ZC: Physical activity interventions in the prevention and treatment of paediatric obesity: Systematic review and critical appraisal. Proc Nutr Soc 2003;62:611–619.
37 Summerbell CD, Ashton V, Campbell KJ, Edmunds L, Kelly S, Waters E: Interventions for treating obesity in children. Cochrane Database Syst Rev 2003;(3):CD001872.
38 Lytle LA, Jacobs DR, Perry CL, Klepp K-I: Achieving physiological change in school-based intervention trials: what makes a preventive intervention successful (Invited Commentary). Br J Nutr 2002;88:219–221.
39 Manios Y, Moschandreas J, Hatzis C, Kafatos A: Evaluation of a health and nutrition education program in primary school children of Crete over a three-year period. Prev Med 1999;28:149–159.
40 Muller MJ, Asbeck I, Mast M, Langnase K, Grund A: Prevention of obesity – more than an intention. Concept and first results of the Kiel Obesity Prevention Study (KOPS). Int J Obes Relat Metab Disord 2001;25(suppl 1):S66–S74.
41 Linardakis M, Sarri K, Bervanaki F, Markatzi I, Hatzis C, Flouri S, Kafatos A: Ten-year evaluation of the initiation of a health education program. Paediatriki 2003;66:436–447.

Prof. Anthony Kafatos
Preventive Medicine and Nutrition Clinic
Department of Social Medicine, University of Crete School of Medicine
PO Box 2208, GR–710 03 Heraklion, Crete (Greece)
Tel. +30 2810 394595, Fax +30 2810 394604, E-Mail kafatos@med.uoc.gr

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 36–41

Epidemiology of Physical Activity from Adolescence to Young Adulthood

Deborah J. Aaron, Yoon-Suk Jekal, Ronald E. LaPorte

University of Pittsburgh, Pittsburgh, Pa., USA

Physical activity (PA) is a major determinant of morbidity and mortality and has been identified as a priority area for promoting health [1]. However, given the documented benefits of achieving and maintaining an active lifestyle, many adults do not meet the recommended levels of physical activity to prevent disease and promote health. Research indicates that there are both physical and psychological benefits associated with increased physical activity in childhood and adolescence. However, it has been proposed by some health promotion experts that physical activity in childhood may also have direct influences on adult health based on several theories of the relation between physical activity during childhood and physical activity during adulthood. As summarized by Malina [2], there are two potential pathways by which promoting physical activity during childhood can influence adult health. First, physical activity patterns established in childhood may persist into adulthood where the relation between physical activity and health has been established. This theory is based on the assumption that physical activity tracks over time and those active children will become active adults. The second pathway is a direct relation between physical activity during childhood and adult health. This is based on the assumption that increasing physical activity in children will have long-term health benefits in adulthood independent of adult physical activity patterns. However, there are little data to support either of these pathways. The purpose of this paper is to present an overview of the epidemiology of physical activity from adolescence to adulthood based on findings from several large longitudinal studies.

Methods

We identified six longitudinal studies that measured physical activity from the adolescent years into young adulthood (table 1). These studies include the Amsterdam Growth and Health Study (AGHS), the Cardiovascular Risk in Young Finns Study (CRYFS), the Danish

Table 1. Description of longitudinal physical activity studies

Study	Sample age at baseline	Follow-up	Physical activity assessment
Amsterdam Growth and Health Study (AGHS) [6–8, 12, 16]	307 boys and girls; aged 13 years	20 years 1977–1997	structured interview, past 3 months
Cardiovascular Risk in Young Finns Study (CRYFS) [5, 10, 15]	3,596 boys and girls; aged 3, 6, 9, 12, 15 and 18 years	12 years 1980–1992	questionnaire, usual activity
Danish Youth and Sports Study (DYSS) [9, 11]	205 boys and girls; aged 15–19 years	8 years 1983–1991	questionnaire, past year
Leuven Longitudinal Study on Lifestyle, Fitness and Health (LLS) [14, 17]	588 boys; aged 13 years	27 years 1969–1996	questionnaire, past year
Northern Ireland Young Hearts Study (NIYHS) [13]	1,015 boys and girls; aged 12 and 15 years	8 years 1989–1998	questionnaire, usual activity
University of Pittsburgh Physical Activity Study (PittPAS) [3, 4]	1,245 boys and girls; aged 12–15 years	14 years 1990–2004	questionnaire, past year

Youth Sport Study (DYSS), the Leuven Longitudinal Study on Lifestyle, Fitness and Health (LLS), the Northern Ireland Young Hearts Study (NIYHS), and the University of Pittsburgh Physical Activity Study (PittPAS). All of these studies except the LLS included both boys and girls. All studies collected baseline data during adolescence and followed the subjects from 8 to 27 years. A questionnaire was used in all studies to assess physical activity with the time-frame including usual activity (CVRYFS, NIYHS), past 3 month recall (AGHS) and past year recall (DYSS, LLS, PittPAS). Using Medline and PubMed data bases, we identified all relevant publications from these six studies that addressed the following three primary questions.

- How does physical activity change from adolescence to adulthood?
- Does physical activity track from adolescent to adulthood?
- Is physical activity during adolescence related to health status in adulthood?

Results

Change in PA from Adolescence to Adulthood

Data from the PittPAS indicated that total physical activity decreased by 43% (11.7–1.9 h/week) over a 10-year period from junior high school to young adulthood with the steepest decline in activity occurring during the adolescent

Table 2. Tracking of physical activity from adolescence to adulthood

Study	Tracking correlation	% remain active	% remain inactive
AGHS [7, 8]	0.34 (overall) 0.14 (males) 0.24 (females) 0.26 (low intensity) 0.14 (moderate intensity) 0.43 (high intensity)	40% (males) 42% (females)	25% (males) 39% (females)
DYSS [9]	0.31 (males) 0.20 (females)	53% (males) 8 % (females)	
CRYFS [10]	0.27 (males) 0.27 (females)	43% (males) 57% (females)	54% (males) 51% (females)
PittPAS [4]	0.21 (overall) 0.24 (males) 0.14 (females)		

years [3]. In both males and females, the decline in PA was primarily due to decreases in high intensity physical activity and participation in team activities. The decline in participation in team activities was more evident among females [4]. During adolescence, 5 of the top 10 activities in males and 4 of the top ten activities in females were team sports. However, in young adulthood a gender difference was evident as only 1 of the top 10 activities in females was a team sport compared to 4 in males. Two other studies also reported large decreases in PA from adolescent to young adulthood. In CRYFS, total PA declined markedly from age 12 to 27 by 57% in males and 28% in females with the steepest decline between ages 12 and 15 years [5]. PA declined by 42% in males and 16% in females between ages 13 and 27 years in the AGHS [6].

Tracking of PA from Adolescence to Adulthood

Tracking is the maintenance of a relative position within a distribution over time. If physical activity tracks during the transition from adolescence to young adulthood it would have important implications for health promotion programs. However, as indicated by the data presented in table 2, there is little evidence to support the hypothesis that PA tracks over this time period. The correlations reported in all studies are weak to moderate, ranging from 0.14 to 0.43. In the PittPAS [4], we also examined the stability of participation in specific activities by determining the predictive value positive (PV+) for activities reported in junior high school compared to those reported in adulthood. The PV+ for specific activities ranged from 0.10 to 0.67 for males and from 0.00 to 0.52 for

Table 3. Relation of physical activity in adolescence to adult health indicators

	Body fatness	Lipids	Blood pressure	Bone density
AGHS [12, 16]	0	0	0	+
LLS [14, 17]	0	0	0	+
NIYHS [13]	0	0	0	?
DYSS [11]	+ (males)	+ (males)	0	?
CVFSS [15]	?	?	?	+

0 = No relationship; + = positive relationship; ? = no published data.

females. These data indicate that there is little stability in the participation in specific activities from adolescence to young adulthood.

Relation of PA in Adolescence to Adult Health

The contribution of physical activity during adolescence has been examined in relation to lipids, blood pressure, body fatness, and bone mass in adulthood (table 3). Four studies examined the association between adolescent physical activity and risk factors for cardiovascular disease (body fatness, lipids and blood pressure) in adulthood. With the exception of the DYSS [11], none of the studies found a significant association between PA levels in adolescence and measures of body fatness, lipids, or blood pressure in adulthood [12–14]. However, data from three studies indicate that physical activity during adolescence is a significant predictor of bone mass in adulthood. The CRYFS reported that bone mineral density was 7.6–10.5% higher in individuals who had been physically active during the adolescent years [15]. Weight-bearing exercise during adolescence was reported as the strongest predictor of bone mineral density at age 27 in participants of AGHS [16]. Data from the LLS indicate that continued participation in high impact sports from adolescence to adulthood was related to higher bone mineral density in adult males [17].

Conclusions

The data from these six longitudinal physical activity studies provide valuable information on the epidemiology of physical activity from adolescence to young adulthood. There is a consistent decline in the volume of physical activity across this time period with the greatest decline being observed in the adolescent years. In addition, the low tracking correlations indicate that physical

activity is not a stable behavior. Taken together, these two conclusions indicate that interventions to promote physical activity or prevent the decline in physical activity must be initiated in the early adolescent years and that repeated interventions may be necessary to maintain adequate levels of PA. Finally, there appears to be little relationship between adolescent physical activity and indicators of cardiovascular risk in young adults. However, there appear to be strong data to support the hypothesis that physical activity during adolescence, in particular weight-bearing physical activity, is related to higher levels of bone mineral density in adulthood.

References

1 US Department of Health and Human Services: Physical Activity and Health: A Report of the Surgeon General. Atlanta, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention; 1996.

2 Malina RM: Physical activity and fitness: Pathways from childhood to adulthood. Am J Hum Biol 2001;13:162–172.

3 Aaron DJ, Storti KL, Kriska AM, Hindes KM, Murray PA, LaPorte RE: Decline in physical activity from adolescence to young adulthood: Physical Activity in Young Adults Study. Med Sci Sports Exerc 2002;34(suppl):S229.

4 Storti KL, Aaron DJ, Kriska AM, Murray PA, Hindes KM, LaPorte RE: Tracking and stability of physical activity from adolescence to young adulthood: Physical Activity in Young Adults Study. Med Sci Sports Exerc 2002;34(suppl):S229.

5 Telama R, Yang X: Decline of physical activity from youth to young adulthood in Finland. Med Sci Sports Exerc 2000;32:1617–1622.

6 vanMechelen W, Twisk JWR, Post GB, Snel J, Kemper HCG: Physical activity of young people: The Amsterdam Longitudinal Growth and Health Study. Med Sci Sports Exerc 2000;32:1610–1616.

7 Twisk JWR, Kemper HCG, vanMechelen W, Post GB. Tracking of risk factors for coronary heart disease over a 14-year period: A comparison between lifestyle and biologic risk factors with data from the Amsterdam Growth and Health Study. Am J Epidemiol 1997;145:888–898.

8 Twisk JWR, Kemper HCG, van Mechelen W: Tracking of activity and fitness and the relationship with cardiovascular disease risk factors. Med Sci Sports Exerc 2000;32:1455–1461.

9 Andersen LB, Haraldsdottir J: Tracking of cardiovascular disease risk factors including maximal oxygen uptake and physical activity from late teenage to adulthood: an 8-year follow-up study. J Intern Med 1993;234:309–315.

10 Raitakari OT, Porkka KVK, Taimela S, Telama R, Rasanen L, Viikari JSA: Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. Am J Epidemiol 1994;140:195–205.

11 Hasselstrom H, Hansen SE, Frobert K, Andersen LB: Physical fitness and physical activity during adolescence as predictors of cardiovascular disease risk in young adulthood: Danish Youth and Sports Study, an eight-year follow-up study. Int J Sports Med 2002;23:S27–S31.

12 Twisk JWR, Kemper HCG, van Mechelen W: The relationship between physical fitness and physical activity during adolescence and cardiovascular disease risk factors at adult age. Int J Sports Med 2002;23:S8–S14.

13 Boreman C, Twisk J, Neville C, Savage M, Murray L, Gallagher A: Associations between physical fitness and activity patterns during adolescence and cardiovascular risk factors in young adulthood: The Northern Ireland Young Hearts Project. Int J Sports Med 2002;23:S22–S26.

14 Lefevre J, Philippaerts R, Delvaux K, et al: Relation between cardiovascular risk factors at adult age and physical activity during youth and adulthood: The Leuven Longitudinal Study on Lifestyle, Fitness and Health. Int J Sports Med 2002;23:S32–S38.

15 Valimaki MJ, Karkkainen M, Lambert-Allardt C, et al: Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass. BMJ 1994;309:230–235.
16 Welten DC, Kemper HCG, Post GB, et al: Weight-bearing activity during youth is a more important factor for peak bone mass than calcium intake. J Bone Min Res 1994;9:1089–1096.
17 vanLangendonch L, Levevre J, Claessens AL, et al: Influence of participating in high impact sports during adolescence and adulthood on bone mineral density in middle-aged men: A 27 year follow-up study. Am J Epidemiol 2003;158:525–533.

Deborah J. Aaron, PhD
155 Trees Hall
University of Pittsburgh
Pittsburgh, PA 15261 (USA)
Tel. +1 412 648 8272, Fax +1 412 648 7092, E-Mail debaaron@pitt.edu

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 42–50

Adolescent Obesity and Physical Activity

Nahla Hwalla[a], *Abla Mehio Sibai*[b], *Nada Adra*[a]

[a] Department of Nutrition and Food Science, Faculty of Agricultural and Food Sciences, and [b]Department of Epidemiology and Population Health, Faculty of Health Sciences, American University of Beirut, Lebanon

In recent years, the prevalence and rise of childhood and adolescent obesity became a matter of major concern not only in developed countries but also in developing ones. In the US, National data from NHANES III demonstrated that the prevalence of adolescent obesity (14–19 years of age) has risen almost 3-fold in a period of 20 years, from 5% in 1976–1980 to 15% in 1999–2000 [1]. Several studies have demonstrated that the higher childhood body mass index (BMI) the greater the risk of becoming an overweight adult with the risk being heightened in adolescence. For example, while an obese 4-year-old child has a 20% chance of becoming an obese adult, the likelihood that obesity in adolescence would persist into adulthood is increased to 80% [2].

Child and adolescent obesity is suspected to be caused by an interaction between genetic, biologic, psychologic, sociocultural and environmental factors. Of the modifiable factors, a decreased energy intake and an increase in energy expenditure were frequently associated with averting overweight and obesity in this age group [2]. Understanding and identifying the underlying factors for obesity is crucial for effective intervention strategies. A recent study in the US indicated that although much of the debate on obesity has focused on diet, evidence suggests that physical activity plays a significant role in obesity for adolescents 12–19 years of age [3].

In Lebanon, data on the magnitude and gravity of adolescent overweight and obesity and their covariates are not available. This study was undertaken to investigate the prevalence of overweight and obesity in children and adolescents, identify its covariates and suggest intervention strategies for prevention and control.

Methodology

Study Design

The data for this paper is based on secondary analysis of an earlier study conducted in Lebanon in 1997. The design and conduct of the survey have been published in detail elsewhere [4]. Briefly, this was a national survey of a sample of 2,104 individuals of all age groups distributed across all the Governorates in Lebanon and was based on the sampling frame of the minicensus (10% of population) of the Population and Housing Survey (PHS) conducted by the Ministry of Social Affairs in 1996 in collaboration with United Nations Fund for Population Activities. The analysis in this paper focused on 792 subjects consisting of 339 children (6–11 years) and 453 adolescents (12–19 years). The University Research Board approved the study protocol.

Interview and Anthropometric Measurements

The subjects were interviewed within the households and anthropometric measurements were taken. The interview provided information on sociodemographic characteristics, physical excercise, and diet. The height, weight, and waist circumference measurements were performed using standard techniques. Body mass index (BMI) was calculated as the ratio of weight in kilogram to the square of height in meters. For comparison purposes, the definitions of overweight and obesity were, respectively, based on sex-specific BMI-for-age CDC reference values, United State's National Health and Nutrition Examination Survey (NHANES III) [1]. Subjects lying above the 85th percentile for age and sex were defined as overweight and those above the 95th percentile were defined as obese. Diet was assessed from mother for children and from the subject him/herself for adolescents.

Statistical Methods

Means, SD and percentiles were calculated for BMI. Multivariate logistic regression analysis was carried out, with percent obese as the dependent variable, physical activity as the main exposure variable with baseline characteristics as co-variates. Engaging in physical exercise was considered present if the child was involved in any leisure-time activity for three or more days during the week preceding the survey. Proportion of energy consumption from fat were divided into tertiles and included in the model as dummy variable with three categories [5]. The Statistical Package for the Social Sciences 10.0 (SPSS for windows) [6] was used for all computations.

Results

Table 1 presents the mean BMI (±SD) of the study adolescent sample, with values corresponding to the 5th, 15th, 50th, 85th, and 95th percentiles by age and gender. Mean BMI increased steadily with increasing age among boys and girls. There was some evidence that mean BMI was higher among girls than boys in the younger age groups and a reverse of this trend in the older ones (12 years and over).

Table 1. Body mass index (mean ± SD and percentiles) by age and gender among the study population

	Age groups						
	6–8	9–11	Total	12–14	15–17	18–19	Total
Boys							
n	77	77	154	80	78	48	206
Mean ± SD	16.2 ± 2.3	17.4 ± 2.7	16.8 ± 2.6	20.6 ± 4.4	22.3 ± 3.6	23.3 ± 3.7	21.8 ± 4.1
5th percentile	13.2	13.7	13.5	14.7	16.6	17.9	15.6
15th percentile	14.2	15.2	14.7	16.0	18.3	19.2	17.5
50th percentile	15.7	16.9	16.2	20.5	22.3	22.8	22.0
85th percentile	18.2	20.5	19.3	24.2	25.7	28.0	25.8
95th percentile	21.9	23.1	22.5	29.5	28.8	30.8	29.1
Girls							
n	92	93	185	96	94	57	247
Mean ± SD	16.5 ± 3.9	17.9 ± 3.2	17.2 ± 3.7	20.2 ± 3.5	21.2 ± 2.8	21.6 ± 3.6	20.9 ± 3.3
5th percentile	13.1	13.6	13.4	15.6	17.5	16.7	16.0
15th percentile	14.2	14.6	14.4	16.4	18.6	18.6	17.7
50th percentile	15.4	17.1	16.1	19.8	20.8	21.0	20.6
85th percentile	18.8	21.2	20.7	23.8	23.7	24.0	23.8
95th percentile	23.8	24.0	23.9	26.2	25.6	27.9	26.3

The prevalence of overweight and obesity for children (6–11 years) and adolescents (12–19 years) as compared to NHANES III are presented in Table 2. Overall, the prevalence of overweight in the total sample of the 6- to 19-year-old population was estimated as 21.7% and obesity as 6.5%. In children aged 6–11 years, overweight and to a lesser extent obesity was higher in girls than boys (25.6 vs. 19.0 and 8.2 vs. 7.2, respectively). This was reversed in adolescence where boys presented a markedly higher prevalence of overweight and obesity than girls (29.3 vs. 13.4 and 9.3 vs. 2.0, respectively). For both genders, there was no consistent relationship between adolescent overweight and obesity with increasing age (data not shown). In comparison with NHANES III data 1999–2000 [1], our data show generally lower prevalence rates for overweight and obesity among both genders with greater differential for obesity than overweight. Figure 1 shows the mean waist circumference of Lebanese adolescents ages 12–19. The data demonstrates a higher mean values for waist circumference among boys than girls across all age groups.

Results of the multivariate regression analysis are presented in Table 3. Obesity was significantly more prevalent in those who do not exercise even after controlling for potential confounders including fat intake and family history of obesity (OR = 2.28, 95% CI = 1.12–4.63). Moreover, obesity was more

Table 2. Prevalence of overweight (BMI ≥85th percentile) and obesity (BMI ≥95th percentile) among study population; comparison with NHANES 1999–2000 [1]

	Age groups		
	6–11 years	12–19 years	total
BMI ≥85th percentile (%)			
Boys			
Lebanese	19.0	29.3	24.9
NHANES III	32.7	30.5	–
Girls			
Lebanese	25.6	13.4	18.7
NHANES III	27.8	30.2	–
Both genders			
Lebanese	22.8	20.8	21.7
NHANES III	30.3	30.4	–
BMI ≥95th percentile (%)			
Boys			
Lebanese	7.2	9.3	8.4
NHANES III	16.0	15.5	–
Girls			
Lebanese	8.2	2.0	4.7
NHANES III	14.5	15.5	–
Both genders			
Lebanese	7.7	5.5	6.5
NHANES III	15.3	15.5	–

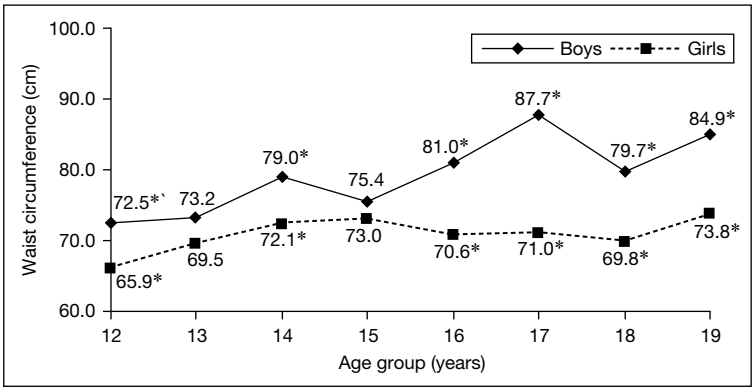


Fig. 1. Waist circumference in Lebanese children aged 12–19 years. *$p < 0.05$.

Table 3. Associations of obesity with baseline covariates: prevalence odds ratios (ORs) and their 95% CI

Variable (reference category)	6–19 years
	OR (95% CI)
Age, years	
6–11	1.0
12–19	0.61 (0.34–1.10)
Gender	
Boys	1.00
Girls	0.41* (0.22–0.77)
Exercise	
Yes	1.00
No	2.28* (1.12–4.63)
Family history of obesity	
No	1.00
Yes	0.58 (0.32–1.05)
Crowding index	
<1person/room	1.00
≥1person/room	1.97* (1.01–3.86)
Energy consumption from Fat, %	
Low (<32)	1.00
Moderate (32–40)	0.51 (0.23–1.13)
High (≥40)	0.58 (0.28–1.22)

*$p < 0.05$.

prevalent among boys and in those with low socioeconomic status as measured by the crowding index.

Discussion

This study presents data on prevalence and covariates of overweight and obesity and on waist circumference from a national sample of Lebanese children of ages 6–19 years. Using BMI, our findings indicate that about 1 in 5 children (6–11 years) is overweight and 6.5% are obese. Adolescent boys in the older age group (12–19 years) showed notably higher prevalence of overweight than that in their girl counterparts and of comparable magnitude to that reported from the US. Obesity was also higher in boys than girls but lower than that of

the US. Using waist circumference, gender differentials among adolescents were similarly pronounced across all age groups.

Comparable to their use in adults, anthropometric measurements such as BMI and waist circumference are simple and easy to obtain for evaluation of the nutritional and health status in children. BMI has been recommended for classifying overweight and obesity in children [1] and a recent study conducted among Swiss children appraised BMI as an 'excellent' proxy measure of adiposity and recommended the new CDC reference values for overweight and obesity [7]. Similarly, waist circumference has been shown to be a key variable correlating with intra abdominal adipose tissue and helping to identify children with metabolic complications such as adverse levels of lipids and insulin [8, 9].

Our estimates of the extent of overweight and obesity among children and adolescents in Lebanon, in particular among boys, are of particular importance as adolescent obesity has been shown to predispose to a range of medical and psychosocial problems. The Harvard Growth Study showed that being overweight during adolescence is a stronger predictor of mortality risk from cardiovascular diseases than being overweight during adulthood [10]. Also, overweight and obesity in children and adolescents predict a broad range of adverse health effects in this age group including hypertension, type 2 diabetes, insulin resistance, menstrual irregularity, and impaired mental health such as depression and low self-esteem [11–12].

Of particular concern is our finding that children who do not exercise were over two times more likely to be obese than children who do. While overall obesity decreased with age, mean BMI showed a sharp increase in the age group 12–14, particularly among boys to the extent that around 30% were classified as overweight, a percentage that corroborated with that seen among their US counterparts (30.5%). With modernization, it is this age group that suffers most form adoption of western lifestyle characterized by heavy reliance on fast food rich in fat, low activity triggered by the wide-spread use of Satellite dishes and computers, and the overall sedentary life-style all of which are key factors affecting nutritional habits and obesity levels. Furthermore, opportunities for promoting physical activity for children in Lebanon are limited. Overall, few schools include physical education in their curricula or oblige their students to participate in physical exercise classes and count these in the cumulative curricula credits. Parks, public beaches and walking/bicycle lanes are scarce to the extent that leisure-time physical activity becomes restricted to a selected affluent population.

Evidence suggests that the 'obesity epidemic' is likely to continue its rise in the years ahead, not only in the developed world but also in the majority of developing countries. Public health professionals in countries of the Eastern Mediterranean Region similarly caution against a major surge in obesity rates and identify obesity as the most pressing health concern [13]. Table 4 reproduces

Table 4. Prevalence of overweight (≥85th percentile) and obesity (≥95th percentile) among adolescents (12–19 years) by gender in selected neighboring countries of the Eastern Mediterranean region compared with the USA and Lebanese data

	≥85th percentile (%)	≥95th percentile (%)
Boys		
USA	30.5	15.5
Lebanon	29.3	9.3
Kuwait[1]	30.0	14.7
Saudi Arabia[2*]	34.3	20.5
United Arab Emirates[4]	–	16.5
Bahrain[3*]	29.8	16.5
Girls		
USA	30.2	15.5
Lebanon	13.4	2.0
Kuwait[1]	31.8	13.1
Saudi Arabia[2*]	28.0	13.0
United Arab Emirates	23.0	9.0
Bahrain[3*]	36.6	18.7
Egypt	35.0	13.0

Age groups: [1]10–14 years; [2]12–20 years; [3]12–17 years; [4]6–16 years.
*Overweight and obesity were calculated according to WHO.

available data on overweight and obesity among adolescence in countries in the region, and compares them with those obtained in the present study. While the majority of countries in the region have reached obesity levels similar to the US (e.g. Kuwait, Saudi Arabia, Bahrain and Egypt) [14–20], obesity among Lebanese adolescents remains lowest in the region especially for adolescent girls. Nevertheless, our earlier study indicated that overall obesity rates in adults are in general greater in women than men (19.0 vs. 14.4%), a trend that became more evident with increasing age and increasing obesity class from I to III [4]. This calls for further studies that examine the age at which women start to gain weight and the various sociocultural and behavioral factors associated with this change.

In conclusion, the results of this study provide the first baseline national data on BMI levels and waist circumference by age and gender in Lebanon. As adult obesity is difficult to treat, identification of adolescents at high risk of obesity at an early age becomes especially important [21]. While further studies are needed for additional advocacy and evidence-based decision-making, it is the time to start implementing multi-component interventions, at the societal

and individual level, for weight control. Public officials, schools and families should work together to provide conditions that promote increased physical activity with a particular focus on adolescent boys.

Acknowledgements

This study was supported by the Ministry of Public Health in Lebanon, the Lebanese National Council for Scientific Research, and the World Health Organization.

References

1 Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL: 2000 CDC growth charts for the United States: Methods and development. Vital Health Stat 2002;11:1–190.
2 American Academy of Pediatrics, Committee on Nutrition: Prevention of pediatric overweight and obesity. Pediatrics 2003;112:424–430.
3 Patrick K, Norman GJ, Calfas KJ, Sallis JF, Zabinski MF, Rupp J, Cella J: Diet, physical activity, and sedentary behaviors as risk factors for overweight in adolescence. Arch Pediatr Adolesc Med 2004;158:385–390
4 Sibai AM, Hwalla N, Adra N, Rahal B: Prevalence and covariates of obesity in Lebanon: Findings from the first epidemiological study. Obes Res 2003;11:1353–1361.
5 Abdul Rahim HF, Holmboe-Ottesen G, Stene LCM, Husseini A, Giacaman R, Jervell J, Bjertness E: Obesity in a rural and an urban Palestinian West Bank population. Int J Obes 2003;27:140–146.
6 SPSS, Inc. Statistical Package for Social Sciences (SPSS) for Windows Release 10.0. Chicago, SPSS, 1999.
7 Zimmerman MB, Gübeli C, Püntener C, Molinari L: Detection of overweight and obesity in a national sample of 6–12 years old Swiss children: Accuracy and validity of reference values for body mass index from the US Centers for Disease Control and Prevention and the International Obesity Task Force. Am J Clin Nutr 2004;79:838–843.
8 Freedman DS, Serdula MK, Srinivasan SR, Berenson GS: Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. Am J Clin Nutr 1999;69:308–317.
9 Freedman DS, Dietz WH, Srinivasan SR, Berenson GS: The relation of overweight to cardiovascular risk factors among children and adolescents: The Bogalusa heart study. Pediatrics 1999;103: 1175–1182.
10 Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH: Long-term morbidity and mortality of overweight adolescents: A follow-up of the Harvard Growth Study of 1922 to1935. N Engl J Med 1992;327:1350–1355.
11 Shinha R, Fisch G, Teague B, et al: Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002;346:802–810.
12 Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P: Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128:608–615.
13 World Health Organization: Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation on Obesity, Geneva, June 1997. Geneva, WHO, 1998, WHO/NUT/NCDI/98.1.
14 Ogden CL, Flegal KM, Carroll MD, Johgnson CL: Prevalence and trends in overweight among US children and adolescents. JAMA 2002;288:1728–1732.
15 Al-Isa AN: Body mass index, overweight and obesity among Kuwaiti intermediate school adolescents aged 10–14 years. Eur J Clin Nutr 2004;[Epub ahead of print].
16 Al-Rukban MO: Obesity among Saudi male adolescents in Riyadh, Saudi Arabia. Saudi Med J 2003;24:27–33.

17 Abahussain NA, Musaiger AO, Nicholls PJ, Stevens R: Nutritional status of adolescent girls in the eastern province of Saudi Arabia. Nutr Hlth 1999;13:171–177.
18 Al-Hourani HM, Henry JK, Lightowler HJ: Prevalence of overweight among adolescent females in the United Arab Emirates. Am J Hum Biol 2003;15:758–764.
19 Al-Sendi AM, Shetty P, Musaiger AO: Prevalence of overweight and obesity among Bahraini adolescents: a comparison between three different sets of criteria. Eur J Clin Nutr 2003;57:471–474.
20 Jackson RT, Rashed M, Saad-Eldine R: Rural urban differences in weight, body image and dieting behavior among adolescent Egyptian schoolgirls. Int J Food Sci Nutr 2003;54:1–11.
21 Labarthe DR, Eissa M, Varas C: Childhood precursors of high blood pressure and elevated cholesterol. Annu Rev Publ Hlth 1991;12:519–541.

Nahla Hwalla, PhD, RD
Department of Nutrition and Food Science
American University of Beirut
PO Box 11–0236, Riad El Solh, Beirut 1107–2020 (Lebanon)
Tel. +961 1 350000 (ext 4540), Fax +961 1 744460, E-Mail nahla@aub.edu.lb

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 51–59

Nutrition and Physical Activity of the Population in Serbia

Mirjana Pavlović[a], *Vera Grujić*[b], *Arne Oshaug*[c]

[a] Public Health Institute, Nutrition Department, Subotica, and [b] Public Health Institute, Novi Sad, Serbia & Montenegro; [c] Akershus University College, Akershus, Norway

Diet and lifestyle has been known to play a key role as a risk factor for non-communicable chronic diseases (NCDs) for many years [1]. Intake of total energy and some nutrients have a considerable impact on the development of NCD linked to unbalanced diets and sedentary lifestyles caused by industrialization, urbanization, and economic change. These changes have led to increased intake of energy-dense diets high in fat, particularly saturated fat, and sugar, and low in complex carbohydrates. When this is combined with a decline in energy expenditure caused by a sedentary lifestyle, the risk for NCDs increases significantly [2]. Globally, NCDs contribute to an ever-increasing proportion of Disability Adjusted Life Years (DALYs). This confirms the importance of nutrition and active lifestyles as important factors in preventing NCD [3]. Previous studies of dietary quality and nutritional status in Serbia show that nutritional risk factors can be related to inadequate diet and lifestyle [4–8]. Physical activity contributes to physical, mental and social health and improves the quality of life of people of all ages and reduces social and health care costs. Therefore, physical activity with nutrition should be considered an essential element of preventing chronic disease, as well as a central part of a healthy lifestyle [3]. The purpose of this study was to assess the nutrition situation related to physical activity in Serbia.

Methods

A representative sample of 863 schoolchildren (435 boys; 428 girls) aged 10–18 in North Backa Region, and a representative sample of an adult population (20 years and above, 9,432–4,458 males and 4,974 females) in Serbia were included in cross-sectional surveys

Table 1. Relations between BMI and lifestyle in schoolchildren (n = 863)

Lifestyle		BMI				
		underweight % (n = 55)	Moderately underweight % (n = 119)	Normal body weight % (n = 571)	Over-weight % (n = 83)	Obesity % (n = 35)
Watching TV	Sometimes	6.4	13.2	65.0	11.8	3.7
	Almost every day	5.7	12.1	68.6	8.5	5.1
	Every day	7.0	15.6	65.0	8.8	3.6
Listening to music**	Sometimes	8.0	17.6	59.3	10.6	4.6
	Almost every day	5.3	10.5	70.6	8.5	5.1
	Every day	3.5	7.8	78.5	8.4	1.8
Physical activity	1/ week, rarely, never	6.3	13.1	66.3	9.7	4.7
	4–7/week	6.4	14.0	66.1	9.6	3.9
Sport activity/ week*	>7 h/week	4.9	11.2	73.4	8.2	2.2
	4–6 h	8.6	10.6	69.3	7.8	3.8
	2–3 h	6.4	13.0	70.0	7.6	3.0
	1 h/week	6.0	17.1	58.0	12.9	6.1

*$p < 0.05$; **$p < 0.01$.

covering dietary assessment and nutritional status measured by anthropometry, and lifestyle including physical activity. The sample size was determined by an estimated frequency questionnaire. Statistical analysis, including stepwise regression analysis and testing significant differences were done using SPSS/PC. NHANES I was used as reference values [9].

Results

The nutritional status of schoolchildren was assessed by body mass index BMI (kg/m^2), and about 6% of the children were underweight (4.9% girls and 7.8% boys), 14% moderate underweight (11.5% boys and 16.2% girls), 66% normal weight (66.9% boys and 65.4% girls), 10% overweight (9.0% boys and 10.2% girls) and 4% obese (4.8% boys, and 3.3% girls) (data not shown).

Table 1 shows that lifestyle factors such as listening to music and involved in sport activities were linked to BMI, while physical activity in general and watching TV were not associated with BMI in this study. Only about 20 percent of the children had some form of physical activity every day (fig. 1), while about 20% 4–6 times weekly, about 40% 2–3 times weekly, once weekly 12 or never about 21% of children. Boys were almost twice as active as girls, and

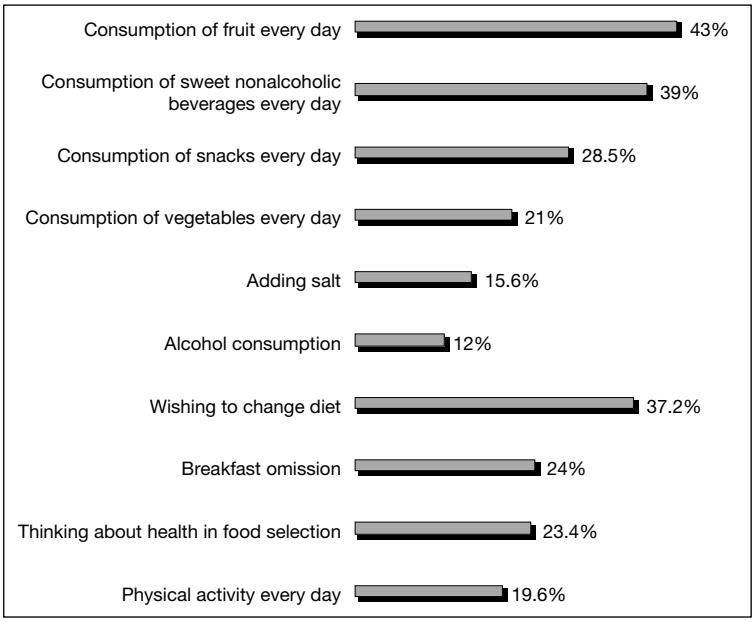


Fig. 1. Eating behavior and lifestyle risk factors in schoolchildren age 10–18 (n = 863).

children from urban areas were more physically active than those from rural areas. Less than 20% of the children were engaged in active sports more than 7 h weekly, and boys were more active (25%) than girls (10%), and children from urban areas more active (20%) than children from rural areas (14%). Most of the children had classes with physical activity in schools two times weekly (93%), and about 17% of the children estimated their physical condition as excellent, 29% as very good, 32% good, 17% moderately good and 4% as bad. During free time almost 40% watch TV and/or video every day, and 19% listen to music daily (data not shown). Figure 1 shows that about 40% of all of the children reported to consume fruit every day, while only about 20% consumed vegetables each day. The consumption of snacks was higher than vegetables, and as many as almost 40% of the children reported to consume sweetened nonalcoholic drinks daily. Not many children were preoccupied with health when choosing food (about 23%), while as many as 24% did not have breakfast daily. About 37% of the children said they wanted to change their dietary habits, of whom the majority were girls ($p < 0.01$). The awareness about nutrition increased with age (data not shown).

Table 2 indicates that there were differences between the groups in meal pattern, and those with obesity problems said they had fewer meals than the

Table 2. Relations between BMI and eating patterns in schoolchildren (n = 863)

Eating patterns		BMI				
		Underweight %	Moderate underweight %	Normal body weight %	Over weight %	Obesity %
Meals/day**	Two	3.1	2.7	65.1	19.3	9.8
	Three	5.8	12.0	66.8	11.1	4.4
	More than three	7.9	18.5	65.4	5.8	2.5
Milk drinks consumption frequency	Never		25.1	74.9		
	Sometimes	7.5	10.8	68.0	9.0	4.7
	One cup a day	6.3	15.9	62.2	11.4	4.2
	Two or more cups a day	5.0	14.6	68.9	8.3	3.2
Fruit consumption frequency*	Rarely	8.5	19.3	51.6	10.9	9.8
	Once a week	4.5	12.5	71.2	10.8	1.0
	2–3 times a week	9.3	10.5	67.6	7.8	4.9
	Every day	3.9	16.3	65.7	10.6	3.4
Vegetable consumption frequency	Rarely	6.4	13.4	66.5	9.9	3.8
	Once a week	10.3	13.4	60.2	14.4	1.7
	2–3 times per week	5.1	13.0	68.6	8.4	4.9
	Every day	6.3	16.2	64.7	8.6	4.2
Consumption frequency of meat and products	Rarely	5.5	10.2	70.1	10.7	3.6
	Once a week	6.1	8.6	69.3	12.7	3.3
	2–3 times a week	6.6	13.5	65.2	10.8	4.0
	Every day	6.3	16.1	66.3	6.7	4.5
Consumption frequency of sweet beverage	Almost every day	6.1	14.1	66.8	9.3	3.8
	Sometimes	6.8	13.7	65.3	10.1	4.1
	Never		9.7	79.9		10.3
Consumption frequency of snacks	Almost every day	6.5	13.8	69.5	6.9	3.3
	Sometimes	6.6	14.1	64.1	10.8	4.4
	Never		3.6	88.3	4.1	4.1
Alcohol consumption**	Never	7.2	15.4	62.9	9.6	4.9
	Sometimes	2.2	6.0	81.8	10.0	
	Every day	n.a.	n.a.	100.0	n.a.	n.a.

*p < 0.05; **p < 0.01.

other groups. Almost a quarter of the children said they did not eat breakfast. Boys said they were drinking more milk than girls and ate more in general. The younger children ate very little fruit, while they ate snacks frequently (data not shown). Table 2 also indicates that fewer of the obese children ate fruits frequently. There seems to be no differences between the various groups (based on BMI) in consumption of meat, sweet beverages, and snacks.

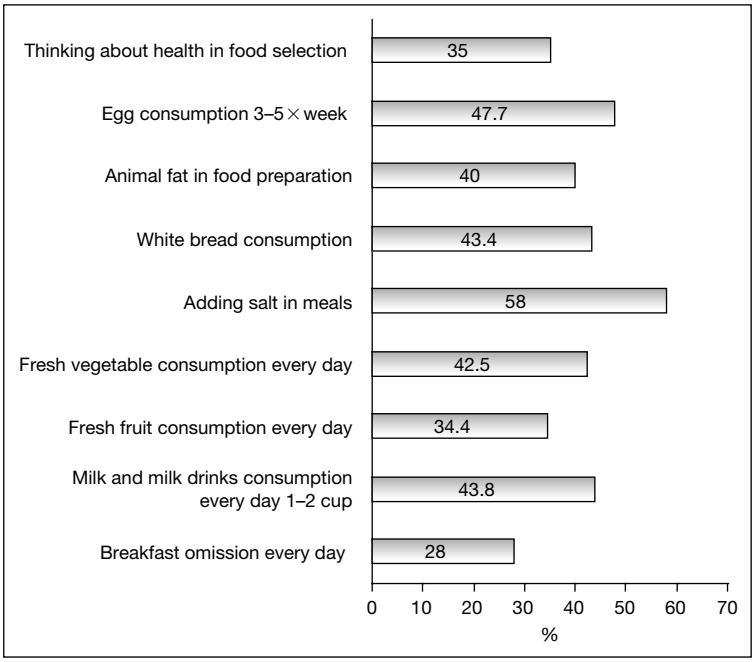


Fig. 2. Dietary patterns in adult population in Serbia (n = 9,432; 4,458 male; 4,974 female).

A regression model with BMI as a dependent variable, with the model: wishing to change diet, alcohol consumption, number of meals/day, thinking about health when selecting food, snacking, and desire for changing own weight gave $R = 0.508$ and $R^2 = 0.258$, a significant association indicating the importance of the independent variables for children's BMI (data not shown).

In the figures 2 and 3 data on the adult population are presented. The results indicate that lunch is the most frequent meal (93%, not shown), but as many as 28% said they did not eat breakfast (fig. 2). This was more usual among women compared to men ($p < 0.001$), younger people compared to older ($p < 0.001$), higher-educated people compared to those with less education ($p < 0.001$) and in urban areas compared to rural ($p < 0.001$) (data not shown). About 42% of adults ate fresh vegetables 6–7 times per week, while about 30% ate vegetables 3–5 times weekly. About 34% said they ate fresh fruits 6–7 times weekly, while 27% only 3–5 times per week. Every day intake of fresh fruit and vegetable were higher among females, younger age groups and higher-educated persons. Consumption of potatoes, especially fried potatoes, was very high (87%), while rice and pasta were eaten 1–2 times per week

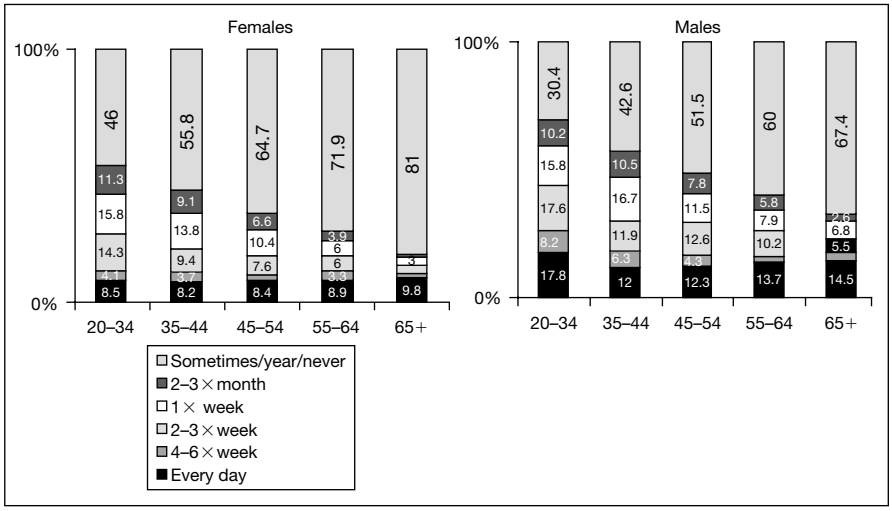


Fig. 3. Physical activity in leisure time in adult population in Serbia by age and gender (n = 9,432; 4,458 male; 4,974 female).

by 71% of the sample. White bread was widely used (43%) as well as use of animal fat in food preparation (40%). Use of animal fat is especially widespread among people with less education (53.7%) and in rural areas (62.0%) where traditional use of fat in the preparation of food prevails. About 35% (41% of females and 31% of males) said they thought about their health when selecting foods, but people from urban areas and with a higher education thought more about it (fig. 2).

Few of those participating in the survey had much physical activity. About 63% of the adult population spends their leisure time mostly sitting, while only 23% said they were physically active. The physically active were mainly males ($p < 0.001$) and the younger compared to the elderly ($p < 0.001$). Only about 10% were physically active every day, about 4% 4–6 times weekly, 9% 2–3 times a week, 8% 1–4 times monthly, and about 60% sometimes during a year or never due to disability or diseases (fig. 3). According to their own opinion, about 60% consider their physical activity as good, and almost 90% of them had a positive attitude about physical activity. Their occupational activity level was moderate-to-heavy according to 38% of the adults, and more than 25% reported having light-sedentary occupation without activity in leisure time (data not shown).

This dietary pattern and low physical activity was reflected in their nutritional status assessed by BMI. The average BMI in the sample was 26. About 39% had a normal nutritional status (BMI 20–24.5), about 37% were overweight (BMI 25–29.9, 43% males; 31% females), about 16% were in obesity

classes I and II (BMI 30–39.9, 14% males; 18% females), while only 1% were classified in obesity class III (BMI > = 40). It is interesting that 29% of obese females and 34% of obese males consider themselves as being normal weight (data not shown).

Discussion

Obesity is a rapidly growing epidemic, now affecting about 30% of the adult population of the WHO European Region. Overweight levels in Europe range from 9 to 41% of women and 10 to 50% of men [2, 3]; in this survey 37% of the adult population were overweight, and 10% of the schoolchildren. The prevalence of overweight and obesity among children in Europe is rising significantly, with up to 27% affected in some regions. In this survey a lower level was found. Based on IOTF on average, the prevalence of childhood overweight and obesity is approximately 10–20% in Europe region, which is much higher than that in the Africa, Asia Pacific, south and central America regions; and it is higher than the Eastern Mediterranean and Middle East Region; but lower than North America. The highest prevalence of overweight and obesity (>20%) is observed in eastern and southern European countries, which was not confirmed in this survey of schoolchildren. Italy probably has the highest prevalence, where a recent survey found that 36% of the 9 years old were overweight or obese. In Greece, the prevalence was 27% in boys and 22% for girls aged 6–17 years. In Spain, over 20% of children and adolescents were overweight or obese. Northern European countries tend to have lower prevalence (approximately 10–20%), for example, in the UK, where about 10–15% of children and adolescents were overweight or obese. In Sweden, the prevalence was about 20% for boys and 10% for girls [10].

Inadequate nutrition habits and lifestyle are mostly acquired in childhood and settled in adolescence. A WHO study among 123,227 schoolchildren (11, 13 and 15 years of age) from 28 countries showed that a majority of the children consumed fruit every day in Portugal (92–93%), Poland (82–85%), Czech Republic (81–85%), but rarely in Greenland (31–38%) and Belgium (46–48%). Snacks were consumed every day by children in North Ireland (41–51%), Scotland (36–44%) and the least in Norway (1–3%) and Sweden (2–3%). Regarding the consumption of sweet non-alcoholic beverages, it was most frequent consumed in North Ireland (75–79%), Israel (65–76%), and the least frequently in Finland (9–19%) and Sweden (15–28%). The level of physical activity in the same study was found to be progressively less, as they grow older. This is the same as found in this study. The proportion of 15-year-olds who reported taking part in sports outside school at least twice a week ranged

from 37 to 66% in girls and from 60 to 90% in boys [11]. This is far higher than found in this survey.

A survey of adults in the EU shows that levels of physical activity are low. An average 32% were not engaged in physical activity in their leisure time in a typical week. In general, southern EU countries had lower levels of physical activity than northern and western countries [12]. In this study, only about 10% of the sample were engaged in physical activity every day during leisure time.

Conclusions

The pattern of diet and physical activity shown in this survey raise concern. Unless something is done to change this pattern, it is likely that situation of NCD will worsen in the years to come. The level of physical activity among both children and adults is too low. The diet and eating patterns are leading to a high level of obesity, and will increase the risk for NCD. Therefore, primary prevention programs are needed, including an effective high-risk strategy in parallel with nutrition and healthy lifestyle promotion programs. Achievement of population goals for nutrition and lifestyle and implementation as specified in the WHO Global Strategy of NCDs Prevention should be placed at the forefront of public health policies and programs, also in Serbia.

References

1 WHO Technical Report Series 916: Diet, nutrition and the prevention of chronic diseases. Report of the Joint WHO, FAO Expert Consultation. Geneva, Switzerland, 2003.

2 The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, World Health Organization, 2002.

3 Food and Health in Europe: A new basis for action, WHO Regional Publications, European Series, No. 96, 2004.

4 Pavlović M, Grujić V: Nutritive risk factors within population; in Dragan Škorić (ed): Proceedings 1st International Symposium 'Food in the 21st Century' 14–17 November 2001, Subotica, Yugoslavia, Institute for Agriculture and Vegetables, Novi Sad, pp 474–481.

5 Pavlović M, Đokić D, Legetić B, Jakovljevic Đ: Nutrition and nutritional status in schoolchildren aged 10–18 from North Bačka Region in Yugoslavia, Book of Abstracts the 8th European Nutrition Conference, Lillehammer, 1999. Scand J Nutr 1999;2S(suppl 34):78.

6 Grujić V: Health status, health needs and usage of the health care in adult population in Republic of Serbia. J Inst Publ Health Serbia 2002;1–2:39–51.

7 Pavlović M, Grujić V: Dietary Patterns, Lifestyle and Obesity in Adolescents in Serbia, 9th European Nutrition Conference. Ann Nutr Metab Abstracts, October 1–4, 2003, Rome, 2003, vol 47, p 51.

8 Pavlović M: Strategy and model of prevention from atherosclerosis. Acta Biol Med Exp 2000;27:37–39.

9 Must A, Dallal GE, Dietz WH: Reference data for obesity: 85th and 95th percentiles of body mass index (w/ht2) and triceps skinfold thickness. Am J Clin Nutr 1991;53:839–846.

10 Lobstein T: Childhood Obesity in Europe: The New Crisis in Public Health. London, International Obesity Task Force, 2003.
11 Currie C (ed): Health and health behavior among young people: International report (http://www.euro.who.int/document/e67880.pdf). Copenhagen, WHO Regional Office for Europe, 2000 Health Policy for Children and Adolescents Series, No.1.
12 Kafatos AG, Codrington CA (eds): EURODIET Reports and Proceedings. Public Health Nutrition, 2001, vol 4 (2A).

Mirjana Pavlović , MD, PhD, RPHNutr
Public Health Institute
Nutrition Department
24000 Subotica, Zmaj Jovina Street 30 (Serbia & Montenegro)
Tel./Fax +381 24 571074, E-Mail mirasu@eunet.yu

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 60–67

Physical Activity and Body Composition

Angela Andreoli, Antonino De Lorenzo

Human Nutrition Unit, University of Rome 'Tor Vergata', Rome, Italy

Public health guidelines focus primarily on the promotion of physical activity and steady state aerobic exercise, which enhances cardiorespiratory fitness and has some impact on body composition (BC). BC is an essential measure of health and fitness for both athletes and the general population.

Research demonstrates that resistance exercise training has profound effects on the musculoskeletal system, contributes to the maintenance of functional abilities, and prevents osteoporosis, sarcopenia, lower back pain, and other disabilities. Recent research demonstrates that resistance training may positively affect risk factors such as insulin resistance, resting metabolic rate, glucose metabolism, blood pressure, body fat, and gastrointestinal transit time, which are associated with diabetes, heart disease, and cancer [1].

Physical activity has an effect on BC, especially on skeletal muscle. Skeletal muscle is the largest nonadipose tissue component at the tissue-system level of body composition in humans and it plays an important role in physical activity and many biochemical processes [2]. Fat-free mass (FFM) has commonly been used as a surrogate measure of skeletal muscle mass but does not always accurately reflect specific changes in muscle mass or differences in muscle mass among individuals. A fairly new approach to assess BC is to measure body cell mass (BCM). BCM is defined as the total mass of 'oxygen-exchanging, potassium-rich, glucose-oxidizing, work-performing' cells of the body [3]. A total body potassium (TBK)-independent BCM prediction model on the basis of an earlier model has been developed by Wang et al. [4]. They have provided a physiologically based, improved, and validated TBK-BCM prediction formula that should prove useful in BC and metabolism research.

Physical activity appears to have a beneficial effect on bone mass. Furthermore, physical activity with greater mechanical loading appears to result in

a greater bone mass than non-weight-bearing activities, and there appears to be a site-specific skeletal response to the type of loading at each bone mineral density site [5]. This has also been demonstrated in a study of girls affected by eating disorders and in athletes of the same age [6].

An assessment of fat-free mass (FFM) and fat mass (FM) provides valuable information about changes in BC with weight gain or loss and physical activity, and during aging. Noninvasive bedside techniques can now be used to evaluate the nutritional status of healthy and ill individuals [7].

Since body mass index has been shown to be an imprecise measurement of fat-free and FM, and provides no information if weight changes occur as a result of a decrease in FFM or an increase in FM. Non-invasive BC methods (i.e. bioelectrical impedance analysis (BIA), air displacement plethysmography) can now be used to monitor FFM and FM with weight gain and loss, and during aging.

Methods to Assess Body Composition

Depending on what information is needed, several methods are available, each with some advantages and limitations [8, 9] to measure BC. Cost of the method (both the instrument itself and the requisite personnel), the eventual stress and danger for radiation exposure for the subject, and the time necessary to obtain the information, as well as the accuracy needed are factors to be considered in the choice of the method.

The measurement of BC is of interest to medical personnel, nutritionists, and sports scientists. The most common and frequently used methods are based on a two-component model comprising FM and FFM because the amount of fat in the body is of special nutritional interest. The three most common methods used to calculate BC based on the two-component model are underwater weighing (UWW), BIA and skinfold thickness measurements.

UWW has been used as the reference method since the beginning of the1950s and is based on the assumption that fat has a density of 0.9 g/cm^3 and the FFM has a constant density of 1.1 g/cm^3 [10].

Skinfold thickness measurement has been used as a simple and inexpensive method to estimate the percentage fat since Durnin and Womersley [11] found a relation between the skinfold thickness measured with caliper and body density measured by UWW. To calculate body fat percentage Siri's 2-components equation was used based on the aforementioned assumed fixed densities for FM and FFM.

BIA is an indirect way to measure total body water (TBW) from total body resistance [12]. BIA is also a relatively simple method and is suitable in field

studies [13, 14]. From the estimation of body water, body fat content has been calculated on the assumption that FFM contains 73.2% water.

The two-component model assumes that there is a fixed proportion of water, protein and mineral in FFM. However, bone mineral mass, water and protein vary among individuals and are influenced by age, sex ethnic and genetic factors, as well as diet and exercise.

A more valid and precise method for measuring BC is dual-energy X-ray absorptiometry (DXA). DXA divides the body into three components: bone, fat-free and bone-free tissue, and fat [15].

A recent method to measure body fat is air-displacement plethysmography. The use of air-displacement plethysmography (BodPod) correlates with the concept of hydrostatic weighing (underwater weighing). Instead of using water to measure body volume, the BodPod uses air displacement to measure body volume [16].

Whole-body counting of ^{40}K enables, using a noninvasive nuclear technique, the in vivo determination of the naturally occurring radioactive isotope of ^{40}K in the human body. Because ^{40}K is 0.012% of natural potassium, it provides an accurate assessment of TBK. Potassium is almost exclusively an intracellular cation (95%) that Moore et al. [3] found chiefly in muscle and viscera (hence, essentially not found in fat, bone, or extracellular water). These authors considered TBK concentrations to be linearly correlated with the size of the BCM. An accurate measure of BCM would prove extremely useful to establish an individual's nutritional state or degree of malnutrition [17].

Factors such as age, gender, level of adiposity, physical activity and ethnicity influence the choice of method and equation. It is also important to evaluate the relative worth of prediction equations in terms of the criterion method used to derive reference measures of BC for equation development [18]. Given that hydrodensitometry, hydrometry and DXA are subject to measurement error and violation of basic assumptions underlying their use, none of these should be considered as a 'gold standard' method for in vivo BC assessment. Reference methods, based on whole-body, two-component BC models, are limited particularly for individuals whose FFM density and hydration differ from values assumed for two-component models. One multi-component model approach adjusts body density (measured via hydrodensitometry) for TBW (measured by hydrometry) and/or total body mineral estimated from bone mineral (measured via DXA). Skinfold (SKF) and BIA are two BC methods used in clinical settings. Unfortunately, the overwhelming majority of field method prediction equations have been developed for specific populations and are based on two-component model reference measures [19]. However, when assumptions generally accepted for the healthy population may not be valid for particular groups of individuals such as the elderly and athletes the multicomponent

models of BC need to be considered. Multicomponent models have been developed in recent years in order to provide estimates of the various components of the FFM, as well as the distribution of the adipose mass. They can be useful in situations where it is likely that the composition of the FFM is altered, when the simple two-component model cannot be applied [20].

Body Composition and Physical Activity

There is considerable interest in the evaluation of BC with regard to exercise and sport, because it is known that BC has a significant effect on athletic performance and that exercise has the potential to alter BC. Nonetheless, fluctuations in body weight alone cannot be adequately interpreted unless the quantitative variations of the components (FFM, FM, and TBW) are taken into account, because each component varies independently.

Information on BC of groups of athletes can be important since BC is an indicator of nutritional status and provides information on acute water homeostasis. Furthermore, BC provides information on specific adaptations to different physical training regimens.

Football (soccer), judo and water polo represent three uniform sports. However, all three are similar in that they are comprised of aerobic and anaerobic components. Thus, assessing and comparing the BC of these similar, yet different, sports would provide new insight into the field of BC.

Presently, the 'gold standard' for quantifying BCM is via measurement of the naturally occurring isotope ^{40}K. Nonetheless, these methods are expensive, time-consuming, and not practical for use in the field.

Bioelectric impedance (BIA) is a method for estimating BC and is one of the most widely used techniques in the study of BC. BCM can be measured by BIA and bioimpedance spectroscopy (BIS) [21, 22], which would allow for increased assessment of BCM because of the ease and inexpensiveness of both BIA and BIS. Furthermore, because BCM represents the functional parameters for metabolism and strength, evaluating BCM in athletes could be a better predictor of athletic performance and health, compared to simply assessing FFM and FM.

Andreoli et al. [23] assessed the impact of different sports on BCM in professional athletes using BIS. Although there were no significant differences in body weight and FFM among the groups, FM, %BF, and BCM varied considerably. They found that BCM was significantly different between the football divisions according to their performance, as well as between control group and all other teams. The BCM of these non-athletes was lower than the BCM of athletes, confirming the high level of fitness of the professional athletes.

Measurement of BCM is the best predictor of muscular efficiency, which could predict athletic performance. Therefore, increases in FFM and BCM are related to increase in muscular efficiency, and the lower BCM reported in non-athletes signifies decreases in muscular efficiency. Thus, the assessment of BCM by BIS could be a practical, as well as extremely useful tool, in evaluating BC and metabolism in athletes. BCM measured by BIS can assist researchers and coaches in more accurately assessing BC in athletes, without considerable time and expense.

Body Composition and Aging

Aging is associated with changes in BC, including an increase and redistribution of adipose tissue and a decrease in skeletal muscle and bone mass, beginning as early as the fourth decade of life. Aging is associated with a decline in bone mass, skeletal muscle mass, strength, and physical work capacity. Women are more likely to suffer from these physical changes than men. These changes have significant implications for the health and functioning of the individual because of their associations with chronic disease expression and severity, as well as geriatric syndromes such as mobility impairment, falls, frailty and functional decline. Therefore, understanding the preventive and therapeutic options for optimizing BC in old age is central to the care of patients in mid-life and beyond. Pharmacological interventions are currently available for maintaining or improving bone mass, and much current interest is focused on anabolic agents that will preserve or restore muscle mass, as well as those that can potentially limit adipose tissue deposition. There is currently sufficient evidence to suggest that a substantial portion of what have been considered 'age-related' changes in skeletal muscle, fat and bone are in fact related either to excess energy consumption, decreased energy expenditure in physical activity, or both factors in combination. In addition, selective underconsumption of certain macro- or micronutrients contributes to the loss of skeletal muscle and bone mass [24].

Aging is associated with a decline in FFM. Sarcopenia is the loss of skeletal muscle mass that occurs to ageing. However, the rate of sarcopenia and the severity of its sequelae vary greatly according to health status, physical activity, and possibly diet [25].

The question is whether age-related changes in BC can be delayed by an active life style. Although no effect of habitual activity level on changes in BC has been observed, training has a positive effect on skeletal muscle function [26].

Sedentary persons who improve their physical fitness are less likely to have an increased risk of cardiovascular disease than are those who remain sedentary.

There now exists a wealth of data demonstrating that physical activity and exercise may improve disease and delay decline in function in the geriatric population. However, many healthcare professionals do not feel adequately prepared to design and prescribe exercise programs for their patients. Healthcare providers are strongly encouraged to promote a less sedentary life style for their older patients, which may improve the quality of life in these older individuals [27].

An accurate measure of BCM would prove extremely useful to establish an individual's state of health or disease over time, possibly assisting with the prevention of sarcopenia. De Lorenzo et al. [28] evaluated BCM in a cohort of Italian men in order to assess differences in BC with age. They did not find differences in body weight among decades; however, TBK, TBK/height, TBK/body weight, and BCM was found significantly lower in the oldest subjects compared to the other groups. Results confirm that there is a major decrease in BCM with age, and in a weight stable subject, BCM may be decreased, which may lead to reduced functional capacity [28].

It is to be noted that since body mass index (BMI) is largely used in sport medicine, an observation should be pointed out here, BMI does not discriminate body fat from FFM nor does it detect changes in these parameters with physical activity and aging. Body FM index (BFMI) and FFM index (FFMI) allow comparisons of subjects with different heights. Kyle et al. [29] evaluated differences in body mass index, BFMI, and FFMI in physically active and sedentary subjects under and over 60 years and determined an association between physical activity, age and BC parameters in a healthy white population between the ages of 18 and 98 years. The results show that the physically active as opposed to sedentary subjects were more likely to have a low BFMI and less likely to have a very high BFMI.

Conclusions

The earlier in life an individual becomes physically active the greater the increase in health benefits; however, becoming physically active at any age will benefit overall health. Improvement in musculoskeletal fitness (for example, through resistance training combined with stretching) is related to an enhanced health status. Thus, maintaining musculoskeletal fitness can increase overall quality of life.

A good approach for many individuals to obtain the recommended level of physical activity is to reduce sedentary behavior by incorporating more incidental and leisure-time activity into the daily routine. Political action is imperative to effect physical and social environmental changes to enable and encourage physical activity.

The current physical activity guideline for adults of 30 min of moderately intense daily activity, preferably every day of the week, is of importance in limiting health risks for a number of chronic diseases including coronary heart disease and diabetes. However, to prevent weight gain or weight regain this guideline is likely to be insufficient for many individuals in the current environment.

Athletic staff should be knowledgeable about the latest guidelines related to weight and appropriate weight control methods so they may guide their athletes using modest, safe approaches that will not negatively affect health or performance.

Regular physical activity has profound effects on BC and helps to maintain and increase skeletal muscle mass, with increased resting metabolic rate and enhanced capacity for lipid oxidation during rest and exercise.

References

1 Winett RA, Carpinelli RN: Potential health-related benefits of resistance training. Prev Med 2001;33:503–513.
2 Wang W, Wang Z, Faith M, Kotler D, Shih R, Heymsfield B: Regional skeletal muscle measurement: evaluation of new dual-energy x-ray absorptiometry model. J Appl Physiol 1999;87: 1163–1171.
3 Moore FD, Olesen KH, McMurray JD, Parker HV, Ball MR, Boyden CM: The Body Cell Mass and Its Supporting Environment. Philadelphia, Saunders, 1963.
4 Wang Z, St-Onge MP, Lecumberri B, Pi-Sunyer FX, Heshka S, Wang J, Kotler DP, Gallagher D, Wielopolski L, Pierson RN Jr, Heymsfield SB: Body cell mass: Model development and validation at the cellular level of body composition. Am J Physiol 2004;286:E123–E128.
5 Andreoli A, Monteleone M, Van Loan M, Promenzio L, Tarantino U, De Lorenzo A: Effects of different sports on bone density and muscle mass in highly trained athletes. Med Sci Sports Exerc 2001;33:507–511.
6 Iacopino L, Siani V, Melchiorri G, Orlandi C, De Luna A, Cervelli V, Andreoli A: Body composition differences in adolescent female athletes and anorexic patients. Acta Diabetol 2003;40(suppl 1): S180–S182.
7 Kyle UG, Genton L, Pichard C: Body composition: What's new? Curr Opin Clin Nutr Metab Care 2002l;5:427–433.
8 Ellis KJ. Human body composition: In vivo methods. Physiol Rev 2000;80:649–680.
9 Deurenberg P, Andreoli A, Borg P, Kukkonen-Harjula K, de Lorenzo A, van Marken Lichtenbelt WD, Testolin G, Vigano R, Vollaard N: The validity of predicted body fat percentage from body mass index and from impedance in samples of five European populations. Eur J Clin Nutr 2001;55:973–979.
10 Fidanza F, Keys A, Anderson JT: Density of body fat in man and other mammals. J Appl Physiol 1953;6:252–256.
11 Durnin JV, Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness: Measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974;32:77–97.
12 Kushner RF, Schoeller DA: Estimation of total body water by bioelectrical impedance analysis. Am J Clin Nutr 1986;44:417–424.
13 Heymsfield SB, Zimian W, Visser M, Gallagher D, Pierson RN: Techniques used in the measurements of body composition: An overview with emphasis on bioelectrical impedance analysis. Am J Clin Nutr 1996;64:S478–S484.
14 De Lorenzo, Andreoli A: Segmental bioelectrical impedance analysis. Curr Opin Clin Nutr Metab Care 2003;6:551–555.

15 Heymsfield SB, Wang J, Heshka S, Kehayias JJ, Pierson RN: Dual-photon absorptiometry: Comparison of bone mineral and soft tissue mass measurements in vivo with established methods. Am J Clin Nutr 1989;49:1283–1289.
16 Dempster P, Aitkens S: A new air displacement method for the determination of human body composition. Med Sci Sports Exerc 1995;27:1692–1697.
17 Forbes GB: Human Body Composition. New York, Springer, 1987.
18 De Lorenzo A, Bertini I, Iacopino L, Pagliato E, Testolin C, Testolin G: Body composition measurement in highly trained male athletes: A comparison of three methods. J Sports Med Phys Fitness 2000;40:178–183.
19 Heyward VH: Evaluation of body composition: Current issues. Sports Med 1996;22:146–156.
20 Heymsfield SB, Wang ZM, Withers R: Multi-component molecular-level models of body composition analysis; in Riche A, Heymsfield SB, Lohman T (eds): Human Body Composition. Champaign, Human Kinetics, 1996, pp 129–147.
21 De Lorenzo A, Andreoli A, Matthie J, Withers P: Predicting body cell mass with bioimpedance by using theoretical methods: A technological review. J Appl Physiol 1997;82:1542–1558.
22 Kotler, DP, Rosenbaum K, Allison DB, Wang J, Pierson RN Jr: Validation of bioimpedance analysis as a measure of change in body cell mass as estimated by whole-body counting of potassium in adults. J Parenter Enteral Nutr 1999;23:345–349.
23 Andreoli A, Melchiorri G, Brozzi M, Di Marco A, Volpe SL, Garofano P, Di Daniele N, De Lorenzo A: Effect of different sports on body cell mass in highly trained athletes. Acta Diabetol 2003;40(suppl 1):S122–S125.
24 Fiatarone Singh MA: Benefits of exercise and dietary measures to optimize shifts in body composition with age. Asia Pac J Clin Nutr 2002;11(suppl 3):S642–S652.
25 Roubenoff R: Sarcopenia: Effects on body composition and function. J Gerontol [A] 2003;58: 1012–1017.
26 Westerterp KR, Meijer EP: Physical activity and parameters of aging: A physiological perspective. J Gerontol [A] 2001;56(spec no 2):7–12.
27 Christmas C, Andersen RA: Exercise and older patients: Guidelines for the clinician. J Am Geriatr Soc 2000;48:318–324.
28 De Lorenzo A, Andreoli A, Battisti P, Candeloro N, Volpe SL, Di Daniele N: Assessment of total body potassium in healthy Italian men. Ann Hum Biol 2004;in press.
29 Kyle UG, Morabia A, Schutz Y, Pichard C: Sedentarism affects body fat mass index and fat-free mass index in adults aged 18 to 98 years. Nutrition 2004;20:255–260.

Angela Andreoli
Human Nutrition Unit, Via Montpellier 1
University of Rome ‘Tor Vergata’
IT–00173 Rome (Italy)
Tel. +39 06 72596415, Fax +39 06 72596407, E-Mail angela.andreoli@uniroma2.it

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 68–74

Syndrome X: Clinical Aspects

D. Labadarios

Department of Human Nutrition, University of Stellenbosch
and Tygerberg Academic Hospital, Tygerberg, South Africa

The current literature concurs that overweight and obesity is associated with a constellation of life-style risk factors, which, collectively, are defined as the metabolic syndrome, which was first described in the late 1980s [1] and is also known as insulin resistance syndrome, dysmetabolic syndrome or syndrome X. The latter is characterized by abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance (table 1) [2], a proinflammatory and prothrombotic state, risk factors which confer an increased risk for type II diabetes and cardiovascular disease. Similar, albeit more stringent, criteria have been recommended by the World Health Organization (WHO) (table 2) [3] in which insulin resistance is a prerequisite for diagnosis, whereas the American Association of Clinical Endocrinologists [4] proposed its own criteria, which could be considered to be less specific in terms of the number of risk factors necessary for the diagnosis of the syndrome. Diagnostically, therefore, there exists significant uncertainty regarding the definition of the syndrome itself and whether the diagnosis of the syndrome affords benefit(s) additional to that (those) derived from the diagnosis and treatment of the syndrome's components. Nevertheless, the early diagnosis of the syndrome may enhance its prevention and avoid its consequences [5]. In this regard, emerging evidence indicates that the syndrome appears to increase the risk for cardiovascular disease [6], although inconsistently so [7], and more definitive outcome data is necessary in order to impart improved perspective on the clinical significance of the syndrome per se.

Irrespective of diagnostic considerations, the syndrome is reported to be present respectively in 1 of 5 and approximately 1 of 7 Americans [8] and nondiabetic Europeans [9] and is emerging as a significant clinical disorder in childhood and adolescence [10] as well as in the developing world [11, 12]. Older age, ethnicity, higher body mass index, postmenopausal status, smoking,

Table 1. The ATP[a] III clinical identification of syndrome X [1]

Risk factor	Recommended cut-off value
Waist circumference, cm	M >102 (>40 in), F >88 (>35 in)
Triglycerides, mg/dl	≥150 (>1.7 mmol/l)
HDL-cholesterol, mg/dl	M ≤40 (≤1.04 mmol/l), F ≤50 (≤1.3 mmol/l)
Blood pressure, mm Hg	M ≥130 systolic ≥85 diastolic
Fasting glucose, mg/dl	≥100 (≥5.5 mmol/l)

[a] The National Cholesterol Education Program's Adult Treatment Panel III; diagnosis of the metabolic syndrome can be made by the presence of 3 of the 5 defined characteristics. M = Male; F = female.

Table 2. WHO diagnostic criteria for the metabolic syndrome [2]

a Insulin resistance, identified by one of the following
Type 2 diabetes
Impaired fasting glucose
Impaired glucose tolerance
Insulin resistance (under hyperinsulinemic, euglycemic conditions glucose uptake below the lowest quartile for background population under investigation)

b Plus any two of the following conditions
Raised arterial blood pressure (≥140/90 mm Hg)
Raised plasma triglycerides (≥150 mg/dl; ≥1.7 mmol/l)
Low plasma HDL cholesterol (≤35 mg/dl; ≤0.9 mmol/l) in men or (≤39 mg/dl; ≤1.0 mmol/l) in women
Central obesity (BMI ≥30 kg/m^2) and/or waist:hip ratio (0.9 in men, 0.85 in women)
Microalbuminuria (urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g)

c Other conditions which may be present but are not required for diagnosis
Hyperuricemia
Coagulation disorders

lower household income, high carbohydrate intake, alcohol abstinence and physical inactivity have been reported [8] to be associated with increased risk for developing the metabolic syndrome. Importantly, the syndrome is also associated with substantial and clinically significant increase in all-cause, cardiovascular as well as diabetic morbidity and mortality [10, 13, 14].

Proposed Predisposing Factors

Although the etiology of the syndrome is not well understood, several factors (insulin resistance, genetics, lifestyles, fetal development and psychosocial stress) have been proposed to be contributing to its development. Among these factors, insulin resistance appears to be of central significance. Factor analysis studies [15] indicate that insulin resistance clusters with measures of glucose, central obesity and usually with dyslipidemia indicating the underlying multifactorial process necessary for the full expression of the syndrome.

Genetic factors are also thought to be important in the pathogenesis of the metabolic syndrome since insulin resistance has been reported in 45% of first-degree relatives of patients with type 2 diabetes compared with 20% of individuals without such family history [16]. Furthermore, first-degree relatives of type 2 diabetics also have an increased waist-to-hip ratio compared to subjects without history.

In terms of environmental influences, a sedentary lifestyle is associated with an increased risk of developing the metabolic syndrome, since moderate and vigorous leisure time physical activity has been reported to decrease the risk of the syndrome by two-thirds and cardiorespiratory fitness was inversely associated with the syndrome independent of BMI and related confounding factors [17]. Dietaryily, it has been proposed that the quantity and quality of dietary carbohydrate may play a crucial role in the development of the syndrome, since high insulinogenic foods may result in postprandial hyperinsulinemia and weight gain, especially in genetically predisposed individuals [18]. In the developing world, especially in countries undergoing the nutrition transition [12, 19], the 'thrifty phenotype' [20], the 'fetal origins' [21] and 'fetal insulin' [22] hypotheses have been proposed to explain the increasing prevalence of obesity, cardiovascular disease and type 2 diabetes mellitus as a consequence of genetic and environmental interaction(s). In this regard, small size at birth, and obesity later in life arising from or related to the significant dietary changes of the nutrition transition, may be predisposing factors to the development of the syndrome. In India for instance, poor intrauterine growth was predictive of a higher prevalence of adiposity at 8 years of age, and the latter was strongly predictive of insulin resistance [23].

The similarities between the metabolic and the Cushing's syndrome [24] have elicited interest in relation to cortisol metabolism as well as the role of increased sympathetic activity and hypothalamic pituitary adrenal (HPA) function, in response to psychosocial stress, in the pathogenesis of the metabolic syndrome. Although the latter has been associated with increased urinary excretion of cortisol metabolites, norepinephrine and a lower heart rate variability [25], which may partly explain [26] the increased cardiovascular mortality in the presence of the metabolic syndrome, future prospective studies will undoubtedly

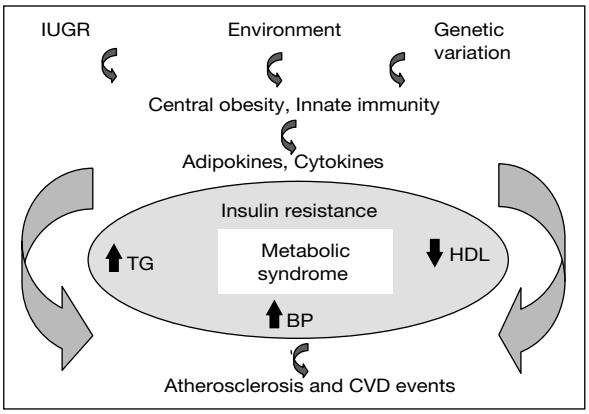


Fig. 1. Proposed origin and relationship of the metabolic syndrome to chronic disease. IUGR = Intrauterine growth restriction; TG = triglycerides; HDL = high-density lipoprotein cholesterol; BP = blood pressure. Adapted from various sources.

afford better perspective on the relationship, if any, of neuroendocrine activation and the metabolic syndrome.

The recurring theme of central obesity as a main component of the metabolic syndrome [8, 9, 12, 23] together with the recent appreciation of the endocrine and paracrine functions of adipose tissue [27] has led to the proposal that chronic inflammation may be an important component of the metabolic syndrome [28]. Certainly, emerging evidence would appear to be supportive (fig. 1) of the role of chronic inflammation being the common underlying link of a number of the, apparently unrelated, components of the metabolic syndrome and its related associations to the so called chronic diseases of the western world [29, 30], including psychosocial stress [31]. In this regard, the recently described antidiabetic, antiatherosclerotic and anti-inflammatory functions of adiponectin [32], a novel adipocytokine, as well as its relation to decreased risk of myocardial infarction [33] would afford additional support for such a proposal. Further more, chronic inflammation [34, 35] could further offer a unifying mechanism [36, 37] of the implications and consequences of the effects of undernutrition early in life in relation to the nutrition related chronic diseases of apparent 'affluence' later in life.

Management

The approach to the treatment of the syndrome includes lifestyle modifications (weight management, physical activity and dietary management

conducive to improving insulin resistance), addressing all modifiable risk factors for coronary heart disease in conjunction with pharmacotherapy, as appropriate, as well as the treatment of glucose intolerance and diabetes.

Despite the lack of consensus on the treatment of the metabolic syndrome, the available evidence would strongly support the urgent need for effective and appropriate management, since the components of the metabolic syndrome, individually and collectively, appear to afford increased risk for coronary heart disease and diabetes [38], and the treatment thereof in the form of exercise [39], dietary [18, 40] and weight [41–43] management are associated with beneficial outcomes. With regard to the dietary management of the syndrome and on the basis of the available evidence, low carbohydrate/high fat diets in relation to weight loss would appear to afford no additional advantage over any other sound method of weight management [44–47], at least in the short term. Nevertheless, although the early diagnosis and management of the metabolic syndrome may prove effective in the better prevention of type II diabetes and cardiovascular disease, more definitive outcomes from any such intervention studies will undoubtedly help establish the efficacy of the current recommendations.

References

1 Reaven GM: Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607.
2 Grundy SM, Brewer HB, Jr, Cleeman JI, et al: Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circulation 2004;109:433–438.
3 World Health Organization: Definition, Diagnosis and Classification of Diabetes mellitus and Its Complications: Report of a WHO Consultation. 1. Diagnosis and Classification of Diabetes mellitus. Geneva, World Health Organization, 1999.
4 Einhorn D, Reaven GM, Cobin RH, et al: American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003;9:237–252.
5 Wilson PWF, Kannel WB, Silbershatz H, D'Agostino RB: Clustering of metabolic factors and coronary heart disease. Arch Intern Med 1999;159:1104–1109.
6 Golden SH, Folsom AR, Coresh, J, et al: Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. Diabetes 2002;51:3069–3076.
7 Resnick HE, Jones K, Ruotolo G, et al: Insulin resistance, the metabolic syndrome and the risk of incident cardiovascular disease in nondiabetic American Indians: The strong heart study. Diabetes Care 2003;26:861–867.
8 Park Y-W, Zhu S, Palaniappan L, et al: The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third national Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 2003;163:427–436.
9 Hu G, Qiao Q, Tuomilehto J, et al, for the DECODE Study Group: Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066–1076.
10 Kohen-Avramoglua R, Theriaultb A, Adeli K: Emergence of the metabolic syndrome in childhood: An epidemiological overview and mechanistic link to dyslipidaemia. Clin Biochem 2003;36:413–420.
11 Misra A, Vikram NK: Insulin resistance syndrome (metabolic syndrome) and obesity in asian Indians: Evidence and implications. Nutrition 2004;20:482–491.

12 Sawaya AL, Martins P, Hoffman D, Roberts SB: The risk between childhood undernutrition and risk of chronic diseases in adulthood: A case study of Brazil. Nutr Rev 2003;61:168–175.
13 Lakka H-M, Laaksonen, De, Lakka TA, et al: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–2716.
14 Bonow RO, Gheorghiade M: The diabetes epidemic: A national and global crisis. Am J Med 2004;116:2S–10S.
15 Meigs JB: Insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. Am J Epidemiol 2000;152:908–911.
16 Groop L, Forsblom, C, Lehtovirta M, et al: Metabolic consequences of a family history of NIDDM (The Botnia Study): Evidence for sex-specific parental effects. Diabetes 1966;45:1585–1593.
17 Laaksonen DE, Lakka H-M, Salonen JT, et al: Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. Diabetes Care 2002;25: 1612–1618.
18 Koop W: High insulinogenic nutrition: An etiological factor for obesity and the metabolic syndrome? Metabolism 2003;52:840–844.
19 Monteiro CA, Conde WL, Popkin BM: The burden of disease from undernutrition and overnutrition in countries undergoing the rapid nutrition transition: A view from Brazil. Am J Publ Health 2004;94:433–434.
20 Hales CN, Barker DJP, Clark PM, et al: Fetal and infant growth and impaired glucose tolerance at age of 64. Br Med J 1991;303:1019–1022.
21 Barker DJP: Fetal origins of coronary heart disease. Br Med J 1995;311:171–174.
22 Hattersley AT, Tooke JE: The fetal insulin hypothesis: An alternative explanation of the association of low birth weight with diabetes and vascular disease. Lancet. 1999;353:1789–1792.
23 Yajnik C: Interactions of perturbations of intrauterine growth and growth during childhood on the risk of adult-onset disease. Proc Nutr Soc 2000;59:257–265.
24 Bjorntorp P, Rosmond R: The metabolic syndrome: A neuroendocrine disorder? Br J Nutr 2000;83 (suppl 1):S49–S57.
25 Brunner EJ, Hemingway H, Walker BR, et al: Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: Nested case-control study. Circulation 2002;106:2659–2665.
26 Liao D, Sloan RP, Cascio WE, et al: Multiple metabolic syndrome is associated with lower heart rate variability: ARIC study. Diabetes Care 1998;21:2116–2122.
27 Mohamed-Ali V, Pinkney JH, Coppack SW: Adipose tissue as an endocrine and paracrine organ. Int J Obes 1998;22:1145–1158.
28 Festa A, D'Agostino R Jr, Howard G, et al: Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102: 42–47.
29 Fernadez-Real JM, Ricart W: Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev 2003;24:278–301.
30 Grundy SM: Inflammation, hypertension, and the metabolic syndrome. JAMA 2003;290: 3000–3002.
31 Black PH: The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav Immun 2003;17:350–364.
32 Matsuzawa Y, Funahashi T, Kihira S, Shimomura I: Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29–33.
33 Pischon T, Girman CJ, Hotamisligil GS, et al: Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730–1737.
34 Lunn PG: The impact of infection and nutrition on gut function and growth in childhood. Proc Nutr Soc 2000;59:147–154.
35 Campbell DI, Elia M, Lunn PG: Growth faltering in rural Gambian children is associated with impaired small intestinal function leading to endotoxemia and systemic inflammation. J Nutr 2003;133:1332–1338.
36 Labadarios D: Malnutrition in the developing world: the lack of food scenario. 10th Nestle Clinical Nutrition Workshop. Home Care Enteral Feeding. Potsdam-Berlin, 2004, in press.

37 Yajnick C: The insulin resistance epidemic in India: Fetal origins, later life, or both. Nutr Rev 2001;59:1–9.
38 Sattar N, Gaw A, Scherbakova O, et al: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in West of Scotland Coronary Prevention Study. Circulation 2003;108:414–419.
39 Katzmarzyk PT, Church TS, Blair SN: Cardiorespiratory fitness attenuates the effects of the metabolic syndrome and all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092–1097.
40 Liu S, Manson JE, Buring JE, et al: Relation between a diet with a high glycemic load and plasma concentrations of high sensitivity C-reactive protein in middle-aged women. Am J Clin Nutr 2002;75:492–498.
41 Reinehr T, Andler W: Changes in the atherogenic risk profile according to the degree of weight loss. Arch Dis Child 2004;89:419–422.
42 McLaughlin T, Abbasi F, Lamendola C, et al: Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908–2912.
43 Tchernof A, Nolan A, Sites CK, et al: Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002;105:564–569.
44 Ornish D: Was Dr Atkins right? Am J Diet Assoc 2004;104:537–542.
45 Foster GD, Wyatt HR, Hill JO, et al: A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med. 2003;348:2082–2090.
46 Samaha FF, Iqbal N, Seshadri P, et al: A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–2081.
47 Bravata DM, Sanders L, Huang J, et al: Efficacy and safety of low-carbohydrate diets: A systematic review. JAMA 2003;289:1837–1850.

Prof. D. Labadarios
Department of Human Nutrition
University of Stellenbosch and Tygerberg Academic Hospital, PO Box 19063
Tygerberg 7505 (South Africa)
Tel. +27 21 938 9259, Fax +27 21 933 2991, E-Mail demetre@sun.ac.za

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 75–83

Metabolic Syndrome: Is There a Pathophysiological Common Denominator?

Lessons Learned from the Pima Indians

P.A. Tataranni

Clinical Diabetes and Nutrition Section, NIDDK, NIH-DHHS, Phoenix, Ariz., USA

The idea that insulin resistance and the resulting hyperinsulinemia cause a cluster of metabolic abnormalities giving rise to a clinical syndrome that greatly increases the risk of cardiovascular disease (CVD) has been debated for several decades [1–4]. As pervasive as the concept has been, more than 15,000 scientific publications later (personal search of PubMed) there is little agreement on what to call the syndrome (metabolic syndrome [5] [for simplicity this name will be used in the rest of manuscript], syndrome X, dysmetabolic syndrome [6], insulin resistance syndrome [4]), how to define it clinically (at least four partially overlapping definitions by the NCEP:ATPIII, WHO, AACE and EGIR were recently discussed at the 1st Annual World Congress on the Insulin Resistance Syndrome [7]) and how to approach it therapeutically [8].

This is perhaps because the pathophysiological underpinnings of the metabolic syndrome are far from being understood. Hyperinsulinemia, increased sympathetic nervous system (SNS) activity and, more recently, elevated intra-adipose tissue concentrations of cortisol are among the abnormalities that continue to be studied as possible common denominators. Notwithstanding this work, the discussion on whether the clustering of obesity, insulin resistance, dyslipidemia, hypertension, and other abnormalities reflects a limited number of underlying etiologic defects or even a single defect has remained very lively throughout the years [8–21].

The Pima Indians of Southwestern Arizona are interesting in this respect because they have one of the highest reported prevalence rates of obesity and T2DM, but not as high a prevalence of hypertension [22] and CVD [23].

The case of the Pimas has been cited in the literature as one of the prime examples for the lack of solid epidemiological evidence supporting the existence of the metabolic syndrome [24]. On the other hand, learning what protects hyperinsulinemic Pimas from fully developing the metabolic syndrome may have great relevance to its treatment in other populations. We have studied the pathophysiological consequences of hyperinsulinemia in the Pima Indians for many years. This manuscript summarizes some of the key findings.

Hyperinsulinemia

The Pima Indians are characterized by marked insulin resistance and hyperinsulinemia [25]. The hyperinsulinemia of the Pimas appears to be an abnormality that is already present in childhood [26] and has serious consequences since it predicts the development of obesity [27] and T2DM [28] in children and T2DM in adults [29]. The reason for the marked hyperinsulinemia remains unknown. To a certain extent, the higher insulin concentration is a secondary adaptation to the high degree of adiposity and insulin resistance. This is unlikely to be the only explanation, however, because Pima Indians are more insulinemic than whites even after accounting for the higher degree of adiposity and insulin resistance [25]. We have hypothesized a role of increased parasympathetic drive to the pancreas [30], but have been unable to conclusively prove it [31].

One of the early clues that insulin and the metabolic syndrome may be physiologically related was provided by the observation in the mid 1960s of an association between hyperinsulinemia and hypertension [1], a finding later confirmed by several others studies [32, 33] but not ours [22, 34, 35]. Saad et al. [22] showed that in Pimas plasma insulin concentrations in the fasting state and after carbohydrate loading were not significantly related with blood pressure after controlling for BMI and glycemia. We also demonstrated that the relationship between insulinemia and blood pressure was racially specific, being present in whites but not in Pimas [34, 35] or blacks [34]. This could indicate that insulinemia is not causally related to variability in blood pressure or, alternatively, that the relationship between hyperinsulinemia and hypertension may be mediated by mechanisms active in whites but not in Pimas or other racial groups. Many such mechanisms have been proposed by which hyperinsulinemia could lead to an increase in blood pressure, including effects on the kidney and the autonomic nervous system [2]. We have been especially interested in the putative stimulatory effect of insulin on the sympathetic nervous system.

The Sympathetic Nervous System

Almost 20 years ago, Landsberg proposed that the hyperinsulinemia associated with obesity-induced insulin resistance leads to increased sympathetic nervous system (SNS) activity, which in turn contributes to increased blood pressure through chronotropic, vasoconstrictive and antinatriuretic effects [36]. While experimental studies in animals have proven this hypothesis correct, the direct neurobiological mechanism through which insulin activates neurons responsible for regulating the SNS remains somewhat obscure [37].

In humans, an association between obesity and SNS activity has been reported by others [38] and us [35]. However, while in whites obesity, hyperinsulinemia, elevated SNS activity and high blood pressure are intercorrelated, in Pimas we observed relationships between obesity and insulinemia and SNS activity and blood pressure, but not insulinemia and SNS activity [35]. This raises the possibility that a failure of insulin to activate the SNS in response to the development of obesity may contribute to the low prevalence of hypertension in this population. It is possible that obese Pimas, who manifest resistance to the action of insulin on peripheral glucose uptake, also become resistant to the central effects of insulin to stimulate sympathetic outflow (fig. 1). The lack of relationship between insulinemia and SNS activity may also explain why, despite being so obese, Pima Indians have a SNS activity that is 20–30% lower than whites [35, 39–41], a desirable characteristic since a low SNS seems to protect against the development of hypertension [42].

Thus, if low SNS activity begets cardioprotection, understanding the neurophysiological mechanisms through which Pimas attain the former would seem highly relevant. Glucocorticoids are known to have both direct and indirect inhibitory effects on central noradrenergic neurons [43] and we have recently uncovered evidence that Pimas are characterized by a high sensitivity of the SNS to the acute inhibitory effect of cortisol [41]. We have, therefore, suggested that this is, at least in part, how Pimas achieve low sympathoexcitation [41].

11β-Hydroxysteroid Dehydrogenase

Another mechanism through which insulin and cortisol may be linked to the pathophysiology of the metabolic syndrome relates to the novel concept of tissue specific metabolism of glucocorticoids [44]. Adipose tissue contains the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11-HSD), which acts in vivo as a reductase, converting inactive cortisone to active cortisol. In rodents, artificially increasing 11-HSD1 activity in adipose tissue by introducing an 11-HSD1 transgene under control of an adipose specific promoter, results in

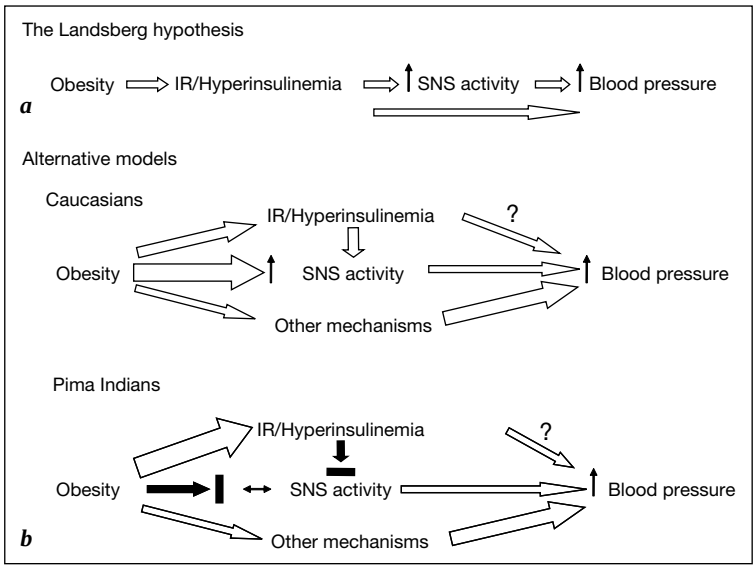


Fig. 1. According to Landsberg's hypothesis [36], hyperinsulinemia associated with obesity-induced insulin resistance leads to increased SNS activity, which in turn contributes to increased blood pressure. Studies in Pima Indians suggest a more complex model in which hyperinsulinemia, SNS activity and other yet unidentified mechanisms can have concomitant but independent effects on blood pressure.

the development of visceral adiposity, hyperglycemia, dyslipidemia and hypertension [45, 46], i.e., a cluster of abnormalities resembling the metabolic syndrome in humans. Conversely, 11-HSD1 knockout mice resist fat accumulation and insulin resistance even when eating a high-fat diet [47]. Based on this and other experimental evidence, it has been suggested that 11-HSD1 in the adipose tissue is a promising target for the treatment of the metabolic syndrome [48].

In humans it was observed that 11-HSD1 expression and activity are up regulated in the adipose tissue [44, 49–51], but not in the liver [44]. The potential pathophysiological importance of adipose-tissue specific dysregulation of glucocorticoid metabolism in the Pimas is supported by the close relationship between high 11-HSD1 expression/activity and insulin resistance [51]. Furthermore, genetic variation in the 11-HSD1 gene has been related to both T2DM [52] and elevated blood pressure in this population [53].

Interestingly, expression and activity of 11-HSD1 also are regulated by insulin and, although the direction of this effect in vitro remains unclear [54–56], we found a positive relationship between insulinemia and 11-HSD1 [51] in the adipose tissue. However, Pimas have lower levels of 11-HSD1 mRNA than

whites, after adjusting for circulating insulin and insulin resistance. Because obese Pimas, like some obese people in general, often have certain cushingoid features (primarily central adiposity with relatively lean extremities), it is somewhat surprising that we have been unable to uncover any systemic [40, 41] or tissue specific [51] cortisol excess in this population. Conversely, it is again tempting to speculate that if adipose-tissue specific dysregulation of 11-HSD1 plays a crucial role in the development of the metabolic syndrome, low level of 11-HSD1 in the adipose tissue may be a peripheral mechanism by which Pimas are protected, at least in part, from some of the deleterious health consequences of hyperinsulinemia.

A Statistical Attempt to Identify the 'Common Denominator'

Factor analysis is a mathematical technique by which a large number of correlated variables can be reduced to fewer factors that represent distinct attributes that account for a large proportion of the variance in the original variables. Thus, factor analysis is well suited for identifying single or multiple components underlying the metabolic syndrome and has been used by others [9–20] and us [56] for this purpose.

Consistent with our clinical physiologic and molecular studies, a factor analysis conducted in close to 2,000 Pima Indians and designed to statistically test the hypothesis that the metabolic syndrome results from a single etiologic abnormality, failed to identify a single factor underlying the correlation structure of the ten variables fed to the model (fasting and 2-hour glucose concentrations, fasting and 2-h insulin concentrations, systolic and diastolic blood pressure, body weight, waist circumference, serum triglycerides, and HDL cholesterol concentrations). Instead, the analysis identified four factors that accounted for 79% of the variance in the original ten variables, each factor reflecting a proposed component of the metabolic syndrome: insulinemia, body size, blood pressure, and lipid metabolism [57]. From this analysis we argued that substantial information about these distinct metabolic processes may be lost by trying to combine them into a single entity [57].

Conclusions

In conclusion, physiologic, molecular and epidemiologic evidence from studies in Pima Indians suggests that the abnormalities constituting the metabolic syndrome are the result of largely independent physiologic processes. Based on the lack of support from our studies, one could conclude that the metabolic

syndrome is an artificial (in pathophysiological terms) construct and that clinical treatment and prevention strategies based on the 'metabolic syndrome' hypothesis may prove sub optimal compared with treatment of the individual components. On the other hand, if a metabolic syndrome exists and Pima are protected against its full development, learning more about the central and/or peripheral mechanisms that afford them this protection may have great relevance to its treatment in other populations.

Acknowledgements

The author wishes to thank Dr. Robert Hanson for his careful review of the manuscript and Ms. Susan Luther for editorial assistance.

References

1 Welborn TA, Breckenridge A, Rubinstein AH, Dollery CT, Fraser TR: Serum-insulin in essential hypertension and in peripheral vascular disease. Lancet 1966;i:1336–1337.
2 Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37: 1595–1607.
3 Ferrannini E, Balkau B: Insulin: In search of a syndrome. Diabet Med 2002;19:724–729.
4 Reaven GM: The insulin resistance syndrome. Curr Atheroscler Rep 2003;5:364–371.
5 Bjorntorp P: Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132–1143.
6 Groop L, Orho-Melander M: The dysmetabolic syndrome. J Intern Med 2001;250:105–120.
7 Bloomgarden ZT: The 1st World Congress on the Insulin Resistance Syndrome. Diabetes Care 2004;27:602–609.
8 Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA: Clinical management of metabolic syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/ American Diabetes Association conference on scientific issues related to management. Circulation 2004;109:551–556.
9 Edwards KL, Austin MA, Newman B, Mayer E, Krauss RM, Selby JV: Multivariate analysis of the insulin resistance syndrome in women. Arterioscler Thromb 1994;14:1940–1945.
10 Donahue RP, Bean JA, Donahue RD, Goldberg RB, Prineas RJ: Does insulin resistance unite the separate components of the insulin resistance syndrome? Evidence from the Miami Community Health Study. Arterioscler Thromb Vasc Biol 1997;17:2413–2417.
11 Meigs JB, D'Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE: Risk variable clustering in the insulin resistance syndrome. The Framingham Offspring Study. Diabetes 1997;46:1594–1600.
12 Gray RS, Fabsitz RR, Cowan LD, Lee ET, Howard BV, Savage PJ: Risk factor clustering in the insulin resistance syndrome. The Strong Heart Study. Am J Epidemiol 1998;148:869–878.
13 Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J: Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. Circulation 1999;100:123–128.
14 Kekalainen P, Sarlund H, Pyorala K, Laakso M: Hyperinsulinemia cluster predicts the development of type 2 diabetes independently of family history of diabetes. Diabetes Care 1999;22: 86–92.
15 Chen W, Srinivasan SR, Elkasabany A, Berenson GS: Cardiovascular risk factors clustering features of insulin resistance syndrome (syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: The Bogalusa Heart Study. Am J Epidemiol 1999;150: 667–674.

16 Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K: Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: The 22-year follow-up results of the Helsinki Policemen Study. Arterioscler Thromb Vasc Biol 2000;20:538–544.
17 Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP: Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. Am J Epidemiol 2000;152:897–907.
18 Chen CH, Lin KC, Tsai ST, Chou P: Different association of hypertension and insulin-related metabolic syndrome between men and women in 8437 nondiabetic Chinese. Am J Hypertens 2000;13:846–853.
19 Hodge AM, Boyko EJ, de Courten M, Zimmet PZ, Chitson P, Tuomilehto J, Alberti KG: Leptin and other components of the Metabolic Syndrome in Mauritius – a factor analysis. Int J Obes Relat Metab Disord 2001;25:126–131.
20 Anderson PJ, Critchley JA, Chan JC, Cockram CS, Lee ZS, Thomas GN, Tomlinson B: Factor analysis of the metabolic syndrome: Obesity vs. insulin resistance as the central abnormality. Int J Obes Relat Metab Disord 2001;25:1782–1788.
21 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C: Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–438.
22 Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH: Insulin and hypertension: Relationship to obesity and glucose intolerance in Pima Indians. Diabetes 1990;39:1430–1435.
23 Nelson RG, Sievers ML, Knowler WC, Swinburn BA, Pettitt DJ, Saad MF, Liebow IM, Howard BV, Bennett PH: Low incidence of fatal coronary heart disease in Pima Indians despite high prevalence of non-insulin-dependent diabetes. Circulation 1990;81:987–995.
24 Jarrett RJ: In defense of insulin: A critique of syndrome X. Lancet 1992;340:469–471.
25 Lillioja S, Nyomba BL, Saad MF, Ferraro R, Castillo C, Bennett PH, Bogardus C: Exaggerated early insulin release and insulin resistance in a diabetes-prone population: A metabolic comparison of Pima Indians and Caucasians. J Clin Endocrinol Metab 1991;73:866–876.
26 Pettitt DJ, Moll PP, Knowler WC, Mott DM, Nelson RG, Saad MF, Bennett PH, Kottke BA: Insulinemia in children at low and high risk of NIDDM. Diabetes Care 1993;16:608–615.
27 Odeleye OE, de Courten M, Pettitt DJ, Ravussin E: Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. Diabetes 1997;46:1341–1345.
28 McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Bennett PH, Knowler WC: Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. Diabetologia 1994;37:617–623.
29 Weyer C, Hanson RL, Tataranni PA, Bogardus C, Pratley RE: A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: evidence for a pathogenic role of relative hyperinsulinemia. Diabetes 2000;49:2094–2101.
30 Weyer C, Salbe AD, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA: Exaggerated pancreatic polypeptide secretion in Pima Indians: Can an increased parasympathetic drive to the pancreas contribute to hyperinsulinemia, obesity, and diabetes in humans? Metabolism 2001;50:223–230.
31 Vozarova de Courten B, Weyer C, Stefan N, Horton M, DelParigi A, Havel P, Bogardus C, Tataranni PA: Parasympathetic blockade attenuates augmented pancreatic polypeptide but not insulin secretion in Pima Indians. Diabetes 2004;53:663–671.
32 Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S: Insulin resistance in essential hypertension. N Engl J Med 1987;317:350–357.
33 Shen DC, Shieh SM, Fuh MM, Wu DA, Chen YD, Reaven GM: Resistance to insulin-stimulated-glucose uptake in patients with hypertension. J Clin Endocrinol Metab 1988;66:580–583.
34 Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M, Ravussin E, Knowler WC, Bennett PH, Howard BV, Bogardus C: Racial differences in the relation between blood pressure and insulin resistance. N Engl J Med 1991;324:733–739.
35 Weyer C, Pratley RE, Snitker S, Spraul M, Ravussin E, Tataranni PA: Ethnic differences in insulinemia and sympathetic tone as links between obesity and blood pressure. Hypertension 2000;36:531–537.
36 Landsberg L: Diet, obesity and hypertension: An hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med 1986;61:1081–1090.

37 Landsberg L: Insulin-mediated sympathetic stimulation: Role in the pathogenesis of obesity-related hypertension (or, how insulin affects blood pressure, and why). J Hypertens 2001;19: 523–528.
38 Scherrer U, Randin D, Tappy L, Vollenweider P, Jequier E, Nicod P: Body fat and sympathetic nerve activity in healthy subjects. Circulation 1994;89:2634–2640.
39 Spraul M, Ravussin E, Fontvieille AM, Rising R, Larson DE, Anderson EA: Reduced sympathetic nervous activity. A potential mechanism predisposing to body weight gain. J Clin Invest 1993;92:1730–1735.
40 Tataranni PA, Cizza G, Snitker S, Gucciardo F, Lotsikas A, Chrousos GP, Ravussin E: Hypothalamic-pituitary-adrenal axis and sympathetic nervous system activities in Pima Indians and Caucasians. Metabolism 1999;48:395–399.
41 Vozarova B, Weyer C, Snitker S, Gautier JF, Cizza G, Chrousos G, Ravussin E, Tataranni PA: Effect of cortisol on muscle sympathetic nerve activity in Pima Indians and Caucasians. J Clin Endocrinol Metab 2003;88:3218–3226.
42 de Courten M, Tataranni PA, Weyer C, Snitker S, Ravussin E, Vozarova B: Higher muscle sympathetic nervous system activity (MSNA) precedes increased systolic blood pressure in Pima Indian males. Diabetes 2003;52:A153.
43 Calogero AE, Bernardini R, Gold PW, Chrousos GP: Regulation of rat hypothalamic corticotropin-releasing hormone secretion in vitro: Potential clinical implications. Adv Exp Med Biol 1988;245:167–181.
44 Rask E, Olsson T, Soderberg S, Andrew R, Livingstone DE, Johnson O, Walker BR: Tissue-specific dysregulation of cortisol metabolism in human obesity. J Clin Endocrinol Metab 2001;86: 1418–1421.
45 Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS: A transgenic model of visceral obesity and the metabolic syndrome. Science 2001;294:2166–2170.
46 Masuzaki H, Yamamoto H, Kenyon CJ, Elmquist JK, Morton NM, Paterson JM, Shinyama H, Sharp MG, Fleming S, Mullins JJ, Seckl JR, Flier JS: Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. J Clin Invest 2003;112:83–90.
47 Kotelevtsev Y, Holmes MC, Burchell A, Houston PM, Schmoll D, Jamieson P, Best R, Brown R, Edwards CR, Seckl JR, Mullins JJ: 11beta-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. Proc Natl Acad Sci USA 1997;94:14924–14929.
48 Masuzaki H, Flier JS: Tissue-specific glucocorticoid reactivating enzyme, 11 beta-hydroxysteroid dehydrogenase type 1 (11 beta-HSD1)–a promising drug target for the treatment of metabolic syndrome. Curr Drug Targets Immune Endocr Metabol Disord 2003;3:255–262.
49 Rask E, Walker BR, Soderberg S, Livingstone DE, Eliasson M, Johnson O, Andrew R, Olsson T: Tissue-specific changes in peripheral cortisol metabolism in obese women: increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity. J Clin Endocrinol Metab 2002;87: 3330–3336.
50 Wake DJ, Rask E, Livingstone DE, Soderberg S, Olsson T, Walker BR: Local and systemic impact of transcriptional up-regulation of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue in human obesity. J Clin Endocrinol Metab 2003;88:3983–3988.
51 Lindsay RS, Wake DJ, Nair S, Bunt J, Livingstone DE, Permana PA, Tataranni PA, Walker BR: Subcutaneous adipose 11 beta-hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians. J Clin Endocrinol Metab 2003;88:2738–2744.
52 Nair S, Lee YH, Lindsay RS, Walker BR, Tataranni PA, Bogardus C, Baier LJ, Permana PA: The 11beta-hydroxysteroid dehydrogenase type 1 gene: genetic polymorphisms are associated with type 2 diabetes in Pima Indians independently of obesity and expression in adipocyte and muscle. Diabetologia 2004;in press.
53 Franks PW, Knowler WC, Nair S, Koska J, Lee YH, Lindsay RS, Walker BR, Looker HC, Permana PA, Tataranni PA, Hanson RL: Interaction between an 11betaHSD1 gene variant and birth era modifies the risk of hypertension in Pima Indians. Hypertension 2004;44:681–688.
54 Bujalska IJ, Kumar S, Stewart PM: Does central obesity reflect 'Cushing's disease of the omentum'? Lancet 1997;349:1210–1213.

55 Hammami MM, Siiteri PK: Regulation of 11beta-hydroxysteroid dehydrogenase activity in human skin fibroblasts: enzymatic modulation of glucocorticoid action. J Cl in Endocrinol Metab 1991;73:326–334.
56 Jamieson PM, Chapman KE, Edwards CR, Seckl JR: 11 beta-hydroxysteroid dehydrogenase is an exclusive 11 beta-reductase in primary cultures of rat hepatocytes: Effect of physicochemical and hormonal manipulations. Endocrinology 1995;136:4754–4761.
57 Hanson RL, Imperatore G, Bennett PH, Knowler WC: Components of the 'metabolic syndrome' and incidence of type 2 diabetes. Diabetes 2002;51:3120–3127.

P.A. Tataranni, MD
CDNS, NIDDK-NIH-DHHS
4212 N 16th St, Rm 541
Phoenix, AZ 85016 (USA)
Tel. +1 602 200 5301, Fax +1 602 200 5335, E-Mail antoniot@mail.nih.gov

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 84–95

Lifestyle-Gene-Drug Interactions in Relation to the Metabolic Syndrome

Len Storlien[a], *Xu Feng Huang*[b], *Linda C. Tapsell*[b], *A. Cecilia Karlsson*[a], *Maria Niklasson*[a], *John Pears*[c], *Björn C.L. Carlsson*[a]

[a]AstraZeneca R&D, Mölndal, Sweden; [b]National Centre of Excellence in Functional Foods & Smart Foods Centre, University of Wollongong, Wollongong, Australia; [c]AstraZeneca R&D, Alderley Park, Macclesfield, UK

Perhaps the major new health care challenge of the current age in both developed and developing countries is the epidemic of obesity. Obesity is a prime driver of the Metabolic Syndrome, a cluster of cardiovascular risk conditions present in one quarter of the adults in the US [1] that predispose the major killers – heart disease, stroke and many cancers. There are several definitions of the Metabolic Syndrome [2] that identify patients at risk with combinations of raised blood pressure, atherogenic dyslipidemia, impaired glucose homeostasis, and visceral obesity. As discussed below, it is becoming increasingly clear that drugs developed for the treatment of these diseases will target pathways altered by lifestyle. Equally, specific macronutrients are ligands to receptors that are now targets for drugs treating lifestyle driven diseases. Added to this complexity is the fact that genetic susceptibility modulates these pathways. We will here discuss this intersection between environment, genes and drugs. A head-on collision or an opportunity for tailored treatment?

Excess corpulence has been recognized throughout history but has become prevalent in the population only in the past couple of decades. Currently in the United States about two-thirds of the adult population are estimated to be either overweight (body mass index, BMI $\geq$25 kg/m^2; weight in kilograms divided by height in meters squared) or obese (BMI $\geq$30) [3]. Argument was made for 'thrifty gene(s)' over 40 years ago [4] but the historical antecedents which led to natural selection of those who could survive times of famine have been most elegantly detailed recently by Prentice [5]. Obesity is a polygenic disease. The heritability is difficult to calculate but has been recently estimated at 30–70% [6]. Clearly, while the genetic makeup of individuals has not changed in the past

30 years, obesity has run rampant. This suggests strongly a shift in environment which has exposed a prevalent genetic predisposition.

Obesity – A Matter of Dietary Fat?

Obesity of course must reflect long-term imbalance between caloric intake and expenditure. The current 'Western' lifestyle can dispose alterations in both. Free access to a high energy dense, palatable and varied food supply encourages overconsumption. When combined with lack of necessity for physical activity to procure that food supply, obesity is a natural, rather than unnatural, outcome.

There is considerable controversy about the dietary variables most responsible for the obesity epidemic. Dietary fat was historically seen as the major problem but more recently the focus has turned to carbohydrates with 'diet gurus' recommending high protein, unlimited fat and severely carbohydrate-limited intake patterns. However, the data are accumulating for a more sophisticated analysis focused on both dietary fat and carbohydrate subtypes. For fats, certainly the case has been made that 'oils ain't oils' – something not in the least surprising to Mediterranean peoples. High saturated fat levels are deleterious and there are numerous mechanisms which have been identified. These have been detailed elsewhere [7], but one of the most interesting is the profound effect of saturated fatty acids in the diet to modulate hypothalamic expressions of neuropeptides of energy balance in the direction that would encourage excess intake [8]. In contrast, polyunsaturated fats (PUFAs) have been shown to be neutral or perhaps even beneficial with respect to total and, importantly, central fat accumulation [9] with contrasting effects (to saturated fats) on neuropeptide expression and a range of other metabolic variables that mechanistically underpin those observations. Of the two major PUFA fat types, the balance between n–6 (omega–6) and n–3 (omega–3) fats equally appears important [10]. On the carbohydrate side, again subtype analysis is very important. Indeed, it is simple sugars and the rise in consumption of fructose-based soft drinks that can be more convincingly linked to obesity than can overall carbohydrate intake [11]. Similarly, if we look at type 2 diabetes, figure 1 shows data from the Nurses Health Study which plots the relative protection from (below the line), or disposition to (above the line), type 2 diabetes if one were to replace only 2% of one type of macronutrient with another [12]. Thus we can see, quite dramatically, that replacing only 2% of saturated fat calories with PUFA, a reduction of almost 20% in diabetes incidence can be achieved, whereas replacing the same amount of PUFA with carbohydrate (type unspecified but obviously important) would result, by this analysis, in an increase of some 15% in diabetes incidence [12]. These are quite startling data and, taken with the wealth

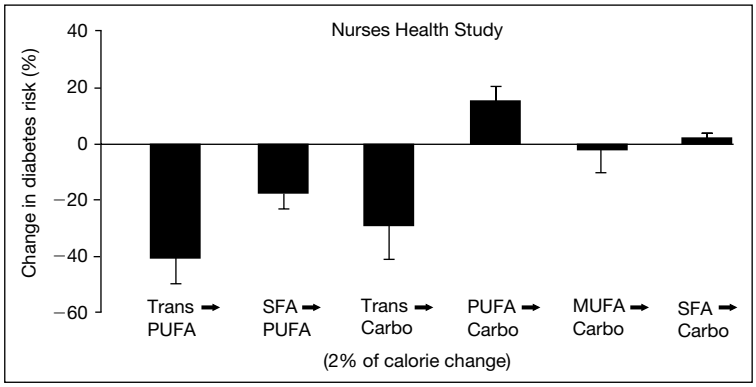


Fig. 1. Figure showing an analysis of the change in diabetes risk which comes about from as little as 2% shift in total calories from one macronutrient, or macronutrient subtype, to another. Trans = Trans fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids; Carbo = carbohydrates; MUFA = monounsaturated fatty acids. From reference Salmerón et al. [12], ©American Society for Clinical Nutrition.

of supporting work around these issues, of major importance to the diet-Metabolic Syndrome issue.

The Link between Gene Polymorphisms and Dietary Lipid: Example of an Interaction

So how do genes link in here? Perhaps the very nicest example is some recent work from the laboratory of O'Rahilly et al. [13]. The background to this study on peroxisome-proliferator-activated receptor-γ (PPARγ) requires some detail because it not only speaks to the issue of gene-nutrient interaction, but PPARγ itself is also a major drug target in treatment of aspects of the Metabolic Syndrome so we will return to it in discussion of the drug part of gene-nutrient-drug interactions.

PPARs are a family of three nuclear hormone receptors (α, γ and δ) which control a multitude of metabolic pathways for lipid and carbohydrate handling [14]. PPARγ activators, of which the thiazolidinediones are the major chemical class on the market, have become the major new treatment for the insulin resistance of diabetes and 'pre-diabetes'. Indeed PPARγ activators are really the first new class of anti-diabetic therapy in many years. Given their enormous importance, and the fact that the endogenous ligands for this vital class of nuclear hormone receptors are long-chain PUFAs, it is critical to understand how PPARγ activators interact with the environment.

This brings us back to the study of O'Rahilly et al. [13]. Basically, they analysed the relationship of frequent polymorphisms of a variant of the PPARγ gene, PPARγ2, on body fatness as indexed by the body mass index (BMI). The clever variation, given that PUFAs are the endogenous ligands, was to assess that relationship in terms of the background diet. Quite remarkably, the relation between one frequent PPARγ2 polymorphism was positive with BMI (i.e., if the individual carried that polymorphism, he or she was more likely to have a higher BMI) but only if the polyunsaturated to saturated fatty acid ratio (PUFA/SAT or more commonly, P/S) of the diet was high. If the P/S ratio was low, then the relationship completely reversed. These are very important data, not least because a major, reasonably new class of anti-diabetics, the thiazolidinediones, target PPARγ. The thiazolidinediones have one major 'side effect' which is worrying for their long-term use. They cause weight gain, a PPARγ2 effect. However, the data of O'Rahilly et al. [13] could mean that the response to the drug may depend on the P/S ratio of the fat component of the specific patient i.e. related to the relative degree of activation by lipids at baseline. In line with this, will the P/S ratio of the fat component consumed during the treatment influence the response? At a first glance this is not likely because thiazolidinediones are high affinity ligands to PPARγ and naturally occurring ligands are likely to be low affinity high abundance ligands. Furthermore, the response to thiazolidinediones appears to be independent of Pro12Ala polymorphism in PPAR γ2 [15]. End of story? Probably not. Nuclear hormone receptors interact with a large number of co-factors that are important regulators of metabolism. Several nuclear hormone receptors compete for the same co-factors, many of these receptors have naturally occurring ligands. Furthermore, small molecule agonists developed for nuclear hormone receptors may have different biological profile depending on how the molecules alters the structure of the receptor and thereby the interaction with co-factors binding to different domains of the receptor. Finally, PPARγ is active as a heterodimer with another nuclear receptor RXR that also can be regulated. Taken together, lipids are endogenous ligands for nuclear receptors and are likely to influence both the efficacy and biological response to drugs that target these systems.

Dietary Fat Profile: Heterogeneity of Individual Responses

Whilst on the topic of insulin sensitivity, it is worth making another point about fatty acids and insulin action. It has been perfectly clear from the 'rodent' literature that increasing omega–3s (or n–3s) in the fatty acid profile of even high fat diets fed to rats had a significant beneficial effect on insulin action [16]. What has been disturbing, and disappointing, is that similar data have not been

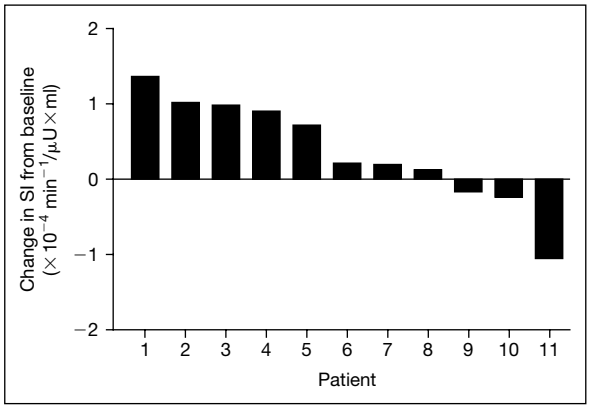


Fig. 2. Changes in insulin sensitivity (Sl, more commonly referred to as Si – on the y-axis) in individual patients following supplementation of the diet with the long chain omega–3 fatty acid docosahexanoic (22:6; DHA). From Lovejoy [18].

forthcoming from human intervention trials. Indeed, it is very difficult to show any beneficial effect, on a treatment group basis, of n–3 fatty acids on insulin action [17]. However, if one looks at the individual data a possibly much more instructive picture emerges. This is shown in figure 2 from the work of Lovejoy [18] where effect of the supplementation with the long-chain n–3 fatty acid docosahexanoic (DHA) on insulin sensitivity in adults is shown plotted as effect by individual. Here we can see that while the overall group effect might not be, and indeed was not, a significant improvement in insulin action with DHA supplementation, in almost half the individuals it was extremely beneficial, in an equal group of no apparent effect and in one individual even deleterious. The question that springs to mind is what are the genetic differences between these individuals that might explain such diversity of effects? Further, can we predict the responders and non-responders to such eminently achievable dietary modifications?

Let us stick with fatty acids and lipid/carbohydrate metabolism for one more example. The sterol regulatory binding proteins (SREBPs) are a major class of metabolic regulators whose ubiquitous control of a range of enzymes is now just being understood [19]. Figure 3 summarizes the multiple levels of control of SREBPs on both cholesterol and fatty acid metabolism. Focusing on the fatty acid side of the figure, we see that elevation of SREBP1 expression/activity positively regulates a range of enzymes which coordinately regulate endogenous lipogenesis (making of new, saturated fatty acids within the body) and delivery of those fatty acids into triglyceride, the storage form of lipid in the body. Thus elevation of SREBP1 activity will be associated with saturated fat

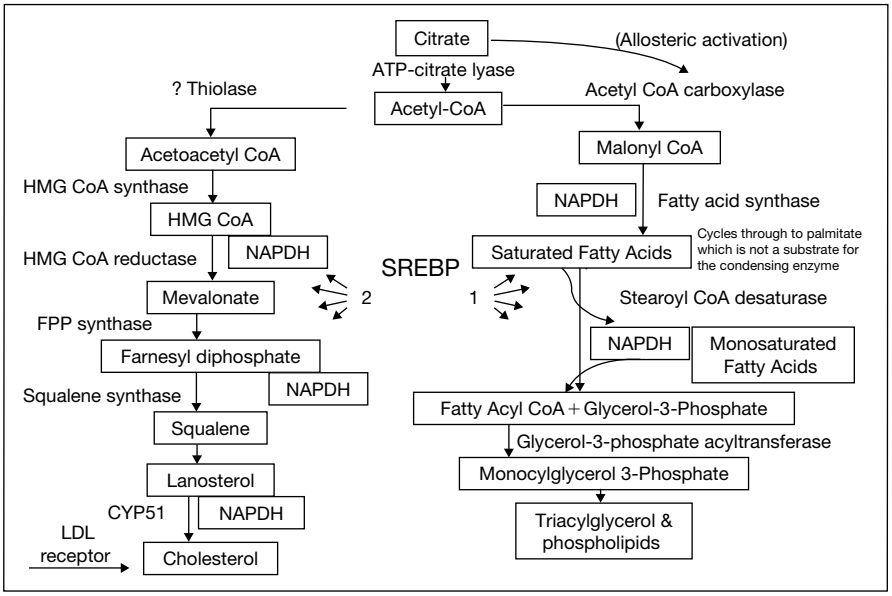


Fig. 3. Illustration of the range of enzymes in both the cholesterol (left side) and triglyceride (right side) metabolism influenced by sterol regulatory element-binding proteins (SREBPs). Adapted from Horton and Shimomura [19].

production and storage. In figure 4 we can see the effects on SREBP1s, in an in vitro cell system, of incubating the test cells with various individual fatty acids. Saturated fatty acids, particularly palmitate (16:0), have perhaps a mildly elevating effect (increasing endogenous lipogenesis and storage) while PUFAs, and in particular, n–3 PUFAs (18:3, α-linolenic) have a dramatic effect to lower SREBP1 activity [20]. The implications for Metabolic Syndrome of this is obvious but less obvious, and currently unexplored, is how the genetic makeup of the individual influences this pattern and indeed how any putative pharmaceutical which might modulate SREBP activity would act if the P/S ratio of the diet were to be altered.

We mentioned earlier the contrasting effects of different dietary fatty acid classes on expression of neuropeptides of energy balance [8]. If this line of thinking is then extended to pharmaceuticals, it can be noted that there is currently only one central nervous system targeted anti-obesity drug in common use. That is sibutramine which is a serotonin/noradrenalin/dopamine combined re-uptake inhibitor [21]. In many ways its development followed out of 2 pharmaceutical agents which were used successfully for many years, fenfluramine and dexfenfluramine, both of which were more specific serotonin reuptake

Fatty acid influence on SREBP
(RNase protection assay – embryonic kidney cells)

Fatty acid	None	16:0	18:0	18:1	18:2	18:3
SREBP-1c	1	1.2	0.9	0.6	0.6	0.1
SREBP-1a	1	1.2	1.0	0.5	0.5	0.1

Fig. 4. This complements figure 3 by showing the influence of the saturated fatty acids (16:0 and 18:0 – neutral or slight induction) on sterol regulatory element-binding protein (SREBP) versus that of unsaturated fatty acids (repression, profound in the case of 18:3 α-linolenic omega–3 fatty acid). Adapted from Hannah et al. [20].

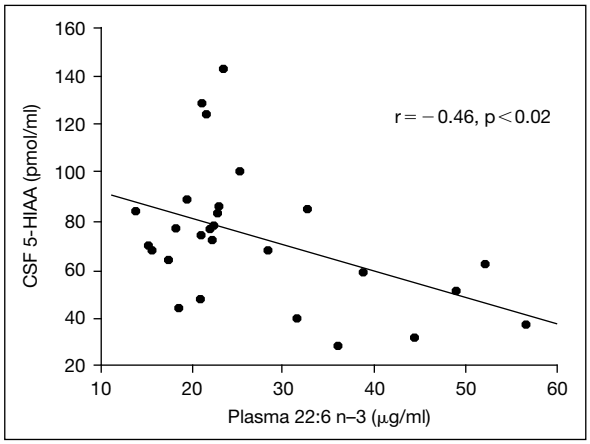


Fig. 5. Relationship between 5-hydroxyindole-3-acetic acid (5-HIAA), the major metabolite of serotonin (and thus an index of serotonin metabolism) in the cerebro-spinal fluid (CSF) in relation to plasma levels of the long chain omega–3 fatty acid docosahexanoic (22:6 n–3; DHA). From Hibbeln et al. [23].

inhibitors whose action was thus to modulate brain serotonergic activity [22]. In this context it is very interesting to note the results from Hibbeln and colleagues who assessed brain serotoninergic activity via assay of the levels of the major serotonin metabolite, 5-HIAA, in cerebrospinal fluid [23]. They did this in the context of understanding the basis of violent behaviors and why, on a world-wide basis, rates of clinical depression are inversely proportional to levels of fish, and hence long-chain n–3 fatty acids like DHA, intake. What you can see from figure 5 is that there is an inverse relationship between DHA levels in

plasma (a reflection of n–3 intake since animals including humans have no capacity for endogenous generation of PUFA) and 5-HIAA as a marker of brain serotonergic activity. While no causality can be ascribed to these correlational data, it is tempting to place such data in the context of the results showing the protective effect of PUFAs on adiposity and other features of the Metabolic Syndrome. Equally of course, when the major current centrally acting drug treatment for obesity is aimed at modulating the serotonergic system, it seems obvious to look for the interaction between dietary n–3 PUFA intake, the P/S ratio of the diet, and effectiveness of drugs such as sibutramine. To our knowledge such interactions have not been explored.

Simple Sugars as Well Promote Fat Storage

Whilst a good deal of the discussion thus far has centered around dietary fats and fat subtypes, an impression should not be given that a similar story cannot be built around carbohydrate subtypes. The low-fat mafia held sway for many years despite the lack of evidence that, as either total intake or as a proportion of calories, fat intake had increased during the time of the explosion of obesity [24, 25]. What has changed is the increase in consumption of simple sugars and in particular fructose intake from sweet drinks [11]. An interesting development over the past few years has been the discovery of carbohydrate response elements in the promoter region of a number of genes. So, just as the role of PUFAs in gene regulation has been clearly recognized [26], it is now becoming clear that simple sugars play a similar gene regulatory role [27]. Unfortunately, while PUFAs play a beneficial role in downregulating genes of endogenous fat production and storage, simple sugars do something of the opposite. This is shown in figure 6, where simple sugars, via carbohydrate response elements, upregulate expression and activity in key genes like fatty acid synthase and ACC which combine to promote the production and storage of fat from these carbohydrate precursors [27]. How polymorphisms in such genes modulate interaction with dietary sugars is currently unknown.

Metabolic Balance – Energy Expenditure Is Important

Finally, whilst dietary variables and the intake side of the equation have been the focus thus far, there is strong evidence that reduced physical activity and energy expenditure play an equally important role in epidemic of obesity, diabetes and the Metabolic Syndrome. This is also new territory to explore in the quest for a way out of the quagmire of this looming medical crisis. Here the

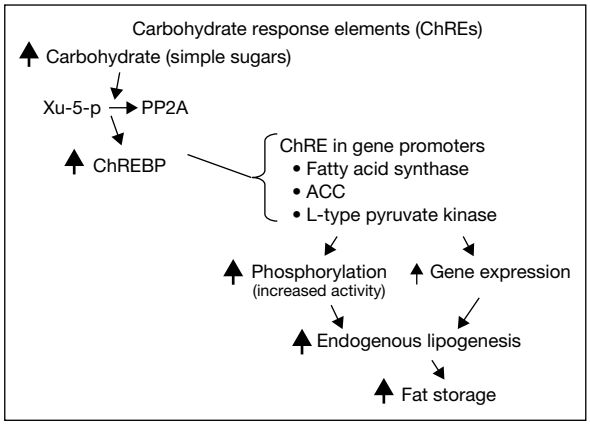


Fig. 6. A limited schematic of how simple sugars can end up as stored fat, emphasizing the role of carbohydrate response elements as gene promoters in this process. This is drawn from the thinking in Veech [27].

focus must be on skeletal muscle, the body's largest 'organ' and a major player in both lipid and carbohydrate metabolism. It is now clear from a body of recent evidence that skeletal muscle oxidative metabolic capacity is reduced in individuals with obesity and diabetes – with reduced oxidative fibers [28], reduced mitochondrial number and size [29] and reduced expression of a range of oxidative-phosphorylation genes [30, 31]. There is some evidence that such impairments already exist in individuals with a strong genetic history of obesity and/or diabetes but undoubtedly lack of physical exercise plays its own independent role. We now have a much better understanding of the metabolic pathways underlying mitochondrial biogenesis and fiber-type distribution and the key control elements. The central role of peroxisome proliferator-activated receptor-γ coactivator 1 (PGC1) is now recognized [32]. It is a coactivator of a number of nuclear hormone receptors and plays a central role in development of cellular oxidative capacity by, inter alia, augmentation of PPAR transcriptional activity. Since, as we noted before, PUFAs are endogenous ligands for PPARs, and PPARγ activators are a major pharma class for treatment of the insulin resistance and dyslipidemia of diabetes and Metabolic Syndrome, the interactions between physical activity, dietary fat profile, genetic makeup and pharmaceutical modification of PGCs will be critical to explore.

A first step along these lines has just been published. This work is by Cambridge University researchers including those noted about who described the very interesting relationships between PPARγ2 polymorphisms, dietary P/S ratio and relation to BMI described above [13]. Taking this work further, they

factored out BMI then analysed the impact of PPARγ2 polymorphisms and dietary P/S ratio plus physical activity level on fasting plasma insulin levels (as a marker of insulin resistance in this nondiabetic study group) [33]. What is very interesting here is that in those individuals who carry the Pro allele, both high physical activity and high P/S ratio of dietary fats are associated with somewhat lower fasting insulin levels. That is, both diet and physical activity had effects and they seemed independent. However, in the Ala allele carriers, both high physical activity and a high dietary fat P/S ratio had to be present in order for low fasting insulin levels to be evident, and when this happened insulin levels were substantially lower [33]. Effectively then, if one were an Ala allele carrier, just increasing physical activity or just increasing dietary P/S ratio wouldn't have much impact on insulin action, but increasing both together should have a powerful beneficial effect. Such work is critical in furthering our understanding of gene-lifestyle interactions – particularly the additional role that physical activity plays.

Why some (many) individuals are prone to physical inactivity is not clear, however, it is a reasonable hypothesis that the genetic predisposition is exacerbated by continued inactivity, a vicious circle making increased habitual exercise more and more unlikely. Appropriate drug and diet intervention to provide activation of the underlying capacity for exercise may be a fruitful way forward.

Conclusion

The era of individualized, tailored medicine is near. With the unraveling of the human genome and the recognition that one size doesn't fit all in relation to either drugs or lifestyle intervention, we are now looking forward to strategies by which treatments are targeted to the individual. Analysis of lifestyle-gene-drug interactions is rightly moving to one of the highest priorities in the pharma industry and should do so as well in those organizations responsible for nutrient supply and physical environment.

References

1 Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–359.

2 Marchesini G, Forlani G, Cerrelli F, Manini R, Natale S, Baraldi L, Ermini G, Savorani G, Zocchi D, Melchionda N: WHO and ATPIII proposals for the definition of the metabolic syndrome in patients with type 2 diabetes. Diab Med 2004;21:383–387.

3 Flegal KM, Carroll MD, Ogden CL, Johnson CL: Prevalence and trends in overweight among US adults, 1999–2000. JAMA 2002;288:1723–1727.

4 Neel JV: Diabetes mellitus: A 'thrifty' genotype rendered detrimental by 'progress'. Am J Hum Genet 1962;14:353–362.

5 Prentice AM: Fires of life: The struggles of an ancient metabolism in a modern world. Nutr Bull 2002;26:13–27.
6 Loos RJF, Bouchard C: Obesity – Is it a genetic disorder? J Intern Med 2003;254:401–425.
7 Kelley DE, Goodpaster BH, Storlien L: Muscle triglycerides and insulin resistance. Ann Rev Nutr 2002;22:325–346.
8 Wang H, Storlien LH, Huang X-F: Effects of dietary fat types on body fatness, leptin, and ARC leptin receptor, NPY, and AgRP mRNA expression. Am J Physiol Endocrinol Metab 2001;282: E1352–E1359.
9 Doucet E, Alméras N, White MD, Després J-P, Bouchard C, Tremblay A: Dietary fat composition and human adiposity. Eur J Clin Nutr 1998;52:2–6.
10 Storlien LH, Higgins JA, Thomas TC, Brown MA, Wang HQ, Huang XF, Else PL: Diet composition and insulin action in animal models. Br J Nutr 2000;83(suppl 1):S85–S90.
11 Bray GA, Nielsen SJ, Popkin BM: Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr 2004;79:537–543.
12 Salmerón J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC: Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–1026.
13 Luan J, Browne PO, Harding A-H, Halsall DJ, O'Rahilly S, Chatterjee KVK, Wareham NJ: Evidence for gene-nutrient interaction at the PPARγ Locus. Diabetes 2001;50:686–689.
14 Ferré P: The biology of peroxisome proliferator-activated receptors: Relationship with lipid metabolism and insulin sensitivity. Diabetes 2004;53(suppl 1):S43–S50.
15 Blüher M, Lubben G, Paschke R: Analysis of the relationship between the Pro12Ala variant in the PPAR-2 gene and the response rate to therapy with pioglitazone in patients with type 2 diabetes. Diabetes Care 2003;26:825–831.
16 Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS: Fish oil prevents insulin resistance induced by high-fat feeding in rats. Science 1987;237:885–888.
17 Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nälsén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson I-B, Storlien LH: Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. Diabetologia 2001;44:312–319.
18 Lovejoy JC: The influence of dietary fat on insulin resistance. Curr Diab Rep 2002;2:435–440.
19 Horton JD, Shimomura, I: Sterol regulatory element-binding proteins: activators of cholesterol and fatty acid biosynthesis. Curr Opin Lipidol 1999;10:143–150.
20 Hannah VC, Ou J, Luong A, Goldstein JL, Brown MS: Unsaturated fatty acids down-regulate SREBP isoforms 1a and 1c by two mechanisms in HEK-293 cells. J Biol Chem 2001;276: 4365–4372.
21 Luque CA, Rey JA: The discovery and status of sibutramine as an anti-obesity drug. Eur J Pharmacol 2002;440:119–128.
22 Vickers SP, Dourish CT, Kennett GA: Evidence that hypophagia induced by *d*-fenfluramine and *d*-norfenfluramine in the rat is mediated by 5-HT2c receptors. Neuropharmacology 2001;41: 200–209.
23 Hibbeln JR, Umhau JC, Linnoila M, George DT, Ragan PW, Shoaf SE, Vaughan MR, Rawlings R, Salem N Jr: A replication study of violent and nonviolent subjects: Cerebrospinal fluid metabolites of serotonin and dopamine are predicted by plasma essential fatty acids. Biol Psychiat 1998;44:243–249.
24 Prentice AM, Jebb SA: Obesity in Britain: Gluttony or sloth? Br Med J 1995;311:437–439.
25 Arnett DK, Xiong B, McGovern PG, Blackburn H, Luepker RV: Secular trends in dietary macronutrient intake in Minneapolis-St. Paul, Minnesota, 1980–1992. Am J Epidemiol 2000;152: 868–873.
26 Jump DB, Clarke SD, Thelen A, Liimatta M, Ren B, Badin M: Dietary polyunsaturated fatty acid regulation of gene transcription. Prog Lipid Res 1996;35:227–241.
27 Veech RL: A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. PNAS 2003;100:5578–5580.
28 Helge JW, Fraser AM, Kriketos AD, Jenkins AB, Calvert GD, Ayre KJ, Storlien LH: Interrelationships betweeen muscle fibre type, substrate oxidation and body fat. Int J Obesity 1999;23: 986–991.

29 Kelley DE, He J, Menshikova EV, Ritov VB: Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002;51:2944–2950.
30 Mootha VK, Lindgren CM, Eriksson K-F, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman BM, Lander ES, Hirshhorn JN, Altshuler D, Groop LC: PGC-1a-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet 2003;34:267–273.
31 Patti ME, Atul JB, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ: Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. PNAS 2003;100:8466–8471.
32 Lin J, Wu H, Tarr PT, Zhang C-Y, Wu Z, Boss O, Michael LF, Puigserver P, Isotani E, Olson EN, Lowell BB, Bassel-Duby R, Speigelman BM: Transcriptional co-activator PGC-1α drives the formation of slow-twitch muscle fibres. Nature 2002;418:797–801.
33 Franks PW, Luan J, Browne PO, Harding A-H, O'Rahilly S, Chatterjee VKK, Wareham NJ: Does peroxisome proliferator-activated receptor R genotype (Pro12ala) modify the association of physical activity and dietary fat with fasting insulin level? Metabolism 2004;53:11–16.

Dr. Len Storlien
AstraZeneca R&D
SE–431 83 Mölndal (Sweden)
Tel. +46 031 776 1230, Fax +46 031 776 3704
E-Mail leonard.storlien@astrazeneca.com

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 96–106

Coronary Heart Disease, Genetics, Nutrition and Physical Activity

Maria Benedetta Donati, Licia Iacoviello

Research Laboratories, Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, Campobasso, Italy

Prevention of coronary heart disease is a major issue in public health all over the world and particularly in developed countries. Indeed, despite major progress recorded during the last decade in the treatment of acute myocardial infarction (MI), still 1 of 3/4 patients with this disease dies before admission for any formal treatment. Therefore, prevention must be the main strategic objective. However, cost-effective prevention is still limited by our imperfect knowledge of the multiple causes of a complex disease such as MI. Traditionally, in preventive cardiology the focus has been concentrated on environmental risk factors and life habits such as smoking, dietary habits, physical activity or acquired diseases such as diabetes, hypertension, dyslipidemia and more recently some infectious diseases. However, it is becoming clear that these factors only partially account for cardiovascular risk. During the last 15 years interest has grown for the genetic determinants of cardiovascular risk. This has been prompted on the one hand by the observation of clustering of the disease cases in families, and on the other by the modulation of intermediate phenotypes belonging to the clotting, glucose, lipid or vascular tone systems.

A number of recent studies have identified candidate genes that might play a role in determining the levels of vascular risk factors and their clustering both in individuals and in families [1–6].

Genetic Modulation of Cardiovascular Risk

Polymorphisms indicate common variants of genes, which are present in at least 1% of the general population. Sometimes up to 50% of the population is

carrying a given polymorphism. One of 300 basepairs of the 3 billion basepairs that characterize an individual varies from person to person. However, only 1% of these changes is functional and accounts for modifications of proteins, although a number of combinations of different functional polymorphisms are possible.

Polymorphisms in many different genes could be linked to interindividual differences in the risk of diseases, through quantitative variations of biochemical and physiological traits that span through the normal range of phenotypic variability [7]. Genetic variation, moreover, might combine with many different environmental exposures to determine an individual's level of resistance or susceptibility to develop a given disease. In the last 10 years, many genetic studies of coronary heart disease have focused on the identification and characterization of those genetic loci contributing to the variation of intermediate traits that are involved in the etiology of the disease.

Variability in protein levels and protein activity in blood, attributable to the presence of polymorphisms, has also been found for proteins such as fibrinogen, considered risk factors for cardiovascular disease [8, 9]. This concept allows making direct associations between these polymorphisms and the risk of disease. As an example, the B2 allele of the *Bcl*I polymorphism of the gene encoding for the β-chain of fibrinogen has been associated with high blood levels of fibrinogen and the risk of familial MI was found to be twice in carriers of this allele. On the contrary, factor VII gene 353Q polymorphism is associated with lower levels of coagulation factor VII and the presence of one of these alleles reportedly reduces the risk of MI by half [2].

However, since polymorphisms only make a relatively small contribution to the overall risk of disease, it may be difficult to fully understand the actual impact of genotypes on the risk of disease. Epidemiological studies have failed so far to make these differences evident. Meta-analyses have shown that the contribution of polymorphisms to the risk of disease is often limited to some specific subgroups. In the case of multifactorial disease, the risk results from an interaction between several environmental and genetic factors. Rather than influencing basal levels of proteins, the presence of polymorphisms may either increase or decrease the susceptibility to disease by modulating the response to environmental factors, such as diet, smoking, physical activity and exposure to infectious agents [10, 11].

In view of the focus of these proceedings, we shall concentrate here on some examples of gene-environment interactions involving nutrition and physical activity in particular, with few considerations on a special model of life-habits/gene interaction, i.e. the European gradient of cardiovascular mortality.

Gene-Environment Impact on Fibrinogen

An individual with a given genetic predisposition might have a stronger response when exposed to a specific stimulus, which translates into a higher variability of the related protein levels. The genetic control of fibrinogen levels has to be considered together with environmental factors, since fibrinogen genotypes may interact with cigarette smoking [12], gender [13, 14] and physical activity [15] in determining the variations in fibrinogen levels.

A different association has been found between −455G/A or *Bcl*I polymorphisms and fibrinogen levels in women or in men [13, 14, 16]. The effect of the A allele of the −455 G/A polymorphism on fibrinogen levels was additive in men, while it showed a dominant behavior in women. When menopausal status and hormone replacement therapy (HRT) were considered, the dominant effect of the A allele was only evident in postmenopausal women not taking hormones, while in both premenopausal and postmenopausal women treated with HRT, the effect of the A allele was additive, as observed in men [14]. These findings suggest that the effects of hormones or other gender-specific factors on the synthesis of fibrinogen are modulated by genetic variance at the promoter levels that can differently regulate the activation/repression of fibrinogen gene transcription.

The fibrinogen genetic background can also regulate the relationship between physical activity and fibrinogen levels. An inverse dose-response relationship has been described between regular physical exercise and fibrinogen levels [17], although intensive, strenuous exercise was associated with an acute rise in fibrinogen levels [15]. The increase lasted several days, probably due to a continuous fibrinogen production. However, this phenomenon varies according to the G/A −455 polymorphism of the fibrinogen β-chain gene. After 2 days of strenuous military exercise, an increase in fibrinogen levels (as compared to the concentration at pre-training) was recorded; an effect significantly stronger in the AA homozygotes than in heterozygotes or GG homozygotes.

Vaisanen et al. [18] showed that physical activity levels explained up to 9% of fibrinogen variance in carriers of the B2 allele of the *Bcl*I β-chain gene polymorphism, while it had only a marginal effect in carriers of the common B1 fibrinogen genotype. Similar results were shown for polymorphisms in the α-chain gene of fibrinogen in postmenopausal women [19] and middle-aged men [20].

Besides their effect on fibrinogen levels, fibrinogen polymorphisms can also modulate the relationship between environmental risk factors and the risk of cardiovascular disease. *Helicobacter pylori* (HP) infection has been associated with a higher risk to develop ischemic heart disease, although the results are controversial [21]. Zito et al. [11] showed that the *Bcl*I polymorphisms of the β-fibrinogen gene modulated the effect of HP on both fibrinogen levels and

the risk of MI. HP, a bacterial agent inducing a life-long infection, was found to be associated with chronically increased plasma levels of fibrinogen, an effect stronger in carriers of the B2 allele. Carriership of the B2 allele also amplified the effect of seropositivity for HP on the risk of MI. Indeed, patients who were both seropositive for HP and carriers of the B2 genotype showed an additional increase in the risk of MI as compared to subjects affected by HP but homozygous for the B1 allele.

The European Gradient of Myocardial Infarction Mortality as a Model of Gene-Environment Interaction

The risk of CAD is differently distributed in Europe: MI mortality is lower in Southern than in Northern European countries [22]. Epidemiological studies have shown that the dietary habits of European populations have an important role in determining the gradient of CAD risk [23]. Indeed, it has been shown that populations consuming low amounts of animal fat or drinking red wine daily had a reduced rate of death for CAD [24]. In general, the low rate of CAD in the Mediterranean regions of Europe stimulated an increasing interest for the potential role of the traditional Mediterranean diet in the prevention of the disease [25, 26]. The dietary profile of the Mediterranean regions is significantly different from that adopted in other Western countries, with particular regard to the use of fat, cereal-derived foods, vegetables and type of alcohol [27–28]. A protective role of the Mediterranean diet has been also shown in subjects at risk for cardiovascular disease [29–32].

Though important, dietary habits are not sufficient to fully explain the difference in CAD risk observed throughout Europe. As already mentioned, in the last years, genetic factors have also been implicated in the development of CAD [1–6]. It has been demonstrated that the genetic background of Europeans is not homogeneous and differences have been observed in the frequency of alleles related to genes of factors relevant for the pathogenesis of atherothrombosis. Actually, genes constantly interact with their environment in determining the pathogenesis of disease. The effect of a gene measured in one environment may differ from its effect in another environment. As an example, the effect of ApoE polymorphism on lipid metabolism may be different among populations with different fat intake [33]. A simultaneous evaluation of the complex interactions between genes and lifestyle habits (particularly nutrition) is required in order to appreciate their true involvement in determining differences in MI prevalence across European countries.

The interactions between genetics and life habits in the cardiovascular risk were the focus of the European study IMMIDIET, which, under the co-ordination

of our group, is evaluating the impact of gene-diet interactions in three European populations at different risk for cardiovascular disease (Southern Italy, Belgium and an area South-East of London). Cultural integration between Italian and Belgian partners in mixed couples deriving from the Italian immigration to Belgian coal mines is also a major point of interest of this study. Food frequency questionnaires (validated in the different Countries starting from the EPIC model) and biomarkers of food intake (lipid composition of red cell membranes, blood levels of micronutrients, markers of oxidation) were used to match dietary habits with the genetic background concerning factors of the hemostatic and inflammatory systems and biochemical indicators of the thrombotic risk in over 1,800 subjects recruited in these three countries through the national networks of General Practitioners.

Specific MI risk factors such as coagulation factor VII and homocysteine are most likely under the combined influence of both dietary factors and genetic polymorphisms. We shall take here the example of factor VII, the pivotal factor of the clotting cascade.

Gene Environment Impact on Coagulation Factor VII

Factor VII is a vitamin K-dependent plasma serine protease that plays a crucial role in the initiation of tissue factor-induced coagulation. Factor VII levels vary over a wide range in the general population [34]. Several environmental factors influence its plasma levels, although explaining only a minor part of its variation among individuals. Age, gender, body mass index, oral contraceptive use and postmenopausal status have all been associated with factor VII levels [35]. Dietary fats and blood lipids are also major determinants of factor VII levels. Factor VII clotting activity (factor VII:c) increases shortly after fat intake, therefore the association between triglycerides and factor VII:c is strongly dependent on the postprandial or fasting status [36].

Factor VII levels are also modulated by polymorphisms in factor VII gene [37]. The gene coding for factor VII has five identified polymorphic sites that may be associated with circulating levels of the gene product, accounting for up to 30% of the variance in factor VII levels in plasma [38–42]. In the promoter, a decanucleotide insertion at position −323 is in strong linkage disequilibrium with a single base substitution (A/G) at codon 353 (Arg/Gln) in exon 8. Two additional promoter polymorphisms arise at −401 (G to T) and −402 (G to A). A further common polymorphism has been described in hypervariable region 4 of intron 7, HVR4, with 3 different length alleles termed H5, H6, and H7. A study of 215 pairs of twins has shown that genetic influences account for 57% of variation in factor VII levels and that there is a significant genetic

correlation between FVII and triglycerides [43]. The Q allele of R353Q polymorphism of factor VII gene, associated with relatively low blood levels of factor VII, has a protective effect on the risk of MI. The presence of the protective alleles reduced the risk of familial MI in the Italian population by about 50% [2]. More recently, the same polymorphisms have been shown to protect Italian patients with a high degree of coronary atherosclerosis against MI [44]. Other studies, however, failed to show conclusive results on the association between factor VII polymorphisms and MI, the severity of coronary artery disease or the risk of stroke [45–48]. The possibility that the protective effect of factor VII polymorphisms depends on different environmental exposure determining the risk is a possible explanation for the discrepancy in the results of different studies. The effect of the Q353 allele in reducing the risk of cardiovascular disease is mainly expressed in smokers, while it is virtually absent in non-smokers [49]. Like air-bags in a car, 'protective' factors might appear unnecessary if the driving style is safe and no accident occurs. In contrast, they show their life-saving effect in the case of hazardous driving leading to a crash. Carrying air-bags, however, should not prevent people from driving carefully!

The 'protective' allele of the factor VII gene is distributed differently among European populations and its distribution in Europe co-varies with the risk of MI [50].

The frequency of the Q allele of R353Q polymorphism ranged between 0.06 and 0.13 in North Europeans at high risk of MI [51, 52] and between 0.15 and 0.29 in Italians, Spanish and Inuit at low risk of MI [2, 51, 53–55]. Similar results were found for the H7 allele of the HVR4 polymorphism [2, 51–55] and the 0-bp allele of 0/10-bp polymorphism [2, 51–55, 56]. Since these rare alleles are associated with low levels of factor VII, their reduced frequency could be in agreement with the higher rate of MI mortality in such countries as compared to the South-European and Inuit populations, supporting a protective role of these polymorphisms in the development of MI.

The R353Q polymorphism may also influence the association of plasma factor VII with triglyceride levels [46, 56–57]; a positive relationship between factor VII and triglyceride levels is present in carriers of the R allele variants but not of the Q allele variants. These findings suggest that subjects carrying the Q allele variant of factor VII are protected from the activation of factor VII in response to dietary fat intake. Indeed, the absolute and the percentage increase in factor VII activation after a fat-rich meal is higher in subjects with the RR genotype than in carriers of the Q allele [58, 59]. On the other hand, the regulation of the relation between factor VII activity and triglycerides by R353Q genotype is not completely clear. A study in Indian adults reported the same finding, but with an opposite effect of the rare allele [60]. Other studies, conducted in subjects in a fasting condition, failed to find any association [61,

62]. Moreover, it is possible that, together with the different ethnical origin of the populations studied and the fasting or non-fasting status, the inclusion of females in the sample and the age of the subjects studied could account for differences among the studies, although the low power of some studies in detecting such a difference should be taken into consideration. In the Rotterdam Study, a large population-based study, Mennen et al. [63] reported a stronger association of both factor VII:c and factor VII:antigen with triglycerides in non-fasting older women carrying the RR genotype, but not in older men.

One of the mechanisms which could explain the effect of dietary fat on factor VII involves the interaction with triglyceride-rich lipoproteins (VLDL). Indeed, the binding of factor VII to VLDL can prolong its half-life and enhance the process of factor VII activation [64, 65]. The amino acid substitution Arg/Gln may alter this interaction and determines a decreased activation of factor VII. However, a direct effect of this polymorphism on factor VII antigen levels could also be proposed; indeed, in transient transfection assays with factor VII cDNA containing the base substitution, the Q allele determined a defective secretion of the molecule from the cells [66].

Conclusions

The application of genetic studies to the pathogenesis of the multifactorial cardiovascular disease has allowed to better explore the impact of crucial environmental factors such as dietary habits or physical activity on vascular risk. Indeed, genetic polymorphisms, rather than influencing the risk per se, may affect the individual response to environmental factors and represent the basis for the well-known interindividual variability in the impact of smoking, nutrition, physical activity or infections on cardiovascular risk. Therefore, a careful approach of gene-environment interaction may optimize the study of nutrition and fitness as major risk factors in cardiovascular prevention strategies.

Acknowledgements

This paper is dedicated to the athletes who will take part in the 2004 Olympic Games, which after over a century will be hosted again in Athens.

The authors thank Giovanni de Gaetano for helpful suggestions.

The authors' work mentioned in this overview has been partially supported by the EU project IMMIDIET QLK1-CT-2000–00100 and the Italian Ministry of Health, contract n.211 RF 2002.

References

1 Cambien F, Poirier O, Lecerf L, Evans A, Cambou JP, Arveiler D, Luc G, Bard JM, Bara L, Ricard S, et al: Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. Nature 1992;359:641–644.

2 Iacoviello L, Di Castelnuovo A, De Knijff P, et al: Polymorphisms in the coagulation factor VII gene and the risk of myocardial infarction. N Engl J Med 1998;338:79–85.

3 Kissebah AH, Sonnenberg GE, Myklebust J, Goldstein M, Broman K, James RG, Marks JA, Krakower GR, Jacob HJ, Weber J, Martin L, Blangero J, Comuzzie AG: Quantitative trait loci on chromosomes 3 and 17 influence phenotypes of the metabolic syndrome. Proc Natl Acad Sci USA 2000;97:14478–14483.

4 Rice T, Rankinen T, Province MA, Chagnon YC, Perusse L, Borecki IB, Bouchard C, Rao DC: Genome-wide linkage analysis of systolic and diastolic blood pressure: the Quebec Family Study. Circulation 2000;102:1956–1963.

5 van Tilburg J, van Haeften TW, Pearson P, Wijmenga C: Defining the genetic contribution of type 2 diabetes mellitus. J Med Genet 2001;38:569–578.

6 Keavney B: Genetic epidemiological studies of coronary heart disease. Int J Epidemiol 2002;31: 730–736.

7 Humphries SE: The genetic contribution to the risk of thrombosis and cardiovascular disease. Trends Cardiovasc Med 1994;4:8–17.

8 Zito F, Di Castelnuovo A, D' Orazio A, Amore C, Donati MB, Iacoviello L: *Bcl*I polymorphism of beta-chain fibrinogen gene is associated with the risk of familial myocardial infarction by increasing fibrinogen levels: A case-control study in a sample of GISSI-2 patients. Arterioscler Thromb Vasc Biol 1997;17:3489–3494.

9 Kluft C: Genetic research stimulates development of individual treatment. Cardiologia 1999;44: 119–124.

10 Humphries SE, Panahloo A, Montgomery HE, Green F, Yudkin J: Gene-environment interaction in the determination of levels of haemostatic variables involved in thrombosis and fibrinolysis. Thromb Haemost 1997;78:457–461.

11 Zito F, Di Castelnuovo A, Amore C, D'Orazio A, Negrini R, De Lucia D, Donati MB, Iacoviello L: *Helicobacter pylori* infection and beta-chain fibrinogen genotype: Modulation of fibrinogen plasma levels and risk of acute myocardial infarction. Thromb Haemost 1999;82:14–18.

12 Thomas A, Lamlum H, Humphries S, Green F: Linkage disequilibrium across the fibrinogen locus as shown by five genetic polymorphisms, G/A-455 (*Hae*III), C/T-148 (*Hin*dIII/*Alu*I), T/G+1689 (*Ava*II), and *Bcl*I (β-fibrinogen) and *Taq*I (α-fibrinogen), and their detection by PCR. Hum Mutat 1994;3:79–81.

13 de Maat MP, de Knijff P, Green FR, Thomas AE, Jespersen J, Kluft C: Gender-related association between beta-fibrinogen genotype and plasma fibrinogen levels and linkage disequilibrium at the fibrinogen locus in Greenland Inuit. Arterioscler Thromb Vasc Biol 1995;15:856–860.

14 Tybjaerg-Hansen A, Agerholm-Larsen B, Humphries SE, Abildgaard S, Schnohr P, Nordestgaard BG: A common mutation (G-455–> A) in the beta-fibrinogen promoter is an independent predictor of plasma fibrinogen, but not of ischemic heart disease. A study of 9,127 individuals based on the Copenhagen City Heart Study. J Clin Invest 1997;99:3034–3039.

15 Montgomery HE, Clarkson P, Nwose OM, Mikailidis DP, Jagroop IA, Dollery C, Moult J, Benhizia F, Deanfield J, Jubb M, World M, McEwan JR, Winder A, Humphries S: The acute rise in plasma fibrinogen concentration with exercise is influenced by the G-453-A polymorphism of the beta-fibrinogen gene. Arterioscler Thromb Vasc Biol 1996;16:386–391.

16 Humphries SE, Ye S, Talmud P, Bara L, Wilhelmsen L, Tiret L: European Atherosclerosis Research Study: genotype at the fibrinogen locus (G-455-A beta) is associated with differences in plasma fibrinogen levels in young men and women from different regions in Europe: Evidence for gender-genotype-environment interaction. Arterioscler Thromb Vasc Biol 1995;15:96–104.

17 Geffken D, Cushman M, Burke G, Polak J, Sakkinen P, Tracy R: Association between physical activity and markers of inflammation in a healthy elderly population. Am J Epidemiol 2001; 153:242.

18 Vaisanen S, Rauramaa R, Rankinen T, Gagnon J, Couchard C: Physical activity, fitness, and plasma fibrinogen with reference to fibrinogen genotypes. Med Sci Sports Exerc 1996;28:1165–1170.
19 Rauramaa R, Vaisanen S, Nissinen A, Rankinen T, Penttila I, Saarikoski S, Tuomilehto J, Gagnon J, Perusse L, Bouchard C: Physical activity, fibrinogen plasma level and gene polymorphisms in postmenopausal women. Thromb Haemost 1997;78:840–844.
20 Rauramaa R, Vaisanen SB, Kuhanen R, Penttila I, Bouchard C: The *Rsa*I polymorphism in the α-fibrinogen gene and response of plasma fibrinogen to physical training: A controlled randomised clinical trial in men. Thromb Haemost 2000;83:803–806.
21 Danesh J, Collins R, Peto R: Chronic infections and coronary heart disease: is there a link? Lancet 1997;350:430–436.
22 Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P: Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet 1999;353:1547–1557.
23 WHO, FAO: Food and health indicators in Europe: Nutrition and health, 1961–1990 (computer program). Copenhagen, World Health Organization Regional Office for Europe, 1993.
24 Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G: Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002;105:2836–2844.
25 Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, et al: The diet and 15-year death rate in the seven countries study. Am J Epidemiol 1986;124:903–915.
26 Trichopoulou A, Costacou T, Bamia C, Trichopoulos D: Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–2608.
27 Ferro-Luzzi A, Branca F: Mediterranean diet, Italian-style: prototype of a healthy diet. Am J Clin Nutr 1995;61(suppl 6):S1338–S1345.
28 Gronbaek M, Deis A, Sorensen TI, Becker U, Schnohr P, Jensen G: Mortality associated with moderate intakes of wine, beer, or spirits. BMJ 1995;310:1165–1169.
29 Ferro-Luzzi A, Strazzullo P, Scaccini C, Siani A, Sette S, Mariani MA, Mastranzo P, Dougherty RM, Iacono JM, Mancini M: Changing the Mediterranean diet: Effects on blood lipids. Am J Clin Nutr 1984;40:1027–1037.
30 Strazzullo P, Ferro-Luzzi A, Siani A, Scaccini C, Sette S, Catasta G, Mancini M: Changing the Mediterranean diet: Effects on blood pressure. J Hypertens 1986;4:407–412.
31 Renaud SC, de Lorgeril M: Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992;339:1523–1526.
32 Ciccarone E, Di Castelnuovo A, Salcuni M, Siani A, Giacco A, Donati MB, de Gaetano G, Capani F, Iacoviello L, on behalf of the GENDIABE investigators: A high score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. J Thromb Haemost 2003;1:1744–1752.
33 Luc G, Bard JM, Arveiler D, Evans A, Cambou JP, Bingham A, Amouyel P, Schaffer P, Ruidavets JB, Cambien F, et al: Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study. Arterioscler Thromb 1994;14:1412–1419.
34 Howard PR, Bovill EG, Pike J, Church WR, Tracy RP: Factor VII antigen levels in a healthy blood donor population. Thromb Haemost 1994;72:21–27.
35 Balleisen L, Bailey J, Epping P-H, Schulte H, van de Loo J: Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population. I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. Thromb Haemost 1985;54:475–479.
36 Mennen LI, Schouten EG, Grobbee DE, Kluft C: Coagulation F VII, dietary fat and blood lipids: A review. Thromb Haemost 1996;76:492–499.
37 Lane DA, Grant PJ: Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. Blood. 2000;95:1517–1532.
38 Green F, Kelleher C, Wilkes H, Temple A, Meade T, Humphries S: A common genetic polymorphism associated with lower coagulation factor VII levels in healthy individuals. Arteroscler Thromb 1991;11:540.
39 Marchetti G, Patracchini P, Papaschini M, Ferrati M, Bernardi F: A polymorphism in the 5′ region of coagulation factor VII gene (F7) caused by an inserted decanucleotide. Hum Genet 1993;90:575.

40 Bernardi F, Marchetti G, Pinotti M, et al: Factor VII gene polymorphisms contribute about one third of the factor VII level variation in plasma. Arterioscler Thromb Vasc Biol 1996;16:72.
41 Pollak ES, Hung HL, Godin W, Overton GC, High KA: Functional characterization of the human factor VII 5′-flanking region. J Biol Chem 1996;271:1738.
42 van't Hooft FM, Silveira A, Tornvall P, et al: Two common functional polymorphisms in the promoter region of coagulation factor VII gene determining plasma factor VII activity and mass concentration. Blood 1999;93:3432.
43 Hong Y, Pedersen NL, Egberg N, de Faire U: Genetic effects for plasma factor VII levels independent of and in common with triglycerides. Thromb Haemost 1999;81:38.
44 Girelli D, Russo C, Ferraresi P, Olivieri O, Pinotti M, Friso S, Manzato F, Mazzucco A, Bernardi F, Corrocher R: Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. N Engl J Med 2000;343:774–780.
45 Heywood DM, Carter AM, Catto AJ, Bamford JM, Grant PJ: Polymorphisms of the factor VII gene and circulating FVII:c levels in relation to acute cerebrovascular disease and poststroke mortality. Stroke 1997;28:816–821.
46 Lane A, Green F, Scarabin PY, et al: Factor VII Arg/Gln353 polymorphism determines factor VII coagulant activity in patients with myocardial infarction (MI) and control subjects in Belfast and in France but is not a strong indicator of MI risk in the ECTIM study. Atherosclerosis 1996;119: 119–127.
47 Heywood DM, Ossei-Gerning N, Grant PJ: Association of factor VII:c levels with environmental and genetic factors in patients with ischaemic heart disease and coronary atheroma characterized by angiography. Thromb Haemost 1996;76:161–165.
48 Wang XL, Wang J, McCredie RM, Wilckeb DEL: Polymorphisms of factor V, factor VII, and fibrinogen genes. Relevance to severity of coronary artery disease. Arterioscler Thromb Vasc Biol 1997;17:246–251.
49 Iacoviello L, Di Castelnuovo A, D'Orazio A, Donati B: Cigarette smoking doubles the risk of myocardial infarction in carriers of a protective polymorphism in the blood coagulation factor VII gene. Thromb Haemost 1999;81:658.
50 Iacoviello L, Zito F, Di Castelnuovo A, de Maat M, Kluft C, Donati MB: The contribution of fibrinogen, fibrinolytic components and factor VII to the risk of cardiovascular disease: Their genetic determinants. Fibrinol Proteol 1998;12:259–276.
51 de Maat MPM, Green F, de Knijff P, Jespersen G, Kluft C: Factor VII polymorphisms in populations with different risk of cardiovascular disease. Arterioscl Thromb Vasc Biol 1997;17: 1918–1923.
52 Bernardi F, Arcieri P, Chiarotti F, et al: Contribution of factor VII genotype to activated FVII levels. Differences in genotype frequencies between Northern and Southern European populations. Arterioscl Thromb Vasc Biol 1997;17:2548–2553.
53 O'Hara PJ, Grant FJ, Haldeman BA, et al: Nucleotide sequence of the gene coding for human factor VII, a vitamin K-dependent protein participating in blood coagulation. Proc Natl Acad Sci USA 1987;84:5158–5162.
54 de Knijff P, Green F, Johansen LG, et al: New alleles in F7 VNTR. Hum Mol Genet 1994;3:384.
55 Lane A, Cruickshank JK, Mitchell J, Henderson A, Humphries S, Green F: Genetic and environmental determinants of factor VII coagulant activity in ethnic groups at differing risk of coronary heart disease. Atherosclerosis 1992;94:43–50.
56 Humphries S, Temple A, Lane A, Green F, Cooper J, Miller G: Low plasma levels of factor VIIc and antigen are more strongly associated with the 10 base pair promoter (-323) insertion than glutamine 353 variant. Thromb Haemost 1996;75:567–572.
57 Humphries SE, Lane A, Green FR, Cooper J, Miller GJ: Factor VII coagulant activity and antigen levels in healthy men are determined by interaction between factor VII genotype and plasma triglyceride concentration. Arterioscler Thromb 1994;14:193–198.
58 Silveira A, Green F, Karpe F, Blomback M, Humphries S, Hamsten A: Elevated levels of factor VII activity in the postprandial state: Effect of the factor VII Arg-Gln polymorphism. Thromb Haemost 1994;72:734–739.
59 Mennen LI, de Maat MP, Meijer G, Zock P, Grobbee DE, Kok FJ, Kluft C, Schouten EG: Postprandial response of activated factor VII in elderly women depends on the R353Q polymorphism. Am J Clin Nutr 1999;70:435–438.

60 Saha N, Liu Y, Heng CK, Hong S, Low PS, Tay JSH: Association of factor VII genotype with plasma factor VII activity and antigen levels in healthy Indian adults and interaction with triglycerides. Arterioscler Thromb 1994;14:1923–1927.
61 Meilahn E, Ferrell R, Kiss J, et al: Genetic determination of coagulation factor VIIc levels among healthy middle-aged women. Thromb Haemost 1995;73:623–625.
62 Heywood DM, Mansfield MW, Grant PJ: Factor VII polymorphisms, factor VII:C levels and features of insulin resistance in non-insulin-dependent diabetes mellitus. Thromb Haemost 1996;75:401–406.
63 Mennen LI, de Maat MPM, Schouten EG, Kluft C, de Jong PTVM, Hofman A, Grobee DE: Coagulation factor VII, serum triglycerides and the R/Q353 polymorphism: Difference between older men and women. Thromb Haemost 1997;78:984–986.
64 Carvalho de Souza J, Soria C, Ayrault-Jarrier M, et al: Association between coagulation factors VII and X with triglyceride rich lipoproteins. J Clin Pathol 1988;41:940–944.
65 Carvalho de Souza J, Bruckert E, Giral P, et al: Coagulation factor VII and plasma trygliceride: Decreased catabolism as a possible mechanism of factor VII hyperactivity. Haemostasis 1989;19:125–130.
66 Hunault M, Arbini AA, Lopaciuk S, Carew JA, Bauer KA: The Arg353Gln polymorphism reduces the level of coagulation factor VII: In vivo and in vitro studies. Arterioscl Throm Vasc Biol 1997;17:2825–2829.

Maria Benedetta Donati, MD, PhD
Research Laboratories
Center for High Technology Research and Education in Biomedical Sciences
Catholic University, IT-86100 Campobasso (Italy)
Tel. +39 0874 312278, Fax +39 0874 312710, E-Mail mbdonati@rm.unicatt.it

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 107–119

Role of Nutrients and Physical Activity in Gene Expression

Raffaele De Caterina[a,b], *Rosalinda Madonna*[a]

[a] Institute of Cardiology and Center of Excellence on Aging, 'G. d'Annunzio' University, Chieti, and [b] CNR Institute of Clinical Physiology, Pisa, Italy

In prokaryotes and lower eukaryotes, the regulation of gene expression in response to changes in nutrients is common and well-documented [1]. In multicellular organisms, nutrients are effectors of more complex functions, such as the stimulation of hormone synthesis and the secretion of neurotransmitters. Nutrients such as fatty acids and their metabolites [2], monosaccharides [3], amino acids [4], nucleotides [5], and vitamins [6] regulate gene expression by interacting directly with transcription factors controlling the expression of specific genes through *cis*-regulatory elements in the promoter region or altering the stability of messenger(m)RNA.

We recently reviewed several examples of regulation of gene expression by micro- and macro-nutrients [7, 8]. We herein expand on the issue of the regulation of gene expression by nutrients during physical activity, and summarize recent insights from our own research into regulation of gene expression by polyunsaturated fatty acids. Finally we will here highlight how the intake of specific nutrients may condition the expression of a specific genotype, an example of the expanding interest in the area of nutrigenetics.

Nutrients, Physical Activity and Gene Expression

The skeletal muscle has a major impact on whole-body metabolic homeostasis, being capable of remarkable adaptation in response to exercise and dietary intervention. Transcriptional activation and increased mRNA stability are the main mechanisms by which exercise increases the expression of many genes in skeletal muscle. Nutrient availability and associated alterations of hormone levels are additional modifiers of skeletal muscle gene expression.

A main subject of nutritional research in these last years has been to identify mechanisms by which alterations of gene expression through nutritional interventions are coupled with changes in skeletal muscle phenotype. Potential stimuli for gene expression during exercise and physical activity include stretch and muscle tension, motor nerve activity, the energy charge of the cells, oxygen tension, circulating hormones and the availability of nutritional substrates.

We will here review a few examples of regulation of gene expression during exercise by lipids and carbohydrates.

Fatty Acids and Gene Expression during Exercise

Dietary regulation of gene expression by fatty acids during exercise is one of the best characterized steps in skeletal muscle adaptation to the energy demands of the muscle. A complex regulation at multiple levels permits the matching of the availability of these fuels to the energy demands of exercising skeletal muscle. Regulation occurs because of changes in substrate availability or changes in hormonal concentrations, and in part reflects the allosteric regulation of specific enzymes [9]. Fatty acid traslocase (FAT/CD36), plasma membrane fatty acid-binding protein (FABPm) and β-hydroxyacyl-CoA dehydrogenase (β-HAD) are examples of genes differentially regulated in response to consumption of a lipid-rich diet during exercise.

FAT/CD36 is present in tissues with a high fatty acid demand, including the heart, the adipose tissue, the intestine and skeletal muscle [10], and acts as a regulator of intracellular fatty acid uptake at times of increased metabolic demand by its recruitment, during muscle contraction, to the plasma membrane from intracellular sites [11]. Cameron-Smith et al. demonstrated that, in well-trained subjects undertaking a matched exercise regimen, the consumption of a fat-rich diet (>65% of energy from lipids and <20% of energy from carbohydrates) for 5 days markedly increases the expression of FAT/CD36 when compared with an iso-energetic high-carbohydrate diet (70–75% of energy from carbohydrates and <15% of energy from fats), modulating the increased expression of the protein occurring with exercise [12]. The investigation carried out by these authors showed 50 and 17% increases in gene and protein abundance of FAT/CD36, respectively, with the high-fat diet compared with the high-carbohydrate diet, suggesting that the role of FAT/CD36 in facilitating skeletal muscle fatty acid uptake during exercise is further finely tuned according to the specific metabolic needs (plasma concentrations of fatty acids), in turn dependent from dietary fat uptake.

FABPm is an important mediator of fatty acid plasma membrane transport, present in tissues with high fatty acid flux [10]. Fasting [13] and endurance training [14] increase the abundance of skeletal muscle FABPm protein by

increasing dietary fatty acid levels. Cameron-Smith et al. showed no increase in FABPm mRNA or protein after 5 days of a high-fat diet in subjects undertaking a matched exercise regimen, arguing that FABPm is regulated differentially from FAT/CD36, with no evidence of an effect of diet on FABPm during exercise [12].

Unlike FABPm, the β-oxidation pathway enzyme β-hydroxyacyl-CoA dehydrogenase (β-HAD) in skeletal muscle has been shown to be under nutritional regulation [15]. Abundance of β-HAD increases 2.6-fold after a high-fat diet compared to a high-carbohydrate diet in well-trained subjects undertaking an exercise regimen, indicating a marked transcriptional activation of this gene [12]. Helge et al. [15] showed that the increase in β-HAD enzyme activity was 120% greater after 7 weeks of a high-fat diet (62% of energy as fat) than after an iso-energetic high-carbohydrate diet (37% of energy as fat) during exercise, and this apparently depended on increased gene expression. Conversely, Peters et al. [16] showed that the consumption of a high-fat diet for 6 days by untrained subjects had little effect on β-HAD enzyme activity relative to the effect of a low-fat control diet (33% of energy as fat). Observations by Kiens et al. [17] underlined that a diet moderately high in fat (53% of total energy), relative to a lower-fat diet (43% of energy as fat), fed for 4 weeks, did not alter β-HAD enzyme activity. Thus, it seems that exercise and diet interact in regulating β-HAD enzyme activity, and that exercise training is permissive for the effect of a high-fat diet on enzyme activity.

The peroxisome-proliferator-activated receptor (PPAR) family of transcription factors has been demonstrated to provide an excellent model to explain the activation of gene expression after a high-fat diet. Signaling to the nucleus by many fatty acids has been shown to occur via the multiple isoforms of PPAR transcription factors [18–20]. It has been demonstrated that selective agonists for the PPAR-α and PPAR-γ isoforms activate the expressions of the FAT/CD36 gene [21, 22], suggesting a role for increased activity of these transcription factors after a high-fat diet (fig. 1). However, PPAR activation alone cannot fully account for the observed regulation also of the β-HAD gene. In fact, there is no evidence for a PPAR response element upstream of the β-HAD coding region in humans [23]. Thus, the mechanisms linking the increased availability of dietary fatty acids to the regulation of β-HAD in human skeletal muscle are far from being understood.

Carbohydrates and Gene Expression during Exercise

Several investigations have shown that plasma levels of three anti-inflammatory cytokines, interleukin (IL)-6, IL-10, and IL-1 receptor antagonist (IL-1ra), are largely augmented after a strenuous exercise [24, 25]. Plasma levels of IL-8, a neutrophil chemotactic and activation protein, were also reported to

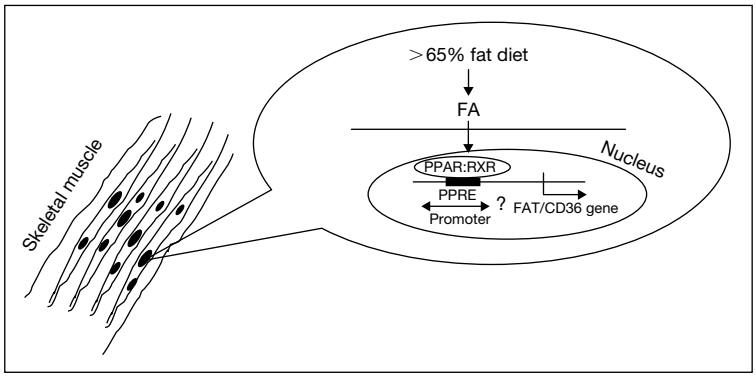


Fig. 1. Example of nutritional regulation of gene expression in skeletal muscle. A high-fat diet increases the expression of FAT/CD36 through the PPAR signaling pathway. PPAR = Peroxisome proliferator-activated receptor; RXR = rexinoid receptor; PPRE = PPAR response element; FAT/CD36 = fatty acid tras locase.

increase after prolonged, intensive exercise [24, 25]. Postexercise plasma levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and IL-1β are slightly increased, with negligible changes reported for the immunomodulatory cytokines IL-2, IL-12, interferon (IFN)-γ and IFN-α [24, 25].

Nieman et al. [26] tested the hypothesis that carbohydrates decrease plasma levels of inflammatory cytokines by influencing muscle glycogen content and cytokine gene expression during prolonged, intensive exercise. In this study, experienced marathon runners were asked to run for 3 h on a treadmill under feeding with carbohydrates or placebo, with muscle biopsies and blood samples obtained before and after exercise. Subjects received 6% carbohydrate or placebo beverages 15–30 min before the run and then during the 3-hour run. The carbohydrate and placebo beverages were identical in sodium (~19 mEq/l) and potassium (~3 mEq/l) concentrations, as well as in their pH value (~3). The study showed that plasma concentrations of IL-6, IL-10 and IL-1ra were lower in endurance athletes who ingested a 6% carbohydrate compared with those taking a placebo beverage (1 liter of beverages per exercise hour). Furthermore, in experienced marathon runners, carbohydrate ingestion attenuated the increase of other inflammatory indices, including blood neutrophil and monocyte counts, granulocyte/monocyte phagocytosis and oxidative burst activity. Earlier studies had shown that the consumption of carbohydrates decreases the release of ACTH, cortisol and epinephrine compared with placebo [27]. Nieman et al. [26] hypothesized that carbohydrate ingestion attenuated anti-inflammatory cytokine production during exercise

through a blood glucose-sympatho-adrenal pathway. Several pieces of evidence have accumulated recently on this issue.

Strarkie et al. [28] reported that carbohydrate ingestion did not affect skeletal muscle IL-6 mRNA expression and the rate of decrease in muscle glycogen content in men who ran for 60 min. In this study, the plasma IL-6 response was decreased by carbohydrate ingestion, suggesting that IL-6 production and its subsequent release from skeletal muscle were attenuated, that IL-6 production from tissues other than skeletal muscle was reduced, or both. Steensberg et al. [29] studied seven men running for 5 h in conditions of muscle glycogen depletion, demonstrating an increase in muscle IL-6 mRNA expression and IL-6 release. Other studies have indicated that IL-6 mRNA expression, the transcription rate of the IL-6 gene, and the release of IL-6 from the working muscle are all enhanced during exercise in the glycogen-depleted state [29, 30]. Febbraio and Pedersen [31] demonstrated that muscle glycogen availability may influence the capability of key signaling molecules to enhance IL-6 gene transcription within skeletal muscle during altered homeostasis. Keller et al. [32] showed that a 180-min run activates the transcription of skeletal muscle IL-6 gene, and that this response is enhanced under conditions whereby muscle glycogen concentrations are low. Helge et al. [30] showed that high IL-6 release was significantly related to exercise intensity, high glucose uptake, arterial plasma epinephrine concentration, and postexercise glycogen concentration. Multiple studies have also shown that epinephrine is an inducer of cytokine release during exercise [25], and that carbohydrate ingestion blunts epinephrine release by increasing blood glucose [27]. Epinephrine plays a key role in exercise-induced changes in lymphocyte number [29]. Thus, it is likely that IL-6 and IL-8 mRNA expressions in the study of Nieman et al. [26] were diminished in the carbohydrate compared with the placebo condition, at least in part due to differences in blood glucose and epinephrine levels.

Polyunsaturated Fatty Acids

Examples of polyunsaturated fatty acid (PUFA)-responsive genes are carnitine palmitoyltransferase [33], peroxisomal acyl-CoA oxidase [34], fatty acyl-CoA synthase [35], mitochondrial 3-hydroxy-3-methylglutaryl (HMG)-CoA synthase [36]. PUFA induce fatty acid oxidation by increasing the expression of mitochondrial L-type carnitine palmitoyltransferase and peroxisomal acyl-CoA oxidase, and by decreasing the sensitivity of the carnitine palmitoyltransferase to malonyl-CoA.

Previous data had indicated that PUFA achieve their effects on lipogenic genes by activating the PPAR family of trascription factors [37]. PPARs possess

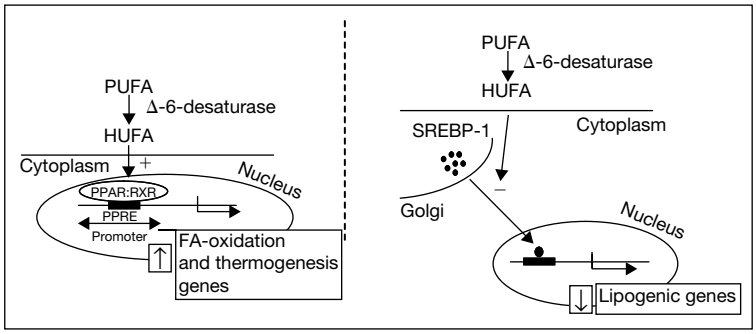


Fig. 2. PUFA regulation of gene expression. On the left, PUFA upregulate the expression of genes of fatty acid oxidation and thermogenesis. On the right, PUFA downregulate lipogenic gene expession. PPAR = Peroxisome proliferator-activated receptor; HUFA = highly unsaturated fatty acids (i.e. longer-chain PUFA, namely arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid); FA = fatty acid; SREBP-1 = sterol response element-binding protein.

a ligand-binding domain, interacting with PUFA, and a zinc-finger DNA-binding domain [38], which mediates the interaction with PPAR response elements, located in the 5′-flanking region of responsive genes, and consisting of a hexameric AGGTCA repeat sequence. The PPAR family includes PPARα, PPARγ1 and 2, PPARδ, and two related lipid-activated transcription factors, LXR and FXR [37]. It has been demonstrated that PPAR binding to the repeat sequence is enhanced when PPARs form a heterodimer with RXR [34] (fig. 2).

Sterol regulatory element-binding proteins (SREBP) are transcription factors binding sterol regulatory elements, and are involved in the sterol regulation of genes involved in cholesterol synthesis [39]. It has been demonstrated that PUFA regulate lipid metabolism by suppressing the expression and nuclear localization of SREBP-1. In fact, the amount of PUFA in the membrane negatively affects the process of proteolytic maturation and nuclear translocation of SREBP [40] (fig. 2). Furthermore, omega−3 and omega−6 PUFA reduce the hepatic abundance of SREBP-1 mRNA by 60–70%, and this in turn leads to a comparable decrease in the amount of precursor SREBP-1 found in the membrane [41]. PUFA do not influence the rate of SREBP-1 gene transcription, but govern SREBP-1 gene expression, by accelerating the rate of SREBP-1 mRNA decay [42]. Therefore, PUFA downregulate lipogenic gene expression by reducing the hepatic content of precursor and mature SREBP-1, whereas they upregulate the expression of genes of fatty acid oxidation and thermogenesis by functioning as ligand activators for PPARα (fig. 2).

Finer Roles for Specific Fatty Acids: The Inhibition of Endothelial Activation by Unsaturated Fatty Acids

Long-chain PUFA and, particularly, omega-3 PUFA, are currently receiving increasing attention as potential anti-atherogenic and anti-inflammatory agents. Research progress in the past 10 years derived from our own research has disclosed potential mechanistic explanations for their preventive or therapeutic use in preventing atherosclerosis and vascular inflammation.

We used human adult saphenous vein endothelial cells activated by cytokines, in an in vitro model of early steps in atherogenesis. The omega−3 fatty acid, docosahexaenoic acid, significantly inhibited the expression of adhesion molecules such as vascular adhesion molecule (VCAM)-1, E-selectin and, to a lesser extent, intercellular adhesion molecule (ICAM)-1 after stimulation with IL-1α and β, TNFα, IL-4 and bacterial lipopolysaccharide (LPS) [43, 44]. Experiments following the fate of ^{14}C-labelled DHA into cell phospholipids showed a significant incorporation of DHA into the phosphatidyl ethanolamine pool, i.e. in a specific and not the most abundant phospholipid pool, likely in the inner plasma membrane, and therefore in a strategic position to alter intracellular signal transduction pathways. This effect was not limited to the expression of transmembrane molecules involved in leukocyte recruitment, but appeared also to occur for other cytokine-activated products, such as the soluble proteins IL-6 and IL-8, involved in either the amplification of the inflammatory response (IL-6), or in the specific chemoattraction for granulocytes (IL-8), and was accompanied by a functional counterpart, i.e. a reduced monocyte or monocytoid cell adhesion to cytokine activated endothelium.

We further analyzed endothelial effects of various fatty acids differing in chain length, number, position (omega−3 vs. omega−6 vs. omega−9) and the *cis/trans* configuration of the double bonds. We concluded that (a) saturated fatty acids are inactive; (b) the potency of PUFA increases with the number of unsaturations; (c) the potency does not depend on chain length; (d) the single double bond present in the monounsaturated fatty acid oleic acid is indeed sufficient to produce all the effects obtainable with higher unsaturated fatty acids, albeit at higher concentrations; (e) for such an effect to occur, even the configuration (*cis* vs. *trans*) of the double bond does not really matter, since oleic acid (18:1 n-9 *cis*) and its *trans* stereoisomer elaidic acid are of equal potency [45].

In order to ascertain mechanisms for these effects, we demonstrated inhibition of nuclear factor (NF)-κB activation by DHA, in parallel with decreased production of hydrogen peroxide by cultured endothelial cells. We could thus document (unpublished results) a decrease in baseline production of hydrogen peroxide (or some of its downstream products) after cell membrane enrichment with DHA, but an even more pronounced dampening, in such conditions, of the

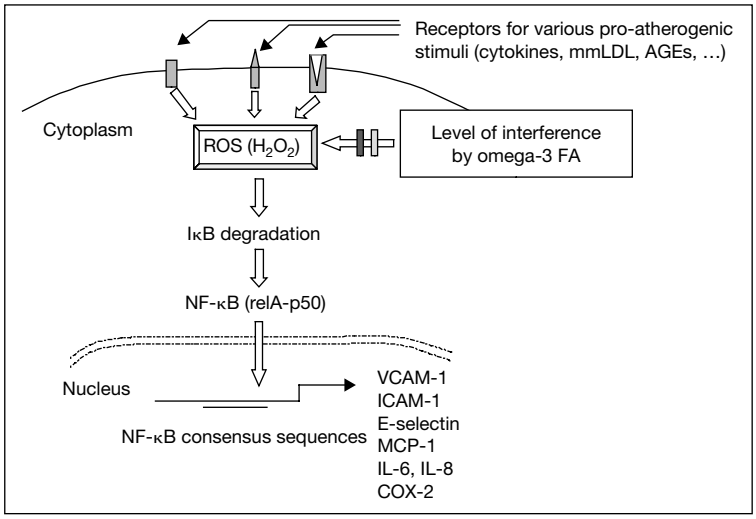


Fig. 3. A model of the putative site of action of omega−3 polyunsaturated fatty acids (omega−3 FA). Omega−3 FA enhance the translocation of nuclear factor-κB (NF-κB) into the nucleus, thus activating the expression of early genes involved in atherogenesis. mm LDL = Minimally modified LDL; AGEs = advanced glycation end products; VCAM-1 = vascular cell adhesion molecule-1; ICAM-1 = intercellular adhesion molecule-1; MCP-1 = monocyte chemoattractant protein-1; IL = interleukin; COX-2 = cyclooxygenase-2. See text for further details.

increase produced by stimulation with cytokines. Saturated fatty acids served as a negative control in these experiments. These findings suggest that a property related to fatty acid peroxidability (the presence of multiple double bonds), usually regarded as a detrimental consequence of PUFA enrichment of cell membranes, is indeed also directly related to the property of inhibiting the release of some reactive oxygen species crucial for cell responsiveness to cytokines. A tentative model of the site of action of omega−3 fatty acids in inhibiting endothelial activation is shown in figure 3.

Interaction between Omega−3/Omega−6 Polyunsaturated Fatty Acids and the Genome: Fatty Acid Intake, 5-Lipoxygenase and Atherosclerosis – An Example of Nutrigenetics

Leukotrienes (LT) are eicosanoids derived through the action of 5-lipoxygenase (5-LO). This enzyme catalyzes the transformation of arachidonic acid into

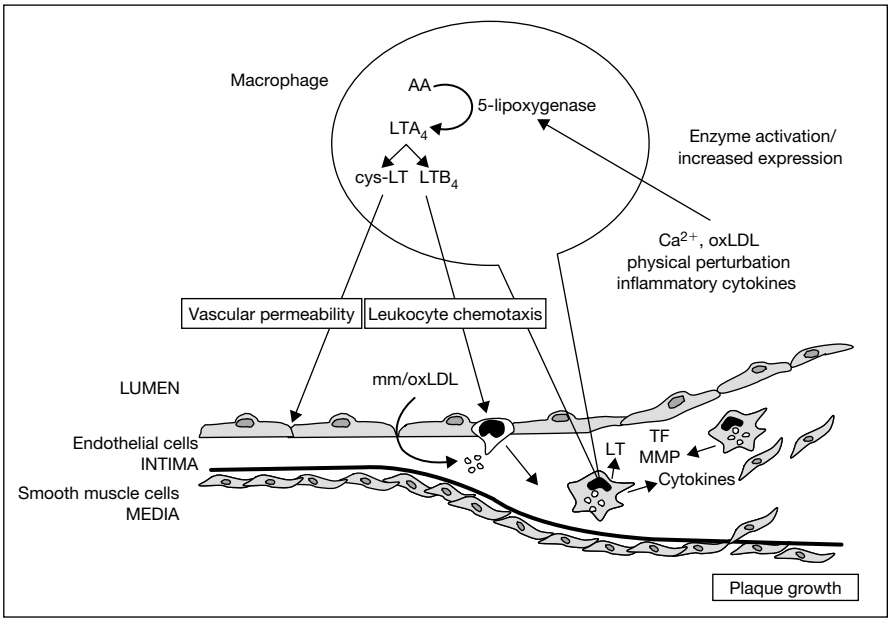


Fig. 4. Main putative roles of 5-lipoxygenase in atherosclerosis. Leukotrienes (LT) may contribute to atherosclerosis by promoting non-specific leukocyte chemotaxis (LTB_4), and by increasing vascular permeability (cysteinyl-LT C_4, D_4 and E_4). The activation and gene expression of 5-lipoxygenase (5-LO) can be increased in inflammatory conditions by different cytokines.

LTA_4, which in turn is either converted into LTB_4, or conjugated to form LTC_4. LTC_4 and its metabolites LTD_4 and LTE_4 are together referred to as 'cysteinyl' (cys)-LT (fig. 4). LTB_4 is a potent chemoattractant for neutrophils, macrophages and other inflammatory cells, while cys-LT increase vascular permeability and contract smooth muscle cells, causing broncho-and vasoconstriction.

In two widely used mouse models of atherosclerosis, the apo-$E^{-/-}$ mice, and the LDL-$receptor^{-/-}$ mice, a locus on mouse chromosome 6 was found to confer almost total resistance to atherogenesis. The 5-LO gene, located in this locus in the mouse, turned out to totally account for this effect, since LDL $receptor^{-/-}$ mice missing even only one of the two allelic copies of the 5-LO gene, had a dramatic decrease (about 26-fold) in lesion development. Also, when bone marrow (supplying circulating blood cells) from 5-$LO^{-/-}$ mice was transplanted into $LDLR^{-/-}$, there was a significant protection from atherosclerosis, suggesting that 5-LO from white blood cells (likely monocyte-macrophages) was necessary for atherogenesis [46, 47].

The important contribution of 5-LO to atherosclerosis may occur because the products of 5-LO, LT, mostly produced by monocyte-macrophages or dendritic cells in the arterial intima, would foster the chemoattraction of monocytes, T cells or other circulating cell types within the vessel wall and/or increase vascular permeability. This would establish a vicious circle by which inflammatory cells, by producing these lipid mediators, beget local vascular inflammation, perpetuating the recruitment of inflammatory cells and the further production of mediators (fig. 4).

Dwyer and coworkers have recently reported that genetic variants of the 5-LO promoter, previously described as associated with variable sensitivity to anti-asthmatic medications, also influence atherosclerosis. Variant genotypes of the 5-LO gene were found in 6% of a cohort of 470 healthy middle aged women and men. Carotid intima-media thickness (IMT), taken as a marker of the atherosclerotic burden, was significantly increased, by 80%, in the variant group compared to carriers of the common allele [48]. The direction of the change in IMT in the variant group is contrary to what one would have expected on the basis of previous findings in vitro, and rather consistent with increased, rather than decreased, 5-LO promoter activity associated with the mutant alleles. This finding thus requires further explanation.

Dwyer et al. also reported, however, on a diet-gene interaction, by which dietary arachidonate intake significantly enhanced the pro-atherogenic effect of the 5-LO gene variants, while intake of omega−3 PUFA (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) blunted this effect [48]. Since EPA and DHA may decrease the formation of LT by competing with arachidonate as substrates for 5-LO and also generate the weaker LT of the 5-series, these findings suggest that the anti-atherogenic effects of fish-derived EPA and DHA might be more prominent in – or perhaps limited to – genotype variants favoring increased 5-LO activity.

Conclusions

There is now ample evidence that nutrients determine variable rate of expression in a wide variety of genes involved in their metabolism (likely a mechanism evolutionarily selected to optimize nutrient utilization), but also affect the body's response to physiological conditions (such as physical exercise) or other changes in the environment, such as those occurring in atherosclerosis and inflammation. Far from being simple sources for the building blocks of our complex organic structures, nutrients definitely need to be considered fine regulators of the responses of our genes to the environment.

References

1 Higgins CF, Peltz SW, Jacobson A: Turnover of mRNA in prokaryotes and lower eukaryotes. Curr Opin Genet Dev 1992;2:739–747.
2 Moustaid N, Sakamoto K, Clarke SD, Beyer RS, Sul HS: Regulation of fatty acid synthase gene transcription. Biochem J 1993;292:767–772.
3 Rutter GA, Tavare JM, Palmer DG: Regulation of mammalian gene expression by glucose. News Physiol Sci 2000;15:149–154.
4 Jefferson LS, Kimball SR: Amino acid regulation of gene expression. J Nutr 2001;131(9 suppl): S2460–S2466.
5 Sanchez-Pozo A, Gil A: Nucleotides as semiessential nutritional components. Br J Nutr 2002;87 (suppl 1):S135–S137.
6 Azzi A, Aratri E, Boscoboinik D, Clement S, Ozer N, Ricciarell R, Spycher S, Stocker A: Vitamins and regulation of gene expression. Bibl Nutr Dieta 2001;55:177–188.
7 De Caterina R, Madonna R, Hassan J, Procopio AD: Nutrients and gene expression. World Rev Nutr Diet. Basel, Karger, 2001, vol 89, pp 23–52.
8 De Caterina R, Madonna R: Nutrients and gene expression. World Rev Nutr Diet. Basel, Karger, 2004, in press.
9 Ruderman NB, Saha AK, Vavvas D, Witters LA: Malonyl-CoA, fuel sensing, and insulin resistance. Am J Physiol Endocrinol Metab 1999;39:E1–E18.
10 Bonen A, Dyck DJ, Luiken JJ: Skeletal muscle fatty acid transport and transporters. Adv Exp Med Biol 1998;441:193–205.
11 Bonen A, Dyck DJ, Ibrahimi A, Abumrad NA: Muscle contractile activity increases fatty acid metabolism and transport and FAT/CD36. Am J Physiol 1999;276:E642–E649.
12 Cameron-Smith D, Burke LM, Angus DJ, Tunstall RJ, Cox GR, Bonen A, Hawley JA, Hargreaves M: A short-term, high fat diet up-regulates lipid metabolism and gene expression in human skeletal muscle. Am J Clin Nutr 2003;77:313–318.
13 Turcotte L, Srivastava A, Chiasson J-L: Fasting increases plasma membrane fatty acid-binding protein (FABP) in red skeletal muscle. Mol Cell Biochem 1997;166:153–158.
14 Turcotte L, Swenberger JR, Tucker MZ, Yee AJ: Training-induced elevation in FABP-m is associated with increased palmitate use in contracting muscle. J Appl Physiol 1999;87:285–293.
15 Helge JW, Kiens B: Muscle enzyme activity in humans: Role of substrate availability and training. Am J Physiol 1997;272:R1620–1624.
16 Peters SJ, Amand TA, Howlett RA, Heigenhauser GJF, Spriet LL: Human skeletal muscle pyruvate dehydrogenase kinase activity increases after a low-carbohydrate diet. Am J Physiol 1998;275: E980–E986.
17 Kiens B, Essen-Gustavsson B, Gad P, Lithell H: Lipoprotein lipase activity and intramuscolar triglyceride strores after long-term high fat and high-carbohydrate diets in physically trained men. Clin Physiol 1987;7:1–9.
18 Duplus E, Glorian M, Forest C: Fatty acid regulation of gene transcription. J Biol Chem 2000;275: 30749–30752.
19 Jump DB, Clarke SD: Regulation of gene expression by dietary fat. Annu Rev Nutr 1999;19: 63–90.
20 Torra IP, Chinetti G, Duval C, Fruchart JC, Staels B: Peroxisome proliferator-activated receptors: From transcriptional control to clinical practice. Curr Opin Chem Biol 2001;12:245–254.
21 Motojima K, Passally P, Peters JM, Gonzalez FJ, Latruffe N: Expression of putative fatty acid transporter genes are regulated by peroxisome proliferator-activated receptor alpha and gamma activators in a tissue- and inducer-specific manner. J Biol Chem 1998;273:16710–16714.
22 Way JM, Harrington WW, Brown KK: Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor gamma activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. Endocrinology 2001;142:1269–1277.
23 Vredendaal PJ, van den Berg IE, Stroobants AK, van der A DL, Malingre HE, Berger R: Structural organization of the human short-chain L-3-hydroxyacyl-CoA dehydrogenase gene. Mamm Genome 1998;9:763–768.

24 Nieman DC, Henson DA, McAnulty SR, McAnulty L, Swick NS, Utter AC, Vinci DM, Opiela SJ, Morrow JD: Influence of vitamin C supplementation on oxidative and immune changes following an ultramarathon. J Appl Physiol 2002;92:1970–1977.
25 Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K: Systemic inflammatory response to exhaustive exercise: Cytokine kinetics. Exerc Immunol Rev 2002;8:6–48.
26 Nieman DC, Davis JM, Henson DA, Walberg-Rankin J, Shute M, Dumke CL, Utter AC, Vinci DM, Carson JA, Brown A, Lee WJ, McAnulty SR, McAnulty LS: Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. J Appl Physiol 2003;94:1917–1925.
27 Murray R, Paul GL, Seifent JG, Eddy DE: Responses to varying rates of carbohydrate ingestion during exercise. Med Sci Sports Exerc 1991;23:713–718.
28 Starkie RL, Nielsen B, Pedersen BK, Moller K, Secher NH: Interleukin-6 release from the human brain during prolonged exercise. J Physiol 2002;542:991–995.
29 Steensberg A, Febbraio MA, Osada T, Schierling P, van Hall G, Saltin B, Pedersen BK: Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. J Physiol 2001;537:633–639.
30 Helge JW, Stallknecht B, Pedersen BK, Galbo H, Kiens B, Richter EA: The effect of graded exercise on IL-6 release and glucose uptake in skeletal muscle. J Physiol 2003;546:299–305.
31 Febbraio MA, Pedersen BK: Muscle-derived interleukin-6: Mechanisms for activation and possible biological roles. FASEB J 2002;16:1335–1347.
32 Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK, Neufer PD: Transcriptional activation of IL-6 gene in human contracting skeletal muscle: Influence of muscle glycogen content. FASEB J 2001;15:2748–2750.
33 Brandt JM, Djouadi F, Kelly DP: Fatty acids activate transcription of the muscle carnitine palmitoyltransferase I gene in cardiac myocytes via the peroxisome proliferator-activated receptor alpha. J Biol Chem 1998;273:23786–23792.
34 Varanasi U, Chu R, Huang Q, Castellon R, Yeldandi AV, Reddy JK: Identification of a peroxisome proliferator-responsive element upstream of the human peroxisomal fatty acyl coenzyme A oxidase gene. J Biol Chem 1996;271:2147–2155.
35 Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J: Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. J Biol Chem 1998;272:28210–28217.
36 Rodriguez JC, Gil-Gomez G, Hegardt FG, Haro D: Peroxisome proliferator-activated receptor mediates induction of the mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase gene by fatty acids. J Biol Chem 1994;269:18767–18772.
37 Clarke SD, Thuiller P, Baillie RA, Sha X: Peroxisome proliferator-activated receptors: A family of lipid-activated transcription factors. Am J Clin Nutr 1999;70:566–571.
38 Issemann I, Green S: Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature 1990;347:645–649.
39 Brown MS, Goldenstein JL: The SREBP pathway: Regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 1997;89:331–340.
40 Worgall TS, Sturley SL, Seo T, Osborne TF, Deckelbaum RJ: Polyunsaturated fatty acids decrease expression of promoters with sterol regulatory elements by decreasing levels of mature sterol regulatory element-binding protein. J Biol Chem 1998;273:25537–25540.
41 Mater MK, Thelen AP, Pan DA, Jump DB: Sterol response element-binding protein 1c (SREBP1c) is involved in the polyunsaturated fatty acid suppression of hepatic S14 gene transcription. J Biol Chem 1999;274:32725–32732.
42 Xu J, Nakamura MT, Cho HP, Clarke SD: Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. J Biol Chem 1999;274:23577–23583.
43 De Caterina R, Cybulsky MI, Clinton SK, Gimbrone MA Jr, Libby P: The omega−3 fatty acid docosahexaenoate reduces cytokine-induced expression of pro-atherogenic and pro-inflammatory proteins in human endothelial cells. Arterioscl Thromb 1994;14:1829–1836.
44 De Caterina R, Cybulsky MA, Clinton SK, Gimbrone MA Jr, Libby P: Omega−3 fatty acids and endothelial leukocyte adhesion molecules. Prostagl Leukotr Ess Fatty Acids 1995;52:191–195.

45 De Caterina R, Bernini W, Carluccio M, Liao J, Libby P: Structural requirements for inhibition of cytokine-induced endothelial activation by unsaturated fatty acids. J Lipid Res 1998;39: 1062–1070.
46 Mehrabian M, Wong J, Wang X, Jiang Z, Shi W, Fogelman A, Lusis A: Genetic locus in mice that blocks development of atherosclerosis despite extreme hyperlipidemia. Circ Res 2001;89:125–130.
47 Mehrabian M, Allayee H, Wong J, Shih W, Wang X-P, Shaposhnik Z, Funk CD, Lusis AJ: Identification of 5-lipoxygenase as a major gene contributing to atherosclerosis susceptibility in mice. Circ Res 2002;91:120–126.
48 Dwyer JH, Allayee H, Dwyer KM, Fan J, Wu H, Mar R, Lusis AJ, Mehrabian M: Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med 2004;350:29–37.

Raffaele De Caterina, MD, PhD
Institute of Cardiology, 'G. d'Annunzio' University – Chieti
C/o Ospedale S. Camillo de Lellis, Via Forlanini 50
IT−66100 Chieti (Italy)
Tel. +39 0871 41512, Fax +39 0871 402817, E-Mail rdecater@unich.it

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 120–128

Physical Activity and Hypertension: An Overview

George P. Rontoyannis

Department of Physical Education and Sports Science,
University of Thessaly, Tricala, Greece

Essential hypertension, i.e. a lasting increase in systolic and diastolic blood pressure (BP) >140 and/or >90 mm Hg, respectively, is an increasingly important medical and public health issue, which affects 25–35% of the adult population and up to 60–70% of those beyond the seventh decade of life in developed and developing countries [1]. High BP is a primary risk factor for stroke, congestive heart failure, renal failure and coronary heart disease, at all ages and in both genders. Because of the health risks of hypertension, prevention and treatment is needed to improve patient outcomes. Since genetic factors contribute only about 30% to blood pressure variance, high BP is a proven modifiable risk factor and hypertension is a preventable and treatable disease. This could be accomplished with control of those conditions, causal and risk factors, associated with hypertension [2].

Many conditions have been associated, some more strongly than others, with the presence of hypertension. A number of important and identified conditions are implicated in the development of hypertension. Some of them cannot be controlled, as for example a positive family history of hypertension, sex and race. Others, including body composition, diet, stress, neural-humoral and renal regulation, may be controlled through lifestyle changes or medication in order to prevent progressive rise of blood pressure and reduce cardiovascular and renal morbidity and mortality.

If adoption of healthy lifestyles by all persons is important, in prehypertensive individuals (BP 120–139/80–89 mm Hg) it is critical, and in hypertensive subjects an indispensable part in the management of the disease. In normal and prehypertensive individuals, lifestyle changes alone may lead, through reducing or minimizing causal factors, to primary prevention or delay of the incidence of hypertension, particularly if prevention strategies are applied early in life [3].

In hypertensive subjects, these behavioral modifications enhance antihypertensive drug efficacy and decrease cardiovascular risk [2].

A number of important causal factors for hypertension, the prevalence of which is high, have been identified. Most of them, such as excess body weight, excess of dietary sodium intake, inadequate intake of fruits, vegetables and potassium, and excess of alcohol intake are related with dietary habits. Another important factor is hypoactivity [2], denoting a level of activity less than that needed to maintain health.

During the latter half of the twentieth century, it became quite clear that the level of physical activity of individuals, at least in Western countries urban populations, had declined to a significant degree. At the same time, there is an epidemic of obesity in children and adults, with prevalence rising progressively throughout childhood and into late middle-age [4]. In USA in 1995 at age 12, 70% of children report participation in vigorous physical activity; by age 21 this activity falls to 42% for men and 30% for women. Furthermore, as adults age, their physical activity levels continue to decline and in 1991, 54% of adults reported little or no regular leisure physical activity [5].

In this paper, we will discuss the primary prevention and treatment of hypertension from the perspective of physical activity, a key component in its management. From the different types of physical activities, we will focus on aerobic exercise and walking in particular, because it is almost unanimously recommended, although, it was shown [6,7] that even resistance exercise seems to reduce resting BP by 3–4%.

Aerobic Physical Activity for Primary Prevention of Hypertension

Perhaps endurance athletes, especially those highly trained, represent the best population sample to study relationship of regular aerobic exercise and the control of BP.

Well-trained young adult and master runners (table 1) have been shown to keep their resting BP below 120/80 mm Hg and within the prehypertension range 120–139/80–89 mm Hg, respectively. In a study [8] in 19 highly trained young adult male runners, the resting average BP was 116/78 mm Hg. In another study [9] the effects of continuing training on the aging process were studied in 128 male master runners, aged from 40 to more than 70 years. The typical athlete was 50 years old and had begun serious training about 20 years earlier. Their mean running distance varied from about 42 to 67 km per week. Their average resting BP varied from 120/77 to 140/83 mm Hg and their maximal average BP during effort varied from 185/81 to 199/88 mm Hg. In two isolated and unique case

Table 1. Physiological characteristics of male elite long- and middle- (L-M) distance and well-trained master runners

Subjects	Age, years	BMI	Fatness, %	Training, km/week	Resting BP, mm Hg
19 elite L-M distance runners [8]	26.2	21.1	3.6	–	116/78
128 male master runners [9]	40–75+	22.1–23	–	40–67	120–140/77–83
1 elite master runner [10]	77	21.9	13.5	–	120/70
1 elite master runner [11]	79	21.8	10.5	35	132/80

studies [10,11], excellent master and regularly trained runners, resting BP of the first one, aged 77 years, was 120/70 mm Hg and of the second, aged 79 years, was 132/80 mm Hg. The second runner used to run from the age of 20 and then, almost without interruption, 35 km with a steady pace, three times per week.

In another study [12], involving young and middle-aged runners, a 6 mm Hg lower systolic and diastolic BP than the age-matched sedentary controls was reported.

Master athletes have much better aerobic power, better stroke volume, and greater peripheral vasodilatory responses compared to their sedentary peers.

Due to regular aerobic training, started relatively early in their life, and conducted for several years or even for decades, some of the main characteristics of these athletes are: the normal BP, the relatively low BMI (range from 21.1 to 23 kg/m^2), the low or very low body fatness (range 3.6–13.5%), and the exceptionally high aerobic power.

In the question whether aerobic exercise can prevent hypertension from developing in normotensive, but not involved in regular physical activity, individuals of both genders and different ages, the findings of three major epidemiological studies [13–15] support this theory. The main conclusions are: (a) that the most active men had significantly lower mean BP than their sedentary peers, and (b) that exercise is inversely associated with the risk of developing hypertension. On the other hand, physical inactivity and low fitness level are associated with higher blood pressure levels and increased incidence of hypertension in a population [16].

In a longitudinal study [13], nearly 15,000 male college alumni have been followed for 6–10 years. Those, who expended less than 2,000 kcal/week in sports, walking, and stair-climbing had one-third greater risk of becoming hypertensive than the others. In another [14] involving 6,000 normotensive men and women, aged 20–65 at entry, it was reported that those with the lower fitness level were 50% more likely to develop hypertension over the following 1–12 years than those with higher fitness. In a third one [17], in nearly 42,000

women aged 55–69, risk reductions of 30% and 10% were found in those who participated in physical activity at high and moderate levels, respectively, over a 2-year period.

Reduced resting BP in 800 normotensive subjects, following an aerobic exercise program, was found in a review of 35 studies, but not in 276 control subjects [18]. A meta-analysis [19], in which the experience of 1,108 normotensive persons, enrolled in 27 randomized controlled trials was included, identified a reduction in systolic BP in those assigned to aerobic exercise compared with the control group.

The average reduction of resting systolic BP (SBP) is expected to be ~3–4 mm Hg [19–21] and ~3 mm Hg of diastolic (DBP), in those engaged in aerobic exercise program, even few weeks after initiation of training. The magnitude of the intervention effect appears to be independent of the intensity of the exercise [21]. This reduction of resting BP represents the long effect of training. However, the immediate effect of an aerobic exercise session on resting BP in normotensive men is a reduction of both SBP and DBP by 8–12 mm Hg that lasts for 20–120 min [22, 23].

Regarding walking, interesting information is provided by two studies. In a study [21] in normotensive men and women, aged 22–59 years, normal walking, reaching 50% VO_2max, for 1 h, 5 days a week, for 4 weeks, lowered systolic BP by 2–3 mm Hg, compared with a period of sedentary living. In another, a prospective study [24], 6,017 normotensive men 35–60 years have been observed for 6–16 years and the relation of walking to work to the risk of hypertension was investigated. The relative risk for hypertension was 0.71 in men whose walk to work lasted 21 min or more, compared with those whose walk to work lasted 10 min or less.

Walking, although exclusively recommended [3] for primary prevention and treatment of hypertension, is seldom specified when exercise is being studied for lowering BP [25], though the human machine seems to be designed and has evolved biologically to perform daily periods of continuous submaximal (aerobic) physical activity, mainly walking [26]. At least 30 min of brisk (5–6 km/h) walking on most, if not all, the days of the week is recommended [3], together with other dietary lifestyle modifications [2, 3].

The above-mentioned results of aerobic training on BP control in athletes and the reduction, though small, of SBP and DBP in normotensive non-athletes, suggest that regular physical activity can help to keep BP within normal levels and lower the incidence of hypertension, even for life, particularly in those in which this lifestyle habit is adopted early in life and was not discontinued. Although aerobic training helps to keep the body mass index (18.5–24.9 kg/m^2) and the body fatness low, which are considered important health risks, prevention of hypertension is, however, independent of changes in

body weight. The BP-lowering effect depends on the initial BP but not on body mass index [27].

Aerobic Physical Activity for Management of Hypertension

Most hypertensive patients have additional cardiovascular risk factors because of increased BP clusters with hyperlipidemia, diabetes, and obesity, each intensifying the risk of hypertension. Treatment should consider the total risk burden. An evaluation of all factors, particularly those involved in the pathogenesis of hypertension, e.g. obesity, excessive sodium intake, stress and inactivity, and an assessment of each patient is needed before deciding upon the need for therapy and the therapy to be given [28]. Exercise and diet often improve multiple risk factors with virtually no side effects and combined or not with pharmacologic treatment can greatly reduce mortality.

According to the JNC 7-Complete Report [2], the ultimate goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Hypertensive patients should begin with lifestyle modifications and if the goal is not achieved pharmaceutical treatment should be used. Treating SBP and DBP to targets that are lower than 140/90 mm Hg is associated with a decrease in cardiovascular complications. In patients with hypertension and diabetes or renal disease, the targeted BP goal is below 130/80 mm Hg.

Review of hypertension and exercise research has indicated that both acute and chronic exercise is effective in the reduction of BP [29].

In mildly hypertensive subjects, short-term aerobic activity decreased BP for 8–10 h after exercise, and average BP was lower on exercise than on non-exercise days [30].

In patients with stage 1 and 2 hypertension, the average reduction in SBP and DBP as a result of long-term effect of moderate-intensity aerobic training is ~10 and ~8 mm Hg, respectively [31, 32]. But even if, as a result of aerobic training, a much smaller reduction of BP is achieved, a dramatic reduction of death incidence from cardiovascular disease will be expected.

The reduction of BP with aerobic training does not appear to be gender-, age-specific [23] or even intensity-specific [32], at least for intensities corresponding between ~40 and ~80% of maximal aerobic power [33]. However, the exercise training program for optimal benefits should consist of 3–5 times per week, 30–60 min per session, at 50–80% of maximum predicted heart rate [31].

In patients with severe hypertension, moderate aerobic training resulted in a decrease in diastolic BP, which was sustained even after reduction in antihypertensive medications [34].

Although the benefits of moderate aerobic training on SBP and DBP control are evident even when total aerobic training lasts only 61–90 and 30–60 min per week, respectively [35]; however, such amount of training may not be sufficient to control other causal factors, as for example excessive body weight and fatness in hypertensives. The exercise program for overweight or obese hypertensives should aim to promote a caloric expenditure of 300–500 kcal per day. Such an approach, combined with a prudent diet, is likely to reduce body weight [31].

Exercise programs should be individualized to meet the patient's needs and abilities. Exercise intensity and duration should be manipulated to promote a safe and effective antihypertention program. Initially, the exercise intensity should be low and the duration short. Both intensity and duration should progressively increase over a period of weeks until the desired goal is achieved. The rate of progression must be tailored to meet the patient's needs and abilities [31].

Regarding the very prolonged (2 years) effects of (mainly) walking in BP control, a much larger reduction in BP at 6 months than at 2 years was reported [36]. Poor adherence of participants in the intervention program was the most likely explanation. Adherence to the intervention program seems to be an essential element for success in achieving and maintain the maximum effect of exercise training in the BP control [19]. As a possible solution to this important problem, as a prerequisite we would suggest that an exercise-dependence state should first be achieved by normotensive and hypertensive individuals in order to remain in an aerobic training program.

A similar exercise-dependence condition is experienced by long-distance runners. Perhaps this explains why they continue running for many years or even for life. In the previous Conference in 2000, we presented [37] the case study (table 2) of an elderly male patient with coronary artery disease and hypertension who developed an exercise-dependence state soon after his walking distance exceeded 8 km per day. Then, the walking dependency was evident by the fact that he doubled his daily walking distance without any further encouragement. Today he is 80 years old and without any interruption he still is in the program for 17 years already. Long-distance brisk walking evolved into a really pleasant and wishful activity for him. Interestingly enough, this extraordinary every day physical activity, combined with appropriate diet, resulted in an excellent management of his coronary artery disease but not of hypertension. In this case, failure to handle hypertension indicates the limitations of lifestyle changes in the management of the disease, at least in elderly patients.

The possible activated mechanisms of the aerobic exercise on BP control are not quite certain; perhaps because hypertension is a heterogeneous disorder, the causes of which are still uncertain [1]. According to Fagard [27] 'the results on hemodynamic changes in response to dynamic training are conflicting; some authors claim that the lowering of blood pressure is based on a reduction of

Table 2. Main physiological characteristics of a male coronary artery disease patient (N.C.), before starting a walking training program (1987) and during a 10-year follow-up: an exercise-dependence state was experienced, when daily walking distance was about 8 km

Subject N.C.	Age		
	63 years (1987)	66 years (1990)	73 years (1997)
Walking distance, km	~1	~8	~10
Walking pace	Slow	easy	brisk
Walking energy expenditure, kcal			379
BMI	27.3		23.6
Body fatness, %			13.6
SBP/DBP, mm Hg	160/90	170/90	160/90

systemic vascular resistance whereas others observed a decrease of cardiac output. Most studies found a decrease of plasma noradrenaline concentrations suggesting a reduction in autonomic nervous activity. Other possible blood pressure-lowering mechanisms have been addressed only rarely in randomized controlled exercise trials.' The same author suggested [27] on this issue that 'future studies should focus on mechanisms involved in blood pressure regulation such as the renin-angiotensin-aldosterone system, prostagladins, endothelial relaxing factor and endothelin, the sympathetic nervous system, insulin sensitivity and finally, genetic polymorphisms that might influence the blood pressure response to physical training'.

Conclusions

Regular aerobic physical activity, mainly walking, is a key component in the prevention and treatment of hypertension.

Exercise training can be expected to decrease SBP/DBP: ~3/3 mm Hg in normotensives, ~6/7 mm Hg in prehypertensives, and ~10/8 mm Hg in hypertensives.

Perhaps the best population samples to study the relationship of aerobic training and the control of blood pressure are those of highly trained athletes and the master endurance athletes.

At least 30 min of brisk walking a day is recommended, but it is doubtful if a minimum walking dose is adequate to control other cardiovascular risk factors.

Exercise may be combined with dietary changes, when needed, to keep blood pressure within the normal level in normotensive individuals and to manage hypertension as well.

Possible activated mechanisms with aerobic training on blood pressure control are still uncertain, and an exercise-dependence state may be a prerequisite for individuals to remain in an exercise program for a long period.

References

1 Staessen JA, Wang J, Bianvhi G, Birkenhaeger WH: Essential hypertension. Lancet 2003;361: 1629–1640.
2 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252.
3 Whelton PK, He J, Appel LJ, Cutler JA, Havas S, et al: Primary prevention of hypertension. Clinical and Public Health Advisory from the National High Blood Pressure Education Program. JAMA 2002;288:1882–1888.
4 Macnair AL: Is inactivity the origin of essential hypertension: Should we all be runners? Nephron Dial Transplant 2000;15:1751–1754.
5 NIH Consensus Statement on Physical Activity and Cardiovascular Health. National Institutes of Health, 1995, vol 13, #3.
6 Kelley G: Dynamic resistance exercise and resting blood pressure in adults: A meta-analysis. J Appl Physiol 1997;82:1559–1565.
7 Kelley GA, Kelley KS: Progressive resistance exercise and resting blood pressure. Hypertension 2000;35:838–843.
8 Pollock ML: Submaximal and maximal working capacity of elite distance runners. 1. Cardiorespiratory aspects. The marathon: Physiological, medical, epidemiological, and psychological studies. Ann NY Acad Sci 1977;31:322.
9 Kavanagh T: The effects of continued training on the aging process. The marathon: physiological, medical, epidemiological and psychological studies. Ann NY Acad Sci 1977;31:656–670.
10 Webb JL, Urner SC, McDaniels J: Physiological characteristics of a champion runner: Age 77. J Gerontol 1977;3:286–290.
11 Rontoyannis GP: Sixty-three years of competitive sport activity. Case study. J Sports Med Phys Fitness 1992;32:332–339.
12 Hagberg JM, Allen WK, Seals DR, et al: A hemodynamic comparison of young and older endurance athletes during exercise, J Appl Physiol 1985;58:2041–2046.
13 Paffenbarger RS Jr, Wing AL, Hyde RT, et al: Physical activity and incidence of hypertension in college alumni. Am J Epidemiol 1983;117:245–257.
14 Blair SN, Goodyear NN, Gibbons LW, Cooper KH: Physical fitness and incidence of hypertension in healthy normotensive men and women. JAMA 1984;252:487–490.
15 Paffenbarger RS, Jung OL, Leung RW, Hyde RT: Physical activity and hypertension: An epidemiological view. Ann Med 1991;23:319–327.
16 Fagard RH: Physical activity, fitness and blood pressure; in Bulpitt CJ(ed): Handbook of Hypertension. Epidemiology of Hypertension. Amsterdam, Elsevier Science BV, 2000, vol 20, pp 191–211.
17 Folsom AR, Prineas RJ, Kaye SA, et al: Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. Stroke 1990;71:701–706.
18 Kelley G, Tran ZV: Aerobic exercise and normotensive adults: A meta-analysis. Med Sci Sports Exerc 1995;27:1371–1377.
19 Whelton SP, Chin A, Xin X, He J: Effect of aerobic exercise on blood pressure: A meta-analysis of randomized control trials. Ann Intern Med 2002;136:493–503.
20 Fagard RH, Tipton CM: Physical Activity, Fitness and Health. Champaign, Human Kinetics Publishers, 1994, pp 633–668.
21 Kingwell BA, Jennings GL: Effects of walking and other exercise programs upon blood pressure in normal subjects. Med J Austr 1993;158:234–238.

22 Boone JB, Levine M, Flynn MG, et al: Opioid receptors modulation of postexercise hypotension. Med Sci Sports Exerc 1992;24:1108–1113.
23 Brown SP, Li H, Chitwood LF, Anderson EP, Boatwright D: Blood pressure hemodynamics and thermal responses after cycling exercise. J Appl Physiol 1993;75:240–245.
24 Hayashi T, Tsumura K, Suematsu C, Okada K, Fujii S, Endo G: Walking to work and risk for hypertension in men: The Osaka Health Survey. Ann Intern Med 1999;131:21–26.
25 Morris JN, Harmann AE: Walking to health. Sports Med 1997;23:306–332.
26 Rontoyannis GP: Diet and Exercise in the Prevention of Cardiovascular Disease. World Rev Nutr Diet. Basel, Karger, 1993, 72, pp 9–22.
27 Fagard RH: Physical activity in the prevention and treatment of hypertension in the obese. Med Sci Sports Exerc 1999;39:S624–S630.
28 Kaplan NM: Management of hypertensive patients with multiple cardiovascular risk factors. Am J Hypertens 2001;14:221S–224S.
29 Tipton CM: Exercise training and hypertension: An update; in Holloczy J (ed): Exercise and Sport Science Reviews. Baltimore, Williams & Wilkins, 1991, pp 447–506.
30 Pescatello LS, Fargo AE, Leach CN, Scherzer HH: Short-term effect of dynamic exercise on arterial blood pressure. Circulation 1991;83:1557–1561.
31 Kokkinos PF, Narayan P, Papademetriou V: Exercise as hypertension therapy. Cardiol Clin 2001;19:507–516.
32 Iwane M, Arita M, Tomimoto S, Satani O, Matsumoto M, Miyashita K, Nishio I: Walking 10,000 steps/day or more reduces blood pressure and sympathetic nerve activity in mild essential hypertension. Hypertens Res 2000;23:573–588.
33 Fagard RH: Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc 2991;33(suppl):S484–S492.
34 Kokkinos PF, Narayan P, Colleran JA, Pittaras A, Notargiacomo A, Reda D, Papademetriou V: Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. N Engl J Med 1995;333:1462–1467.
35 Ishikawa-Tanaka K, Toshiki O, Tanaka H: How much exercise is required to reduce blood pressure in essential hypertensives: A dose-response study. Am J Hypertens 2003;16:629–633.
36 Wing RR, Venditi E, Jakicic JM: Lifestyle intervention in overweight individuals with a family history of diabetes. Diabetes Care 1998;21:350–359.
37 Rontoyannis GP: Effectiveness of walking in handling patients with cardiovascular disease and/or metabolic disease. Unpublished oral presentation at the 4th International Symposium on Nutrition and Fitness, Ancient Olympia, Greece,. May 25–29, 2000.

George P. Rontoyannis, MD, Professor of Sports Medicine
Department of Physical Education and Sports Science
University of Thessaly,
Karies 42 100, Tricala (Greece)
Tel. +30 24310 47047, Fax +30 24310 47042, E-Mail grontog@pe.uth.gr

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 129–138

Omega–3 Fatty Acids and Ventricular Arrhythmias

Alexander Leaf [a,c], *Jing X. Kang* [a], *Yong-Fu Xiao* [b]

Departments of Medicine, [a] Massachusetts General Hospital and [b] Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass., USA

The first investigators to demonstrate the antiarrhythmic effects of ω–3 fish oil fatty acids were two Australians, Peter McLennan and John Charnock. In the late 1980s they were publishing their simple and clear experiments. They subjected young rats to a diet in which they could control the major fat component for a period of 3 or 4 months. Then they simply ligated the coronary arteries of the rats and counted the numbers of rats, which died of irreversible ventricular fibrillation (VF). When the rats were fed a diet in which the major fat component was saturated fatty acids, an arrhythmic mortality of over 40% was observed. When the dietary fat was olive oil (a monounsaturated fatty acid) there was no significant change in mortality from VF. A diet of plant seed oil, safflower seed, reduced the mortality by a significant 70%, but when the fat was tuna fish oil no arrhythmic deaths occurred [1].

Since there are very few things in medicine reported to be such an effective treatment, we wanted to see whether we could confirm these findings. But first let me digress briefly to describe the polyunsaturated fatty acids to which we will be referring. Polyunsaturated fatty acids are essential in at least two ways: First, they are essential since we cannot make them in our bodies, but must get them from our diets. Second, they are absolutely essential for optimal development and function of brain and heart. They come in our diet in two forms. The most prevalent today are plant seed oils of which the parent compound is linoleic acid, an 18-carbon fatty acid with two C = C double bonds. Since it is 6 carbon atoms back from the methyl end of the fatty acid before the first double bond is encountered this is an ω–6 fatty acid. This 18-carbon linoleic acid can be further elongated and desaturated in our bodies to a 20-carbon fatty acid with 4 double bonds, the familiar arachidonic acid, which we know as the precursor of prostaglandins, leukotrienes, lipoxins and epoxinginase products,

many of which are potent cell messengers. But in the chloroplasts of green leaves and in the phytoplankton in the ocean, linoleic acid can be further desaturated to the α-linolenic acid, an 18-carbon fatty acids but with 3 C = C double bonds, which is the parent compound of the ω–3 class of polyunsaturated fatty acids. This is because only 3 carbons back from the methyl end that the first double bond is encountered making this the ω–3 class of polyunsaturated fatty acids. In our bodies and in that of fish this α-linolenic acid can be further elongated and desaturated to EPA (eicosapentaenoic acid, C20:5ω–3) and to DHA (docosahexaenoic acid, C22:6ω–3), the most unsaturated fatty acid normally encountered in our diet and the storage form of ω–3 fatty acids in heart and brain. The EPA and DHA are the two physiologically active compounds in fish oil, we will show you. Like arachidonic acid, EPA is converted by the same enzymes to form another series of important products, which also serve as cell messengers, but often with opposing effects from the products from arachidonic acid.

To return to our interests in seeing if we could confirm the findings of Charnock and McLennan, we turned to Prof. George E. Billman at the Ohio State University Department of Physiology since he had a highly reliable dog model of sudden cardiac death. Dr. Billman operates on a dog tying off the left main anterior descending coronary artery to create a large anterior ventricular infarct. At the same operation, he leaves a hydraulic cuff around the left circumflex coronary artery and exteriorizes this so that he can occlude this artery later at will. During the month he allows the dog to recover from the MI and surgery he trains it to run on a treadmill.

Figure 1 shows one of our early experiments [2]. Because the dog is running on the treadmill, its pulse rate is rapid. When he occludes the left circumflex coronary artery, within 2 min a ventricular flutter occurs which deteriorates into VF. As soon as the dog loses consciousness, it is defibrillated. The same dog is brought back into the laboratory 1 week later and the same protocol is repeated except that just before the left circumflex coronary is occluded a phospholipid emulsion containing free ω–3 fish oil fatty acids was infused intravenously. Now when the left circumflex coronary artery was occluded, you see that no arrhythmia occurred. After 1 week a second control experiment was performed. This time an infusion of an emulsion of soybean oil, which contains no free ω–3 fatty acids, was infused and within 2 min the dog developed ventricular fibrillation.

Table 1 summarizes our dog experiments. 10 of the 13 dogs tested with the fish oil emulsion were protected from VF ($p < 0.005$). With these results I felt that the experiments in rats by McLennan and Charnock were confirmed though we infused the fish oil fatty acids and they did feeding experiments. Since there are many constituents in fish oil, we wanted to find which one or

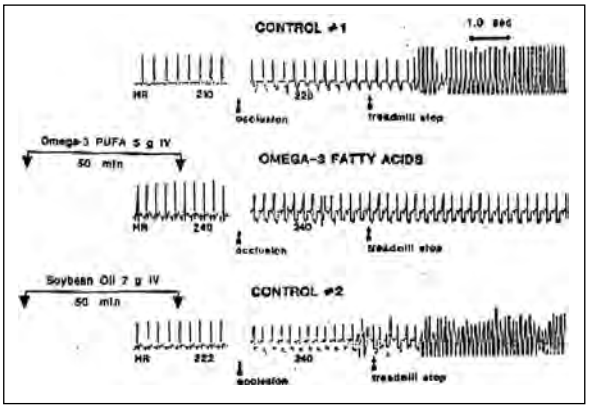


Fig. 1. Prevention of ischemia-induced sudden cardiac death in a prepared dog by intravenous omega–3 PUFA.

Table 1. Prevention of ischemia-induced fatal ventricular arrhythmias by ω–3 fatty acids in a dog model of sudden cardiac death

ω–3 PUFAs	Number of dogs tested		p value
	Total	Protected	
Fish oil concentrate[1]	13	10	<0.005
EPA[2]	7	5	<0.02
DHA[3]	8	6	<0.004
α-LNA[4]	8	6	<0.004

[1]72% ω–3 PUFA with free EPA, 33.9% and DHA 25% (Pronova Biocare a.s. Lysaker, Norway; EPAX 6000FA).
[2]98.4% free EPA; 1.1% free DHA (Pronova Biocare).
[3]90.8% free DHA; 0.9% free EPA (Pronova Biocare).
[4]>99% free α-linolenic acid (Nu-Check-Prep, Elysion, Minn., USA).

more molecules might account for the protection. So we infused pure EPA and pure DHA, each alone, and each proved to provide significant protection [3].

By this time we realized that the fish oil fatty acids must be modifying the electrical currents in the heart, since arrhythmias are uncontrolled electrical events generated in the ion channels of the sarcolemma. So we started to determine the electrophysiology of the fast voltage-dependent Na^+ current which

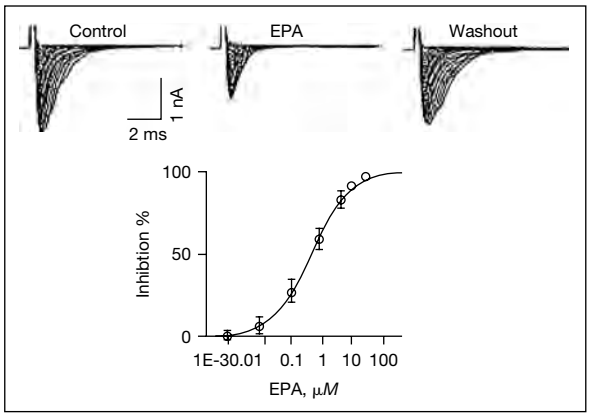


Fig. 2. Inhibition of I_{Na} of human cardiac Na^+ channel α-subunit expressed in human embryonic kidney cells in the absence and presence of EPA (5 μ*M*).

initiates action potentials in cardiomyocytes [4]. Figure 2 shows that the Na^+ current in human myocardial ion channels are inhibited by 5 μ*M* EPA [5]. This is a very potent action of the ω–3 fatty acids as seen in the current-concentration relationship shown in the lower part of figure 2. There it can be seen that at some 10–20 n*M* concentration of EPA, there is already a significant inhibition of the Na^+ current.

How does this action of the ω–3 fish oil fatty acids prevent the fatal ischemia-induced arrhythmias you saw in the dog experiments? Unfortunately, the scope of this brief essay does not permit me to show you the details of the electrophysiology involved in the protective action of the ω–3 fatty acids on fatal arrhythmias [6].

With a MI heart cells in the central core of the ischemic tissue rapidly depolarize and die. The cells at the periphery of the ischemic tissue in juxtaposition with the remaining normally perfused myocardium do not die; however, they become partially depolarized. These partially depolarized cells are the mischief-makers, which initiate fatal arrhythmias [6]. Their resting membrane potentials instead of being –90 mV, as in healthy heart cells, may now be –75 or –70 mV. Thus, their resting membrane potentials are close to the threshold for the gating (opening) of the fast inward sodium current and positive Na^+ rushes into the cells depolarizing the cells and initiating an aberrant action potential. If this occurs at a vulnerable moment in the electrical cycle of the heart it may induce an arrhythmia, especially in the presence of nonhomogeneous conduction of action potentials through the ischemic myocardial tissue, this is likely to be a reentrant fatal VF. But the ω–3 fish oil fatty acids by shifting the steady

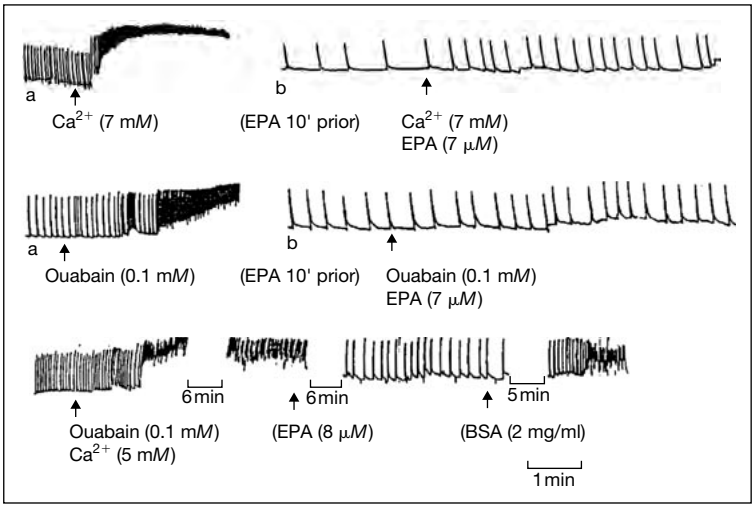


Fig. 3. Prevention of arrhythmias in cultured neonatal rat cardiomyocytes by ω–3 fatty acids.

state inactivation far to the left as they inhibit the Na^+ current will eliminate from function these partially depolarized myocytes, thus preventing the ischemia-induced fatal ventricular arrhythmias [6].

Not all fatal arrhythmias are due, however, to dysfunction of Na^+ currents. To pursue further possible causes of fatal ventricular arrhythmias, we turned to studies with cultured neonatal rat heart cells [7]. This proved to be a fine preparation of heart cells with which to observe the function of heart cells in vitro and their responses to known cardiac toxins. It is easy to remove the hearts quickly from 1-day-old rat pups and to separate the individual cardiac myocytes enzymatically suspending them in a culture medium. This suspension of heart cells may then be plated directly on a microscope coverslip. By the second day in culture, the cells have become adherent to the microscope cover slip and under the microscope they are a pretty sight. There will be several individual clumps of cells in a field. Each clump is beating spontaneously, rhythmically and simultaneously, mimicking in vitro their behavior in the intact heart. We built an edge-monitor so that we could observe and record the beating of a single cell in a clump of cells. Figure 3 shows heart cells beating fairly regularly and the amplitude of each contraction. We decided to test all the cardiac toxins we knew – some 12 – which produce fatal arrhythmias in humans and observe their effects on the function of these isolated heart cells and then the response of their function to the ω–3 fatty acids. In figure 3, we show the results of our tests with two such cardiac toxins: elevated serum Ca^{2+} concentration and the cardiac

glycoside, ouabain. When we suddenly increased the concentration of Ca^{2+} from its normal serum concentration to the high concentration in the medium perfusing the cells, you see the cells go into contracture and the beating rate was greatly accelerated. The myocytes cannot relax in diastole because of the high $[Ca^{2+}]_i$ concentration and when we looked at cells we found that rather than beating regularly, the cells were beating arrhythmically, actually fibrillating in vitro. But if we first exposed the cells to the fatty acid, EPA or DHA, their beating rate slowed down and then when we increased the Ca^{2+} concentration to 7 m*M*, no arrhythmias occurred. In the next lower line you see exactly the same responses of the cells to the cardiac glycoside ouabain, which is known to cause fatal ventricular fibrillation in animals and humans by elevating the cytosolic free Ca^{2+} excessively. In the last line, my colleague added both high Ca^{2+} and toxic ouabain to the superfusate bathing cells on a coverslip, on which cells were beating regularly. This induced a violent fibrillation. When EPA was added to the perfusate, in a short time the arrhythmias was terminated and cells returned to a fairly regular beating pattern. Delipidated bovine serum albumin was then added to the perfusate. Albumin contains 3 binding sites for fatty acids with such high binding affinity that they can extract the fatty acids from the heart cells and you see that still in the presence of the high Ca^{2+} concentration and ouabain the arrhythmia resumed. This simple experiment taught us two important facts. First, the fact that we could withdraw the free ω–3 fatty acids from the heart cells and the arrhythmia returned indicated that the fatty acids had not bonded covalently or by strong ionic binding to any constituent within the heart cell membrane or we would not have been able to withdraw the fatty acid with the delipidated albumin. Apparently all the fatty acid need do is to partition, or dissolve in the hospitable hydrophobic environment provided by the hydrophobic acyl chains of the long fatty acids within the phospholipid bilayer of the heart cells' plasma membranes, to confer their antiarrhythmic action on the heart cells. Second, only the free ω–3 fatty acids with their negatively charged carboxyl group at one end are antiarrhythmic. When we added the ethyl ester of the fatty acid to our preparation it had no acute antiarrhythmic effect [7].

The reason that the ω–3 fatty acids prevented these arrhythmias is that we have found that they inhibit the L-type inward Ca^{2+} currents [8]. This is shown in figure 4. By inhibiting the entry of Ca^{2+} through the L-type calcium channels in the heart the ω–3 fatty acids prevent the overload of free Ca^{2+} in the cytosol of the heart cell and thereby prevent these arrhythmias.

Although we have found that these fatty acids affect conductance of other ion channels in the heart cell plasma membranes, at the present we think it is their effects on the fast voltage-dependent Na^+ channels and the L-type Ca^{2+} channels, which are the channels primarily responsible for the antiarrhythmic effects of these fish oil fatty acids.

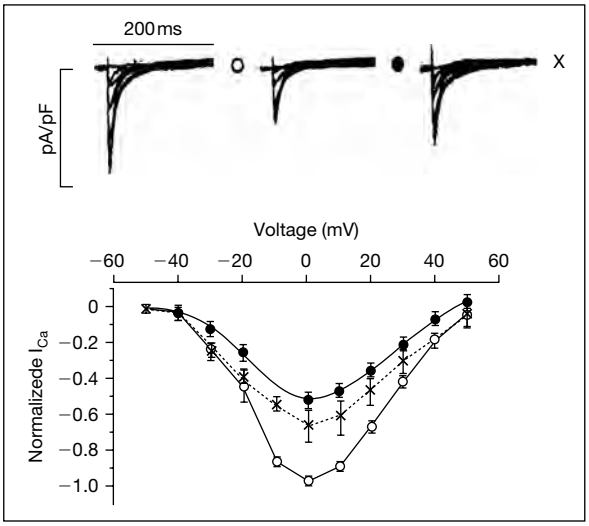


Fig. 4. Inhibition of $I_{Ca,L}$ of adult rat cardiomyocyte by EPA (1.5 μ*M*).

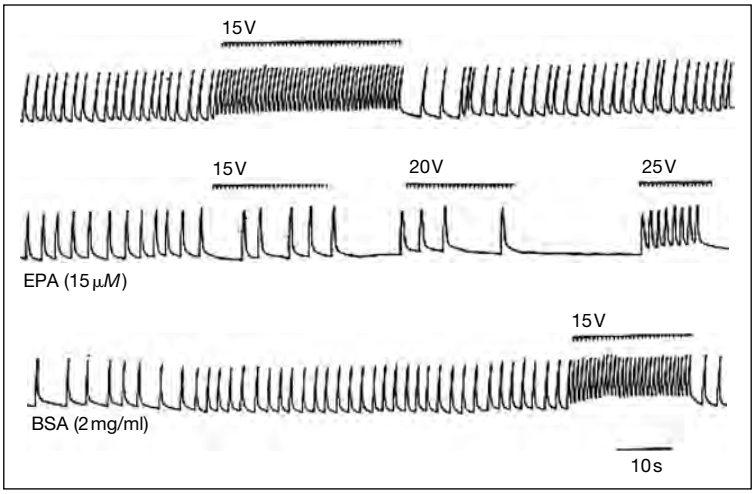


Fig. 5. Electrical stabilization of neonatal cardiomyocyte by ω–3 fatty acids.

In order to convince ourselves that effect of these actions on heart cells were stabilizing electrically the heart cells making them resistant to developing arrhythmias, we did a simple experiment illustrated in figure 5 [9]. With a coverslip on which clumps of neonatal cardiac myocytes are seen to be contracting

quite regularly, two platinum electrodes connected to an external voltage source were placed across the coverslip and dipped into the medium perfusing the cells so that we could stimulate the cells with external electric currents at will. You see in the top line that it was easy to increase the beating rate 2- to 3-fold with stimuli from an external voltage source of 15 V. When the external field was turned off the beating rate returned to the control rate. The second line, shows the same coverslip and cells. When EPA was added to the perfusion fluid the beating rate began to slow down and now the cells paid no attention to stimuli delivered at 15 V or 20 V. At 25 V the heart cells began to respond to the external stimuli, but only to every other stimulus. In the third line, still the same cells, delipidated bovine serum albumin was added to the perfusion fluid and extracted the EPA from the heart cells. The beating rate returned to the control and now the cells responded as they had initially to stimuli delivered at 15 V. When one considers that this is a direct effect of the ω–3 fatty acids on every individual myocyte in the heart in the absence of any neural or hormonal control of the beating rate of the cells, one can sense what a potent potential antiarrhythmic effect these ω–3 fish oil polyunsaturated fatty acids can exert on the heart. Saturated or unsaturated fatty acids lack these effects on the heart.

Evidence of Antiarrythmic Effects of ω–3 Fish Oil Fatty Acids in Humans

While we were doing these experiments to try to determine the mechanism of the antiarrhythmic effects demonstrated in animals, there were at least two important clinical trials and many epidemiologic studies performed. The first study was by Burr et al. [10] in the UK reported in 1989, who simply advised 1,015 men who had just had a MI to eat fish, oily fish at least twice weekly compared with a matched cohort not given such advice. At the end of 2 years, there was a 29% reduction in all causes of death due to reduced ischemic heart disease deaths in those advised to eat fish. There was no reduction in nonfatal MIs in those given fish advice compared with those not given such advice. This study was done before the antiarrhythmic actions of the fish oils were generally recognized. Today this study is interpreted as a reduction in mortality from fatal arrhythmias, since there were fewer deaths among those advised to eat fish than among those not so advised, despite the higher incidence of nonfatal MIs among those advised to eat fish.

Another larger study was reported in 1999, the GSSI-Prevenzione [11]. In this study 5,666 men who had just had an MI were randomized to one capsule daily containing 850 mg fEPA plus DHA in addition to a healthy diet and currently recommended antiarrhythmic therapy compared with a matched control

cohort of 2,828 men. At the end of 3.5 years those receiving the fish oil supplement had a significant reduction in all causes of mortality due to a reduction in cardiovascular deaths. These beneficial effects were found surprisingly to result largely from an unexpected 45% reduction in sudden cardiac deaths, which was not a stated primary end point of the study.

Because none of these better studies had been designed with the primary stated endpoint to be prevention of sudden cardiac death, we undertook a further clinical trial, which was started 4 years ago. The aim of this study was to learn in a group of 402 patients with implanted cardioverter defibrillators (ICDs) for a prior episode of cardiac arrest and, therefore, they were at very high risk for fatal ventricular arrhythmias, would be protected from such arrhythmias by a daily supplement of fish oil versus an olive oil placebo for a study period of 12 months. Despite the unfortunate discontinuation of their prescribed oil supplement before completion of 12 months in the study by 42% of enrollees, the statistical analysis revealed a definite reduction in the time to the first arrhythmic event in the subjects receiving the fish oil supplement compared with those receiving the olive oil supplement.

This study supports the current advice of the American Heart Association that every one, young and old, should be eating at least one meal weekly of oily fish to maintain a healthy heart. For those who have experienced symptoms of coronary heart disease, arrhythmias or those with a family history of coronary heart disease a supplement of fish oil containing 1,000 mg of EPA plus DHA should be ingested daily.

Finally, the potential public health benefit of what we have shown is very considerable, because today there is 300,000–400,000 sudden cardiac deaths annually in the United States alone and millions more world wide. Furthermore, none of the antiarrhythmic drugs produced by the pharmaceutical industry, despite expenditure of hundreds of millions of dollars, is both effective and safe. Whereas the fish oil fatty acids have been part of the human diet for hundreds of thousand of years and they are safe. As shown here they also are effective antiarrhythmic agents, as effective as any produced by the pharmaceutical industry. Thus, at the present time fish oil is the best available treatment to prevent fatal ventricular arrhythmias. If further studies confirm what we have shown, then fish oil fatty acids should be recognized and advised by all cardiologists and physicians as the optimal current prevention for the risk of sudden cardiac death.

Acknowledgements

Experiments reported herein have been supported in part research grants DK38165 from NIDDK, by HL 62284 and HL62154 from NHLBI of the National Institutes of Health of the US Public Health Services.

References

1 McLennon PL: Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. Am J Clin Nutr 1993;57:207–212.

2 Billman GE, Hallaq H, Leaf A: Prevention of ischemia-induced fatal ventricular arrhythmias by ω6 fatty acids. Proc Natl Acad Sci USA 1994;91:4427–4430.

3 Billman GE, Kang JX, Leaf A: Prevention of sudden cardiac death by dietary pure omega–3 polyunsaturated fatty acids in dogs. Circulation 1999;99:2452–2457.

4 Xiao Y-F, Kang JX, Morgan JP, Leaf A: Blocking effects of polyunsaturated fatty acids on Na^+ channels of neonatal rat ventricular myocytes. Proc Natl Acad Sci USA 1995;92:11000–11004.

5 Xiao Y-F, Wright SN, Wang GK, Morgan JP, Leaf A: Fatty acids suppress voltage-gated Na^+ currents in HEK293t cells transfected with the α-subunit of the human cardiac Na^+ channel. Proc Natl Acad Sci USA 1998;95:2680–2685.

6 Xiao Y-F, Wright SN, Wang GK, Morgan JP, Leaf A: Coexpression with β1-subunit modifies the kinetics and fatty acid block hH1α Na^+ channels. Am J Physiol Heart Circ Physiol 2000;279: H35–H46.

7 Kang JX, Leaf A: Effects of long-chain polyunsaturated fatty acids on the contraction of neonatal rat cardiac myocytes. Proc Natl Acad Sci USA 1994;91:9886–9890.

8 Xiao Y-F, Gomez AM, Morgan JP, Lederer WJ, Leaf A: Suppression of voltage-gated L-type Ca^{2+} currents by polyunsaturated fatty acids in adult and neonatal rat ventricular myocytes. Proc Natl Acad Sci USA 1997;94:4182–4287.

9 Kang JX, Leaf A: Protective effects of free polyunsaturated fatty acids on arrhythmias induced by lysophosphatidylcholine or palmitoylcarnitine in neonatal rat cardiac myocytes. Eur J Pharmacol 1996;297:97–106.

10 Burr M, Gilbert JF, Holliday RM, Elwood PC, Fehily AM, Rogers S, Sweetnam PM, Deadman MN: Effect of changes in fat, fish and fibre intakes on death and myocardial infarction: Diet and reinfarction trial (DART). Lancet 1989;334:757–761.

11 GISSI-Prevenzione Investigators: Dietary supplementation with n3 polyunsaturated fatty acid and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354: 447–455.

A. Leaf, MD
Massachusetts General Hospital, East, Bldg 149
13th Street, Charlestown, MA 02129 (USA)
Tel. +1 617 726 5908, Fax +1 617 726 6144, E-Mail aleaf@partners.org

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 139–143

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

Franca Marangoni, Claudio Colombo, Claudio Galli

Department of Pharmacological Sciences, University of Milan, Milan, Italy

The relationship between fat consumption and health has been assessed in several epidemiological and clinical studies carried out in the last decades. In particular, the intake of n–3 polyunsaturated fatty acids (PUFA) with the diet has been positively associated with health promotion, e.g. optimal infant development [1, 2], cardiovascular protection [3], prevention of neurodegenerative diseases [4] and behavioral disorders [5], and improvement of immune defenses [6].

However, data on the fatty acid composition of circulating lipids [7, 8] in large population studies, in confirmation of dietary fat intakes and habits, are limited, due to operational difficulties associated with blood collection in a large number of subjects, and in the complexity and costs of the conventional analytical methods, involving health personnel and medical facilities, and the application of time-consuming and relatively costly procedures (preparation of samples, lipid extraction, etc.).

We have recently developed a method that is rapid, substantially less expensive than the conventional one, applicable to large population groups, does not require the intervention of specialized personnel in the collection of samples, in order to analyze the fatty acid (FA) composition of lipids in a drop of blood [9]. Briefly, the drop of blood is obtained by punching the fingertip with an automatic lancing device equipped with a lancet, and blood (20–40 μl) is absorbed on a strip of chromatographic paper containing butylated hydroxytoluene (BHT) (100 μl) as antioxidant. The sample, when dry, is then either immediately processed, or stored at 4°C. The sample can be maintained up to 60 days at room

temperature without any detectable modification of the FA profile. Gas chromatographic analysis of FA followed the direct methylation of the sample.

The above analytical approach greatly facilitates studies devoted to the screening and follow-up of population groups of particular interest, e.g. infants, pregnant women, elderly people, sick persons, not easy to analyze through conventional approaches and, for this reason, not yet adequately investigated.

The data obtained with the new method are superimposable with those obtained with the conventional one, and all requirements (reproducibility, comparison between FA data in whole blood samples processed with the new procedure versus those obtained in samples processed according to the conventional procedure, etc.) were appropriately checked. Analysis of FA of whole blood lipids gives, predictably, somewhat different FA profiles in comparison with that of plasma lipids, due to the presence of erythrocytes, providing a relatively higher proportion of long chain PUFAs, esterified in membrane phospholipids (PL). On the other hand, this type of measurement, more than providing information on the impact of nutritional, metabolic and lifestyle parameters on the FA profile of selected lipid pools, e.g. phospholipids, triglycerides and cholesterol esters, describes the general FA status in the whole lipid pool in the circulation, including major cellular compartments, the erythrocytes, in addition to the typical plasma lipid classes.

Subjects

100 healthy subjects, aged between 22 and 72, 46 males and 54 females, all working at the Department of Pharmacological Sciences in Milan, and including students, technicians, researchers, administrative personnel, and professors, were recruited. They gave informed consent and were asked to fill-in a questionnaire on dietary intakes and lifestyle habits. Collection of all samples was carried out rapidly over a few days.

The detailed procedure from the collection of samples to the final analysis has been previously described [9].

Results and Discussion

The average FA composition of the whole blood samples of the 100 subjects subjected to analysis is presented in table 1. The data, in line with those reported in a vast literature for FA in plasma lipids – except for predictably somewhat higher PUFA levels due to the contribution of red blood cell phospholipids – are rather homogeneous, especially for the FA that are not strictly dependent upon the intakes, which is the case for PUFAs. We have then subdivided the subjects into groups according to different criteria. Values of percentage levels of selected FA that are statistically significant are reported in table 1.

Table 1. Average FA composition of the whole blood samples of the 100 subjects subjected to analysis

Number of subjects 100	Average ± SD	Meat consumption		Fish consumption		Salmon supplementation		Gender		Pregnancy		Cigarette smoke	
		Low 33	High 66	Low 40	High 47	T0 5	3 weeks 5	M 46	F 54	No 34	Yes 4	No 80	Yes 11
Fatty acids													
16:0	25.31±4.23												
18:0	13.92±4.75									24.82	29.27[c]		
20:0	0.57±0.19												
22:0	1.29±0.50												
24:0	1.35±0.58												
16:1	2.74±1.25												
18:1 n–9	21.03±3.53												
18:1 n–7	2.19±0.73							21.81	20.34[b]				
20:1	0.29±0.11												
24:1	1.60±0.72												
18:2 n–6	16.74±5.86					18.90	17.87[b]	15.52	17.83[b]				
20:3 n–6	1.15±0.40					1.51	1.31[b]					1.20	0.86[b]
20:4 n–6	6.65±2.47	6.37	8.30[a]			9.32	8.51[a]			7.29	4.01[c]	6.91	4.93[c]
22:4 n–6	1.03±0.49									0.99	0.40c		
22:5 n–6	0.31±0.23					0.63	0.47[a]					0.33	0.15[c]
18:3 n–3	0.61±0.43												
20:5 n–3	0.59±0.47					0.59	1.16[a]			0.63	0.28[c]		
22:5 n–3	0.87±0.57												
22:6 n–3	1.75±0.95			1.22	2.01[c]					2.01	1.29[c]	1.83	1.30
SFA	42.44±6.56												
MUFA	27.86±4.10							28.94	26.89[b]				
PUFA	29.70±8.13									32.15	23.58[c]		
UI	116.71±22.13									122.22	96.28[c]		

Low meat = 1 serving/week; high meat = 2–3 servings/week. Low fish: <1 serving/week; high fish: 2–3 servings/week. Salmon = 200 g/week × 3 weeks. SFA = Saturated fatty acids; MUFA = mono-unsaturated fatty acids; PUFA = polyunsaturated fatty acids; UI unsaturation index. Statistically significant differences: [a]$p < 0.05$, [b]$p < 0.002$, [c]$p < 0.001$.

Dietary Habits. Subjects were subdivided, on the basis of data provided by dietary questionnaires, into low and heavy consumers of fish or meat. Docosahexaenoic acid (DHA), mainly contained in fish, was the FA most influenced by fish consumption, as shown by the significantly higher levels in subjects who ate fish once or twice per week, versus those who had less than one portion of fish per week. On the other hand, arachidonic acid (AA) levels were significantly higher in blood lipids of subjects who consumed more meat (two or more portion per week) versus low (1 portion per week) meat consumers. The significantly higher AA levels in those who consumed more meat may be attributed to higher intakes of AA.

We have also checked the effects of the controlled consumption of fish on whole blood FA. Five male subjects, aged 25–43 years consumed 200 g/week of salmon providing 900 mg n–3 FA/day for three weeks. Analyses were carried out at T_0 and at 3 weeks and significant differences were observed in all PUFA levels: reduction of all n–6 FA and increments in n–3 FA, especially in eicosapentaenoic acid (EPA) levels (almost doubling).

Anthropometric and Physiological Conditions

Gender. We have evaluated the differences in FA levels between men (46, aged 23–72 years) and women (56, aged 22–73 years): significantly lower levels of oleic acid (OA) and total MUFA, and higher levels of linoleic acid (LA) are present in women vs. men. At present these difference cannot be attributed to specific factors.

Physiological Conditions. Comparisons of the FA status in non-pregnant (34, aged 26–40 years) and pregnant (4, aged 30–40 years) women show significantly lower levels of all long chain PUFA (LCP), especially EPA, associated with elevation of 16:0. These differences are in line with those reported in the literature [10, 11] and indicate a greater demand/utilization of PUFA during pregnancy.

Lifestyles. A final factor that we have considered concerns lifestyle habits, namely cigarette smoking. By comparing subjects who smoked more than 5 cigarettes/day (11 smokers) versus non-smokers (80 non-smokers), it was found that levels of LCP of both series are significantly lower in smokers. This observation is in line with previous reports of lower PUFAs in smokers [12] and with the observation that PUFA levels are reduced in breast milk of smoking mothers [13].

Conclusions

The reported results led us to conclude that the newly described method is valid, non-invasive, time- and cost-saving, and that it can be applied to the FA

analysis of large numbers of samples. Applications of the method to evaluate the impact of dietary habits, of the controlled FA intake, of physiological parameters and conditions, and of life style factors on the FA status in the circulation, reveal its usefulness in epidemiological and prospective studies, and in controlled trials, on the effects of dietary interventions.

References

1 Innis SM, Gilley J, Werker J: Are human milk long-chain polyunsaturated fatty acids related to visual and neural development in breast-fed term infants? J Pediatr 2001;139:532–537.
2 Larque E, Demmelmair H, Koletzko B: Perinatal supply and metabolism of long-chain polyunsaturated fatty acids: Importance for the early development of the nervous system. Ann NY Acad Sci 2002;967:299–310.
3 Hu FB, Willet WC: Optimal diets for prevention of coronary heart disease. JAMA 2002;288: 2569–2588.
4 Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH: Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 2000;35:1305–1312.
5 Brunner J, Parhofer KG, Schwandt P, Bronisch T: Cholesterol, essential fatty acids, and suicide. Pharmacopsychiatry 2002;35:1–5.
6 Kew S, Banerjee T, Minihane AM, Finnegan YE, Muggli R, Albers R, Williams CM, Calder PC: Lack of effect of foods enriched with plant- or marine-derived n-3 fatty acids on human immune function. Am J Clin Nutr 2003;77:1287–1295.
7 Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick D S: n–3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 2003;77:319–325.
8 Laidlaw M, Holub BJ: Effects of supplementation with fish oil-derived n–3 fatty acids and gamma-linolenic acid on circulating plasma lipids and fatty acid profiles in women. Am J Clin Nutr 2003;77:37–42.
9 Marangoni F, Colombo C, Galli C: A method for the direct evaluation of the fatty acid status in a drop of blood from a fingertip in humans: Applicability to nutritional and epidemiological studies. Analyt Biochem 2004;326:267–272.
10 Matorras R, Ruiz JI, Perteagudo L, Barbazan MJ, Diaz A, Valladolid A, Sanjurjo P: Longitudinal study of fatty acids in plasma and erythrocyte phospholipids during pregnancy. J Perinat Med 2001;29:293–297.
11 Otto SJ, van Houwelingen AC, Badart-Smook A, Hornstra G: Comparison of the peripartum and postpartum phospholipid polyunsaturated fatty acid profiles of lactating and nonlactating women. Am J Clin Nutr 2001;73:1074–1079.
12 Simon JA, Fong J, Bernert JT Jr, Browner WS: Relation of smoking and alcohol consumption to serum fatty acids. Am J Epidemiol 1996;144:325–334.
13 Agostoni C, Marangoni F, Grandi F, Lammardo AM, Giovannini M, Riva E, Galli C: Earlier smoking habits are associated with higher serum lipids and lower milk fat and polyunsaturated fatty acid content in the first 6 months of lactation. Eur J Clin Nutr 2003;57:1466–1472.

Claudio Galli
Department of Pharmacological Sciences
University of Milan
9, Via Balzaretti, IT–20133 Milan (Italy)
Tel. +39 2 50318309, Fax +39 2 50318384, E-mail claudio.galli@unimi.it

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 144–151

Measurement Error in the Assessment of Interaction between Dietary and Genetic Factors in Cohort Studies of Cancer

Sheila A. Bingham

Medical Research Council, Dunn Human Nutrition Unit,
Welcome Trust/MRC Building, Cambridge, UK

There is a large body of evidence to show that the marked international differences in the occurrence of cancer are mainly due to environmental factors, such as diet [1, 2]. Many dietary factors are associated with cancer prevention or causation; these factors range from traditional nutrients such as antioxidant vitamins, fat, and plant polysaccharides, to foods, such as vegetables, meat and fruit, to phytochemicals such as glucosinolates, phytoestrogens and carotenoids, and to contaminants such as heterocyclic amines and aflatoxins [1, 2]. However, causal associations require evidence of individual risk from exposure to particular items of diet. This entails accurate measures of the habitual diet of very large numbers of free-living individuals, one of the most difficult and challenging problems in nutrition. Furthermore, the complexity of the subject has increased markedly in recent years with the need to assess risks from non nutritional items, such as phytochemicals and contaminants, which vary markedly from one food to another and for which databases of food levels may not be published.

Despite strong international associations between diet and cancer, and high estimates of attributable risk from diet in westernized societies, within-population estimates of relative risks between dietary factors and chronic disease such as cancer are rarely greater than 1.5 for most foods or dietary items [1, 2]. It is difficult to ascribe causality to these low estimates, in comparison with relative risks in the order of 15 for smoking and lung cancer, for example. Furthermore, the inability to produce consistent estimates for even major nutrients or foods and cancer risk prompted the suggestion that attempts to measure diet in epidemiology had reached its limits [3]. Since that time, it has been realized that

two main factors may contribute to these low and inconsistent within-population estimates; genetic susceptibility and measurement error in dietary assessment.

Gene Environment Interactions in Nutritional Epidemiology

Between 50,000 and 250,000 of common variants of genes, or single nucleotide polymorphisms (SNPs), are estimated to be involved with disease risk [4]. There have been numerous association studies of these variants in cancer, and it has even been suggested that case control analyses of candidate genes could obviate the need for complex prospective studies of gene environment interactions, the so-called 'Mendelian randomisation' approach [5]. The absence of altered risk from polymorphisms in the N acetyl gene required for the activation of heterocyclic amines, formed when meat is cooked at high temperatures, has been taken as evidence that these compounds are not important in affecting risk of large bowel cancer [6]. However, genetic associations will not be revealed if the risk conferred by them is only apparent in populations exposed to the relevant environmental exposure, as for example in the case of alcohol dehydrogenase and oral cancer [7]. Furthermore, unexpected effects of such studies, such as the apparent protective effect in colorectal cancer of the MTHFR variant, which is associated with low folate levels, has only emphasised the need for careful measures of dietary exposure where this is possible [8]. Although it is assumed that there is an interaction between nutrition, genetic polymorphisms and cancer risk, there has so far been inconsistency in the ability to replicate results with either single polymorphisms or haplotype analyses [4]. This may be because the right gene may not have been chosen, and the need for quality control in genotyping has only recently been appreciated. Furthermore, studies have been carried out in comparatively small populations, so that the reported elevated risks associated with an interaction may have been based on very small numbers of subjects. Findings might thus have arisen by chance or have been missed due to lack of statistical power.

Very large sample sizes are required for prospective studies of gene-environment interactions in cancer, and they can only be studied in epidemiological cohorts that have measured environmental exposures, collections of biological material, and a sufficient number of disease endpoints. Such was the approach behind the large prospective collaborative project carried out in ten different European countries in the main EPIC, which currently includes 519,978 individuals. Diet has been measured by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. Over 20,000 cases of cancer have occurred since the study was started [9].

Measurement Error in Nutritional Epidemiology

Misclassification error in dietary assessment will increase sample size requirements markedly; with only a 20% loss in sensitivity in dietary assessment, the required sample size for interactive investigations may more than double [10]. These errors arise from the assessment of the frequency of food consumption, portion size, daily variation, and failure to report usual diet, due to either changes in habits whilst taking part in an investigation, or misreporting of food choice or amount. When translated into food constituents, by using data bases of food tables, further errors are incurred. In populations with a complex food supply, databases may contain values for a few thousand food items only. This compares with several hundreds of thousands of foods marketed. In less complex societies, resources for extensive food analyses may not be available and data bases will be less comprehensive.

The presence of measurement errors has generated much controversy and discussion as to the most 'accurate' method of dietary investigation. Numerous studies, comparing results of one dietary assessment method with another, presumed more accurate, method on the same individuals have been conducted. However, unless food consumption can be independently observed, the 'true' value for assessing validity is unknown because all traditional methods, even weighed records, rely on food consumption as reported by the individuals.

In large prospective epidemiologic studies, it is now common practice to correct for measurement error in the assessment of relative risk by regression calibration, when the correction factors are derived by comparison of the method in use, such as a FFQ, with a 'reference' method, such as a record. This practice relies on the assumptions that errors in the reference instrument are uncorrelated with both 'true' intake and errors in the method in use. However, errors associated with the method under investigation may be correlated with those of the reference method, so that correction for regression dilution is substantially underestimated [11].

Types of Biological Markers

The ability to assess measurement error associated with dietary assessment, and correct for it, has only become possible with the advent of biological markers in biological specimens such as blood, urine or hair, that reflect intake sufficiently closely to act as objective indices of true intake.

Several 'concentration' biomarkers (including serum vitamins) are available to compare with estimates of dietary intake [12]. However, there are few 'recovery' biomarkers that are sufficiently accurate to validate the accuracy of

dietary assessment methods. Prior calibration studies under controlled conditions, for example a metabolic suite, are necessary to ascertain that the predictability of the biomarker in humans consuming varying diets is at least as good as the dietary intake method which is being validated and that they are independent of the errors associated with a dietary survey method being tested. Few biomarkers of dietary intake have been studied in this way; they include doubly labeled water used for example in the OPEN study [13, 14] and urine markers of potassium and nitrogen [15, 16].

Biomarkers could also replace estimates of intake based on traditional methods. The usefulness of these 'replacement' biomarkers is illustrated in a follow up study of markers of aflatoxin exposure in relation to liver cancer. The range of aflatoxin contamination of foods is very great, so that use of food tables of average levels of contamination is unlikely to reflect individual exposure. Relative risks of cancer from aflatoxin consumption were only 0.9 and insignificant (confidence intervals 0.4–1.9) for individuals classified to have had high dietary exposure, as assessed by an interview of the frequency of consumption of 45 foods. However, aflatoxin exposure biomarkers in urine samples obtained from individuals in the cohort were able to detect substantial and significant relative risks for liver cancer in the order of 6–10. The estimated relative risk was 59.4 (16.6–212.0) in individuals positive for urine biomarkers of both aflatoxin and hepatitis B [17].

24-Hour Urine Nitrogen and Potassium

In initial studies to assess the validity of several different methods of dietary assessment in UK cohorts of the EPIC study, 160 women were asked to complete 16 days of weighed food records over 1 year, as 4 repeated 4-day records. The volunteers were also asked to provide eight 24-hour urine collections, as 4 repeated 2-day collections, and completeness of the urine collections was assessed using the *p*-aminobenzoic acid (PABA) check method [16]. During the year, different methods of dietary assessment were completed by the volunteers and it was shown that correlations were greater between the biomarker 24-hour urine nitrogen and estimates of nitrogen intake from records, than from estimates of intake from other methods including FFQ [18, 19]. A similar pattern was evident with potassium [18, 19]. For this reason, three methods of dietary assessment, an FFQ, a food diary and a simple 24-hour recall were used to assess diet in the UK arms of EPIC [20].

In a more recent study, repeat biomarker estimates were also obtained from EPIC participants over a 9-month period. Urinary nitrogen, potassium and sodium were estimated from 2–6 complete 24-hour urine collections in 134 subjects and

plasma ascorbic acid from 2–3 fasting blood samples in 118 subjects. As before, PABAcheck was used to verify the completeness of the 24-hour urine collections [16]. Subjects completed two FFQ and two 7-day food diaries, and the second diary and FFQ were sent at varying times over the course of the study. 24-Hour urine samples were not collected during the time that subjects were recording their dietary intake, making it more likely that any errors between the dietary method and biomarker were completely independent of each other. As before, in both men and women, results calculated from the 7-day food diary were much closer to estimates of output from urinary biomarkers than those calculated from the FFQ [21].

The design of this study also allowed error variance analysis to be conducted from the repeated dietary intake measures and the repeated urine collections. Marked differences in error variances associated with the different dietary assessments were shown. The most accurate method, the 7-day food diary, had substantially less error variance than the FFQ. Using the urine biomarkers as indices of 'true' intake, the correction factors for measurement error of relative risk estimates from the dietary assessment methods could be estimated. Correction factors for regression dilution from the food diary were only 1.8–2.0, whereas those for the FFQ were too large to use with confidence (4.8 for potassium and 9.0 for nitrogen). Furthermore, the confidence limits around these estimates for the FFQ became impossibly wide, 1.7–16.2 for nitrogen for example [11]. Similar conclusions have been reached using the doubly labeled water technique in addition to 24-hour urine nitrogen [14].

Calibration

Another way to correct for measurement error is to increase the heterogeneity of the population and study different populations with diverse dietary practices. Values for the regression correction factor seen for a dietary instrument derive both from the error variances and the underlying between individual variation in the study population. If the latter is increased, the correction factor will become smaller, which underlines the importance of variation across study populations [11]. Such was the approach to attempt to reduce measurement error in EPIC Europe [11]. Diet was measured by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. A second dietary measurement was taken from an 8% random sample (36,000 individuals) of the cohort using a computerized 24-hour diet recall method (EPIC SOFT) in order to calibrate the questionnaires. 1,103 volunteers of both genders from 12 centres also provided complete 24-hour urines for biomarker analysis and the high (0.72) sex-partial Spearman correlation between mean

urinary and dietary nitrogen suggests that confidence can be placed in the validity of the calibration method used [22].

Effects on End Points

In the first main finding from the main EPIC study, the effect of dietary fibre on risk of colorectal cancer was investigated. 1,065 colorectal cancers for analysis have developed in EPIC since recruitment in 1992–1998, and dietary fibre in foods was significantly and inversely related to large bowel cancer incidence (adjusted relative risk = 0.75 (C.I. 0.59–0.95)) for the highest versus the lowest quintile of intake. The protective effect was greatest for the left side of the colon, and least for the rectum. After calibration with the more detailed dietary data from the EPIC SOFT, the adjusted relative risk for the highest versus lowest quintile of fibre from food intake was 0.58 (0.41–0.85). These findings are in accord with expectations according to possible mechanisms behind a protective effect of fibre in the colon. They do however contrast with recent FFQ-based cohort studies in homogeneous populations, which have not found a relationship [23].

Within the homogeneous population of EPIC Norfolk 168 incident breast cancer cases have arisen. The food diaries and FFQ from these cases and four matched controls have been coded and the effects on cancer risk compared. 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, 1.219 (1.061–1.401; $p < 0.005$) but not with saturated fat measured using the FFQ 1.100 (0.941–1.285) $p < 0.229$ [24]. These findings may explain the enigma of apparent lack of effect shown in FFQ-based prospective studies of fat intake in breast cancer, whereas all other data is generally consistent with a positive relationship between incidence of breast cancer and fat consumption [24].

Future Work

Some biomarkers for the validation of methods for assessing dietary intake have been developed. There is a need for a greater variety of dietary biomarkers to be developed to reflect wider aspects of diet, and two more, 24 h urine thiamine and sucrose look promising [25]. At present, the doubly labeled water technique, and 24-hour urine nitrogen and potassium are in routine use for validation studies. Using these biomarkers, it has been shown that there could be substantial attenuation of diet effects and loss of statistical power in epidemiological studies in homogeneous populations where relatively inaccurate methods of dietary

assessment have been used. Attenuation and loss of power, together with genetic variation in response, could account for the inability of existing studies to show causal links between diet and chronic disease such as cancer. Some of this measurement error can be overcome by studying populations whose dietary habits are more heterogeneous than single populations, but biomarker studies suggest that improved, more detailed, methods of dietary assessment will be necessary if causal associations between diet, genotype, biomarkers, and disease are to be established in future large scale epidemiological studies.

References

1 Potter J (ed): World Cancer Research Fund, Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, American Institute for Cancer Research, 1997.
2 Great Britain: Committee on Medical Aspects of Food and Nutrition Policy. Working Group on Diet and Cancer. Nutritional Aspects of the Development of Cancer. Report of the Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy. Report on Health and Social Subjects; 48. London, Stationery Office Department of Health, 1998.
3 Taubes G: Epidemiology faces its Limits Science 1995;269:164–169.
4 Rebbeck TR, Ambrosone CB, Bell DA, Chanock SJ, Hayes RB, Kadlubar FF, Thomas DC: SNPs, Haplotypes, and Cancer (Meeting Report). Cancer Epidemiol, Biomarkers Prev 2004;13: 681–687.
5 Clayton D, McKeigue PM: Epidemiological methods for studying genes and environmental factors in complex diseases Lancet 2001;358:1356–1360.
6 Sachse C, Smith G, Wilkie MJV, Barrett JH, Waxman R, Sullivan F, Forma D, Bishop T, Wolf R: A pharmacogenetic study to investigate the role of dietary carcinogens in the etiology of colorectal cancer. Carcinogenesis 2002;23:1839–1849.
7 Harty LC, Caporaso NE, Hayes RB, Winn DM, Bravo-Otero E, Blot WJ, Kleinman DV, Brown LM, Armenian HK, Fraumeni JF Jr, Shields PG: Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers. J Natn Cancer Inst 1997;89:1698–1705.
8 Little J, Khoury MJ: Mendelian randomisation: A new spin or real progress? Lancet 2003;363: 930–931.
9 Bingham S, Riboli E: Is diet important in cancer pathogenesis? The European Prospective Investigation of Cancer (EPIC). Nat Rev Cancer 2004;4:206–215.
10 Garcia-Closas M, Rothman N, Lubin J: Misclassification in case-control studies of gene-environment interactions: Assessment of bias and sample size. Cancer Epidemiol Biomarkers Prev 1999;8: 1043–1050.
11 Day NE, McKeown N, Wong MY, Welch A, Bingham S: Epidemiological assessment of diet: a comparison of a 7 day diary with a food frequency questionnaire. Int J Epidemiol 2001;30: 309–331.
12 Kaaks RJ: Biochemical markers as additional measurements in studies of the accuracy of dietary questionnaire measurements: Conceptual issues. Am J Clin Nutr 1997;65:S1232–S1239.
13 Prentice AM, Coward WA, Davies HL, Murgatroyd PR, Black AE, Goldberg GR, Ashford J, Sawyer M, Whitehead RG: Unexpectedly low levels of energy expenditure in healthy women. Lancet 1985;i:1419–1422.
14 Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, Bingham S, Schoeller DA, Schatzkin A, Carroll RJ: Structure of dietary measurement error: Results of the OPEN biomarker study. Am J Epidemiol 2003;158:14–21.
15 Bingham SA, Cummings JH: Urine nitrogen as an independent validatory measure of dietary intake: A study of nitrogen balance in individuals consuming their normal diet. Am J Clin Nutr 1985;42:1276–1289.

16 Bingham SA, Williams R, Cole TJ, Price CP, Cummings JH: Reference values for analytes of 24-h urine collections known to be complete. Ann Clin Biochem 1988;25:610–619.
17 Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, Wogan GN, Groopman JD: A follow-up study of urinary markers of alflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. Cancer Epidemiol Biomarkers Prev 1994;3:3–10.
18 Bingham SA, Cassidy A, Cole TJ, Welch A, Runswick SA, Black AE, Thurnham D, Bates C, Khaw KT, Key TJ: Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. Br J Nutr 1995;73:531–550.
19 Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thurnham DI, Key TJ, Roe L, Khaw KT, Day NE: Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. Int J Epidemiol 1997;26(suppl 1):S137–S151.
20 Bingham S, Welch A, McTaggart A, Mulligan A, Runswick AA, Luben R, Oakes S, Khaw KT, Wareham N, Day NE: Nutritional Methods in the European Prospective Investigation of Cancer in Norfolk. Publ Health Nutr 2001;4:847–858.
21 McKeown NM, Welch AM, Runswick SA, Luben R, Mulligan A, McTaggart A, Day NE, Bingham SA: The use of biological markers to validate self reported dietary intake in a random sample of the European Prospective Investigation into cancer (EPIC) UK Norfolk Cohort. Am J Clin Nutr 2001;74:188–196.
22 Slimani N, Bingham SA, Runswick S, et al: Group level validation of protein intakes estimated by 24-hour diet recall and dietary questionnaires against 24-hour urinary nitrogen in the EPIC Calibration Study. Cancer Epidemiol Biomarkers Nutr 2003;12:784–795.
23 Bingham SA, Day NE, Luben R, et al: Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): An observational study Lancet 2003;361:1496–1501.
24 Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day NE: Fat and breast cancer: are imprecise methods obscuring a relationship? Report from the EPIC Norfolk prospective cohort study. Lancet 2003;362:212 –214.
25 Tasevska N, Runswick S, Bingham S: Can urinary sugars and thiamine be used as biomarkers to assess measurement error in dietary intake data? Proc Nutr Soc 2005;in press.

Sheila A. Bingham, MD
Medical Research Council
Dunn Human Nutrition Unit, Welcome Trust/MRC Building
Hills Road, Cambridge CB2 2XY (UK)
Tel. +44 1223 252760, Fax +44 1223 252765, E-Mail sab@mrc-dunn.cam.ac.uk

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 152–157

Cancer Frequency in Poor Rural Communities Consuming a Very Limited Diet

Miriam Muñoz Rivera[a], *Adolfo Chávez*[b], *Roxana Rosales*[b], *Virginia Melo*[c]

[a] National Cancer Institute, Morelos State University, [b] National Institute of Medical Sciences and Nutrition, and [c] Metropolitan University, Tlalpan, Mexico

Cancer is a painful and costly disease that is on the rise in practically every country of the world [1]. In most medium-developed countries – those undergoing socio-economic and epidemiological transition, as is the case of Mexico – cancer has become one of the leading health threats [2]. It ranks second only to cardiovascular diseases among the causes of death [3].

There are many factors involved in the increased rates of cancer in Mexico: some are indirect, such as the increase in the percentage of older adults, more susceptible to cancer, and more diagnostic facilities. Other factors are more direct, such as changes in diet, increased exposure to radiation, viral contamination, and perhaps other factors not well known [4].

Some recent studies show how lifestyle changes, especially in diet, are contributing to the increase in cancer [5]. It is now widely accepted that the rise in several chronic diseases, such as obesity, diabetes, hypertension, and thromboembolic disease are very sensitive to population lifestyle changes, as related, in part, to the greater percentage of elderly persons, urbanization, diet change, sedentarism, and other [6].

It is almost certain that many forms of cancer are related to an abundant diet, rich in fat and animal foods [7], and inappropriate forms of food preparation [8], and this type of diet is typical of what is referred to as 'dietary modernization,' which has expanded throughout the world, including formerly marginal populations, until very recently consumed a self-produced 'limited diet,' consisting of few foods, usually grains [9].

The population that is the poorest and most marginal in development and modernization in Mexico is essentially genetically and culturally indigenous [10]. They are people mostly isolated in spite of 500 years of contact with Western culture. They still speak their own languages; live in the mountains, forests, or deserts, eating basically corn tortillas, poorly complemented with beans and various local plants. They go to local markets to buy small amounts of sugar, salt, and sometimes meat.

During the past 40 years, most of the indigenous population has begun to change, slowly at first, and then more rapidly in the last 20 years. This has been due to their receiving information and products by road, radio, and recently by television. They now try to use fat to cook their food, especially beans, and instead they often try pastas, since they are easier to prepare and taste better [11]. These people are purchasing beer, soft drinks, packaged breads, pastries, and crackers, as well as fried corn, wheat, or potato products. Recently, they have been sold small amounts of imported lard, pork rinds, packaged plump hens, and entrails, which have been very well received although consumed in keeping with their scarce resources. The situation now represents a dietary transition, which is now making way for what could be considered an incipient change in lifestyle and the base for an epidemiological transition – both a decrease in infant mortality due to infection and malnutrition, and an increase in obesity, diabetes, and hypertension [12].

This study was carried out in three rural research centers, located near and up to 100 miles from Mexico City, and maintained for various purposes by the National Nutrition Institute. At 6 communities of these centers, cancer detection through semi-longitudinal observations were performed. The shortest time being three years and the longest, six years. The objective was to learn the prevalence and incidence of cancer among adults in order to find out if some registered changes in blood cholesterol and arterial pressure, the same as in morbidity due to obesity and diabetes and in mortality due to these chronic diseases are followed by the presentation of the types of cancer linked to diet.

Material and Methods

The personnel of three rural research centers located in indigenous areas performed a survey on the prevalence of cancer in six communities. They asked about family histories about cancer. People in these communities still consumed more than 60% of the energy from tortillas plus very limited amounts of other kinds of products, but including some industrialized cakes and fried cereal, sugar and fat foods, Therefore they consumed a limited and deficient diet. The families were periodically interviewed for as long as the research centers remained in existence, an average of 4.5 years. The total number of families directly observed

were 1,165, comprised 2,635 adults older than 25 years of age. A subsample of the families was asked about their dietary habits and food consumption during the 24 h prior to the interview. Physical activity was also studied in a sub-sample.

In every community a medical service from the research center existed, where consultations were provided at the request of the regional population, all them were routinely asked about the presence of cancer. Physicians and other local health service personnel were also frequently interviewed. The total population under indirect control, all inhabitants of a region with 2,810 families, were questioned on the presence of cancer, and morbidity and mortality registrations were surveyed over a period of 10 years.

The Dietary Transition of the Communities

The surveys on food consumption during the 24 h prior to the interview showed few changes in relation to the known indigenous diet. In all communities, corn provided between a minimum of 60% and a maximum of 76% of daily calories. As in every study previously known, caloric consumption was low, between 1,810 and 1,960 calories per person, per day. However, several circumstances, besides poverty and frugality, explain the very low figures. Indigenous populations continue to have many children; half the population is less than 16 years old, which means that the recommended caloric intake is low (between 2,000 and 2,150). These populations are short in stature and, above all, have many habits for saving physical energy.

The survey on physical activity showed that they do not work as much as one would expect for an agricultural population; they only work half a year, and at this season they lose weight and suffer frequent food shortages, they have to ration and gather food such as plants and insects, which rarely ever appear on the surveys taken at home. Outside the planting time, half the adults do not work, and the other half migrates to irrigated agricultural areas or neighboring cities where they work more intensely, though only for few weeks. The women do more work, because they constantly carry water and take care of the house and children.

Beans continue to be the second food most commonly eaten, although nearly half the time they are replaced by pasta, soup and, at other times, by nopal (opuntia cladodes) or other gathered greens (quelites). Pulque is consumed in every community – on average, close to half a liter per person per day (420 ml). This drink provides quite a few calories.

Egg consumption has increased to perhaps one or two per person per week; however, the average situation does not reflect the situation as a whole, since, even in poverty, there are inequalities. The truth is nearly half the families very rarely eat eggs. Similarly, the use of cooking fat has increased,

although perhaps only for half of the population. They especially like lard and pork rinds, which are usually imported, although two of the six communities slaughter a pig every Saturday. Also now, unlike in the past, milk consumption has begun to appear on surveys, due to the fact that there are now industrial forms for easier conservation. Nevertheless, it was more common (12%) to find its consumption among adults, for breakfast, than among children, at the age of weaning (8%).

There has been a significant increase in the consumption of soft drinks, beer, and grain products in the form of breads, cakes, and cookies, and in the form of fried foods (including potato chips). Stores are filled with these products, yet the surveys reflect a low consumption of them (8% of the energy in school age). Perhaps they do not appear in the surveys, in part, due to these products being consumed outside the home, or that people are not stating them as part of their diet.

The percentage of the family diet corresponding to 'non-indigenous' foods barely surpasses 20%, which allows one to conclude that the dietary transition has just begun in these communities. This situation is not due so much to cultural preferences as it is to poverty, since families with more resources quickly replace beans with pasta, cook with more fat, and eat more meat and industrial 'junk foods', everybody but especially young people are quite addicted to soft drinks, sugar breads, sweets and many fried 'junk' products. There is clearly an eagerness for already cooked, high-energy foods with a high concentration of sugar, fat, and salt.

Results on Cancer Prevalence

Among the 1,165 families comprising 2,635 adults, covering 4.5 years of control, only three cases of cervico-uterine cancer were found among post-menopausal women and two cases of stomach cancer in men. In the indirect information of the 2,810 families with medical control in the region through the 10-year surveillance provided by the population itself and the local doctors, only 2 additional cases (cervical-uterine and stomach cancers) were confirmed, giving a total of 7 cancer cases detected.

From the epidemiological point of view, in the direct survey, 1.9 of every 1,000 adults was found to have cancer, during the 4.5 years of observation. The actual incidence of cancer was at a rate of 0.42 per year, per 1,000 adults observed.

In the extended sample in the area, and considering 10 years of interviewing and seeking information from public health records, and local doctors and medical services, the incidence of cancer was four times lower, of 0.10 cases per year, per 1,000 adults.

Comments

The prevalence of cancer found through the direct survey is not actually low; however, it is important to note that the five cases diagnosed had forms of cancer frequently linked to infections, the papilloma virus, and campylobacter bacteria. Moreover these types of cancer prevalence is high, if it is considered that the studied population is very young – only 119 of the 2,635 adults observed were confirmed to have more than 65 years old.

Considering the incidence in the population observed, that is, the occurrence of new cancer cases per year, then the rates are low. In 4.5 years of observation, only the same 5 cases were found, the reason for which the rate is 0.42/thousand persons/year.

In the 2,810 families of the 6 communities comprising 10 years of surveillance, only 7 cases were found, a rate of 0.1 per 1,000 adults, per year. This figure is low; however, to judge their importance, it must be considered the low percentage of older adults and the lack of precise diagnoses among this type of population. Apart from the persons diagnosed with cancer, it is important to mention that there are some other causes of death among older adults that are registered giving names of indigenous traditional causes. Those persons which died 'of old age', 'sadness', 'bad liver,' or other terms that generally mean that the elderly person stopped eating could have been cancer cases.

Conclusions

It cannot be said that forms of cancer having the possibility of being related to changes in lifestyle and diet do not exist in the indigenous population, as it is still very recent and hard to make proper diagnoses. Nevertheless, no case was found in such an extensive survey, and through a surveillance program and search among the medical registration which included a significant number of families, many of the people observed and studied by the authors were physicians or research personnel.

It is quite possible that the incipient changes in diet and lifestyle found among this population, which has also begun to spread to most of the rest of the indigenous groups, are already contributing to the occurrence of obesity, diabetes, and hypertension, but probably not yet to forms of cancer not linked to infections. Nevertheless, it is important to continue observing the communities, with the support of greater diagnostic facilities, in order to evaluate the evolution of the relationship between the progressive lifestyle changes, especially in diet, and the possibility of a significant increase in the incidence of cancer.

References

1 Coleman M, Estéve M, Damieck P: Trends in cancer incidence and mortality. IARC Sci Publ 121. Lyon, International Agency for Research on Cancer, 1993.
2 Wheelan SL, Parkin DM, Masuyer E: Patterns of cancer in five continents. IARC Sci Publ 102. Lyon, International Agency for Research in Cancer, l999.
3 Muñoz de Chavez M, Chavez A: The diet that prevents cancer: Recommendations for Mexico. Int J Cancer 1998;(suppl II):85–89.
4 Chávez A, Muñoz de Chávez M, Roldán JA, Madrigal H: The Food and Nutrition Situation of Mexico, a report of the 1960–1990, tendencies of food consumption, nutritional status and applied programs tendencies. México, Ed Instituto Nacional de Nutrición, 1992.
5 Potter JD, Chavez A, et al: Food Nutrition and the Prevention of Cancer: A Global Perspective. Washington, World Cancer Research Fund/American Institute of Cancer Research, 1997.
6 National Academy of Science: National Research Council (US) Committee and Diet and Healthy Diet and Health Implications for Reducing Chronic Diseases Risk. Washington, National Academy Press, 1989.
7 Willett WC, Trichopoulos D: Nutrition and cancer: A summary of the evidence. Cancer Causes Control 1996;7:178–180.
8 Skog K: Looking procedures and food mutagens: A literature review. Food Chem Toxicol 1993 31:655–675.
9 Ávila A, Shamah T, Chávez A: Encuesta Nacional de Alimentación y nutrición en el medio rural. México, Ed Instituto Nacional de la Nutrición-SEDESOL-DIF-SSA-IMSS-INI y UNICEF, 1997.
10 Roldán JA, Chávez A, Ávila A, Muñoz M, Álvarez A: La desnutrición a nivel municipal de acuerdo a un indicador mixto de estado nutricional. México, Ed Instituto Nacional de Nutrición, 2000.
11 Chávez A, Muñoz de Ch M, Roldán JA, Ávila A: La Nutrición en México y la transición epidemiológica. México, Ed Instituto Nacional de la Nutrición, 1997.
12 Saucedo AG, Chávez VA, García GV: Salud y nutrición en la Sierra Tarahumara. Estud Antropol Biol 2003;11:343–364.

M. Muñoz Rivera, MD
Instituto Nacional de Cancerología
San Fernando No. 20
Tlalpan, DF México 14000 (México)
E-Mail achavez@quetzal.innsz.mx

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 158–165

Omega–6/Omega–3 Polyunsaturated Fatty Acids Ratio and Breast Cancer

Philippe Bougnoux, Virginie Maillard, Véronique Chajès

'Nutrition, Growth and Cancer', INSERM EMI-U 0211, University François-Rabelais, Tours, France

There is epidemiological support that the long-chain ω–3 polyunsaturated fatty acids (PUFA), including eicosapentaenoic acid (20:5 ω–3) and docosahexaenoic acid (22:6 ω–3), which originate from animal marine sources, exert protective effects against breast cancer. Animal studies have generally concluded that ω–6 PUFA, provided by corn and other common seed oils, have tumor-promoting effects at several sites whereas ω–3 PUFA, provided by fish oils, are protective [1]. This oversimplified pattern has been questioned by several experimental data [2, 3], and several reports support the hypothesis that fatty acids interact with other components of lipids [4] and that, among fatty acids, the balance between ω–6 and ω–3 PUFA may influence the outcome of breast cancer more than the individual amount of each class of PUFA.

The evolutionary aspects of diet with emphasis on the ratio of ω–6 to ω–3 fatty acids has been reviewed by Simopoulos [5]. In the diet of our ancestors, the ratio of ω–6 to ω–3 essential fatty acids was 1 to 2/1 with higher levels of EPA, DHA and arachidonic acid than today's diet. Today, this ratio is about 4 to 1 in Japan, and varies from 15 to 1 in current United Kingdom and northern Europe to 16.74 to 1 in current United States, indicating that Western diets are depleted in ω–3 fatty acids [6]. The depletion of ω–3 PUFA in Western diets is the consequence of agribusiness, modern agriculture and aquaculture [7]. The high ratio of ω–6 to ω–3 PUFA is the consequence of excessive production of vegetables oils and of the substitution of saturated fat and butter with oils high in ω–6 PUFA to lower serum cholesterol levels, without taking into consideration their adverse effect on overall human metabolism. Only the diet of Crete or the traditional diet of Greece resembles the Paleolithic diets in terms of fiber, antioxidants, saturated fat, monounsaturated fat, and the ratio of ω–6 to ω–3 PUFA is close to 1 to 1 [6]. There is evidence that diet, and specifically a

balanced ω–6 to ω–3 PUFA ratio, may have a protective effect on cancer incidence in humans.

There are two families of essential fatty acids, the ω–6 and ω–3 families. Linoleic acid (18:2 ω–6), the essential fatty acid of the ω–6 family, is the major ω–6 fatty acid in diet. Alpha-linolenic acid (18:3 ω–3) is the essential fatty acid of the ω–3 family. In the body, linoleic acid is metabolized to arachidonic acid (20:4 ω–6), and alpha-linolenic acid is metabolized to eicosapentaenoic acid (20:5 ω–3, EPA) and docosahexaenoic acid (22:6 ω–3, DHA). The ω–3 and ω–6 fatty acids cannot be converted in the human body, and are important components of cell membranes. One of the main functions of PUFA in the body is as a precursor for eicosanoids; which are mediators of inflammation and cellular growth. PUFA are converted to prostaglandins (PG) by cyclo-oxygenases and to leukotrienes (LT) by lipoxygenases. Arachidonic acid (20:4 ω–6) and EPA compete for cyclooxygenases and lipoxygenases, resulting in the production of eicosanoids with opposing effects. In general, 20:4 ω–6-derived eicosanoids (2-series PG and 4-series LT) have proinflammatory effects, whereas EPA-derived eicosanoids (3-series PG and 5-series LT) have anti-inflammatory effects. Since there is competition and opposition of PUFA in the body, research has been conducted to determine the importance of the dietary ω–6/ω–3 fatty acids ratio, rather than the absolute level of individual PUFA, in cancer prevention [8]. A balanced ω–6/ω–3 ratio in the diet is essential for normal growth and development and should lead to decreases in cardiovascular disease and cancers.

Breast cancer incidence rates vary greatly across countries. Despite associations of hormonal, reproductive and genetic factors with breast cancer risk, most of the variation in occurrence across populations does not appear to be attributable to established risk factors. Among preventable causes of cancer, dietary factors estimates have been accounting for between 20 and 60% according to the sites [9, 10]. Among dietary factors, fat consumption has received extensive attention. Cohort studies, however, provide little evidence that total fat consumption independent of its energy contribution strongly influences breast cancer risk [11, 12].

Most of the epidemiological studies investigating potential protective effects of ω–3 PUFA on breast cancer risk addressed fish consumption. The preponderance of ecological studies supported an inverse association of fish consumption with breast cancer [13–15]. While case-control studies and cohort studies were less consistent [16–19], several studies reported a significant negative association between estimated consumption of fish or other seafood and postmenopausal disease [20–23]. One study reported no association of overall fish intake with breast cancer risk, but an inverse association of poached fish with breast cancer [24].

In spite of the interest in whether a high intake in ω–3 PUFA and/or a high ratio of ω–3 PUFA to ω–6 PUFA is associated with a decreased risk of breast

cancer, most of the studies examined the association between estimated dietary intakes of total saturated, monounsaturated and polyunsaturated fat and breast cancer risk, without data on the type of PUFA [25]. In one case-control study conducted in Finland in a population of 73 breast cancer patients and 55 patients with benign breast disease, the dietary intake of long-chain ω–3 PUFA (eicosapentaenoic acid, docosahexaenoic acid) was significantly lower in breast cancer patients than in controls, particularly in postmenopausal women [26]. In the Netherlands Cohort Study on Diet and Cancer, a significant inverse association was found between dietary alpha-linolenic acid intake and breast cancer risk, whereas no association was found for long-chain ω–3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid [27].

Several population-based studies were undertaken to investigate the relation between ω–3 and ω–6 PUFA composition and breast cancer risk, using biomarkers of past dietary intake of PUFA.

A prospective cohort study, aimed at evaluating whether ω–3 PUFA protect against breast cancer, was conducted in Sweden [28]. The ω–3 PUFA levels of phospholipids in prediagnostic sera of 196 women who developed breast cancer were compared to those of 388 referents. No significant association between ω–3 PUFA levels and breast cancer risk was found. The same lack of association between ω–3 PUFA levels or the ratio of ω–3 to ω–6 PUFA in serum phospholipids and breast cancer risk were already reported in a case-control study conducted in Oslo, Norway, in 87 women who developed breast cancer and 235 women who were free of any diagnosed cancer [29]. Within a cohort of women in the New York University Women's Health Study, the fatty acid composition of serum phospholipids was determined among 197 breast cancer patients and 197 matched controls [30]. No significant association was found between ω–3 or ω–6 PUFA levels and breast cancer risk, total PUFA (ω–6 and ω–3 PUFA) showed a weak protective effect. No data on the effect of ω–6 to ω–3 PUFA ratio on breast cancer risk was provided.

The relationship between erythrocyte membrane fatty acids and postmenopausal breast cancer risk was investigated in a prospective study of hormones, diet and breast cancer risk (the ORDET study) conducted in northern Italy. In a cohort of 4,052 postmenopausal women, 71 cases of invasive breast cancer were identified, and two matched control women were randomly selected from among cohort women. A non-significant inverse association was found between long-chain ω–3 PUFA levels in erythrocyte membranes and breast cancer risk [31]. In this study, no data on the relationship between the ratio of ω–6 to ω–3 PUFA and breast cancer risk was provided (fig. 1).

Since adipose tissue has been shown to best reflect dietary exposures for the essential fatty acids (with the linoleic acid, alpha-linolenic acid, and long-chain ω–3 PUFA) [32, 33], several studies used the fatty acid composition of

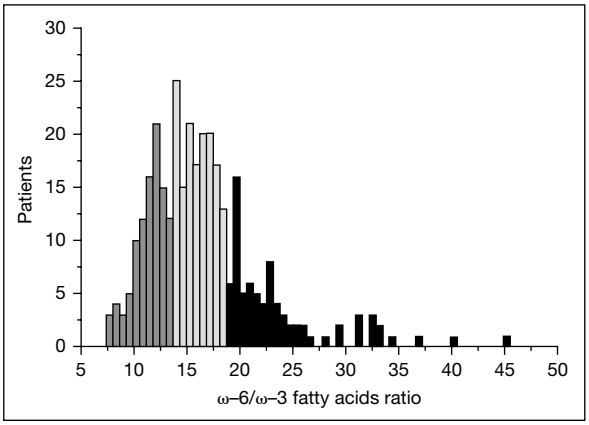


Fig. 1. Distribution of French women according to ω–6/ω–3 fatty acids ratio in the adipose tissue. Breast adipose tissue from 329 patients treated for a benign (controls) or malignant (cases) breast tumor was analyzed for fatty acid composition. Tertiles are indicated by different shadings.

adipose tissue samples as a biomarker to investigate the relation between exposure to ω–3 and ω–6 PUFA and breast cancer. The determination of fatty acid profiles in the adipose tissue offers the advantages over questionnaire methods of dietary assessment in case-control studies of being free from recall bias and, unlike serum levels of fatty acids, not being potentially altered by recent changes in diet that may occur due to the disease.

In one case-control study conducted in Boston, the association between fatty acid composition of subcutaneous adipose tissue and risk of breast cancer has been investigated in 380 postmenopausal women with newly diagnosed stage I or II breast cancer and 176 postmenopausal women with proliferative breast disease [34]. No consistent associations were found between any of the series of fatty acids or the individual fatty acids (including long-chain ω–3 PUFA) in adipose tissue and breast cancer risk. The same lack of association between ω–3 PUFA in subcutaneous abdomen and breast adipose tissues was observed in another case-control study conducted in New York on 154 women with invasive breast carcinoma and 125 control women with benign breast disease [35]. In one case-control study conducted in Finland in 73 women with breast cancer and 55 control women with benign breast disease, the level of docosahexaenoic acid (22:6 ω–3) of phospholipids in breast adipose tissue was significantly lower in cases than in controls among postmenopausal women [26]. A positive correlation was also found between dietary intake of docosahexaenoic acid and its level in phospholipids of breast adipose tissue. No difference was found in the level of linoleic

acid or long-chain ω–6 PUFA in breast adipose tissue between cases and controls. However, none of these three studies addressed the association of the balance between ω–3 and ω–6 PUFA with breast cancer risk.

In the European Community Multicenter Study on Antioxidants, Myocardial Infarction and Cancer of the breast (EURAMIC), the fatty acid content of adipose tissue from the subcutaneous buttock in postmenopausal breast cancer cases and controls from five European countries (Germany, Switzerland, the Netherlands, Northern Ireland, Spain) was used to explore the hypothesis that ω–3 PUFA levels were inversely associated to breast cancer risk and that the inverse association depended on background levels of ω–6 PUFA [36]. Inverse associations between breast cancer risk and total adipose tissue ω–3 PUFA levels (EPA, DHA and alpha-linolenic acid) appeared in three centers (Zeist, Corelaine, Zurich), with the second and third tertiles having odds ratios below 1.0. However, only one inverse association reached statistical significance (Zurich). In contrast, a positive association was observed in two other centers (Malaga, Berlin), reaching statistical significance in one center (Malaga). The same patters of associations were observed when restricting the analyses to long-chain ω–3 PUFA. Alpha-linolenic alone showed a non-significant inverse association with breast cancer risk in two centers (Corelaine, Zurich) and a non-significant positive association in the three others centers. Pooling all centers gave little evidence of an inverse association with breast cancer for total ω–3 PUFA, long-chain ω–3 PUFA and alpha-linolenic acid. Total ω–6 PUFA (linoleic acid, dihomo-gamma-linolenic acid, arachidonic acid) showed a strong positive association with breast cancer in one center (Malaga). No associations or weak inverse associations were observed in the other centers. Pooling all centers yielded weak evidence of a positive association between ω–6 PUFA and breast cancer risk. The ratio of total ω–3 PUFA to ω–6 PUFA or the ratio of long-chain ω–3 PUFA to ω–6 PUFA was inversely associated with breast cancer risk in four of five centers. In Spain, the ratio of long-chain ω–3 PUFA to ω–6 PUFA showed a significant inverse association with disease, despite both ω–3 and ω–6 PUFA exhibiting significant positive associations with breast cancer. In pooled analyses, the effect estimates for total ω–3 PUFA, long-chain ω–3 PUFA and alpha-linolenic acid were higher when considering the relation to ω–6 PUFA rather than absolute levels. The strongest inverse association with breast cancer was reported for the ratio of long-chain ω–3 PUFA to ω–6 PUFA, with evidence of a dose-response pattern. In our case-control study conducted in central France, we investigated the association between ω–3 and ω–6 PUFA, the ratio ω–3 PUFA to ω–6 PUFA and the risk of breast cancer [37]. We examined the fatty acid composition in breast adipose tissue from 241 patients with invasive breast carcinoma and from 88 control patients with benign breast disease. We found significant inverse associations between individual levels of

Table 1. Estimated relative risk (odds ratio, adjusted) of breast cancer and 95% CI by adipose tissue ω–3 and ω–6 fatty acid levels from the whole population (n = 329)

Fatty acids	Odds ratio* (95%)			p for trend
	1st tertile (low)	2nd tertile	3rd tertile (high)	
18:2 ω–6	1.00	1.60 (0.76–3.36)	2.31 (1.15–4.67)	0.06
20:4 ω–6	1.00	0.87 (0.41–1.84)	0.98 (0.42–2.29)	0.32
Total ω–6	1.00	1.50 (0.71–3.21)	2.29 (0.12–4.69)	0.07
18:3 ω–3	1.00	0.97 (0.50–1.90)	0.39 (0.19–0.78)	0.01
22:6 ω–3	1.00	0.84 (0.40–1.75)	0.31 (0.13–0.75)	0.016
Total ω–3	1.00	0.91 (0.45–1.87)	0.40 (0.17–0.94)	0.001

*Adjusted for age at diagnosis, height, BMI (as continuous variables), menopause (pre- and post-) and menopausal status-BMI interaction.

ω–3 PUFA (alpha-linolenic acid, docosahexaenoic acid) and the relative risk of breast cancer (table 1). However, the strongest inverse association with breast cancer was found for the ratio of long-chain ω–6 PUFA to ω–3 PUFA.

This set of data supports the idea that the protective effect of ω–3 PUFA depends on background levels of ω–6 PUFA. Thus, it may be the balance between ω–3 and ω–6 PUFA rather than the individual amount of each class of PUFA which influence the outcome of breast cancer.

References

1 Bougnoux P: n–3 polyunsaturated fatty acids and cancer. Curr Opin Clin Nutr Metab Care 1999;2: 121–126.

2 Cohen LA, Chen-Backlund JY, Sepkovic DW, Sugie S: Effect of varying proportions of dietary menhaden and corn oil on experimental rat mammary tumor promotion. Lipids 1993;8:449–456.

3 Sasaki T, Kobayashi Y, Shimizu J, Wada M, In'nami S, Kanke Y, Takita T: Effects of dietary n–3 to n–6 polyunsaturated fatty acid ratio on mammary carcinogenesis in rats. Nutr Cancer 1998;30: 137–143.

4 Cognault S, Jourdan ML, Germain E, Pitavy R, Morel E, Durand G, Bougnoux P, Lhuillery C: Effect of an alpha-linolenic acid-rich diet on rat mammary tumor growth depends on the dietary oxidative status. Nutr Cancer 2000;36:33–41.

5 Simopoulos AP: Importance of the ratio of omega–6/omega–3 essential fatty acids: evolutionary aspects. World Rev Nutr Diet. Basel, Karger, 2003, vol 92, pp 1–22.

6 Simopoulos AP: The Mediterranean diets: What is so special about the diet of Greece? The scientific evidence. J Nutr 2001;131:3065S–3073S.

7 Simopoulos AP: The importance of the ratio of omega–6/omega–3 essential fatty acids. Biomed Pharmacother 2002;56:365–379.

8 Rose DP, Connolly JM: Omega–3 fatty acids as cancer chemopreventive agents. Pharmacol Ther 1999;83:217–244.

9 Doll R, Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191–1308.
10 Doll R: The lessons of life: Keynote address to the nutrition and cancer conference. Cancer Res 1992;52:2024s–2029s.
11 Willett WC, Hunter DJ, Stampfer MJ, et al: Dietary fat and fiber in relation to risk of breast cancer. JAMA 1992;268:2037–2044.
12 Hunter DJ, Spiegelman D, Adami H, et al: Cohort studies of fat intake and the risk of breast cancer-a pooled analysis. N Engl J Med 1996;334:356–361.
13 Kaizer L, Boyd NF, Kriukov V, Tritchler D: Fish consumption and breast cancer risk: An ecological study. Nutr Cancer 1989;12:61–68.
14 Sasaki S, Horacsek M, Kestleloot H: An ecological study of the relationship between dietary intake and breast cancer mortality. Prev Med 1993;22:187–202.
15 Guo W, Chow W, Zheng W, et al: Diet, serum markers and breast cancer mortality in China. Jpn J Cancer Res 1994;85:572–577.
16 Ingram DM, Nottage E, Roberts T: The role of diet in the development of breast cancer: A case-control study of patients with breast cancer, benign epithelial hyperplasia and fibrocystic disease of the breast. Br J Cancer 1991;64:187–191.
17 Toniolo P, Riboli E, Shore R, Pasternack BS: Consumption of meat, animal products, protein, and fat and risk of breast cancer: A prospective cohort study in New York. Epidemiology 1994;5:391–397.
18 Yuan JM, Wang QS, Ross RK, et al: Diet and breast cancer in Shanghai and Tianjin, China. Br J Cancer 1995;71:1353–1358.
19 Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S: Fish consumption and cancer risk. Am J Clin Nutr 1999;70:85–90.
20 Malik IA, Sharif S, Malik F, et al: Nutritional aspects of mammary carcinogenesis: A case-control study. J Park Med Assoc 1993;43:118–120.
21 Landa MC, Frago N, Tres A: Diet and the risk of breast cancer in Spain. Eur J Cancer Prev 1994;3:313–320.
22 Hirose K, Kazuo T, Hamajima N, et al: A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. Jpn J Cancer Res 1995;86:146–154.
23 Braga C, La Vecchia C, Negri E, Franceschi S, Parpinel M: Intake of selected foods and nutrients and breast cancer risk: An age- and menopause-specific analysis. Nutr Cancer 1997;28: 258–263.
24 Vatten LJ, Solvoll K, Løken EB: Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. Int J Cancer 1990;46:12–15.
25 Smith-Warner SA, Spiegelman D, Adami HO, et al: Types of dietary fat and breast cancer: A pooled analysis of cohort studies. Int J Cancer 2001;92:767–774.
26 Zhu ZR, Ågren S, Männistö S, et al: Fatty acid composition of breast adipose tissue in breast cancer patients and in patients with benign breast disease. Nutr Cancer 1995;24:151–160.
27 Voorrips L, Brants H, Kardinaal A, Hiddink G, van den Brandt P: Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: The Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002;76:873–82.
28 Chajès V, Hultén K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, Riboli E: Fatty acid composition in serum phospholipids and risk of breast cancer: An incident case-control study in Sweden. Int J Cancer 1999;83:585–590.
29 Vatten LJ, Bjerve KS, Andersen A, Jellum E: Polyunsaturated fatty acids in serum phospholipids and risk of breast cancer: A case-control study from the Janus Bank in Norway. Eur J Cancer 1993;29A:532–538.
30 Saadatian-Elahi M, Toniolo P, et al: Serum fatty acids and risk of breast cancer in a nested case-control study of the New York University Women's Health Study. Cancer Epidemiol Biomarkers Prev 2002;11:1353–1360.
31 Pala V, Krogh V, Muti P, Chajès V, Riboli E, Micheli A, Saadatian M, Sieri S, Berrino F: Erythrocyte membrane fatty acids and subsequent breast cancer: A prospective Italian study. J Natl Cancer Inst 2001;93:1088–1095.
32 London SJ, Sacks FM, Caesar J, et al: Fatty acid composition of subcutaneous adipose tissue and diet in postmenopausal US women. Am J Clin Nutr 1991;54:340–345.

33 Kohlmeier L, Kohlmeier M: Adipose tissue as a medium for epidemiologic exposure assessment. Environ Health Perspect 1995;103:99–106.
34 London SJ, Sacks FM, Stampfer MJ, Henderson IC, et al: Fatty acid composition of the subcutaneous adipose tissue and risk of proliferative benign breast disease and breast cancer. J Natl Cancer Inst 1993;85:785–793.
35 Petrek JA, Hudgins LC, Levine B, Ho M, Hirsch J: Breast cancer risk and fatty acids in the breast and abdominal adipose tissues. J Natl Cancer Inst 1994;86:53–56.
36 Simonsen N, Van't Veer P, Strain JJ, Martin-Moreno JM, et al: Adipose tissue omega–3 and omega–6 fatty acid content and breast cancer in the EURAMIC study. Am J Epidemiol 1998;147: 342–352.
37 Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, Lavillonnière F, Body G, Le Floch O, Chajès V: n–3 and n–6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France. Int J Cancer 2002;98:78–83.

Philippe Bougnoux
INSERM EMI-U 0211
CHU Bretonneau, 2bis Blvd Tonnellé
F–37044 Tours (France)
Tel. +33 247 366179, Fax +33 247 366226, E-Mail bougnoux@med.univ-tours.fr

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 166–175

Fish, ω–3 Polyunsaturated Fat Intake and Cancer at Selected Sites

Alessandra Tavani[a], *Silvia Franceschi*[b], *Fabio Levi*[c], *Carlo La Vecchia*[a,d]

[a] Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy; [b] International Agency for Research on Cancer, Lyon, -France; [c] Registre Vaudois des Tumeurs, Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland; [d] Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milano, Italy

Ecological studies have suggested inverse relations between fish and ω–3 polyunsaturated fatty acid (PUFA) intake and the risk of cancer at several sites [1–3], but the issue is still discussed [4–6].

Fish and ω–3 PUFA intake has been inversely related with risk of cancer of the oral cavity and pharynx [7], in most [6, 8–10], but not all studies [11, 12], and with risk of cancer of the esophagus [6, 13–15]. Data are inconclusive for colorectal cancer, with at least a cohort [16] and a case-control study [17] showing an inverse association with fish intake, and at least three case-control studies finding no relation [18–20]. At least two prospective studies, one in women [21] and one in men [22], and two case-control studies [6, 23] found an inverse relation between colon cancer risk and fish intake, while two prospective studies showed no relation [24, 25]. A case-control study on rectal cancer reported an inverse association with fish consumption [6].

With reference to breast cancer, a prospective study on Norwegian women reported no relation with overall fish intake, but an inverse association with poached fish [26]; the Nurses' Health Study cohort found no relation between ω–3 fats from fish and breast cancer risk [27], and a study on Swedish women found no association with fish intake [28]. Of three case-control studies, one from Spain found an inverse association of breast cancer risk with fish intake [29], one from the USA reported an inverse association only in postmenopausal women [30], and one from Italy found no relation [6]. A nested case-control study of the New York University Women's Health Study found that while total PUFAs (ω–3 and ω–6) were suggestive of a small protection, neither individual ω–3 PUFAs nor ω–6 ones were related to breast cancer risk [31]. Another study found no association of ω–3 fatty acid intake with a mammographic pattern

showing extensive fibrosis, which may be associated with a proliferative process [32]. The information on ovarian cancer is scanty and controversial, with two case-control studies reporting elevated risk with fish consumption [33, 34] and one showing an inverse trend [6].

Inverse associations with risk have also been reported from cohort and case-control studies for cancer of the larynx [7], stomach [35], pancreas [36], gallbladder [37], bladder [38], kidney [39] and thyroid [40], and a panel report, published in 1997, concluded that fish consumption may protect against cancers of the colon, rectum and ovary [41].

In the present paper, we review the data on fish and ω–3 PUFA intake and cancer risk from a network of case-control studies conducted in Italy and Switzerland.

Methods

Data were obtained from two series of hospital-based case-control studies. Each series had the same design, inclusion criteria and similar questionnaire [6, 42]. The first series was conducted between 1983 and 1996 in northern Italy and included patients below age 80 with incident, histologically confirmed cancers of oral cavity/pharynx (n = 181), esophagus (n = 316), stomach (n = 745), colon (n = 828), rectum (n = 498), liver (n = 428), gallbladder (n = 60), pancreas (n = 362), larynx (n = 242), breast (n = 3,412), endometrium (n = 750), ovary (n = 971), prostate (n = 127), bladder (n = 431), kidney (n = 190), thyroid (n = 208), lymphomas (n = 280) and multiple myeloma (n = 120) [6]. The comparison group involved overall 7,990 patients. For the second series, information was collected between 1991 and 2001 in several areas of northern, central and southern Italy; studies on oral cavity/pharynx, esophagus, colon, rectum and breast were conducted also in the Swiss Canton of Vaud [42]. Cases were patients below age 80 with incident, histologically confirmed cancers of oral cavity/pharynx (n = 736), esophagus (n = 395), colon (n = 1,394), rectum (n = 886), breast (n = 2,900), ovary (n = 1,031) and prostate (n = 1,294). Controls were over 5,000 patients admitted to hospital for a wide spectrum of acute non-neoplastic conditions.

Interviewers used a structured questionnaire including information on socio-demographic factors, anthropometric variables, smoking, alcohol and other lifestyle habits, a problem-oriented medical history, physical activity and history of cancer in relatives.

For the first series of studies information was based on a food frequency questionnaire including a single question on average weekly consumption of fish [40]. For the second series of studies, the questionnaire included questions on 78 foods or food groups [42] and information on fish derived from weekly frequency of consumption and portion size of three items: mixed Mediterranean fish and seafood, including clams, mussels (0.94 g of ω–3 PUFAs per portion); other fish, including cuttlefish, octopus, squid (0.49 g of ω–3 PUFAs per portion); and canned tuna, mackerel and sardines (0.34 g of ω–3 PUFAs per portion). Content in ω–3 PUFAs (including eicosapentaenoic and docosahexaenoic acids) and total energy intake were computed using tables of food composition [43, 44] taking into account the differences in food habits between Italy and Switzerland. In the Italian studies, the mean national composition of fish dishes (including shrimp, cuttlefish, squid, mussels, clams and other seafood) was based on the mean national consumption figures and was used to obtain

Table 1. Odds ratios (OR) and their 95% CI for selected cancers according to fish intake: Italy, 1991–2001

Cancer site	Number of cases	Fish intake		
		1 portion/week	>1 portion/week	p, trend
Oral cavity/pharynx	181	0.8 (0.6–1.2)	0.5 (0.3–0.9)	0.009
Esophagus	316	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.001
Stomach	745	0.8 (0.7–1.0)	0.7 (0.5–0.8)	0.0003
Colon	828	0.7 (0.6–0.8)	0.6 (0.5–0.7)	<0.00001
Rectum	498	0.8 (0.7–1.0)	0.5 (0.3–0.6)	<0.00001
Liver	428	0.9 (0.7–1.2)	1.0 (0.7–1.3)	0.75
Gallbladder	60	1.2 (0.7–2.2)	0.6 (0.3–1.4)	0.44
Pancreas	362	0.7 (0.5–0.9)	0.7 (0.5–1.0)	0.018
Larynx	242	0.7 (0.5–1.0)	0.7 (0.4–1.0)	0.019
Breast	3412	1.1 (0.9–1.2)	1.0 (0.8–1.1)	0.75
Endometrium	750	0.6 (0.5–0.8)	0.8 (0.6–0.9)	0.002
Ovary	971	0.9 (0.7–1.0)	0.7 (0.6–0.9)	0.002
Prostate	127	1.0 (0.6–1.4)	0.7 (0.4–1.1)	0.16
Bladder	431	1.1 (0.9–1.4)	1.4 (1.0–1.8)	0.024
Kidney	190	0.9 (0.6–1.2)	0.9 (0.6–1.3)	0.527
Thyroid	208	1.2 (0.8–1.6)	1.1 (0.7–1.6)	0.655
Hodgkin disease	80	0.8 (0.5–1.3)	0.7 (0.4–1.4)	0.294
Non-Hodgkin lymphoma	200	1.0 (0.8–1.4)	0.7 (0.5–1.1)	0.294
Multiple myeloma	120	0.9 (0.6–1.3)	0.5 (0.3–0.9)	0.040
Controls	7,990	–	–	–

Reference category was <1 portion of fish per week. OR adjusted for age, sex, area of residence, education, body mass index, alcohol and smoking. Modified from Fernandez et al. [42].

the coefficient for computing ω–3 PUFA [45]. In the Swiss studies, the coefficients were calculated on the basis of local consumption. The correlation coefficient for reproducibility of questions on fish was 0.59 [46] and that for validity of ω–3 PUFAs was 0.64 [47].

Data Analysis

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for fish or for subsequent quintiles of ω–3 PUFA intake were derived using unconditional multiple logistic regression [48] (in the first series of studies and in unmatched studies, i.e. breast, ovarian, prostate and colorectal cancers of the second series) or conditional one (in studies matched on age, sex and study center, i.e. upper aero-digestive tract cancers of the second series). Frequency of fish and ω–3 PUFA intake was also introduced as a continuous variable; this model gave an estimate of the OR relative to an increase of 1 portion of fish per week or 1 g of ω–3 PUFAs per week. All regression models included terms for age, sex, area of residence/study center, education, body mass index, smoking and alcohol, plus other variables as indicated in tables 1 and 2.

Table 2. Odds ratios (OR)[a] and their 95% confidence intervals for selected cancers according to ω–3 polyunsaturated fatty acids (PUFA): Italy and Switzerland, 1991–2001

Cancer site	Number of cases: controls	Quintiles of intake				
		2nd	3rd	4th	5th (highest)	p, trend
Oral cavity/ pharynx[b]	736:1,772	0.9 (0.7–1.2)	0.7 (0.5–0.9)	0.6 (0.4–0.8)	0.5 (0.3–0.7)	<0.0001
Esophagus[b]	395:1,066	0.8 (0.5–1.2)	0.7 (0.5–1.1)	0.6 (0.4–0.9)	0.5 (0.3–0.7)	0.0005
Large bowel[c]	2,280:4,765	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.8 (0.7–0.9)	0.7 (0.6–0.9)	<0.0001
Colon[c]	1,394:4,765	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.8 (0.6–0.9)	0.7 (0.5–0.8)	<0.0001
Rectum[c]	886:4,765	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.009
Breast[d]	2,900:3,122	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.003
Ovary[d]	1,031:2,411	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.8 (0.7–1.1)	0.6 (0.4–0.7)	<0.0001
Prostate[b]	1,294:1,451	1.2 (0.9–1.5)	1.1 (0.8–1.4)	1.4 (1.1–1.8)	1.5 (1.2–1.9)	0.001

[a]Reference category: 1st quintile of PUFA intake (lowest). The upper cut-off points for the quintiles of intake (g/week) ranged between: 0.47–0.55 for the 1st quintile, 0.83–0.89 for the 2nd, 1.06–1.28 for the 3rd and 1.46–1.89 for the 4th. Modified from Tavani et al. [43].

[b]OR adjusted for age, sex, study center, education, body mass index, energy intake, alcohol and smoking.

[c]OR adjusted for age, sex, study center, education, body mass index, energy intake, alcohol, smoking and physical activity.

[d]OR adjusted for age, study center, education, body mass index, energy intake and parity.

Results

Fish and Cancer Risk

The distribution of cases of selected cancers and controls, with the corresponding OR and 95% CI, according to fish consumption is shown in table 1. There was a consistent pattern of protection towards several digestive tract cancers, such as those of the oral cancer/pharynx, esophagus, stomach, colon and rectum, for which the OR for an increment of one serving per week of fish was 0.5–0.7 and the trends in risk were statistically significant. The OR were 1.0 and 0.6 for liver and gallbladder cancer, with no trend in risk, and the OR was 0.7 for cancers of the pancreas and larynx with an inverse trend in risk. Among female cancer, the OR was 1.0 for breast cancer and 0.8 and 0.7 for those of the endometrium and ovary, with an inverse trend in risk. No association and no trend in risk was found for cancers of the prostate (OR 0.7), bladder (OR 1.4), kidney (OR 0.9), thyroid (OR 1.1), and for Hodgkin disease (OR 0.7) and non-Hodgkin lymphoma (OR 0.7). The OR for multiple myeloma was 0.5, with a significant trend in risk.

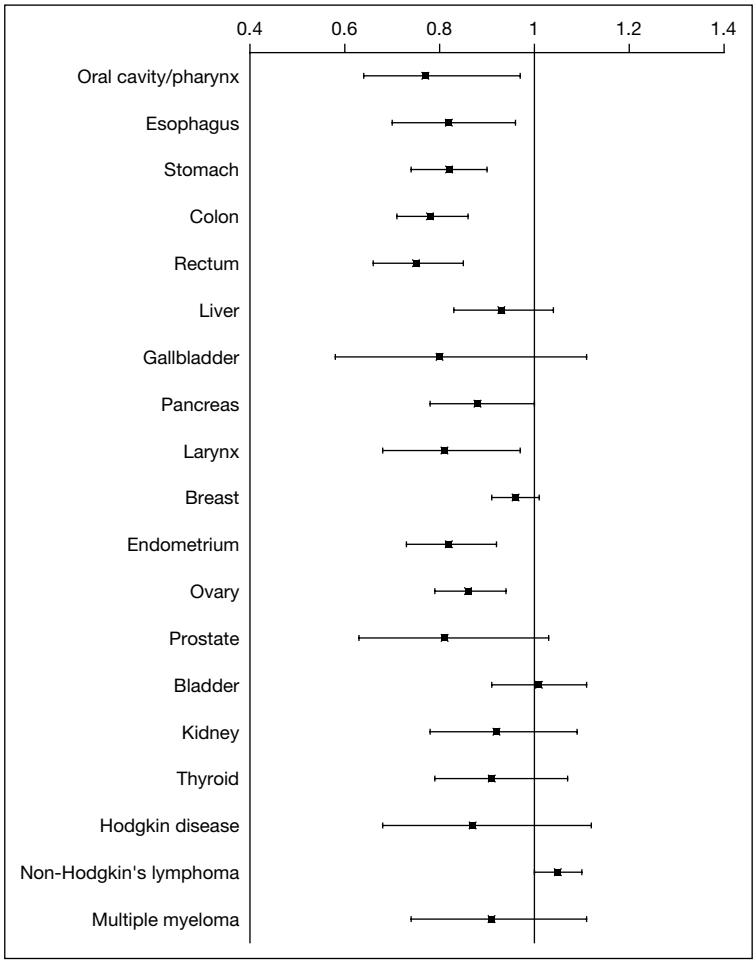


Fig. 1. Continuous odds ratios and 95% confidence interval for an increment of 1 portion/week of fish.

The continuous OR for an increase of 1 portion/week of fish are reported in figure 1. The OR were consistently below unity for digestive tract cancers (OR 0.7–0.8) and were 0.8 for gallbladder, laryngeal and prostate cancer; 0.9 for hepatic, pancreatic, endometrial, ovarian, thyroid cancer, and for Hodgkin disease and multiple myeloma; 1.0 for breast, bladder and kidney cancer and for non-Hodgkin lymphoma. The risk of cancer at selected sites according to fish consumption was consistent across strata of age, sex, education, smoking, alcohol and body mass index.

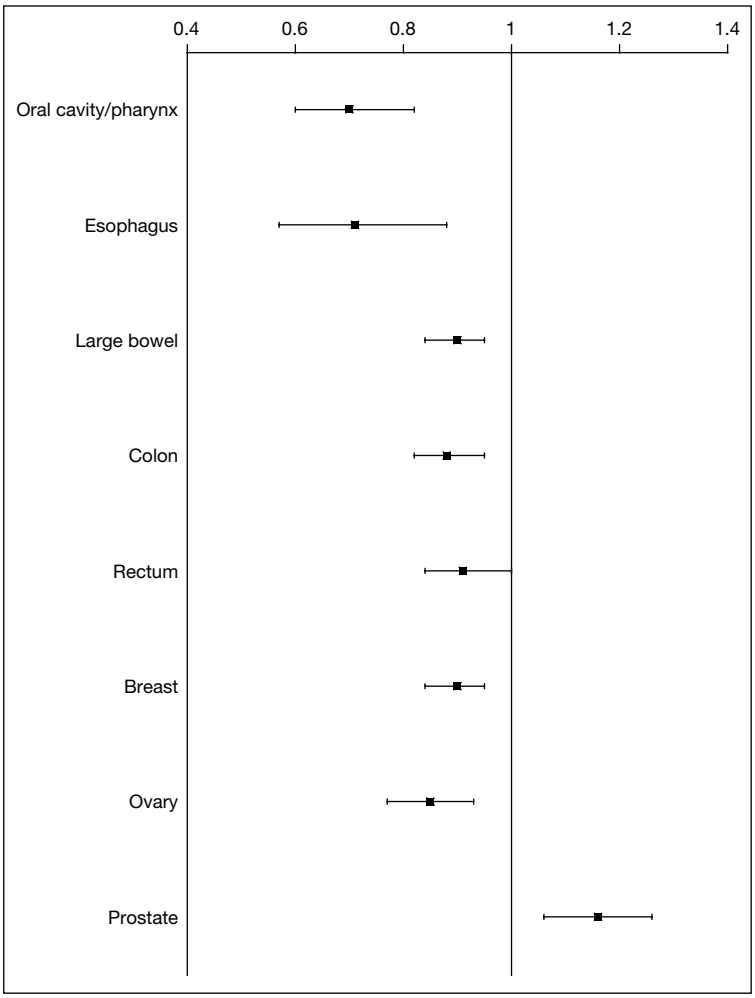


Fig. 2. Continuous odds ratios and 95% confidence interval for an increment of 1 g/week of ω–3 polyunsaturated fatty acids.

ω–3 PUFAs and Cancer Risk

Table 2 shows the OR of cancer at selected sites for subsequent quintiles of ω–3 PUFA intake. Compared to patients with the lowest quintile of intake, the multivariate OR for those with the highest ω–3 PUFA intake was 0.5 for oral/pharyngeal and for esophageal cancer, 0.7 for colon cancer, 0.8 for rectal and breast cancer, and 0.6 for ovarian cancer; all the estimates were significant, except for cancer of the rectum and breast, which were of borderline

significance, and the inverse trends in risk were significant for all cancer sites. Prostate cancer risk was slightly associated to ω–3 PUFA intake (OR 1.5), with a borderline significant trend in risk.

The continuous OR for an increase of 1 g/week of ω–3 PUFAs are reported in figure 2. The OR were consistently below unity for all cancers, except prostate cancer: 0.7 for oral/pharyngeal and esophageal cancer; 0.9 for colon, rectal breast and ovarian cancer; 1.2 for prostate cancer. The risk of cancer at selected sites according to an increase of 1 g/week of ω–3 PUFA intake was consistent across strata of age, sex, smoking and alcohol.

Discussion

The data from this integrated network of studies confirm that fish and ω–3 PUFA consumption is a favourable indicator of the risk of several common cancers, mainly those of the digestive tract. The results are less clear for breast cancer, as fish consumption was not related to the risk in the first study, while ω–3 PUFA intake was inversely related in the second study, and for prostate cancer, which was not related to fish intake in the first study and showed a slight positive association with ω–3 PUFAs in the second study. The inverse relation between fish/ω–3 PUFAs and cancers of the digestive tract was not explained by sociodemographic factors, total energy intake and selected other covariates, as it was consistently found in different strata. We cannot exclude that allowance for other variables specific for each cancer site might modify some of the risk estimates, but further allowance for physical activity or exogenous hormones did not materially modify the risk estimates for colorectal, breast or ovarian cancer. Residual confounding remains, however, plausible, because fish and ω–3 PUFAs could be markers for a more favourable dietary pattern or healthier lifestyle and of a lower consumption of meat, which is a potential risk factor for digestive tract cancers [49].

As dietary PUFAs of the ω–3 series are rapidly incorporated into cell membranes and profoundly influence several biological responses [50], multiple mechanisms may be involved in their preventive activity. These include suppression of neoplastic transformation, cell growth inhibition, influence on the immune system and inflammation [51, 52], enhanced apoptosis and antiangiogenicity [53]. Animal studies have shown that diets rich in ω–3 PUFAs have diminished tumorigenesis [54], and that they decrease the number and size of tumors and increase the time elapsed before appearance of tumors [55]. In the colon ω–3 PUFAs may act through the prostaglandin pathway [56, 57], and influence the activity of enzymes and proteins related to intracellular signalling and cell proliferation [58], and in the breast they suppress cell growth and metastases in mouse models [59].

In conclusion, this investigation points to fish and ω–3 PUFA intakes as important potential factors in the nutritional etiology of several common cancers. Together with the favorable effect of fish and ω–3 PUFA intake on the cardiovascular system [60, 61], this indicates that fish can be a better substitute for meat intake [49] in the western diet. The finding that an increase of 1 portion per week of fish or 1 g per week of ω–3 PUFAs significantly lowers the risk of cancer at several sites suggests that the protection on carcinogenesis is exerted at relatively low doses, as observed also for myocardial infarction [62].

Acknowledgements

This work was partially supported by the Italian Association for Cancer Research, Italian and Swiss Leagues Against Cancer, Italian Ministry of Education (COFIN 2003). We thank Ms Paola Bonifacino for editorial assistance.

References

1 Caygill CP, Hill MJ: Fish, n–3 fatty acids and human colorectal and breast cancer mortality. Eur J Cancer Prev 1995;4:329–332.
2 Caygill CP, Charlett A, Hill MJ: Fat, fish, fish oil and cancer. Br J Cancer 1996;74:159–164.
3 Grant WB: An ecologic study of dietary and solar ultraviolet-B links to breast carcinoma mortality rates. Cancer 2002;94:272–281.
4 Willett WC: Specific fatty acids and risk of breast and prostate cancer: dietary intake. Am J Clin Nutr 1997;66(suppl):1557S–1563S.
5 de Deckere EA: Possible beneficial effect of fish and fish n–3 polyunsaturated fatty acids in breast and colorectal cancer. Eur J Cancer Prev 1999;8:213–221.
6 Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S: Fish consumption and cancer risk. Am J Clin Nutr 1999;70:85–90.
7 Notani PN, Jayant K: Role of diet in upper aerodigestive tract cancers. Nutr Cancer 1987;10:103–113.
8 McLaughlin JK, Gridley G, Block G, Winn DM, Preston-Martin S, Schoenberg JB, Greenberg RS, Stemhagen A, Austin DF, Ershow AG: Dietary factors in oral and pharyngeal cancer. J Natl Cancer Inst 1988;80:1237–1243.
9 Gridley G, McLaughlin JK, Block G, Blot WJ, Winn DM, Greenberg RS, Schoenberg JB, Preston-Martin S, Austin DF, Fraumeni JF Jr: Diet and oral and pharyngeal cancer among blacks. Nutr Cancer 1990;14:219–225.
10 Tavani A, Gallus S, La Vecchia C, Talamini R, Barbone F, Herrero R, Franceschi S: Diet and risk of oral and pharyngeal cancer: An Italian case-control study. Eur J Cancer Prev 2001;10:191–195.
11 Winn DM, Ziegler RG, Pickle LW, Gridley G, Blot WJ, Hoover RN: Diet in the etiology of oral and pharyngeal cancer among women from the southern United States. Cancer Res 1984;44:1216–1222.
12 De Stefani E, Ronco A, Mendilaharsu M, Deneo-Pellegrini H: Case-control study on the role of heterocyclic amines in the etiology of upper aerodigestive cancers in Uruguay. Nutr Cancer 1998;32:43–48.
13 Ziegler RG, Morris LE, Blot WJ, Pottern LM, Hoover R, Fraumeni JF Jr: Esophageal cancer among black men in Washington, D.C. II. Role of nutrition. J Natl Cancer Inst 1981;67:1199–1206.
14 Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M, Faivre J: Diet and squamous-cell cancer of the oesophagus: A French multicentre case-control study. Int J Cancer 1998;76:7–12.
15 Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, Russell RM, Weisenburger DD, Tucker KL: Dietary patterns and adenocarcinoma of the esophagus and distal stomach. Am J Clin Nutr 2002;75:137–144.

16 Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E: Prospective study of diet and female colorectal cancer: The New York University Women's Health Study. Nutr Cancer 1997;28:276–281.
17 Haenszel W, Locke FB, Segi M: A case-control study of large bowel cancer in Japan. J Natl Cancer Inst 1980;64:17–22.
18 Le Marchand L, Wilkens LR, Hankin JH, Kolonel LN, Lyu LC: A case-control study of diet and colorectal cancer in a multiethnic population in Hawaii (United States): Lipids and foods of animal origin. Cancer Causes Control 1997;8:637–648.
19 Levi F, Pasche C, La Vecchia C, Lucchini F, Franceschi S: Food groups and colorectal cancer risk. Br J Cancer 1999;79:1283–1287.
20 Boutron-Ruault MC, Senesse P, Faivre J, Chatelain N, Belghiti C, Méance S: Foods as risk factors for colorectal cancer: a case-control study in Burgundy (France). Eur J Cancer Prev 1999;8:229–235.
21 Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE: Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323:1664–1672.
22 Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC: Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390–2397.
23 Iscovich JM, L'Abbé KA, Castelleto R, Calzona A, Bernedo A, Chopita NA, Jmelnitzsky AC, Kaldor J: Colon cancer in Argentina. I: Risk from intake of dietary items. Int J Cancer 1992;51:851–857.
24 Gaard M, Tretli S, Løken EB: Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. Eur J Cancer Prev 1996;5:445–454.
25 Goldbohm RA, van den Brandt PA, van't Veer P, Brants HA, Dorant E, Sturmans F, Hermus RJ: A prospective cohort study on the relation between meat consumption and the risk of colon cancer. Cancer Res 1994;54:718–723.
26 Vatten LJ, Solvoll K, Løken EB: Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. Int J Cancer 1990;46:12–15.
27 Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, Speizer FE, Rosner B, Willett WC: Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281:914–920.
28 Terry P, Suzuki R, Hu FB, Wolk A: A prospective study of major dietary patterns and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2001;10:1281–1285.
29 Landa MC, Frago N, Tres A: Diet an the risk of breast cancer in Spain. Eur J Cancer Prev 1994;3:313–320.
30 Ambrosone CB, Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE, Laughlin R, Nemoto T, Shields PG: Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. Int J Cancer 1998;75:825–830.
31 Saadatian-Elahi M, Toniolo P, Ferrari P, Goudable J, Akhmedkhanov A, Zeleniuch-Jacquotte A, Riboli E: Serum fatty acids and risk of breast cancer in a nested case-control study of the New York University Women's Health Study. Cancer Epidemiol Biomarkers Prev 2002;11: 1353–1360.
32 Jakes RW, Duffy SW, Ng F-C, Gao F, Ng E-H, Seow A, Lee H-P, Yu Mc: Mammographic parenchymal patterns and self-reported soy intake in Singapore Chinese women. Cancer Epidemiol Biomarkers Prev 2002;11:608–613.
33 Mori M, Miyake H: Dietary and other risk factors of ovarian cancer among elderly women. Jpn J Cancer Res 1988;79:997–1004.
34 Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK: Reproductive, genetic, and dietary risk factors for ovarian cancer. Am J Epidemiol 1988;128:771–777.
35 Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J, Adami H-O: Diet and risk of gastric cancer. A population-based case-control study in Sweden. Int J Cancer 1993;55:181–189.
36 Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM: A case-control study of diet and cancer of the pancreas. Am J Epidemiol 1991;134:167–179.
37 Kato K, Akai S, Tominaga S, Kato I: A case-control study of biliary tract cancer in Niigata Prefecture, Japan. Jpn J Cancer Res 1989;80:932–938.
38 Chyou P-H, Nomura AM, Stemmermann GN: A prospective study of diet, smoking, and lower urinary tract cancer. Ann Epidemiol 1993;3:211–216.

39 McLaughlin JK, Gao YT, Gao RN, Zheng W, Ji BT, Blot WJ, Fraumeni JF Jr: Risk factors for renal-cell cancer in Shangai, China. Int J Cancer 1992;52:562–565.
40 Franceschi S, Levi F, Negri E, Fassina A, La Vecchia C: Diet and thyroid cancer: A pooled analysis of four European case-control study. Int J Cancer 1991;48:395–398.
41 World Cancer Research Fund, American Institute for Cancer Research: Food, nutrition and the prevention of cancer: A global perspective. Washington, America Institute for Cancer Research, 1997, pp 452–459.
42 Tavani A, Pelucchi C, Parpinel MT, Negri E, Franceschi S, Levi F, La Vecchia C: n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer 2003;105:113–116.
43 Salvini S, Parpinel M, Gnagnaella P, Maisonneuve P, Turrini A (eds): Banca Dati di Composizione degli Alimenti per Studi Epidemiologici in Italia. Milano, Istituto Europeo di Oncologia, 1998.
44 Carnevale E, Miuccio F: Tabelle di Composizione degli Alimenti. Roma, Istituto Nazionale della Nutrizione, 1989.
45 Turrini A, Saba A, Lintas C: Study of the Italian reference diet for monitoring food constituents and contaminants. Nutr Res 1991;11:861–874.
46 Franceschi S, Negri E, Salvini S, Decarli A, Ferraroni M, Filiberti R, Giacosa A, Talamini R, Nanni O, Panarello G, La Vecchia C: Reproducibility of an Italian food frequency questionnaire for cancer studies: Results for specific food items. Eur J Cancer 1993;29A:2298–2305.
47 Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, La Vecchia C, Negri E, Salvini S, Falcini F, Giacosa A: Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 1996;6:110–118.
48 Breslow NE, Day NE: Statistical Methods in Cancer Research, The Analysis of Case-Control Studies. Lyon, IARC Scientific Publication, 1980, vol I, No 32.
49 Tavani A, La Vecchia C, Gallus S, Lagiou P, Trichopoulos D, Levi F, Negri E: Red meat intake and cancer risk: A study in Italy. Int J Cancer 2000;86:425–428.
50 Alexander JW: Immunonutrition: The role of omega-3 fatty acids. Nutrition 1998:14:627–633.
51 Grimble RF: Nutritional modulation of immune function. Proc Nutr Soc 2001;60:389–397.
52 Grant WB: Fish consumption, cancer, and Alzheimer disease. Am J Clin Nutr 2000;71:599–603.
53 Rose DP, Connolly JM: Omega–3 fatty acids as cancer chemopreventive agents. Pharmacol Ther 1999;83:217–244.
54 Cave WT Jr: Dietary n–3 (omega–3) polyunsaturated fatty acid effects on animal tumorigenesis. FASEB J 1991;5:2160–2166.
55 Simopoulos AP: Omega–3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991;54:438–463.
56 Hill MJ: Mechanisms of diet and colon carcinogenesis. Eur J Cancer Prev 1999;8(suppl 1):S95–S98.
57 Singh J, Hamid R, Reddy BS: Dietary fat and colon cancer: modulation of cyclooxygenase-2 by types and amount of dietary fat during the postinitiation stage of colon carcinogenesis. Cancer Res 1997;57:3465–3470.
58 Bartsch H, Nair J, Owen RW: Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: Emerging evidence for their role as risk modifiers. Carcinogenesis 1999;20:2209–2218.
59 Rose DP, Connolly JM: Effects of dietary omega–3 fatty acids on human breast cancer growth and metastases in nude mice. J Natl Cancer Inst 1993;85:1743–1747.
60 Marckmann P, Grønbaek M: Fish consumption and coronary heart disease mortality: A systematic review of prospective cohort studies. Eur J Clin Nutr 1999;53:585–590.
61 GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico): Dietary supplementation with n–3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. Lancet 1999;354:447–455.
62 Tavani A, Pelucchi C, Negri E, Bertuzzi M, La Vecchia C: n–3 polyunsaturated fatty acids, fish, and nonfatal acute myocardial infarction. Circulation 2001;104:2269–2272.

Alessandra Tavani, BiolSciD
Istituto di Ricerche Farmacologiche 'Mario Negri'
Via Eritrea, 62, IT–20157 Milano (Italy), Tel. +39 02 39014 460, Fax +39 02 39001916,
E-Mail tavani@marionegri.it

Simopoulos AP (ed): Nutrition and Fitness: Obesity, the Metabolic Syndrome, Cardiovascular Disease, and Cancer. World Rev Nutr Diet. Basel, Karger, 2005, vol 94, pp 176–188

Cancer Risk Reduction by Physical Exercise

Andreas Willer

III. Medizinische Universitätsklinik, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Mannheim, Deutschland

The worldwide burden of cancer is increasing; thus, in the year 2000, more than 10 million people developed cancer, and 6.2 million people died of cancer [1]. Therefore, efficient cancer prevention offers a promising benefit for public health and minimizes economic damage which results from costly treatment and early death.

The currently available data suggest that more than 50% of all cancers in developed countries can be prevented by changing the individual's behavior: reduction of tobacco use, increase of physical activity, controling weight, improving diet, limiting alcohol, getting routine cancer screening tests, avoiding excessive sun exposure and practicing safer sex [2]. The majority of individuals in developed countries is remarkable inactive [3]; furthermore, it is believed that increased physical activity positively influences other health risk factors such as tobacco use, body weight and diet; therefore, and since it also results in prevention of cardiovascular diseases, increased physical activity seems to have the largest impact on improvement of public health [4].

Epidemiologic studies have accumulated considerable evidence linking increased physical activity to reduced occurrence of cancers chiefly of breast and colon [5–7]. This review focuses on the impact of physical activity for reduction of the individual cancer risk (table 1).

Influence of Physical Activity on Different Cancers

Breast Cancer

Obesity, which is a BMI ≥30, endogenous hormones and physical inactivity have been identified as risk factors for breast cancer [8, 9]. However, the

Table 1. Selected studies and reviews providing evidence for a decreased cancer risk due to increased physical activity

Cancer type	Evidence level	
	2	3
Breast, ovarian, endometrial cancer		Kramer 1996, r [10]
Breast cancer	Adams, 2001, cs, n = 704 [70] Friedenreich, 1998, r, 21 studies [16] Gammon, 1998, r, 16 studies [15] Rockhill, 1999, cs, n = 3,137 [60] Thune, 1997, cs, n = 351 [17] Thune, 2001, r, 41 studies [74] Patel, 2003, cs, n = 1,520 [75] Thompson, 1997, animal trial [76]	Bernstein, 1994, cc, n = 545 [71] Friedenreich, 2001, cc, n = 1,233 [72] McTiernan, 1998, r [5] Mezzetti, 1998, cc, n = 2,569 [20] Moradi, 2000, cc, n = 3,347 [73] Verloop, 2000, cc, n = 918 [18]
Ovarian cancer		Cottreau, 2000, cc, n = 767 [27] Zhang, 2004, cc, n = 254 [26]
Endometrial cancer	Moradi, 1998, cs, n = 12,332 [22] Terry, 1999, cs, n = 133 [23] Colbert, 2003, cs, n = 253 [67]	Goodman, 1997, cc, n = 332 [24] Hirose, 1996, cc, n = 145 [77] Kalandidi, 1996, cc, n = 145 [78] Levi, 1993, cc, n = 274 [79] Olson, 1997, cc, n = 232 [25] Shu, 1993, cc, n = 268 [80] Sturgeon, 1993, cc, n = 405 [81]
Colon cancer	Colditz, 1997, r [45] Macfarlane,1994, r [83] Martinez, 1997, cs, n = 2,249 [44] McTiernan, 1998, r [5] Rissanen, 1999, r, 18 studies [84] Sternfeld, 1992, r, 18 studies [85] Thune, 1996, cs, n = 335 [42] Thune, 2001, r, 48 studies [74]	Evans, 2002, cc, n = 512 [82] Slattery, 1997, cc, n = 2,073 [46] Slattery, 2003, cc, n = 952 [66]
Lung cancer	Thune, 1997, cs, n = 464 [55]	Kubik, 2002, cc, n = 269 [86] Mao, 2003, cc, n = 1,128 [56]
Prostate cancer	Hartman, 1998, cs, n = 317 [49] Wannamethee, 2001, cs, n = 969 [48]	
Renal cell cancer	Mahabir, 2004, cs, n = 210 [54]	Menezes, 2003, cc, n = 305 [53]
Hemopoietic malignancies	Davey, 2000, cs, n = 2,859 deaths [57]	

The evidence level classification and recommendations are based on guides of the 'Evidence-Based Medicine Working Group' [87, 88] and the 'Oxford Centre for Evidence-Based Medicine' (http://minerva.minervation.com/cebm/). cs = Cohort study; cc = case control study; r = review.

underlying mechanisms by which these factors support carcinogenesis have not yet been completely understood. It is likely that endogenous hormones such as estrogen [10] and probably also growth factors such as insulin-like growth factor (IGF) play a crucial role in the development of breast cancer but also other estrogen dependent cancers (ovarian, endometrial) [10, 11]. Physical activity has been proposed to reduce circulating estrogen levels thus resulting in a reduced occurrence of these cancers [10].

The effect of physical activity on reduction of breast cancer risk can be explained by several mechanisms which decrease hormone and/or growth factor levels and which may act in concert. Obesity decreases estrogen binding and supports the synthesis of estrogens [11]. Therefore, body weight reduction, e.g. by physical exercise, decreases estrogen levels either directly [10] or indirectly via a decrease of IGF-1 [12]. Since high levels of IGF-1 have been found in women with breast cancer [13], IFG may also have direct influence on breast cancer development. In premenopausal women, physical activity probably modifies menstrual function by reducing the number of ovulatory menstrual cycles via a hormone-related mechanism and thus decreases the cumulative life time exposure to progesterone and estrogen [9, 10]. Experimental studies support this hypothesis [14].

The majority of studies report an association of increased physical activity and reduced risk for breast cancer. The risk reduction is 12–60% among pre- and postmenopausal women [15]. Specific subgroups with high levels of physical exercise may experience a particularly great risk reduction; these women are lean (BMI below 22.8), parous and premenopausal [16]. In contrast, the BMI was found to be inversely correlated to the breast cancer risk [17–20]. This suggests that avoiding or modifying these risk factors can significantly contribute to breast cancer prevention (table 1).

However, the results of some studies that analyzed the association of physical activity and breast cancer risk were inconsistent which may be due to methodological limitations and confounding factors [9]. Major problems of epidemiologic studies include the assessment of physical activity in different ways and for restricted periods as well as the inability to measure physical activity with enough precision to detect a protective correlation [18, 21]. Therefore, the design for future studies should incorporate standardized methods to measure physical activity; also, the studies should respect subgroups of women with differences in breast cancer risk factors such as hormone replacement status [21].

The National Cancer Institute (NCI) informs that ‘studies suggest that exercise may be associated with reduced breast cancer risk’ (level of evidence 3) (date last modified 03/2004). Based on level 3 evidence, a level ‘B’ recommendation can be given to increase physical activity for breast cancer prevention.

Endometrial Cancer

Since endometrial cancer belongs to the 'estrogen-dependent' cancers, diminished estrogen life time exposure, e.g. by physical exercise can be expected to result in a reduced cancer risk. The mechanisms that are responsible for reduced estrogen exposure are described in the breast cancer section above.

Large cohort and case control studies have shown a moderate inverse relationship between increased physical exercise and cancer occurrence. The risk reduction in women who exercise regularly is about 40% (table 1) [22–25].

The NCI concludes from the published studies that there is evidence (level 3) that physical activity – among other factors – is associated with a decreased risk of endometrial cancer (date last modified 02/2004). Based on level 3 evidence, the level of recommendation to practice physical activity for prevention of endometrial cancer is 'B'.

Ovarian Cancer

Until recently, it was not clear if modification of estrogen exposure results in a reduction of the risk for ovarian cancer, as has been shown for breast and endometrial cancer. However, a study published in 2004 revealed an association of sedentary behavior and increased ovarian cancer risk, suggesting that physical activity is likely to reduce the cancer risk [26]. Another study reported a 27% risk reduction for cancer in the group of women with the highest level of physical activity when compared to the group with the lowest activity [27]. Nevertheless, it is not clear if the women in the high activity group had a low-fat diet which by itself seems to be associated with a lower risk for ovarian cancer development (table 1) [28].

The NCI gives no information, if ovarian cancer can be prevented by increased physical activity (date last modified 03/2004). Based on the studies published so far, the level of evidence that increased physical exercise can prevent ovarian cancer is 3, resulting in a recommendation level 'C' for increased physical activity to reduce the cancer risk.

Colorectal Cancer

There is good evidence that modifiable factors such as inadequate physical activity, obesity, high fat diet, alcohol and smoking increase the risk for colorectal carcinomas [29]. The simultaneous presence of several risk factors further increases the cancer risk. Among these factors, physical inactivity and obesity have been strongly and consistently reported to be associated with an increased risk for colon cancer [8]. Also, chemokines such as IGF and possibly prostaglandins are likely to contribute to carcinogenesis. However, the underlying mechanisms have not yet been completely identified.

Obese (BMI ≥30) premenopausal women and obese men have a two-fold increased risk for cancer when compared to slimmer individuals [30, 31]. There are several mechanisms which can explain the association of obesity and colon cancer risk and which can be modulated [32]. Insulin levels are positively correlated to obesity [33]. High insulin levels decrease IGF-1 binding protein and thus increase the levels of free IGF-1 [34]. IGF-1 has been positively associated with the colorectal cancer risk in women and men [35–37], probably because IGF-1 promotes tumor development [38, 39]. Prolonged aerobic exercise and a diet low in calories increase IGF-1-binding protein and thus decrease IGF levels [12]. Furthermore, prostaglandin levels, which are elevated in obesity [40] and which are associated with colon cancer in animals [41], can be decreased by physical exercise [40] and non-steroidal anti-inflammatory drugs [39]. Additionally, a faster gastrointestinal transit time has been hypothesized to have a protective effect on cancer occurrence [42, 43]. Thus, weight reduction in obese individuals, optimization of diet and/or increased physical activity are expected to decrease the colon cancer risk.

Despite of different methods for assessing the amount of physical activity, and despite of different types of physical activity, there is remarkably consistent evidence that individuals who are highly physically active have a reduced risk for colon cancer. The risk reduction is reportedly 40–50% and up to 63% in individuals practicing vigorous lifetime leisure activity (table 1) [42, 44–46]. However, some studies such as one on physicians showed no inverse correlation of physical activity and colon cancer risk. The reasons for this null finding may be misclassification of the physical activity or an increased surveillance effect for colon cancer in the study population [47].

The NCI informs that physical activity is one of the factors for which there is evidence of benefit for colorectal cancer prevention (date last modified 03/2004). The level of evidence that colorectal cancer can be prevented by increased physical activity is 3, resulting in a recommendation level ‘B’. Therefore, it is recommended to increase physical activity and maintain lean body weight to prevent colon cancer.

Prostate Cancer

Obesity and sedentary life style have been implicated as risk factors for prostate cancer [8]. Studies investigating the influence of increased physical activity on cancer risk showed inconsistent results. About half of the studies report an average risk reduction of 20% [39, 48, 49], whereas other did not find a risk reduction [50, 51] or even an increase of cancer risk [51]. However, methodological limitations can be identified in most of the studies [51]. Interestingly, one recent study showed that physical exercise results in low

insulin and IGF-1 levels and high IGF-1-binding protein levels which induce apoptosis in prostate cancer cells in vitro [52].

Since the literature provides no clear evidence for a beneficial effect of physical activity on prostate cancer risk reduction, the NCI gives no information about a possible cancer prevention by physical activity (date last modified 02/2004). Thus, due to the controversial study results, there is no evidence that increased physical activity can prevent prostate cancer.

Bladder Cancer

Vigorous physical activity resulted in a significant increase of bladder cancer [48].

Renal Cell Carcinoma

Physical activity may be associated with a decreased risk up to 50% of developing renal cell carcinoma [53, 54].

Lung Cancer

Physical exercise can reduce lung cancer risk by 18–41% dependent chiefly on the dose level of physical activity and less on the histopathologic subtype [55, 56]. However, it is not clear why, in one study, there was no risk reduction for squamous cell carcinoma or for women (table 1) [55]. Since the study results are not consistent, the NCI does not provide any information for prevention of lung cancer by physical activity (date last modified 02/2004).

Leukemia and Malignant Lymphoma

A significant inverse relationship between increased physical activity and cancer-related mortality including hemopoietic malignancies has been observed (table 1) [57].

Other Cancers

Due to a lack of study results on oral, esophageal and gastric cancer, the NCI does not provide any recommendations for prevention of these cancers by increased physical exercise (date last modified 02/2004).

Nonspecific Effects of Physical Activity on Cancer Prevention

The natural nonspecific immune function may be enhanced by physical activity through the cumulative effects of repeated exercise bouts [43]. Thus, the NK cell activity increases with training [58]. In contrast, an association of other healthy life style habits with beneficial effects of physical activity on

cancer risk seems unlikely; however, endurance athletes usually are non-smokers, and regular leisure time activity is associated with a high economic status which tends to reduce exposure to airborne carcinogens both at work and at home [11].

Adverse Effects of Physical Activity

An impairment of the immune system may result from exercise-mediated increases in cortisol, and prostaglandin levels may depress the cellular immune system; however, acute and chronic alterations induced by moderate exercise intensity are rather small, and their practical relevance remains debatable [11].

Level of Physical Exercise Required for Cancer Risk Reduction

The optimum of exercise intensity required for achieving cancer risk reduction has been identified for a fraction of cancers [59]. An inverse dose-response gradient of physical activity or fitness and morbidity such as cancer is described by most prospective observational studies [10, 17, 44, 60, 61]: a linear gradient with a steep slope at low levels of fitness and an asymptote in the upper part of the fitness distribution. Although the evidence level is only 3 due to the study design, the levels of correlation are strikingly consistent. It is nevertheless impossible to distinguish if activity or fitness is more relevant for health [61].

A dose-dependent negative correlation between cancer risk and physical activity has been found in breast cancer [10, 17, 60], colon cancer [44, 61] and lung cancer [56]. At least 4 h of (moderate to) vigorous physical activity per week are consistently reported to yield in a maximum of cancer risk reduction for colon [42, 44, 61], breast [10, 17, 60] and lung cancer [56]. Aerobic physical activity such as biking or walking is recommended which engages large muscle groups [62]. A ‘moderate’ intensity of physical activity is for example biking 4 miles within 15 min, a more ‘vigorous’ intensity is practiced in less time, according to the Centers of Disease Control, USA.

Critical Life Time Period for Practicing Increased Physical Activity in order to Reduce Cancer Risk

Only a few studies investigated in which life time period increased physical activity must be practiced in order to yield the greatest effect on cancer risk

reduction. The development of human cancers from initiation to a clinically manifest disease usually takes several years, if not decades [63–65]. Also, physical exercise is believed to exert its beneficial influence rather at the time of cancer initiation than in developing cancer [9]. Therefore, the maximum benefit of physical exercise can be expected when it is practiced years before the peak of cancer incidence is observed in the sedentary controls. Indeed, this hypothesis seems to be supported by several studies on estrogen-dependent cancer such as breast cancer and colon cancer. In the case of estrogen-dependent cancer, diminished estrogen exposure by physical exercise may be responsible for cancer prevention; this means that for postmenopausal women the time period for increased physical activity which is critical for breast cancer risk reduction seems to be at an age of less than 45 years [16, 17]. In the case of colon cancer, a recent study demonstrated that the most pronounced effect of physical exercise on cancer risk reduction was observed in the group of individuals practicing vigorous activity over the last 20 years [66]. In contrast, physical activity in the recent past is not associated with a reduced risk for breast [60] or endometrial cancer [67], respectively. In another study carried out in 1997, however, a similar age- or time period-dependent beneficial effect of physical activity had not been found; increased physical activity at different life time periods were associated with an approximately equal risk reduction [46].

Recommendations and Future Aspects

In general, physical activity is associated with cancer risk reduction. In more detail, the evidence for a causal relationship between increased physical activity and a reduced risk for developing colon, breast and endometrium cancer is found to be convincing, for ovarian and lung cancer to be probable, for prostate cancer to be possible, for renal cell cancer and hematopoietic cancers to be currently insufficient to make any definitive conclusions [7, 68, 69]. Increased physical activity results in a decrease of the number of breast, endometrium and colon cancers for about 40% through different biological mechanisms that need to be further investigated. Additionally, the benefit of physical exercise applies not only to risk groups, but to the whole population and, importantly, decreases not only the individual risk of developing cancer, but also the risk of developing cardiovascular diseases [57]. Thus, the American Cancer Society has published guidelines on nutrition and physical activity for cancer prevention; these guidelines are consistent with those from the American Heart Association for the prevention of coronary heart disease as well as for general health promotion [4].

However, the evaluation of studies on physical activity and cancer risk reduction is hampered by different physical activity histories and other confounding factors; it is for example not clear to which extent a general 'healthy life style', which includes avoiding modifiable risk factors such as physical inactivity, obesity and smoking, contributes to the cancer risk reduction. Therefore, future studies on physical activity should use standardized methods for measuring physical activity and to identify the appropriate activity; they should further focus on elucidation of underlying biologic mechanisms and confounding factors. Thus, for reducing the individual risk for the most common human cancers, specific large-scale community interventions do not seem to be justified at the moment; instead, the currently available data allow the recommendation of modification of the individual's behavior towards a 'healthy life style' including 4 h of physical exercise weekly which should be moderate or, preferentially, vigorous.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P: Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–156.
2 Stein CJ, Colditz GA: Modifiable risk factors for cancer. Br J Cancer 2004;90:299–303.
3 US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Physical Activity. 1999 Promoting Physical Activity: A Guide for Community Action. Champaign, Human Kinetics, 1999.
4 Byers T, Nestle M, McTiernan A, Doyle C, Currie-Williams A, Gansler T, Thun M: American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2002;52:92–119.
5 McTiernan A, Ulrich C, Slate S, Potter J: Physical activity and cancer etiology: associations and mechanisms. Cancer Causes Control 1998;9:487–509.
6 Lee IM: Physical activity and cancer prevention – data from epidemiologic studies. Med Sci Sports Exerc 2003;35:1823–1827.
7 Willer A: Reduction of the individual cancer risk by physical exercise. Onkologie 2003;26: 283–289.
8 Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO: Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001;91:421–430.
9 Friedenreich CM, Rohan TE: A review of physical activity and breast cancer. Epidemiology 1995;6:311–317.
10 Kramer MM, Wells CL: Does physical activity reduce risk of estrogen-dependent cancer in women? Med Sci Sports Exerc 1996;28:322–334.
11 Shephard RJ, Shek PN: Associations between physical activity and susceptibility to cancer: possible mechanisms. Sports Med 1998;26:293–315.
12 McCarty MF: Up-regulation of IGF binding protein-1 as an anticarcinogenic strategy: Relevance to caloric restriction, exercise, and insulin sensitivity. Med Hypotheses 1997;48:297–308.
13 Agurs-Collins T, Adams-Campbell LL, Kim KS, Cullen KJ: Insulin-like growth factor-1 and breast cancer risk in postmenopausal African-American women. Cancer Detect Prev 2000;24: 199–206.
14 Latikka P, Pukkala E, Vihko V: Relationship between the risk of breast cancer and physical activity: An epidemiological perspective. Sports Med 1998;26:133–143.

15 Gammon MD, John EM, Britton JA: Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst 1998;90:100–117.
16 Friedenreich CM, Thune I, Brinton LA, Albanes D: Epidemiologic issues related to the association between physical activity and breast cancer. Cancer 1998;83(suppl 3):600–610.
17 Thune I, Brenn T, Lund E, Gaard M: Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269–1275.
18 Verloop J, Rookus MA, van der KK, van Leeuwen FE: Physical activity and breast cancer risk in women aged 20–54 years. J Natl Cancer Inst 2000;92:128–135.
19 Ueji M, Ueno E, Osei-Hyiaman D, Takahashi H, Kano K: Physical activity and the risk of breast cancer: A case-control study of Japanese women. J Epidemiol 1998;8:116–122.
20 Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S: Population attributable risk for breast cancer: Diet, nutrition, and physical exercise. J Natl Cancer Inst 1998;90:389–394.
21 Ainsworth BE, Sternfeld B, Slattery ML, Daguise V, Zahm SH: Physical activity and breast cancer: Evaluation of physical activity assessment methods. Cancer 1998;83(suppl 3):611–620.
22 Moradi T, Nyren O, Bergstrom R, Gridley G, Linet M, Wolk A, Dosemeci M, Adami HO: Risk for endometrial cancer in relation to occupational physical activity: A nationwide cohort study in Sweden. Int J Cancer 1998;76:665–670.
23 Terry P, Baron JA, Weiderpass E, Yuen J, Lichtenstein P, Nyren O: Lifestyle and endometrial cancer risk: A cohort study from the Swedish Twin Registry. Int J Cancer 1999;82:38–42.
24 Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN: Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res 1997;57:5077–5085.
25 Olson SH, Vena JE, Dorn JP, Marshall JR, Zielezny M, Laughlin R, Graham S: Exercise, occupational activity, and risk of endometrial cancer. Ann Epidemiol 1997;7:46–53.
26 Zhang M, Xie X, Lee AH, Binns CW: Sedentary behaviours and epithelial ovarian cancer risk. Cancer Causes Control 2004;15:83–89.
27 Cottreau CM, Ness RB, Kriska AM: Physical activity and reduced risk of ovarian cancer. Obstet Gynecol 2000;96:609–614.
28 Risch HA, Jain M, Marrett LD, Howe GR: Dietary fat intake and risk of epithelial ovarian cancer. J Natl Cancer Inst 1994;86:1409–1415.
29 Shike M: Diet and lifestyle in the prevention of colorectal cancer: an overview. Am J Med 1999;106:S11-S15.
30 Terry PD, Miller AB, Rohan TE: Obesity and colorectal cancer risk in women. Gut 2002;51: 191–194.
31 Shike M: Body weight and colon cancer. Am J Clin Nutr 1996;63(suppl 3):S442–S444.
32 Quadrilatero J, Hoffman-Goetz L: Physical activity and colon cancer: A systematic review of potential mechanisms. J Sports Med Phys Fitness 2003;43:121–138.
33 Bruce WR, Giacca A, Medline A: Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomarkers Prev 2000;9:1271–1279.
34 Powell DR, Suwanichkul A, Cubbage ML, DePaolis LA, Snuggs MB, Lee PD: Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. J Biol Chem 1991;266:18868–18876.
35 Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ: Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–625.
36 Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, Colditz GA, Speizer FE, Hankinson SE: A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9: 345–349.
37 Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R: Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut 2002;50:642–646.
38 Giovannucci E: Insulin, insulin-like growth factors and colon cancer: A review of the evidence. J Nutr 2001;131(suppl 11):S3109–S3120.
39 The Scientific Program Committee: Physical activity across the cancer continuum: Report of a workshop. Cancer 2002;95:1134–1143.

40 Martinez ME, Heddens D, Earnest DL, Bogert CL, Roe D, Einspahr J, Marshall JR, Alberts DS: Physical activity, body mass index, and prostaglandin E2 levels in rectal mucosa. J Natl Cancer Inst 1999;91:950–953.
41 Mutoh M, Watanabe K, Kitamura T, Shoji Y, Takahashi M, Kawamori T, Tani K, Kobayashi M, Maruyama T, Kobayashi K, Ohuchida S, Sugimoto Y, Narumiya S, Sugimura T, Wakabayashi K: Involvement of prostaglandin E receptor subtype EP(4) in colon carcinogenesis. Cancer Res 2002;62:28–32.
42 Thune I, Lund E: Physical activity and risk of colorectal cancer in men and women. Br J Cancer 1996;73:1134–1140.
43 Hardman AE: Physical activity and cancer risk. Proc Nutr Soc 2001;60:107–113.
44 Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA: Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 1997;89:948–955.
45 Colditz GA, Cannuscio CC, Frazier AL: Physical activity and reduced risk of colon cancer: implications for prevention. Cancer Causes Control 1997;8:649–667.
46 Slattery ML, Potter J, Caan B, Edwards S, Coates A, Ma KN, Berry TD: Energy balance and colon cancer–beyond physical activity. Cancer Res 1997;57:75–80.
47 Lee IM, Manson JE, Ajani U, Paffenbarger RS Jr, Hennekens CH, Buring JE: Physical activity and risk of colon cancer: the Physicians' Health Study (United States). Cancer Causes Control 1997;8:568–574.
48 Wannamethee SG, Shaper AG, Walker M: Physical activity and risk of cancer in middle-aged men. Br J Cancer 2001;85:1311–1316.
49 Hartman TJ, Albanes D, Rautalahti M, Tangrea JA, Virtamo J, Stolzenberg R, Taylor PR: Physical activity and prostate cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (Finland). Cancer Causes Control 1998;9:11–18.
50 Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG: Case-control study of lifetime total physical activity and prostate cancer risk. Am J Epidemiol 2004;159:740–749.
51 Oliveria SA, Lee IM: Is exercise beneficial in the prevention of prostate cancer? Sports Med 1997;23:271–278.
52 Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA: A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. Prostate 2003;56:201–206.
53 Menezes RJ, Tomlinson G, Kreiger N: Physical activity and risk of renal cell carcinoma. Int J Cancer 2003;107:642–646.
54 Mahabir S, Leitzmann MF, Pietinen P, Albanes D, Virtamo J, Taylor PR: Physical activity and renal cell cancer risk in a cohort of male smokers. Int J Cancer 2004;108:600–605.
55 Thune I, Lund E: The influence of physical activity on lung-cancer risk: A prospective study of 81,516 men and women. Int J Cancer 1997;70:57–62.
56 Mao Y, Pan S, Wen SW, Johnson KC: Physical activity and the risk of lung cancer in Canada. Am J Epidemiol 2003;158:564–575.
57 Davey SG, Shipley MJ, Batty GD, Morris JN, Marmot M: Physical activity and cause-specific mortality in the Whitehall study. Publ Health 2000;114:308–315.
58 Shinkai S, Konishi M, Shephard RJ: Aging, exercise, training, and the immune system. Exerc Immunol Rev 1997;3:68–95.
59 Shephard RJ: Absolute versus relative intensity of physical activity in a dose-response context. Med Sci Sports Exerc 2001;33(suppl 6):S400–S418.
60 Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Colditz GA: A prospective study of recreational physical activity and breast cancer risk. Arch Intern Med 1999;159:2290–2296.
61 Blair SN, Cheng Y, Holder JS: Is physical activity or physical fitness more important in defining health benefits? Med Sci Sports Exerc 2001;33(suppl 6):S379–S399.
62 Adami HO, Day NE, Trichopoulos D, Willett WC: Primary and secondary prevention in the reduction of cancer morbidity and mortality. Eur J Cancer 2001;37(suppl 8):S118–S127.
63 Li FP: Second malignant tumors after cancer in childhood. Cancer 1977;40(4 suppl):1899–1902.
64 Tronko MD, Bogdanova TI, Komissarenko IV, Epstein OV, Oliynyk V, Kovalenko A, Likhtarev IA, Kairo I, Peters SB, LiVolsi VA: Thyroid carcinoma in children and adolescents in Ukraine after the

Chernobyl nuclear accident: Statistical data and clinicomorphologic characteristics. Cancer 1999;86:149–156.
65 Varady E, Deak B, Molnar ZS, Rosta A, Schneider T, Esik O, Eckhardt S: Second malignancies after treatment for Hodgkin's disease. Leuk Lymphoma 2001;42:1275–1281.
66 Slattery ML: Physical activity and colorectal cancer. Sports Med 2004;34:239–252.
67 Colbert LH, Lacey JV, Jr., Schairer C, Albert P, Schatzkin A, Albanes D: Physical activity and risk of endometrial cancer in a prospective cohort study (United States). Cancer Causes Control 2003;14:559–567.
68 Friedenreich CM: Physical activity and cancer prevention: from observational to intervention research. Cancer Epidemiol Biomarkers Prev 2001;10:287–301.
69 Marrett LD, Theis B, Ashbury FD: Workshop report: Physical activity and cancer prevention. Chron Dis Cancer 2000;21:143–149.
70 Adams-Campbell LL, Rosenberg L, Rao RS, Palmer JR: Strenuous physical activity and breast cancer risk in African-American women. J Natl Med Assoc 2001;93:267–275.
71 Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK: Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–1408.
72 Friedenreich CM, Courneya KS, Bryant HE: Relation between intensity of physical activity and breast cancer risk reduction. Med Sci Sports Exerc 2001;33:1538–1545.
73 Moradi T, Nyren O, Zack M, Magnusson C, Persson I, Adami HO: Breast cancer risk and lifetime leisure-time and occupational physical activity (Sweden). Cancer Causes Control 2000;11: 523–531.
74 Thune I, Furberg AS: Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. Med Sci Sports Exerc 2001;33(suppl 6):S530–S550.
75 Patel AV, Callel EE, Bernstein L, Wu AH, Thun MJ: Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. Cancer Causes Control 2003;14: 519–529.
76 Thompson H, Zhu Z, Banni S, Darcy K, Loftus T, Ip C: Morphological and biochemical status of the mammary gland as influenced by conjugated linoleic acid: implication for a reduction in mammary cancer risk. Cancer Res 1997;57:5067–5072.
77 Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, Kuzuya K, Nakamura S, Tokudome S: Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. Jpn J Cancer Res 1996;87:1001–1009.
78 Kalandidi A, Tzonou A, Lipworth L, Gamatsi I, Filippa D, Trichopoulos D: A case-control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. Oncology 1996;53:354–359.
79 Levi F, La Vecchia C, Negri E, Franceschi S: Selected physical activities and the risk of endometrial cancer. Br J Cancer 1993;67:846–851.
80 Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA: Physical activity and risk of endometrial cancer. Epidemiology 1993;4:342–349.
81 Sturgeon SR, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD: Past and present physical activity and endometrial cancer risk. Br J Cancer 1993;68:584–589.
82 Evans RC, Fear S, Ashby D, Hackett A, Williams E, Van D, V, Dunstan FD, Rhodes JM: Diet and colorectal cancer: an investigation of the lectin/galactose hypothesis. Gastroenterology 2002;122: 1784–1792.
83 Macfarlane GJ, Lowenfels AB: Physical activity and colon cancer. Eur J Cancer Prev 1994;3: 393–398.
84 Rissanen A, Fogelholm M: Physical activity in the prevention and treatment of other morbid conditions and impairments associated with obesity: Current evidence and research issues. Med Sci Sports Exerc 1999;31(suppl 11):S635–S645.
85 Sternfeld B: Cancer and the protective effect of physical activity: The epidemiological evidence. Med Sci Sports Exerc 1992;24:1195–1209.
86 Kubik AK, Zatloukal P, Tomasek L, Petruzelka L: Lung cancer risk among Czech women: A case-control study. Prev Med 2002;34:436–444.

87 Hayward RS, Wilson MC, Tunis SR, Bass EB, Guyatt G: User's guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA 1995;274:570–574.
88 Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ: For the Evidence-Based Medicine Working Group. User′s guides to the medical literature. IX. A method for grading health care recommendations. JAMA 1995;274:1800–1804.

PD Dr. A. Willer
III. Medizinische Universitätsklinik
Fakultät für Klinische Medizin Mannheim der Universität Heidelberg
Wiesbadener Strasse 7–11, DE–68305 Mannheim (Germany)
Tel. +49 621 383 4115, Fax +49 621 383 4201
E-Mail andreas.willer@med3.ma.uni-heidelberg.de

Author Index

Subject Index