Longevity and well-being:
the role of diet

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people, environment, science, economy

D ear Reader,
Over the last one hundred years, life expectancy from birth in Western countries has doubled.

Various factors have contributed to this result: the progress made by medicine, innovations in the pharmaceutical field, better hygienic and sanitary conditions and, last but not least, a healthy lifestyle and a healthy diet. This close relationship is recognized by the entire scientific community and has been shown by us in our previous works.

The reality of today, however, is characterized by the rapid and progressive development of overweight conditions and obesity, especially among the younger population; this situation, if not stopped, could result in a deterioration of what has been acquired in terms of the lengthening and, above all, in the quality of life.

Therefore, with this document, we have tried to understand the extent of scientific knowledge that is available today regarding the link between proper nutrition, lifestyle and longevity, where by "longevity," the BCFN means a long life lived fully in good health.

First of all, we highlighted the important relationship between diet, lifestyle and the prevention of major non-communicable diseases. The increase of the period of time "without disease" is fundamental to the quality of life for everyone, and it is likewise important to the sustaining of health care spending in the future. But we went even further, shedding light upon two recent and innovative research areas in which nutrition and lifestyle can make a significant contribution: cellular inflammation and calorie restriction.
Adopting a correct behavior, ultimately, allows people to live better today, but also and especially, to live better and longer tomorrow.

It is our hope that the BCFN addresses each of you in sharing the knowledge that, for a healthier life, eating better is possible and it is an option left to the free choice of each of us.

Enjoy your read,
Guido Barilla

THE VISION OF THE BARILLA CENTER FOR FOOD & NUTRITION

TO OFFER A VARIETY OF HIGHLY SCIENTIFIC CONTRIBUTIONS AND BECOME A VALUABLE SERVICE TO THE INSTITUTIONS, THE SCIENTIFIC COMMUNITY, THE MEDIA AND CIVIL SOCIETY OVER TIME; A MEETING POINT FOR ANYONE WHO CARES ABOUT FOOD, THE ENVIRONMENT, SUSTAINABLE DEVELOPMENT AND ITS IMPLICATIONS ON PEOPLE'S LIVES.

THE FUTURE OF FOOD IS GROWING WITH US
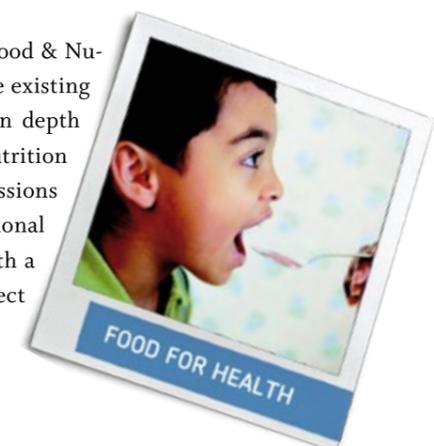
THE BARILLA CENTER
FOR FOOD & NUTRITION

T he Barilla Center for Food & Nutrition (BCFN) is a center of multidisciplinary analysis and proposals which aims to explore the major issues related to food and nutrition on a global scale.

Created in 2009, BCFN intends to listen to the demands emerging from society today by gathering experience and qualified expertise on a worldwide level and promoting a continuous and open dialogue. The complexity of the phenomena under investigation has made it necessary to adopt a methodology that goes beyond the boundaries of different disciplines. These topics under study are broken down into four areas: *Sustainable Growth for Food, Food for Health, Food for All* and *Food for Culture*. The areas of analysis involve science, the environment, culture and the economy; within these areas, BCFN explores topics of interest, suggesting proposals to meet the food challenges of the future.
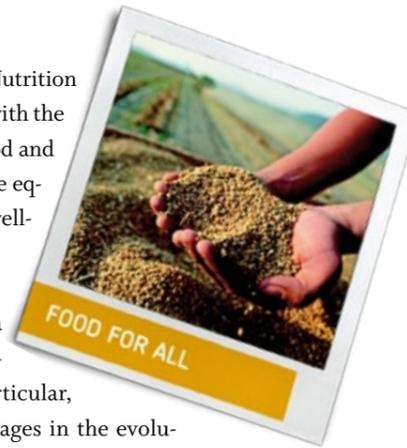

FOOD FOR
SUSTAINABLE GROWTH

In the field of *Food for Sustainable Growth*, the Barilla Center for Food & Nutrition focuses on the issue of the optimization of natural resources within the framework of the food and agricultural sector. More specifically, the studies conducted so far have identified some critical issues and have evaluated the environmental impact of food production and consumption, putting forward a series of proposals and recommendations for individual and collective lifestyles which may have a positive effect on the environment and on natural resources.

In the field of *Food for Health*, Barilla Center for Food & Nutrition has decided to start its research work by analyzing the existing relationship between nutrition and health. It has studied in depth the recommendations provided by the most distinguished nutrition institutes in the world and the results of ad hoc panel discussions with some of the most accredited scientists at the international level. As a result, it has been able to provide civil society with a clear set of concrete proposals for more easily adopting a correct lifestyle and a healthy diet.

FOOD FOR HEALTH

In the field of *Food for All*, the Barilla Center for Food & Nutrition deals with the issue of food accessibility and malnutrition with the aim to reflect how to promote better governance of the food and agricultural sector on a global scale, in order to have a more equitable distribution of food and a better impact on social well-being, health and the environment.

FOOD FOR ALL

In the *Food for Culture* area, the Barilla Center for Food & Nutrition aims the relationship between man and food. In particular, BCFN has traced the most significant stages in the evolution of the man-food relationship, refocusing on the fundamental role of the Mediterranean diet.

FOOD FOR CULTURE

In line with this approach, the activities of BCFN are guided by the Advisory Board, a body composed of experts from different but complementary sectors, which makes proposals, analyzes and develops the themes, and then drafts concrete recommendations.

One or more advisors have been individuated for each specific area: Barbara Buchner (expert on energy, climate change and the environment) and John Reilly (economist and expert on environmental issues) for the area *Food for Sustainable Growth*; Mario Monti (economist) for the area *Food For All*; Umberto Veronesi (oncologist), Gabriele Riccardi (nutritionist) and Camillo Ricordi (immunologist) for the area *Food for Health* and Claude Fischler (sociologist) for the area *Food for Culture*.

In the area of *Food for Health*, the Barilla Center for Food & Nutrition has conducted in-depth studies over a three year period on the link between health and diet, detailing the most important aspects. The issues included concerned the role of nutrition in the prevention of major non-communicable diseases (cardiovascular diseases, metabolic diseases, tumors) and on the prevalence of overweight conditions and obesity, the characteristics of a healthy diet for children and the contribution of nutrition in slowing down the aging process, in order to ensure a long and healthy life.
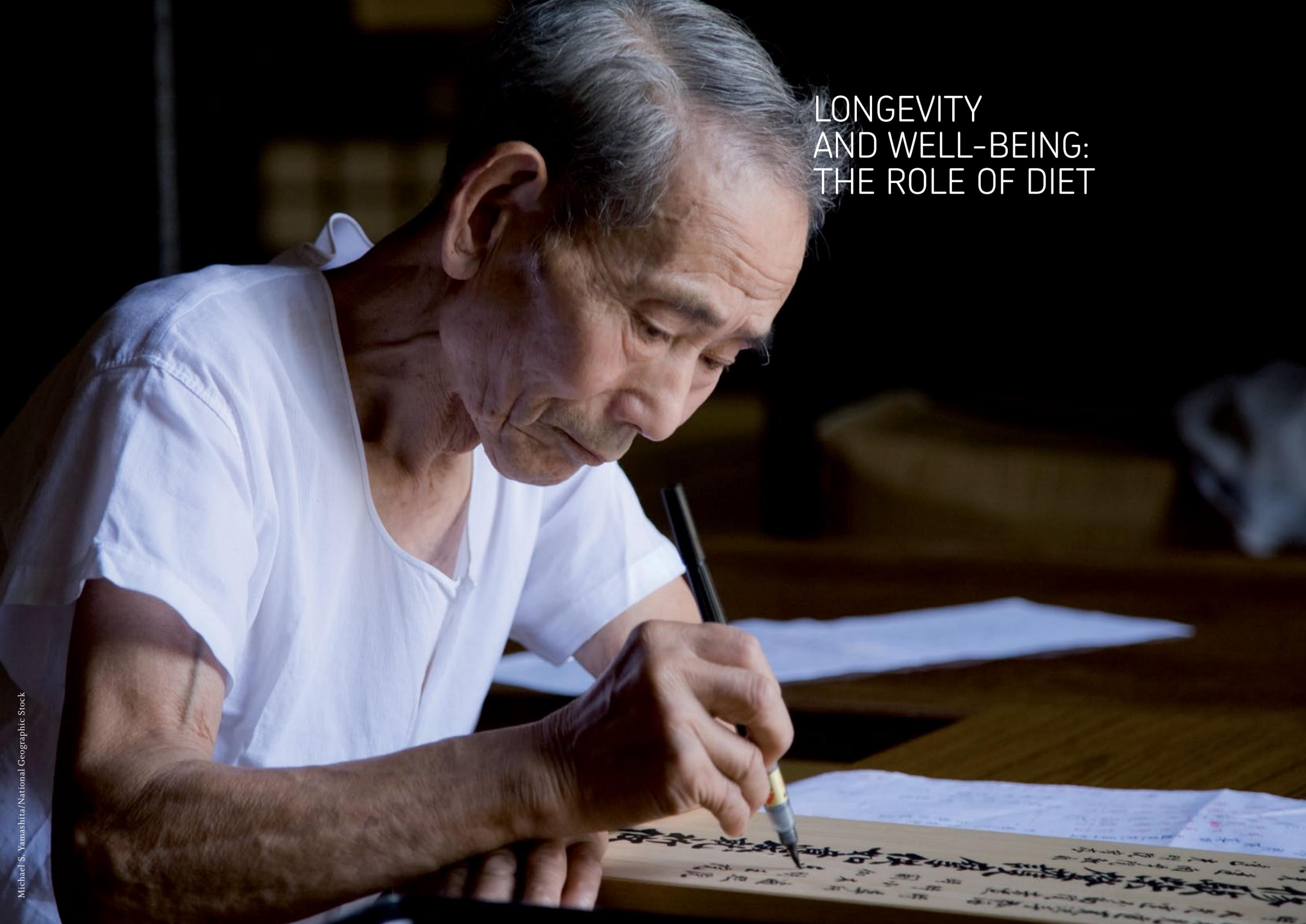
The document that we present here is part of that sphere of activity seeking to investigate the issue of longevity, taken to be understood as "a long life in good health": is it possible that a healthy lifestyle and good eating habits can help slow down the aging process? What are the scientific community's most reliable theories to explain the aging processes and the role that diet plays in slowing them down? What lessons can we learn concerning our everyday lives? These are the main questions to which we have tried to give an answer.

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LONGEVITY AND WELL-BEING: THE ROLE OF DIET

EXECUTIVE SUMMARY

This paper ideally concludes a process started by the Barilla Center for Food & Nutrition with the position papers *Food and Health* in 2009 and H*ealthy Growth and Nutrition in Children* in 2010. The reason this document was prepared stems from the desire to understand and to propagate the extensive scientific knowledge available today regarding the link between proper nutrition, lifestyle and longevity, where by *longevity* the Barilla Center for Food & Nutrition means "a long life in good health."

THE AGING OF THE POPULATION IS A KEY ISSUE FOR THE PRESENT AND THE FUTURE

- In the last 100 years, life expectancy in Western countries has almost doubled, going from 45 years at the end of the 1800s to around 80 years in 2010. The percentage of elderly people (older than 65) has also increased significantly: for example, in Italy it has increased from 4% in 1900 to 20.6% in 2010 and this percentage should reach 34% in 2050. The same growth trend in the proportion of elderly people is occurring worldwide. It is estimated that *in 2050, the over-65 population, globally, will consist of 1.9 billion people*.
- *About 80% of the people over 65 are now suffering from at least one chronic disease, while about 50% suffer from two or more chronic conditions* (cardiovascular and cerebrovascular diseases, tumors, diabetes mellitus, hypertension, chronic lung disease). In addition, the current epidemic of overweight conditions and obesity (especially abdominal), also in the younger population, is associated with a significantly increased risk of developing cardiovascular disease, diabetes and cancer.
- In light of the current scenario, it is essential to study and implement interventions to reduce the "gap" between the lifespan and the duration of healthy life (healthspan). If this is not done, we may experience, on average, an *old age characterized by a greatly reduced quality of life for a significantly longer time*. Moreover, all this may have *significant consequences on the sustainability of national health systems*. The increase in the elderly population means rising costs in health spending, both public and private, worldwide.

IT IS POSSIBLE TO TAKE ACTION FOR SLOWING DOWN THE AGING PROCESSES

- *Aging* is a process caused by the *gradual accumulation over time of damage to the DNA, cells and organs throughout the body due to the failure of the repair mechanisms for that damage*.

The accumulation of this damage causes a progressive decline of many vital physiological functions and structures of the body.

- *The potential longevity* of each individual *is closely linked to the proper functioning of cells that play roles concerning the protection and continuous repair* within the body. These cells may, however, exhaust their ability to replicate – and, therefore, their potential for repairing – more or less quickly throughout life, depending on several factors.
- Two of the main areas of *cross-cutting and innovative* research on the determinants of healthy longevity are:
  → the area of research concerning the *state of inflammation of the body's cells* which, according to modern theories, seems to be at the root of many chronic diseases. States of cellular inflammation that are progressive and constant over time result in full-blown disease, impacting negatively on the aging process and accelerating it. *The model of diet and lifestyle that one adopts can also greatly influence the inflammatory state of the organism* and, thus, affect the health of the individual in various stages of life.
  → the area of research concerning the analysis of a *dietary approach characterized by a reduction of calorie intake* – with the proper intake of all the nutrients required as to quality and quantity – that can have an effect on the physiological and biochemical processes of the organism and a *positive impact on the lengthening of life expectancy in good health*.
- From the *review of the evidence emerging from the main international studies* on the links between inflammation, aging and food choices, it is clear that:
  → the dietary model has a role, in positive or negative, on the inflammatory responses of the organism, with effects leading to the onset of chronic diseases and consequently, on the longevity and quality of life. *The diet adopted, therefore, can be a determining factor in the reduction or slowing of the inflammatory states produced by situations of obesity, diabetes and the presence of cardiovascular disease*.
  → calorie restriction, combined with a proper intake of nutrients, seems to be able to produce additional positive effects on slowing down the aging process, as shown in numerous studies conducted on animals. *However, there is still no scientific data to clearly demonstrate that caloric restriction has an effect upon the lengthening of the maximum human lifespan*. With a view to longevity, it is advisable for people who have a normal weight to maintain an ideal weight and avoid the accumulation of fat in the abdomen, with a complete, moderately low-calorie diet and a regimen of regular physical activity.

DIET PLAYS A CENTRAL ROLE IN THE PROCESSES OF AGING

- There is a significant *link between diet and the contrasting of aging processes*. The molecular, metabolic and hormonal alterations caused by an excessive and chronic caloric intake and an incorrect dietary model and lifestyle play a central role in the processes of aging.
- It is possible to identify a "puzzle" of the aspects upon which to act in order to establish *an integrated set of eating habits and lifestyles for longevity in good health*: correct calorie intake, proper intake of macronutrients (carbohydrates, fats and proteins) and micronutrients (such as phytochemicals), and regular physical exercise.
- The *Mediterranean diet* is one of the most balanced diets and – with an intake of about 2,000 calories a day – allows for an ingestion of all the essential macro and micro nutrients. It therefore provides a significant contribution toward the prevention of chronic diseases, affecting the states of cellular inflammation due to improper diet and increasing life expectancy in good health.

SOME IDENTIFIABLE PRIORITIES FOR FUTURE HEALTH AND WELL–BEING

- In 2009-2010, the BCFN identified some guidelines that can be summarized in three key concepts: *learn, inform, act*. The work carried out concerning the relationship between diet and longevity has allowed us to confirm and integrate these thoughts. In particular, priority should be given to:

1 Promoting the further expansion of scientific knowledge available on the relationship between diet and health

It is necessary to undertake further studies on the mechanisms of aging and cell repair; to conduct more in-depth studies on the gene-nutrient-disease relationships; to promote systematic research on the topic of caloric restriction; to foster further studies of the dietary models that, for various reasons, have already provided very important evidence regarding the prevention of chronic diseases and healthy aging.

2 Facilitating the diffusion of correct information and nutrition education to promote the adoption of appropriate eating habits and lifestyles

An intensive communication effort by governments, scientific societies, the medical profession and private companies is needed. There are lifestyles that constitute an insurance for an adulthood and advanced age to be lived out in good health: there must be an adequate level of information concerning this topic.

3 Structuring policies and social and health interventions to concretely promote the spreading of healthy eating habits, also looking to the best international practices in this field

We must find – and employ in an integrated manner by all parties involved and according to a systematic logic – new and more effective ways of transmitting the scientific knowledge in the field of nutrition and health, so that it may be translated into concrete action in the direction of diverse, wide-ranging projects that can have a real impact on people's behavior.

James L. Stanfield/National Geographic Stock

1. INTRODUCTION
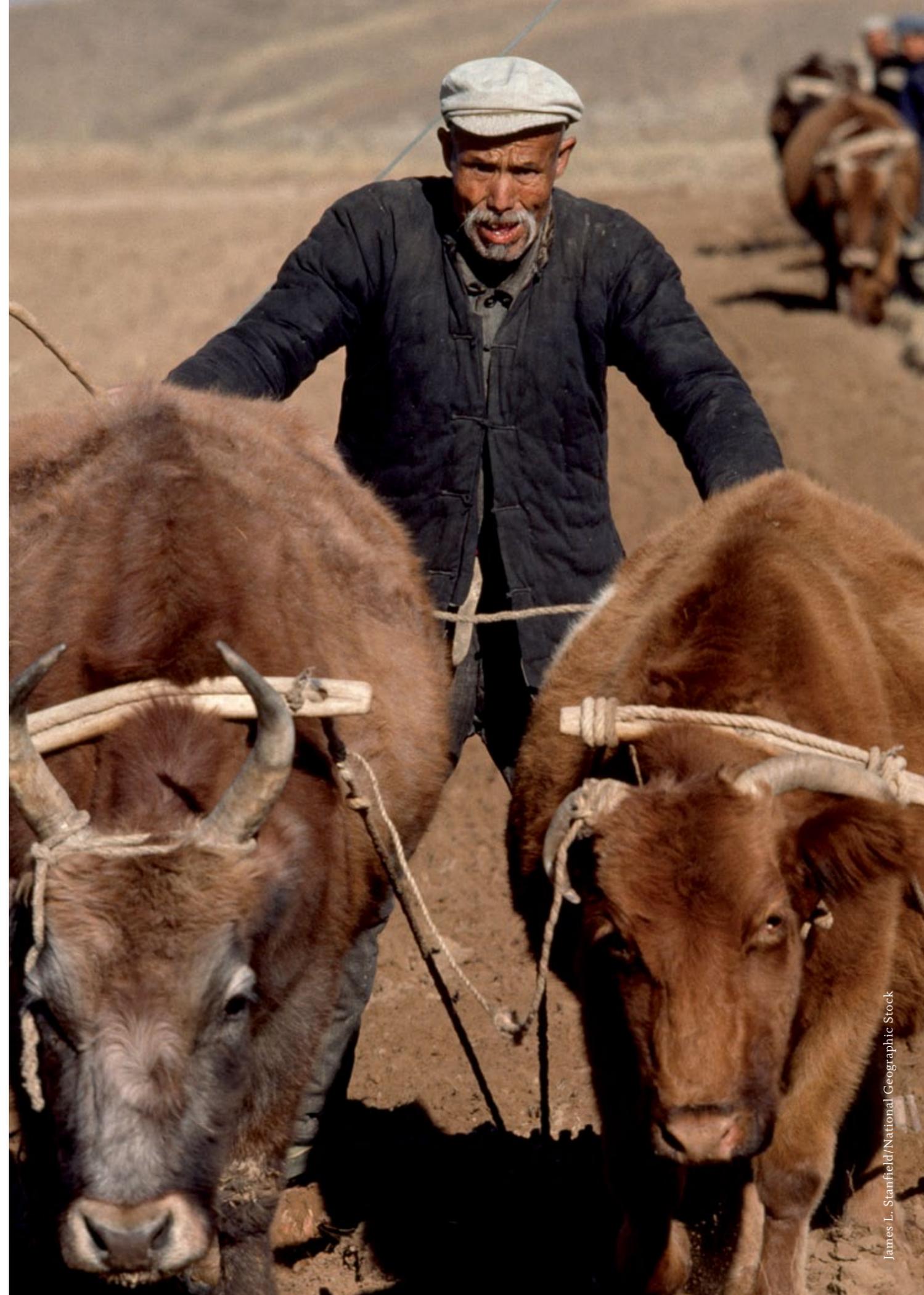
N In 2025, according to estimates by the United Nations, there will be more than 8 billion people in the world, mainly because of the increase in average life expectancy.

Figure 1.1. **Increase in life expectancy (1850–2000)**

Source: Christensen *et al.*, Lancet, 2009.

In fact, life expectancy at birth has almost doubled over the last 100 years, from 45 years of age at the end of the 1800s to approximately 80 years of age in 2010. In Italy, the percentage of the elderly has dramatically increased, going from 4% in 1900 to 20.6% in 2010. In 2050, people over 65 years of age should account for 34% of the Italian population; one out of three people will be elderly. The same growth trend in the proportion of elderly people is occurring worldwide.
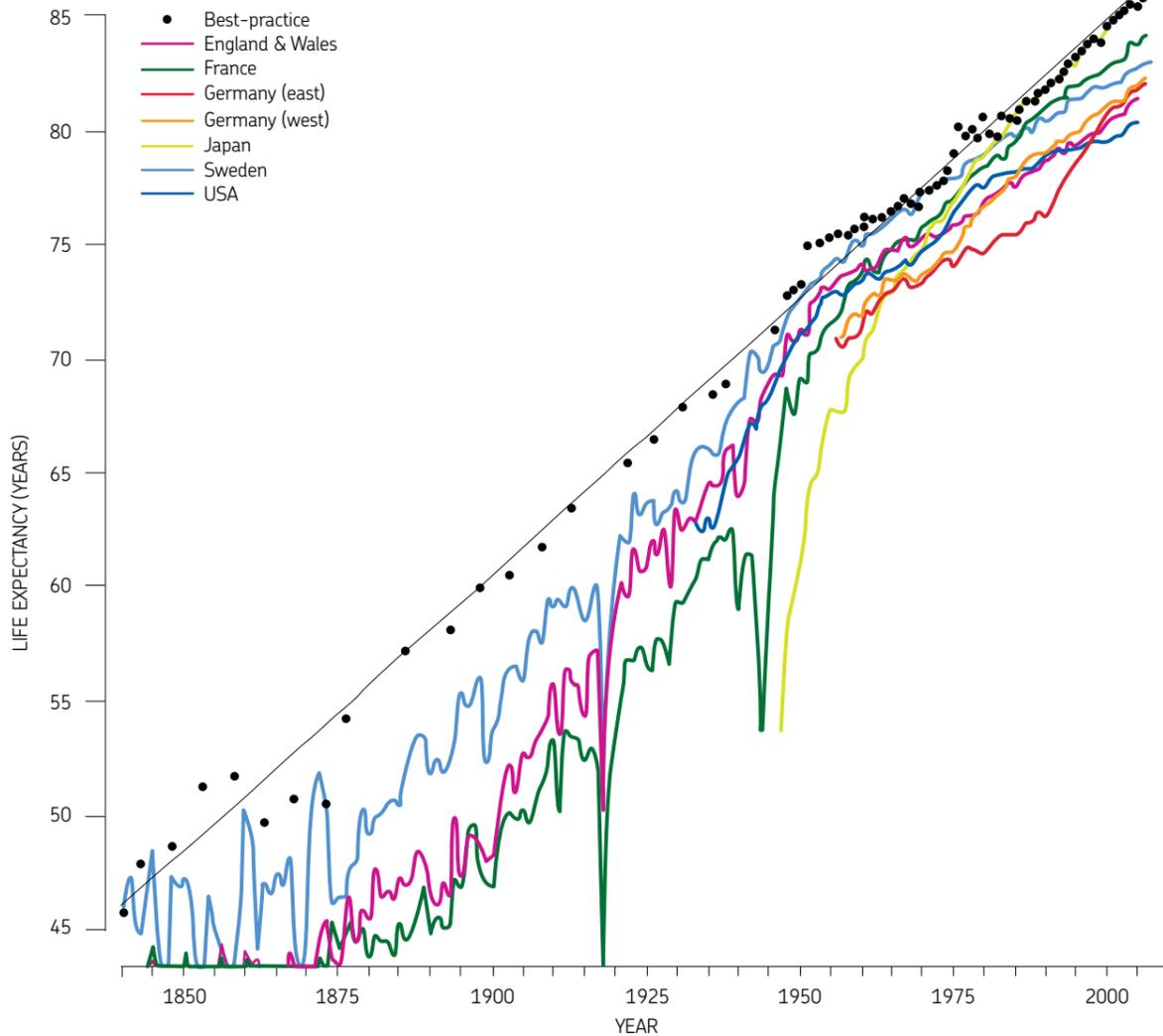
From 1950 to 2010, the elderly population worldwide grew at an average annual rate of 13%, showing a growth trend that gives no sign of stopping. It is estimated that in 2050, the over-65 population will number 1.9 billion people.

These demographic changes are very worrisome and could undermine the health systems of many countries, both industrialized and developing: about 80% of the elderly (over 65) is affected by at least one chronic disease, and about 50% suffer from two or more chronic conditions (such as cardiovascular and cerebrovascular diseases, tumors, mellitus diabetes, hypertension and chronic lung diseases).[1]

These numbers will increase in light of the epidemic of obesity and mellitus diabetes currently in progress, even in the younger population. Overweight conditions and obesity (especially abdominal) are associated with an increased risk of developing cardiovascular disease and cancer. These diseases are responsible, altogether, for about 70% of the causes of death in many industrialized countries and developing countries. In addition, abdominal obesity is a powerful risk factor for the development of type 2 mellitus diabetes, which in turn is a risk factor for the development of various diseases such as cardiovascular disease, diabetic nephropathy and diabetic retinopathy (the leading cause of blindness in industrialized countries). After 20 years of mellitus diabetes, about 40% of patients develop diabetic nephropathy, which over the years leads to renal failure, whose only treatment is dialysis, followed by renal transplantation.

In light of these demographic changes, the epidemic of obesity and the deterioration in lifestyle (sedentary lifestyle, atherogenic high-calorie food, cigarette smoke, etc.), it has, therefore, become essential to study and implement interventions aimed at the prevention of chronic diseases associated with aging and at the improvement of the quality of life, i.e., to reduce the "gap" between the lifespan and the duration of healthy life (health span). More than ever, it is necessary to identify and adopt lifestyles that promote healthy aging (or successful aging), to ensure that individuals can remain physically and mentally healthy, happy, active, strong, independent and socially useful for the longest time possible, ideally for the duration of their lives.

Without corrective action on lifestyles, a longer life may no longer imply the achievement of a better life. We may experience, on average, an old age characterized by a greatly reduced quality of life for a significantly longer time.

As Professor Gabriele Riccardi also reminded us (at the Second International Forum on Food and Nutrition, organized by the BCFN in 2010), "It is absolutely necessary to progress toward a style of living that is capable of ensuring an extension of a better quality of life and, especially, to lengthen the disease free period of life. What counts is not just living a long life but living longer in reasonably good health, thus being able to live one's life with dignity."

To achieve this ambitious goal, it is necessary to address the problem of aging and its associated diseases with a preventive and integrated approach. The strategy of fighting a single disease only when it comes to medical attention is conceptually wrong and does not adequately address the challenge of reducing the gap between lifespan and health span.

Aging, in fact, is a process caused by the gradual accumulation over time of damage to the DNA of cells and organs throughout the body, due to the failure of the repair mechanisms

LIFE EXPECTANCY AT BIRTH HAS ALMOST DOUBLED OVER THE LAST 100 YEARS

IN 2050, THE OVER-65 POPULATION WILL NUMBER 1.9 BILLION PEOPLE

ABOUT 80% OF THE ELDERLY (OLDER THAN 65 YEARS OF AGE) IS AFFECTED BY AT LEAST ONE CHRONIC DISEASE

A REDUCTION OF THE "GAP" BETWEEN THE LIFESPAN AND THE DURATION OF HEALTHY LIFE IS ESSENTIAL TO PROMOTING HEALTHY AGING

A LONGER LIFE MAY NO LONGER IMPLY THE ACHIEVEMENT OF A BETTER LIFE BUT RATHER, A GREATLY REDUCED QUALITY OF LIFE FOR A SIGNIFICANTLY LONGER TIME

A PREVENTIVE AND INTEGRATED APPROACH

The main theories on aging

Aging is a complex process that involves significant changes at the genetic level of proteins, tissue structures and the physical abilities of older individuals, as compared to those of the same species who are younger.

And it is precisely on the processes of aging that many scientific discoveries of new biomarkers have been concentrated, in an attempt to understand the multitude of biochemical processes at the basis of the physiology and "pathophysiology" that contribute to aging. There is also the desire to develop potential interventions to slow degeneration and disability in humans and animals.

Over the past 50 years, several theories on aging have been developed; they can be divided into three main groups:
– the "use it or lose it" dogma, according to which our mental and physical abilities are used to a lesser extent as aging advances, to the point of gradually losing them over time;
– the theory that attributes the responsibility of aging to genetic mutations that cannot be repaired through normal repair mechanisms of the genes, leading to irreversible changes in the function of tissue, cancer, the accumulation of proteins and other disorders;
– the *paradigm of mitochondrial dysfunction,* according to which, with the passage of time, the mitochondrial DNA undergoes irreversible mutations with various biochemical effects (such as, for example, an increase in the production of oxygen-reactive species with dysfunctions in the metabolic process of oxygenating respiration), with resulting consequences on the aging processes.

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for the damage. The accumulation of this damage causes a progressive decline of many physiological functions and vital structures of the body.

Recent studies have shown that lifestyles (nutrition, physical activity, exposure to cigarette smoke, toxic and radioactive substances, pollution, etc.), heavily influence the aging process. For example, a high-calorie diet, rich in animal fats and low in nutrients (vitamins, minerals, phytochemicals) and a sedentary lifestyle promote the onset of obesity, mellitus diabetes, hypertension, cardiovascular disease and cancer, as well as an acceleration of aging processes. In contrast, significant scientific evidence has shown that a mild low-calorie diet rich in nutrients is able to slow the aging process and prevent most chronic diseases associated with aging.

LIFESTYLES HEAVILY INFLUENCE THE AGING PROCESS

Even though we cannot prevent or reverse the natural aging process, we can, however, take decisive action on environmental (or secondary) aging and influence the processes of intrinsic (or primary) aging. It is possible, in fact, to slow down the natural aging processes and, most importantly, to take action on chronic diseases associated with them (obesity, diabetes, metabolic syndrome, cancer, cardiovascular disease, hypertension and inflammatory processes). Therefore, what clearly emerges in this context is the central role of nutrition and lifestyle in preventing the onset of these diseases, in mitigating their effects and then, ultimately, in promoting higher quality longevity.

**ALTHOUGH THE NATURAL AGING PROCESS CANNOT BE PREVENTED, WE CAN, INSTEAD, TAKE ACTION ON ENVIRONMENTAL AGING
THE CENTRAL ROLES OF NUTRITION AND LIFESTYLE**

In particular, it is possible to consider that different interventions and approaches effectively contribute to "slowing down the aging process" when they are able – simultaneously – to extend the average and maximum life of an organism and – equally – to decelerate numerous physiological and structural changes (depending on age) in organs and tissues.

In this light, authoritative studies have shown that the adoption of an overall healthy lifestyle and, in particular, of an adequate diet, can ultimately constitute a significant intervention in favor of healthy longevity, confirming the fact that a lot can be done to prevent and mitigate the negative effects that many factors, starting with chronic diseases, have and will have on longevity and its quality.

In particular, a recent study by a group of Australian researchers[2] on a sample of 7,989 male participants, aimed at measuring the impact of their behavior on the increase in mortality risk, has verified how the adoption of a "healthy lifestyle" – from the point of view of diet, alcohol consumption, smoking and physical activity – is an important factor for preventing mortality, since it allows for a lengthening of the average life by nearly five years.

A GROUP OF AUSTRALIAN RESEARCHERS VERIFIED THAT ADOPTING A "HEALTHY LIFESTYLE" HELPS PREVENT MORTALITY

In fact, as shown in figure 1.2, the participants in the study who adopted a lifestyle which is as healthy as possible, and who were given a score equal to or greater than 5, also recorded an average life expectancy which was higher than those who, because of their lifestyle, were given a score of less than 4.

This evidence has been confirmed by numerous other studies,[3] which have identified the key factors for healthy aging as four kinds of behavior, with special attention given to eating behavior and the adoption of a low-calorie diet[4] characterized by a significant fruit content.

Among the analyses conducted, of particular relevance was a study conducted in the UK – on a sample of 20,244 men and women between 45 and 79 years of age[5] – which highlighted how the adoption of this behavior can lead to an increase in life expectancy of 14 years. A recent study in 2009 also emphasized how maintaining the current trend of increasing obesity (+0.5%/year) and a decrease in smoking (-1.5%/year) can affect the average life expectancy (Figure 1.3).

THE ADOPTION OF A CORRECT EATING BEHAVIOR AND LIFESTYLE LEADS TO AN INCREASE IN LIFE EXPECTANCY

In light of these considerations, the BCFN has decided to undertake – throughout 2011 – a course of study on the relationship between longevity and well-being and the role played by eating in this regard.

The choice of this area of investigation for 2011 appears to be in perfect continuity with the work of the BCFN during the 2009-2010 period: after having investigated the rela-
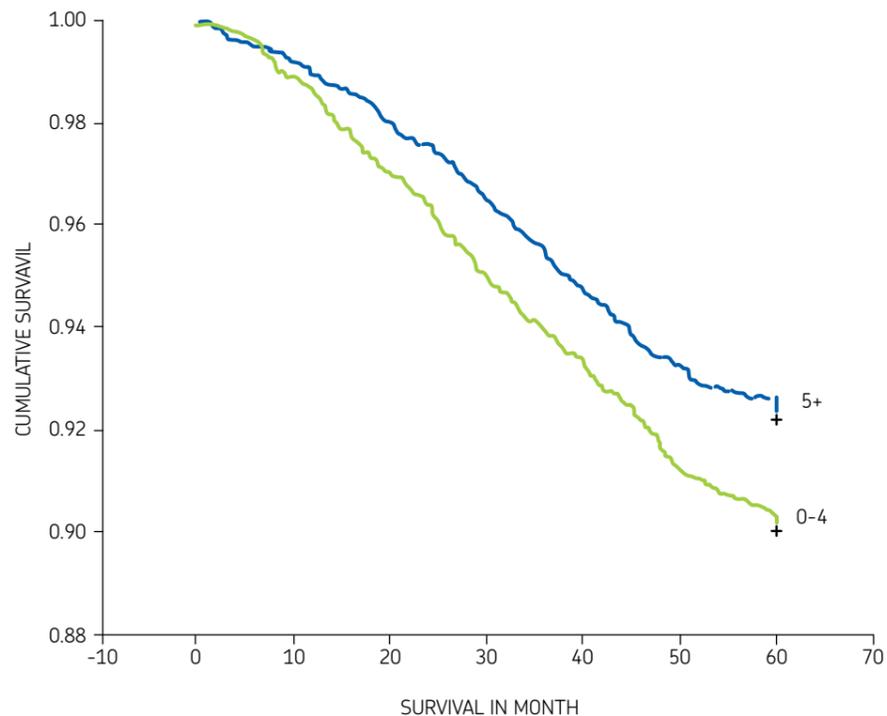
IT IS INTERESTING TO ANALYZE THE RELATIONSHIP BETWEEN LONGEVITY AND WELL-BEING AND THE ROLE THAT EATING HAS IN THIS REGARD

Figure 1.2. Survival curves (Kaplan – Meier) associated to men's lifestyle with scores of 0 – 4 and 5+

Source: Spencer C.A. *et al., A simple lifestyle score predicts survival in healthy elderly men,* Elsevier, Amsterdam, 2005.

tionship between nutrition and health, with particular attention given to those diseases that have now truly become contemporary "epidemics" (obesity, cardiovascular diseases, diabetes, cancer), in 2010 the BCFN dealt with the issue of the link between nutrition and healthy growth in the different stages of a child's life, from infancy to elementary school age, up to adolescence.

In 2011, it was, therefore, decided to "close the circle" of the reflections upon these issues, ideally completing the quest begun in 2009, with an analysis of the relationship between diet and longevity with regard to health.

The topic seems to be of primary importance, not only for the medical-scientific world, but also for the political-institutional world, which is now forced to confront the growing problems of the economic sustainability of the health and social systems and which, more

Figure 1.3. **Changes in predicted life expectancy if the current trends of increasing obesity and decreasing smoking remain unchanged**

MERGEFORMAT	CHANGE, 2005–2020					
	SMOKING STATUS ALONE		BMI ALONE		BOTH SMOKING STATUS AND BMIS	
	Life expectancy	Quality– adjusted life expectancy	Life expectancy	Quality– adjusted life expectancy	Life expectancy	Quality– adjusted life expectancy
HISTORICAL 15-YEAR RATE OF CHANGE (BASELINE)	0,31	0,41	-1,02	-1,32	-0,71	-0,91

Source: Stewart S.T. *et al.,* in the "New England Journal of Medicine," 2009.

importantly, is facing a progressive decline in the quality of life of average citizens, particularly in developed countries.

As we have already mentioned, it is no longer enough to focus on living longer, without living the second part of one's life – maturity – in good health. The quality of life is a value that no one wants to renounce, whether as individuals or as a society, and it is an essential foundation for the truly sustainable progress of countries.

THE QUALITY OF LIFE IS A VALUE THAT NO ONE WANTS TO RENOUNCE

This raises more questions about what information to give people regarding which approach to adopt for healthy eating at every stage of their life, what role nutrition plays in the mechanisms of aging, and which educational approaches are to be used in the early years of life. In the background, the issue remains of how to broadly and effectively propagate the eating habits that science now tells us are correct, even and especially in relation to the achievement of health in the last years of life.

The Mediterranean model appears, once again, to be a paradigm of diet to be observed closely, and which is even more attractive today than in the past, in that it provides diet guidelines for living well and, above all, for living in the fullness of one's faculties for an entire lifetime.

THE MEDITERRANEAN MODEL IS A PARADIGM OF DIET TO BE OBSERVED CLOSELY

There are many key aspects of the relationship between longevity and well-being that the BCFN has sought to study in depth; they are summarized as follows:

- the *issue of an aging population, current demographic and vital statistics, trends and future prospects* (Chapter 2);
- the *issue of chronic and emerging diseases* (obesity, diabetes, cancer, cardiovascular diseases, neurodegenerative diseases and osteoporosis), which are increasingly more widespread and with increasingly evident impacts, also long-term (Chapter 2);
- the *relationship between nutrition, well-being and longevity*, and causal links existing between these variables (Chapter 3);
- the *topic of the most significant (and innovative) factors/approaches in determining the achievement of healthy longevity*, including, in particular, the processes of inflammation and caloric restriction regimens (Chapter 4);
- the identification of a *limited number of proposals for the promotion and adoption of lifestyles and diets that can promote a long and healthy life* (Chapter 5).

THE BCFN HAS IDENTIFIED THE FOUR KEY ASPECTS OF THE RELATIONSHIP BETWEEN LONGEVITY AND WELL-BEING

Our hope is to be able to contribute - through this document and the moments of confrontation that will arise from it - to a greater awareness of the importance of adopting healthy lifestyles and eating habits, from childhood to old age, in exchange for a healthy life, lived in the fullness of one's physical and mental faculties until the very last years of life.

Living longer and better is possible. And it is within everyone's reach.

2.1 DEMOGRAPHY AND LONGEVITY: A POPULATION THAT IS GROWING AND GETTING OLDER AND OLDER

ACCORDING TO UN ESTIMATES, BY AROUND 2025, THE WORLD POPULATION WILL EXCEED 8 BILLION PEOPLE

THERE IS A WIDESPREAD AGING OF THE GLOBAL POPULATION AND, THUS, A PHENOMENON CALLED "POPULATION SHIFT" IS EXPECTED

According to UN estimates, by around 2025, the world population will exceed 8 billion people. These estimates are considered reliable by most scholars, unlike those that go even farther and predict greater difficulty in possible social, economic and cultural changes.

In general, there is a widespread aging of the global population and, thus, a phenomenon called "population shift" is expected: the number of people between the ages of 10 and 14 will decline between 2000 and 2020, while there will be a large increase in the population between 50 and 60 years of age. The child dependency ratio (the ratio of the number of people between 0-14 years of age and the number of people aged 15-64) will have gone from 0.472 in 2000 to 0.374 by 2020; while the old age dependency ratio (the population over 65 and those aged 15 to 64 years) will have grown from 0.110 in 2000 to 0.145 in 2020.

Figure 2.1. **Expected changes in the age groups worldwide between 2000 and 2020**
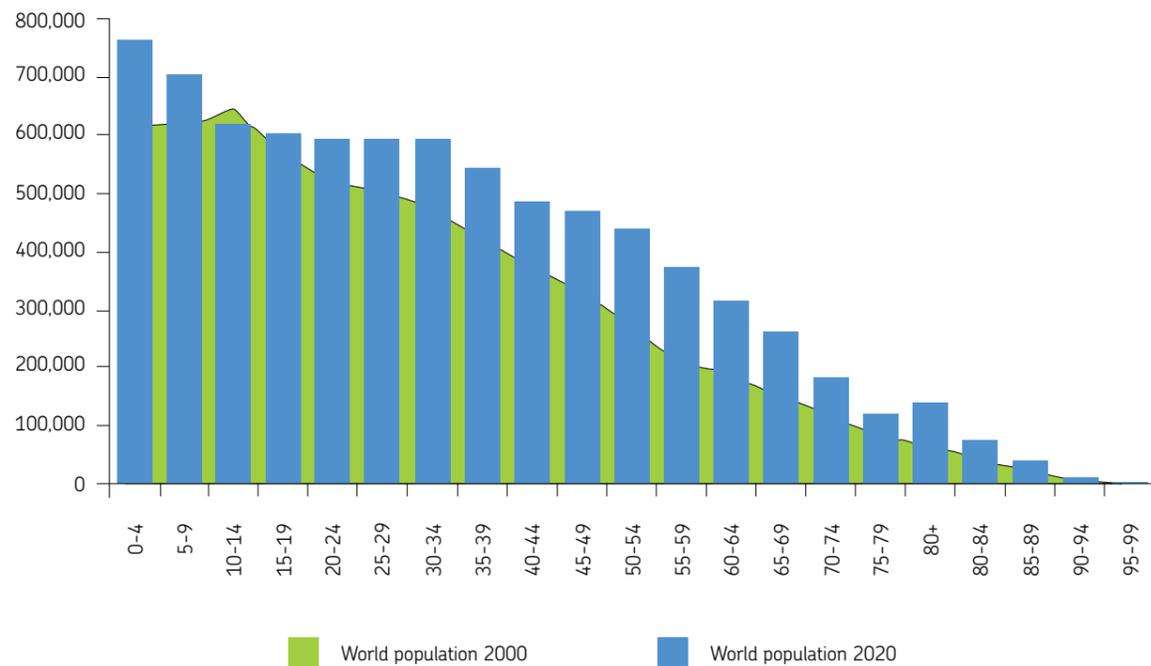
Source: The European House–Ambrosetti elaboration of UN data, *World Population Prospect*, 2010.

Looking at the pyramid of the world's population according to age groups, you will notice a radical evolution between 1980 and 2020. The overall trend is that of an enlargement of the pyramid, which is significantly concentrated in its "medium high" range, with an increase in the median range (between 20 and 40 years) and – above all – in the over-60 population, which will have tripled in 2020, compared to 1980.

Figure 2.2. **Pyramid of the world population relative to the years 1980, 2000, 2010 and 2020**
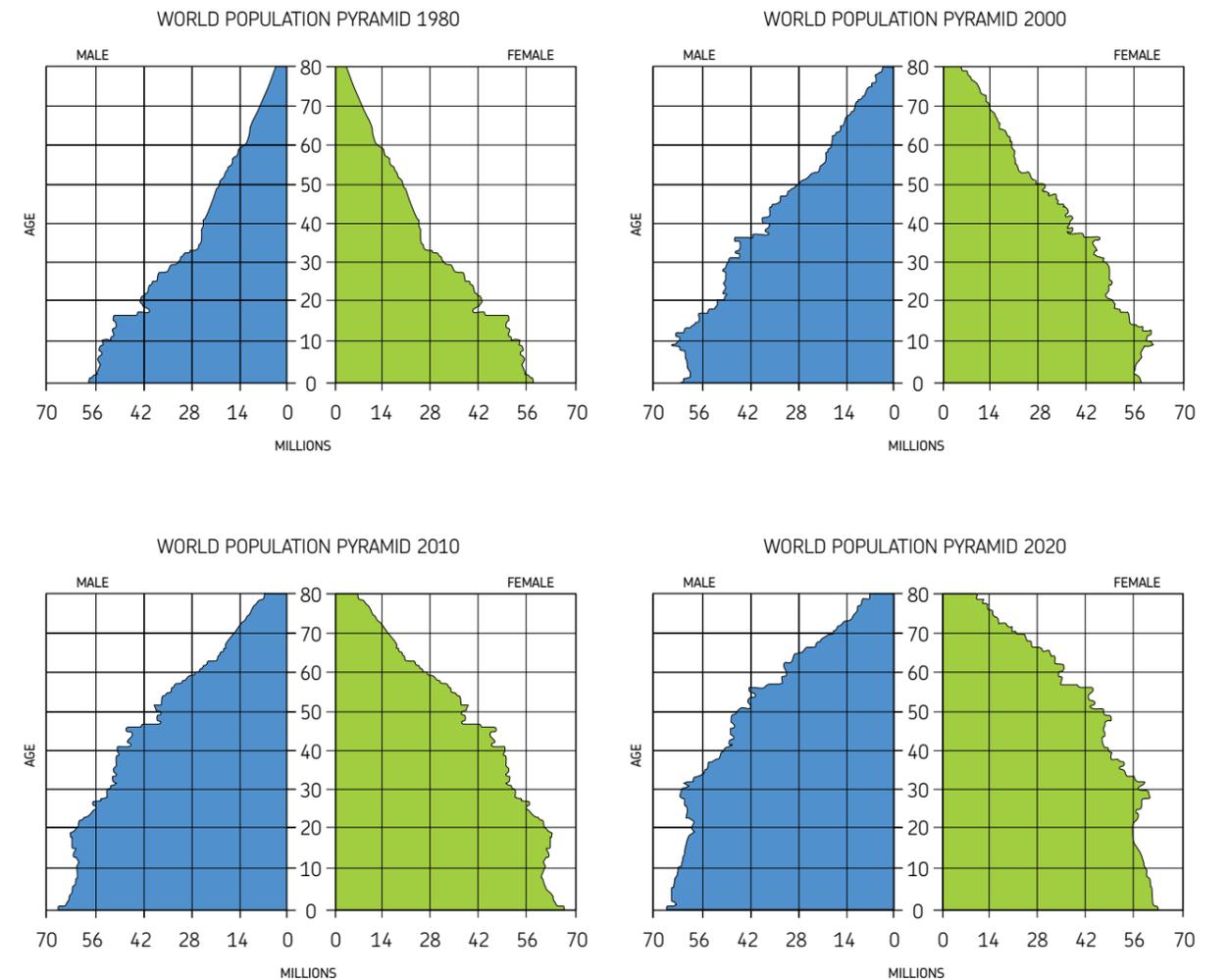
Source: The European House–Ambrosetti elaboration of UN data, *World Population Prospect*, 2010.

In Italy, the population grew very slowly for decades, after reaching a peak in the decade from 2000 to 2010, it has begun to slow down again. Estimates indicate that the population growth between 2020 and 2030 will register less than 0.1% on average per year. The share of working age people (people between 15-64 years) has been slowly decreasing for many decades. In the period between 2010 and 2030, there will be a further reduction of 4.5%, which is the equivalent of about 1.8 million people. From this we derive that there will be about 31 million people over 50 years of age in 2030, or 19 million more than in 1980.[1]

IN ITALY, THE POPULATION GREW VERY SLOWLY FOR DECADES, AFTER REACHING A PEAK IN THE DECADE FROM 2000 TO 2010, IT HAS BEGUN TO SLOW DOWN AGAIN

Figure 2.3. **Changes in the population in Italy between 2010 and 2030**
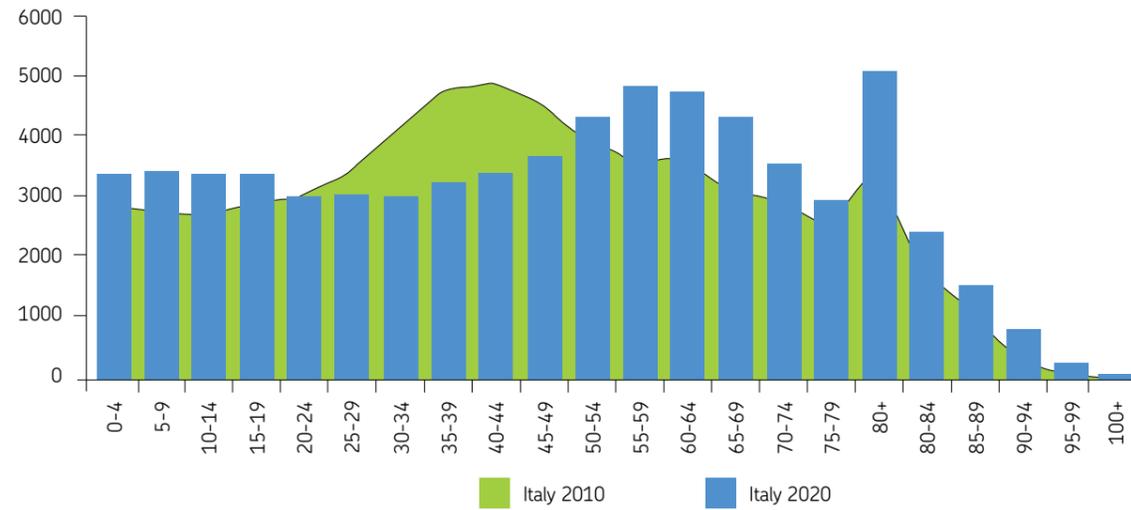
Source: The European House–Ambrosetti elaboration of UN data, *World Population Prospect,* 2010.

Figure 2.4. **Comparison of births and deaths in industrialized countries[2] between 1950 and 2050**

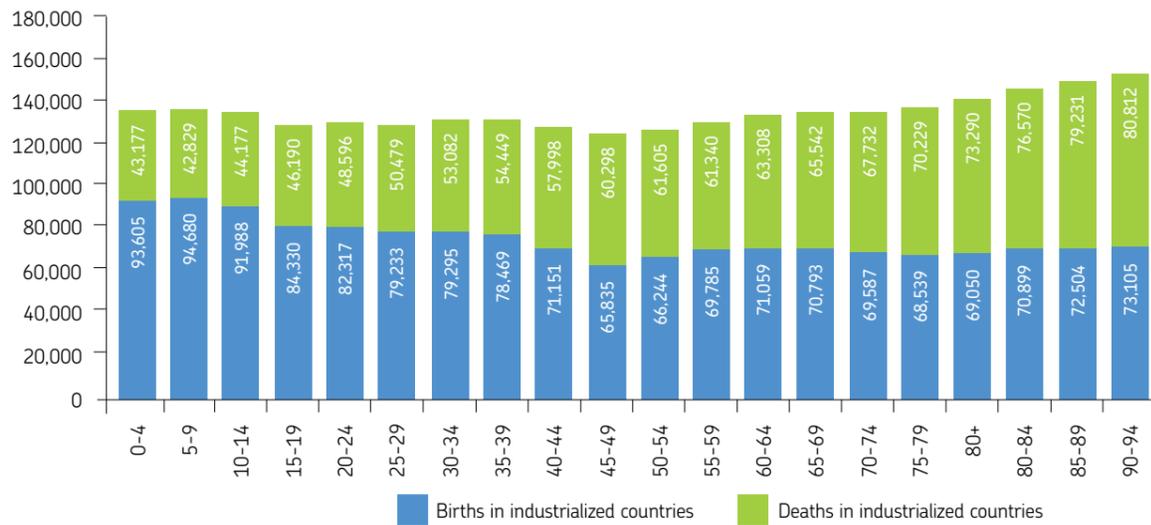| Age	Births	Deaths
0-4	93,605	43,177
5-9	94,680	42,829
10-14	91,988	44,177
15-19	84,330	46,190
20-24	82,317	48,596
25-29	79,233	50,479
30-34	79,295	53,082
35-39	78,469	54,449
40-44	71,151	57,998
45-49	65,835	60,298
50-54	66,244	61,605
55-59	69,785	61,340
60-64	71,059	63,308
65-69	70,793	65,542
70-74	69,587	67,732
75-79	68,539	70,229
80+	69,050	73,290
80-84	70,899	76,570
85-89	72,504	79,231
90-94	73,105	80,812

Births in industrialized countries — Deaths in industrialized countries

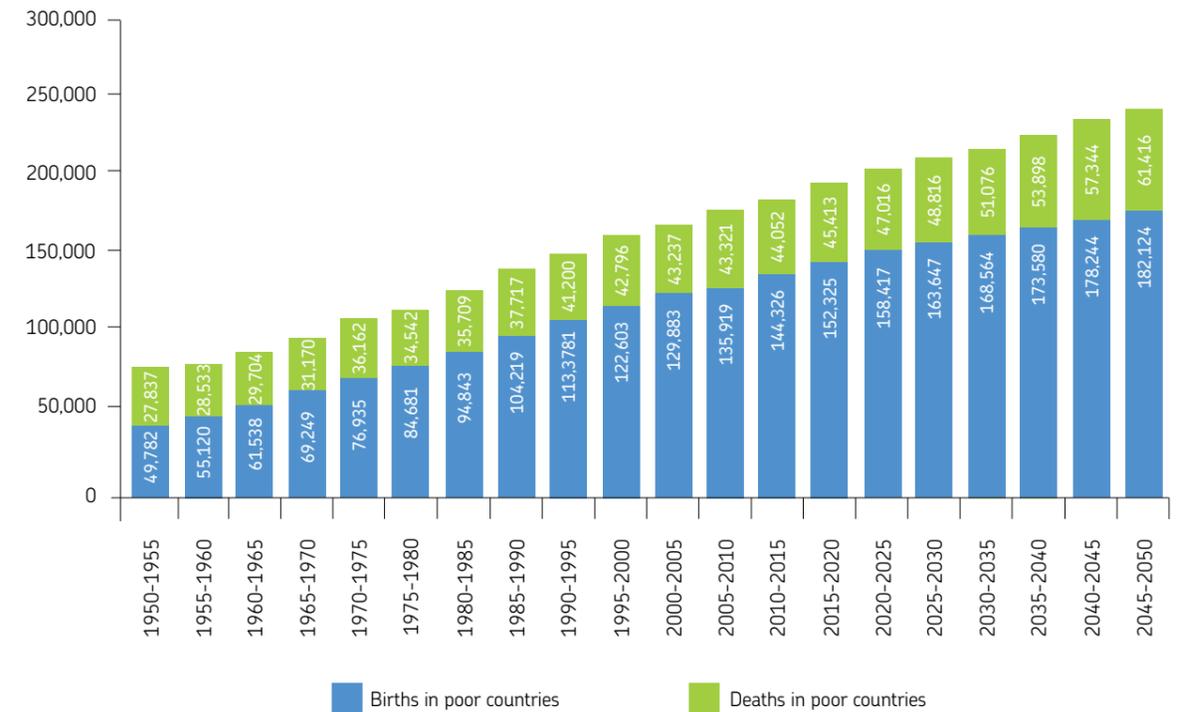Source: The European House-Ambrosetti elaboration of UN data, *World Population Prospect,* 2010.

In analyzing the demographic variables, we must first consider the important differences between advanced countries, which have almost reached the "zero point" of growth, and developing countries, contributing instead to 90% of the population growth today.

Figure 2.4 shows that in industrialized countries, there is an almost perfect equality between the number of births and deaths. Figure 2.5, instead, highlights the strong population growth registered in poor or developing countries.

SCHOLARS SPEAK OF THREE STAGES OF DEMOGRAPHIC TRANSITION

To explain the profound differentiation and the imbalance of demographic regimens in the last century, scholars speak of three[3] stages of demographic transition (Landry, Notestein). The first phase is the one in which mortality decreases while the birth rate is still high

Figure 2.5. **Comparison of births and deaths in developing countries[4] between 1950 and 2050**

Period	Births	Deaths
1950-1955	49,782	27,837
1955-1960	55,120	28,533
1960-1965	61,538	29,704
1965-1970	69,249	31,170
1970-1975	76,935	36,162
1975-1980	84,681	34,542
1980-1985	94,843	35,709
1985-1990	104,219	37,717
1990-1995	113,3781	41,200
1995-2000	122,603	42,796
2000-2005	129,883	43,237
2005-2010	135,919	43,321
2010-2015	144,326	44,052
2015-2020	152,325	45,413
2020-2025	158,417	47,016
2025-2030	163,647	48,816
2030-2035	168,564	51,076
2035-2040	173,580	53,898
2040-2045	178,244	57,344
2045-2050	182,124	61,416

Births in poor countries — Deaths in poor countries

Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

and average life expectancy is increasing. This phase is recorded in developing countries, particularly in Africa south of the Sahara, the Muslim countries and in Southeast Asia.

In an intermediate situation, i.e., the second stage, there are the Latin American countries, China and India.

And lastly, in the third and final stage, there are countries such as Italy, the U.S., Canada, Australia, New Zealand, Japan and South Korea. This phase is characterized by a decrease in mortality (due to the improvement of sanitary conditions), but it also corresponds to a sharp decline in the birth rate.

Thanks to global economic growth, a general improvement of living conditions and scientific progress, the global average life expectancy[5] has been constantly increasing since the beginning of the 21st century: in 2010, it stood at 70.14 years of age for women and 65.71 for men. However, it all depends on the starting point, and this testifies to the fact that there are countries that are rapidly growing with regard to life expectancy, but that do not yet have sufficient conditions for their economic and social development. In Bangladesh, for example, male life expectancy in 2020 will reach age 71, only three years younger than Europeans, despite being a country that is partially suffering from inadequate sanitary facilities and has difficulty finding basic medicines.

The world values are, in fact, driven by the high average of Western countries and the high growth rates of life expectancy experienced by emerging economies. A selection of the 10 OECD countries with the highest life expectancy is shown in Figure 2.7. Of these, five out of ten are European countries, two are Asian, followed by Australia and, in North America, only Canada.

THANKS TO GLOBAL ECONOMIC GROWTH AND A GENERAL IMPROVEMENT OF LIVING CONDITIONS, THE AVERAGE LIFE EXPECTANCY HAS BEEN CONSTANTLY GROWING SINCE THE BEGINNING OF THE 21ST CENTURY

Figure 2.6. **World life expectancy, comparison of male and female populations between 1950 and 2030**
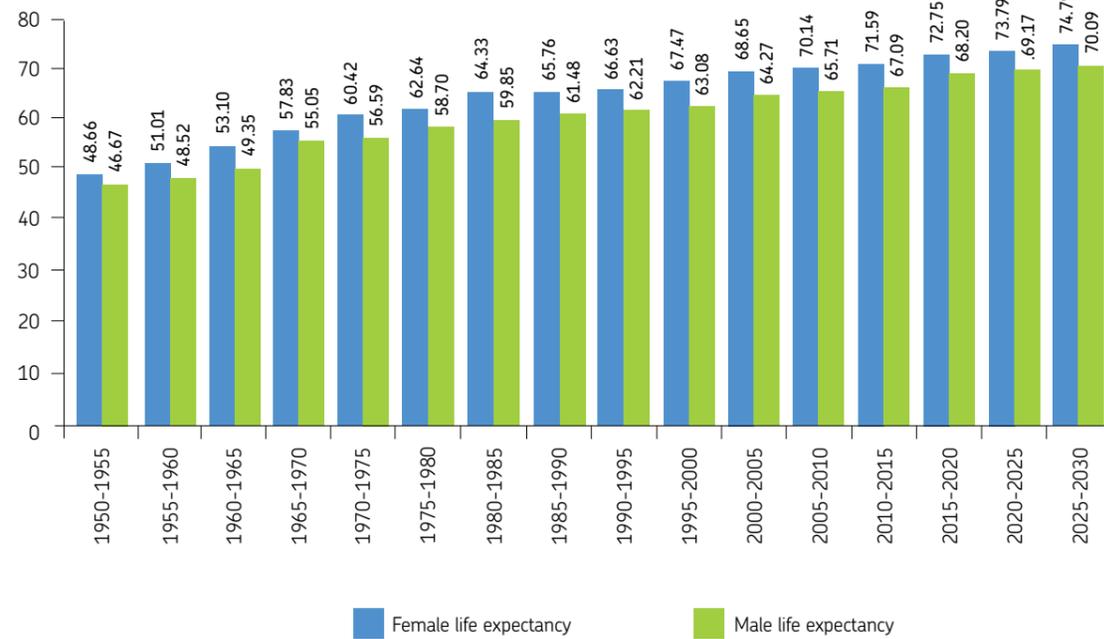
Female life expectancy   Male life expectancy

Source: The European House–Ambrosetti elaboration of UN data, World Population Prospect, 2010.

Figure 2.7. **Life expectancy in the top 10 OECD countries, comparison of the male and female populations (2010)**

Males   Females
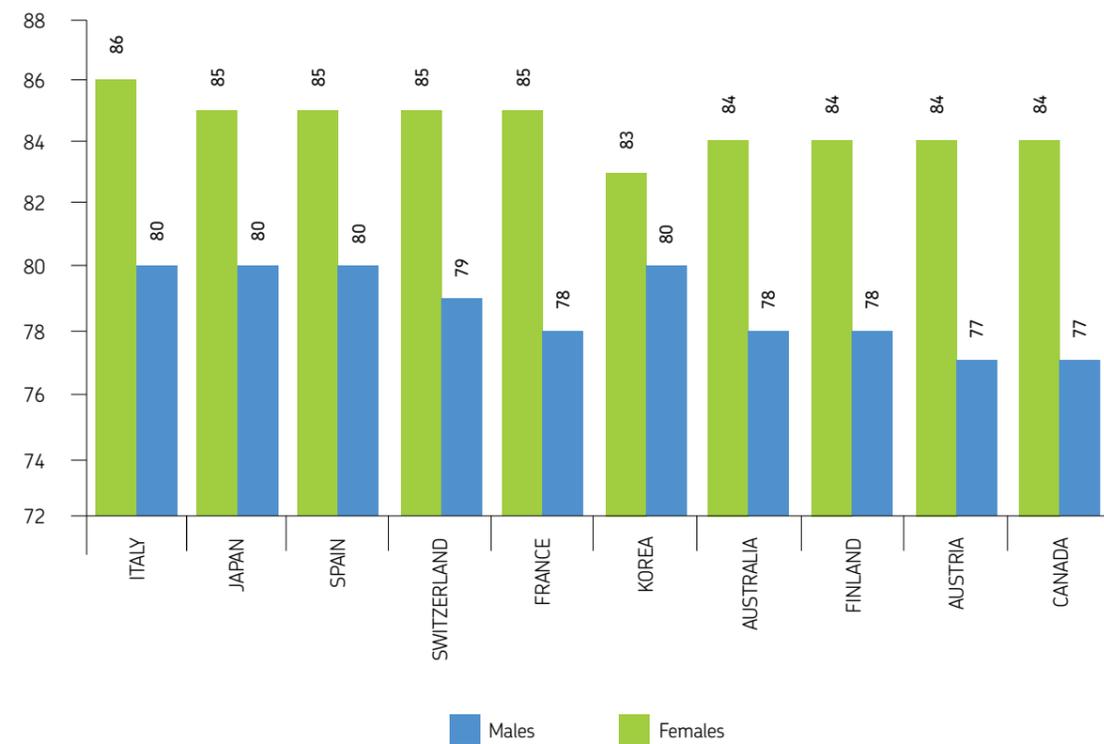
Source: The European House–Ambrosetti elaboration of OECD data from 2010.

The U.S., unique among developed countries, is beginning to experience, in some of its states, a decline in life expectancy at birth. In fact, a recent study[6] showed that states such as Mississippi, Arkansas, Kentucky, Tennessee, Oklahoma, Alabama and Louisiana are undergoing a gradual decline in life expectancy, particularly with regard to women, among whom the highest rates of obesity and smoking are recorded. Particularly in Mississippi, the state with the highest obesity rate, life expectancy is only 67 for men and 74 for women, much lower values than those of the countries shown in Figure 2.7. The graph in Figure 2.9 shows, however, that China has almost doubled its life expectancy between 1950 and 2011. This will lead to a rapidly aging population, accelerated, among other things, in part by the effects of the one-child policy adopted in China since 1979.

The effect of the aging of the Chinese population is due to the drop in the average annual birth rate between 1950 and 2010 (-3%). A number of factors have contributed to this phenomenon, and one in particular was the birth control policy implemented in 1979. Another phenomenon is that of the over-65 population, which between 2005 and 2010 already exceeded the number of infants (114 million people aged over 65 compared to 83 million babies).

The gradual aging of the population has become a common phenomenon in both developed and developing countries. The UN estimates predict that by 2050, one-third of the population in industrialized nations and one-fifth in developing countries will be aged sixty or older. Figure 2.10 shows how, between 1950 and 2010, the elderly population in the world increased at an average annual growth rate of 13%. Moreover, it is estimated that in 2050, the over-65 population will consist of 1.9 billion people.

This phenomenon will have a very significant impact on economic, political and social structures worldwide, since an increasing share of the population over 65 years of age involves, in fact, an increase in economic inactivity and greater reliance upon the younger population. Europe has the highest dependency ratio in the world, and estimates indicate that it will grow to reach 48% in 2050. This growth is not only due to the increase in the number of elderly, but also to a reduction of the population of working age (typically between 15 and 64). Both the developed countries and those in the developing world will face major challenges with regard to pensions and health care. In fact, because of global aging and the higher incidence of chronic diseases, the costs of care and medical equipment will increase. For example, in China there will be a sharp increase in pension costs, which are predicted to reach $1600 billion by 2050.[7] Figure 2.11 shows the sharp rise in the old age dependency ratio in developed countries, as compared to developing countries, where the rate has remained substantially unchanged over the past 60 years. This phenomenon is due to the marked aging of the population in industrialized countries, as shown in Figure 2.8. The UN predicts that, globally, the old age dependency ratio will rise from 11.5% today to 25.4% in 2050. Without further changes in other key parameters, the rapid aging of the population will lead to an increase in demand for pension benefits and assistance for hospitalization.

In addition, today, chronic diseases are the leading cause of death worldwide. But between 2005 and 2015, it is expected that deaths from such diseases will grow 17%.[8] These chronic and infectious diseases significantly worsen the quality of life and stimulate the emergence of high costs, both for emergencies and for long-term hospital care. Estimates indicate that in both lowincome countries and in middle-income countries, the demand for medicines and equipment for the treatment of these diseases will grow and this will have an impact on both the public and private sectors.

Finally, the World Bank estimates that the workforce in high-income countries reached

SOME STATES IN THE U.S. ARE BEGINNING TO EXPERIENCE A DECLINE IN LIFE EXPECTANCY, ESPECIALLY AMONG WOMEN

CHINA HAS ALMOST DOUBLED ITS LIFE EXPECTANCY BETWEEN 1950 AND 2011, WHICH WILL LEAD TO A RAPIDLY AGING POPULATION

AN INCREASINGLY HIGH PROPORTION OF THE POPULATION WILL LEAD TO AN INCREASE IN ECONOMIC INACTIVITY AND RELIANCE UPON THE YOUNGER POPULATION

THE RAPID AGING OF THE POPULATION WILL LEAD TO AN INCREASE IN DEMAND FOR PENSION BENEFITS
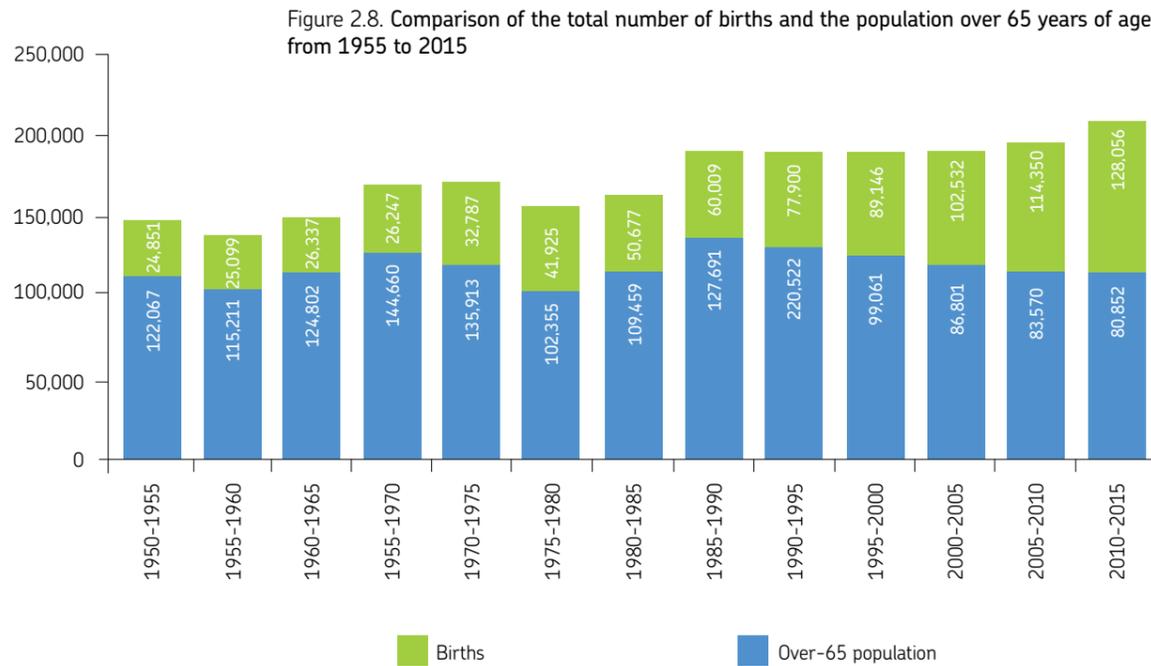
AN INCREASE IN DEATHS FROM CHRONIC DISEASES IS EXPECTED, TO BE FOLLOWED BY THE CORRESPONDING INCREASES IN OPERATING COSTS FOR THE TREATMENT OF THESE DISEASES

THE WORKFORCE
IN HIGH-INCOME
COUNTRIES REACHED
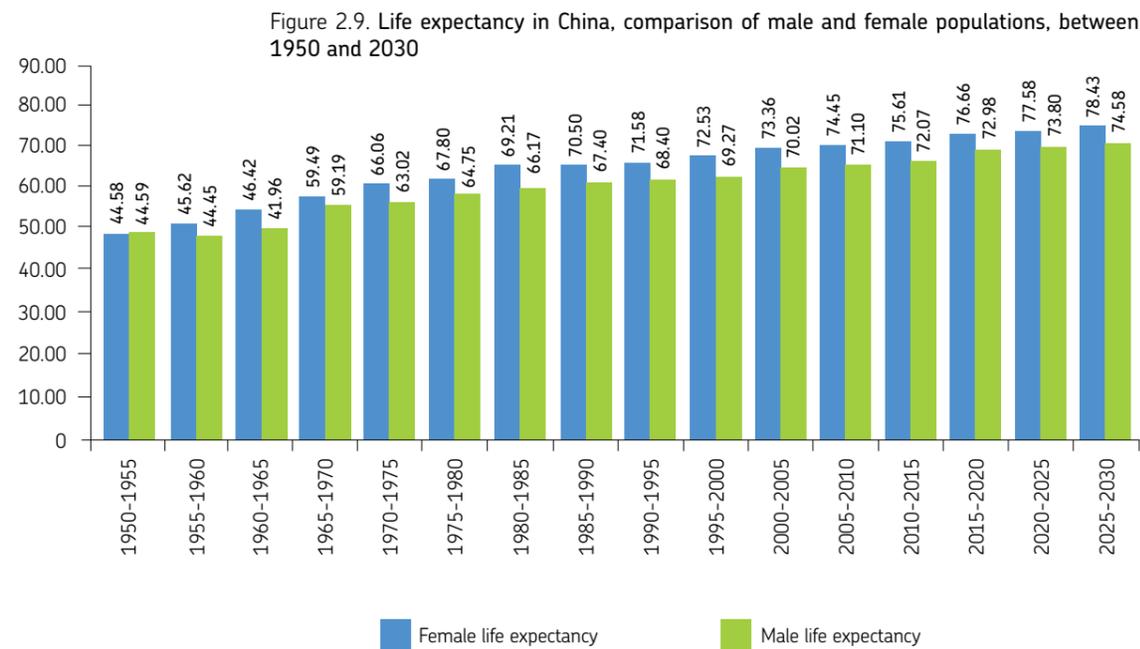ITS PEAK IN 2010,
FOLLOWED BY
A SIGNIFICANT
REDUCTION.

its peak in 2010, after which it began to drop, significantly weakening the financial sustainability of pension systems.

In conclusion, in light of the above, we can say that, in general, the increase in the elderly population leads to a significant expansion of spending on health, both public and private, worldwide.

Figure 2.13 shows the growth of the share of the GDP devoted to health spending on

Figure 2.8. **Comparison of the total number of births and the population over 65 years of age, from 1955 to 2015**

Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

Figure 2.9. **Life expectancy in China, comparison of male and female populations, between 1950 and 2030**

Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

Figure 2.10. **Composition of the world population by age groups, "<65" and "> 65," between 1950 and 2050**
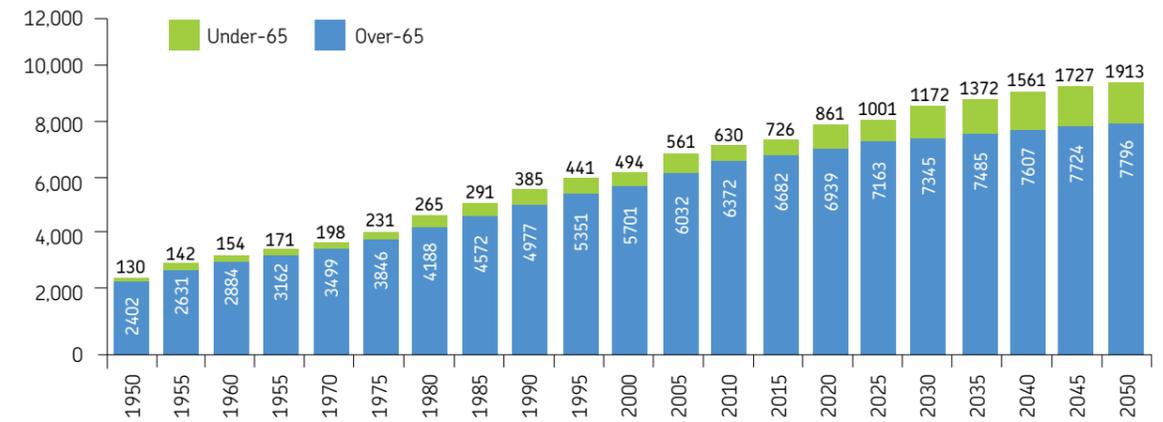
Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

Figure 2.11. **Ratio of the over-65 population and the working-age population (15-64) worldwide, between 1950 and 2010**

Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

Figure 2.12. **Composition of the population of industrialized countries of the different "<65" and ">65" age groups, between 1950 and 2050**
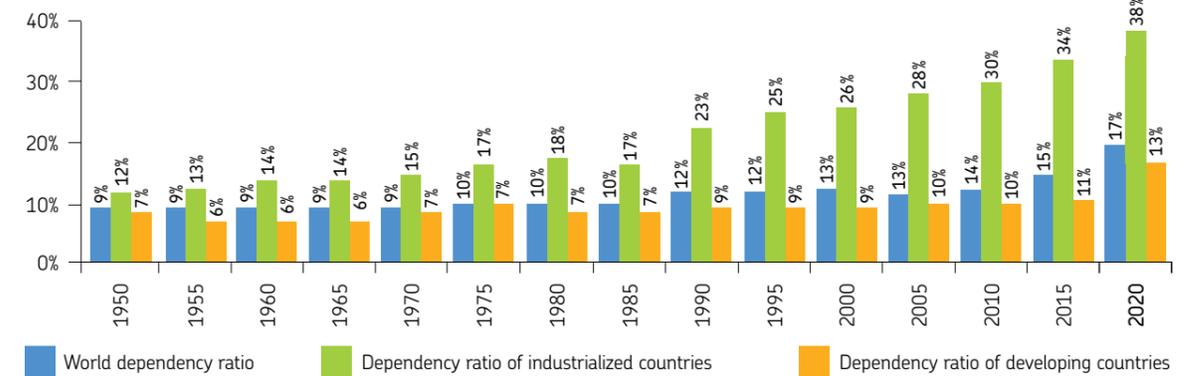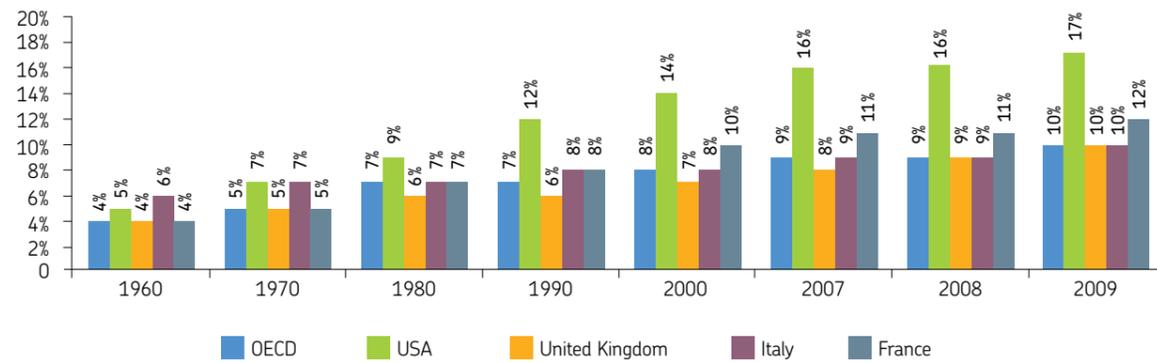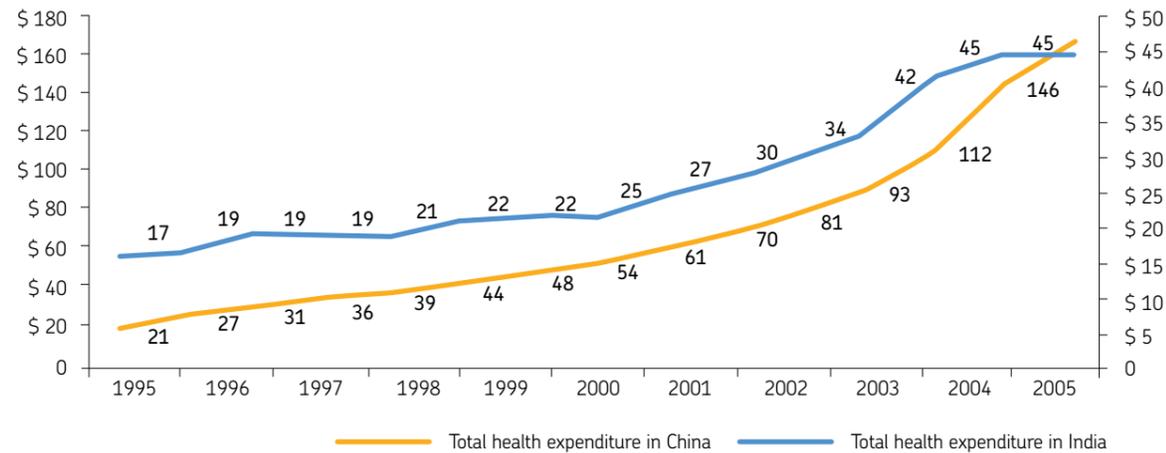

Source: The European House-Ambrosetti elaboration of UN data, World Population Prospect, 2010.

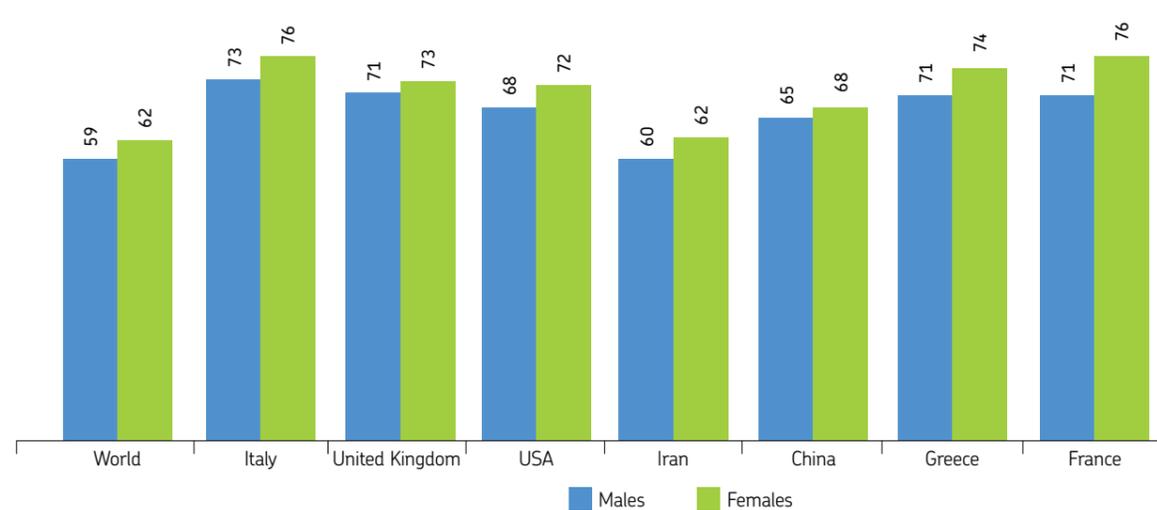Figure 2.13. **Share of the GDP of total health expenditure between 1960 and 2010**

Legend: OECD, USA, United Kingdom, Italy, France

Source: The European House–Ambrosetti elaboration of OECD data, 2009.

Figure 2.14. **Total health expenditure per capita in U.S. dollars in China and India, between 2009 and 1995**

Total health expenditure in China — Total health expenditure in India

Source: The European House–Ambrosetti elaboration of OECD data, 2009.

Figure 2.15. **Life expectancy in good health of selected countries and compared with global data (2010)**

	Males	Females
World	59	62
Italy	73	76
United Kingdom	71	73
USA	68	72
Iran	60	62
China	65	68
Greece	71	74
France	71	76

Source: The European House–Ambrosetti elaboration of WHO data, 2009.

average in OECD countries and in some representative countries. In the U.S., 17.4% of the GDP (about $2,500 billion U.S.) is spent on health, compared to 5% in 1960. Even in Italy, there is a phenomenon of growth, albeit more modest, with a passage from 6% of the GDP in the '60s to around 10% today (about €180 billion).

As seen in Figure 2.14, China and India also have large increases in health spending in terms of the GDP per capita.

The challenge on a global level for the next years will be to make sustainable the huge costs linked to aging, through programs of "active aging" that provide for a greater involvement of the population belonging to that age group, which tends to be considered unproductive in economic and social activities. This can be achieved through an increase in the years of life which are lived in good health.

Figure 2.15 shows that countries with greater health care costs are also those that can provide citizens with a better life expectancy in good health.

THE CHALLENGE ON A GLOBAL LEVEL FOR THE NEXT YEARS WILL BE TO MAKE SUSTAINABLE THE HUGE COSTS LINKED TO AGING, THROUGH PROGRAMS OF "ACTIVE AGING"

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2.2 MAJOR DISEASES AND LONGEVITY: EVOLUTION AND SOCIO-ECONOMIC IMPACT

NON-COMMUNICABLE DISEASES NOW REPRESENT THE GREATEST RISK TO HUMAN HEALTH GLOBALLY, AS WELL AS A HUGE SOCIO-ECONOMIC BURDEN FOR SOCIETY

Non-communicable diseases, particularly cardiovascular diseases, cancer and diabetes, now represent the greatest risk to human health globally, as well as a huge socio-economic burden for society. It is estimated that 80% of the manifestations of these diseases could be prevented by eliminating risk factors such as tobacco use, unhealthy eating patterns and habits (diet), physical inactivity and excessive alcohol consumption. On the contrary, without proper prevention, the burden of these diseases on global health could increase by 17% in the coming years.[9] With the evolution of age, the prevalence of these diseases, which are often accompanied by neurodegenerative diseases and osteoporosis, becomes progressively higher. The following chapter presents the latest data available in scientific literature regarding the diffusion, mortality and socio-economic impact of these diseases, whose onset is associated, with variable intensity, to the diet. Therefore, it will be dealing with: *diabetes and metabolic syndrome, cardiovascular disease, cancer, osteoporosis, neurodegenerative diseases*.

Before describing in detail the scenario of these diseases, an overview of the phenomenon of obesity and overweight conditions is provided below; the occurrence of this phenomenon is a major risk factor and, in particular, it is becoming increasingly widespread in youth.

2.2.1 Obesity and overweight conditions

ALMOST ALL OF THE COUNTRIES IN THE WORLD ARE EXPERIENCING AN EXPONENTIAL GROWTH OF OBESITY AND OVERWEIGHT CONDITIONS

Almost all of the countries in the world are experiencing an exponential growth of obesity and overweight conditions. The European Association for the Study of Diabetes has even acknowledged the treatment of obesity as "the most important public health problem worldwide."

Figure 2.16 clearly shows that the U.S. has the highest share of obese population[10] in the world. Approximately 34% of the adult population (i.e., more than 60 million people) appears to meet the criteria identified to define situations of obesity.

In Asian countries, the phenomenon is growing but at much lower rates (3% of the adult population in Japan and 4% in South Korea), mainly due to the composition of their low-calorie diet. Instead, the trend in China is of concern because of its rapid growth: in 2004, there were 60 million obese Chinese and 200 million who were overweight; in 2009 the figures had passed to 100 million obese people and 310 million overweight people.

IT IS WELL ESTABLISHED BY NOW THAT THE RATE OF OBESITY INCREASES WITH THE PER CAPITA INCOME

It is well established by now that the rate of obesity increases with the per capita income, even though in rich countries, the poorest people have a higher prevalence of the disease because of the high cost of a healthy and diversified diet.

Farrell Grehan/National Geographic Stock

IN HIGH-INCOME COUNTRIES, THE PICTURE RELATING TO OBESITY IS WORSE: CHILDREN AND YOUNG PEOPLE ARE ALSO INCREASINGLY BECOMING OVERWEIGHT

Moreover, in high-income countries, obesity and overweight conditions no longer seem to be widespread mainly in adults and in middle-aged subjects, but pathologies are occurring with increasing frequency in children and young people, outlining a severe and worsening picture.

The level of the overweight condition at a young age is crucial with regard to the probability of developing severe illnesses and discomforts in adulthood. In particular, type 2 diabetes – once considered a disease of elderly adults – may now be found, and increasingly so, among children and young people.

Figure 2.16. **Overweight conditions (figure 1) and obesity (figure 2) in some countries, 2008 (% adult population)**
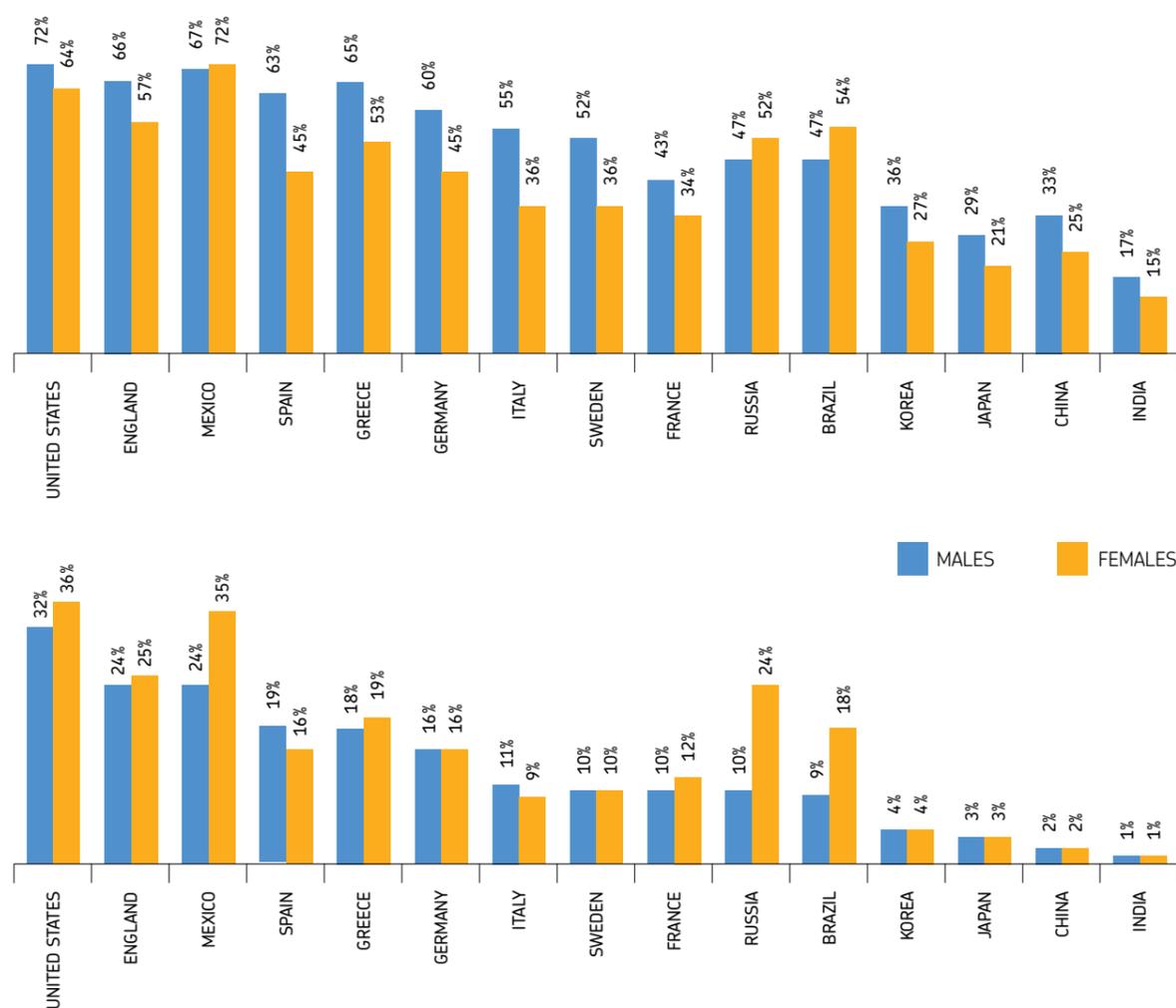
Source: The European House–Ambrosetti elaboration of *Obesity and the economics of prevention*, OECD data, 2010.

2.2.2 Diabetes and metabolic syndrome

Diabetes appears to be one of the most widespread chronic diseases in the world, particularly in highly industrialized countries; it is one of the most significant and costly social illnesses of our time, mainly because of its chronic character, the tendency to establish long-term complications and the gradual shift toward a younger age of onset.

The causes of the emergence of what has been described as an epidemic are to be found in four main factors:
- the *proliferation of bad eating habits*;
- the *growth in the number of obese/overweight people*;
- the *emergence of increasingly sedentary lifestyles*;
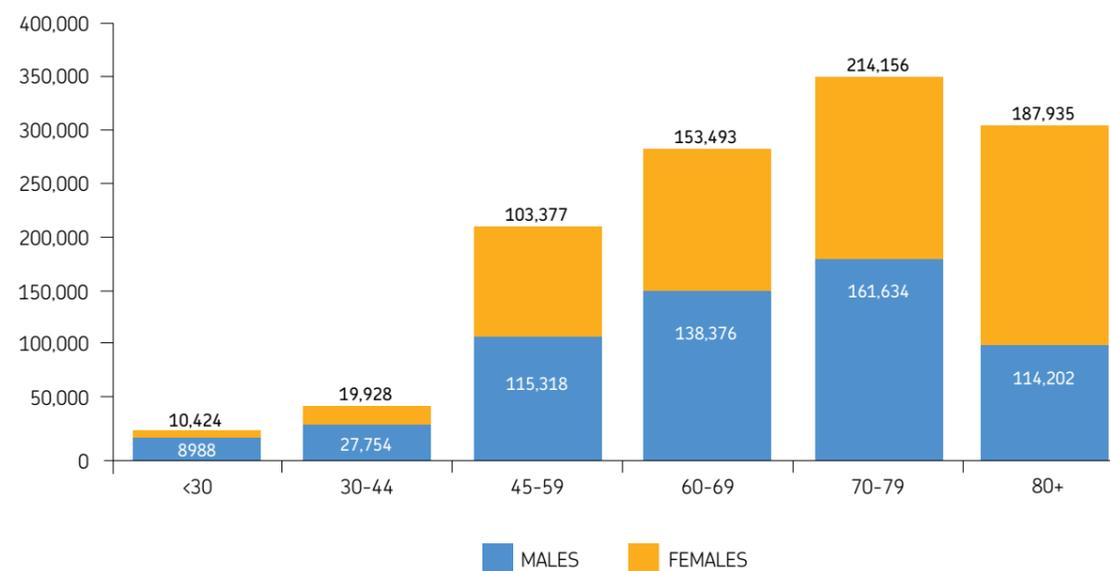- the *aging of the population*.

With reference to 2009, among people aged 20 to 79 years, the estimated prevalence worldwide of the disease is 5.9%, amounting to 302 million patients, with a 34% increase compared to 2003.

Every year, there are more than 7 million new cases of diabetes in the world (one every five seconds).

The prevalence of diabetes will grow both in industrialized and in developing countries. In China, for example, it has been estimated that there were about 39.8 million people with diabetes in 2007, or 4.3% of the population; in 2025, this number is expected to have grown to just under 60 million (5.6% of the population), with a 50% increase in the number of cases. A more worrisome trend of growth is expected in India, where the number of people affected with diabetes, currently 40.8 million (6.2% of the population), is expected to reach 69.8 million (7.6% of the population) in 2025.

The prevalence and mortality linked to this disease grow dramatically with increasing age. Figure 2.17 shows the distribution by age of deaths due to or caused by diabetes (including the various complications).

DIABETES APPEARS TO BE ONE OF THE MOST WIDESPREAD CHRONIC DISEASES IN THE WORLD; IT IS ONE OF THE MOST SIGNIFICANT AND COSTLY SOCIAL ILLNESSES OF OUR TIME

EVERY YEAR, THERE ARE MORE THAN 7 MILLION NEW CASES OF DIABETES IN THE WORLD (ONE EVERY 5 SECONDS)

Figure 2.17. **Worldwide absolute mortality caused by diabetes, by age group (2008)**

Source: The European House–Ambrosetti elaboration of WHO data, 2010.

IN ITALY, THE PROGRESSION IN THE PREVALENCE OF DIABETES IN THE LAST 10 YEARS SHOWS A TREND OF STEADY GROWTH

In Italy, the progression in the prevalence of diabetes in the last 10 years shows a trend of steady growth: the rough rate recorded an increase from 3.9% in 2001 to 4.9% in 2010, while the standardized rate rose from 3.9% to 4.5%.[11]

Also with reference to Italy, the data clearly shows that the prevalence of diabetes increases with age, reaching 19.8% in people aged 75 or older.

Figure 2.18. **Trends in the prevalence of diabetes in Italy (% total population, 2001–2010)**
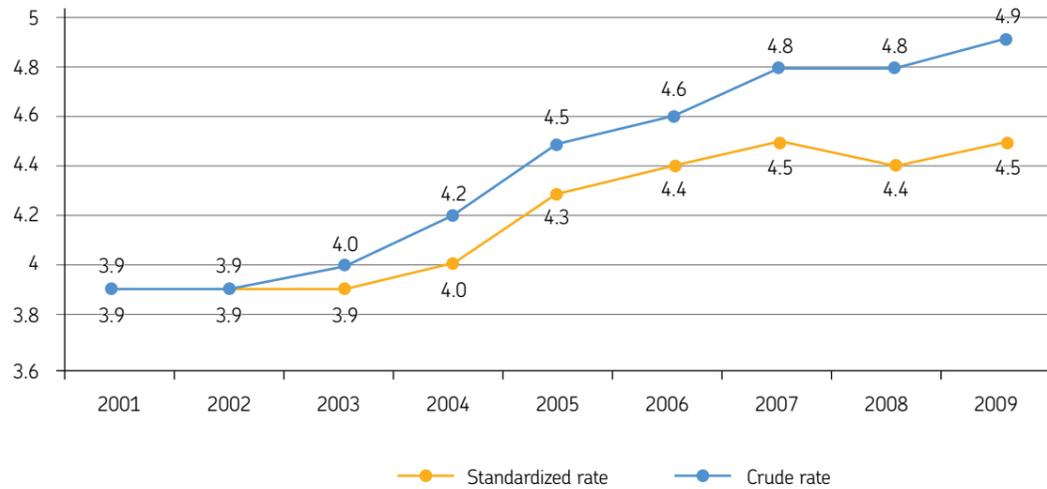
Source: The European House–Ambrosetti elaboration of ISTAT/ISS data, 2010.

Figure 2.19. **Prevalence of diabetes by gender and age group (2010)**
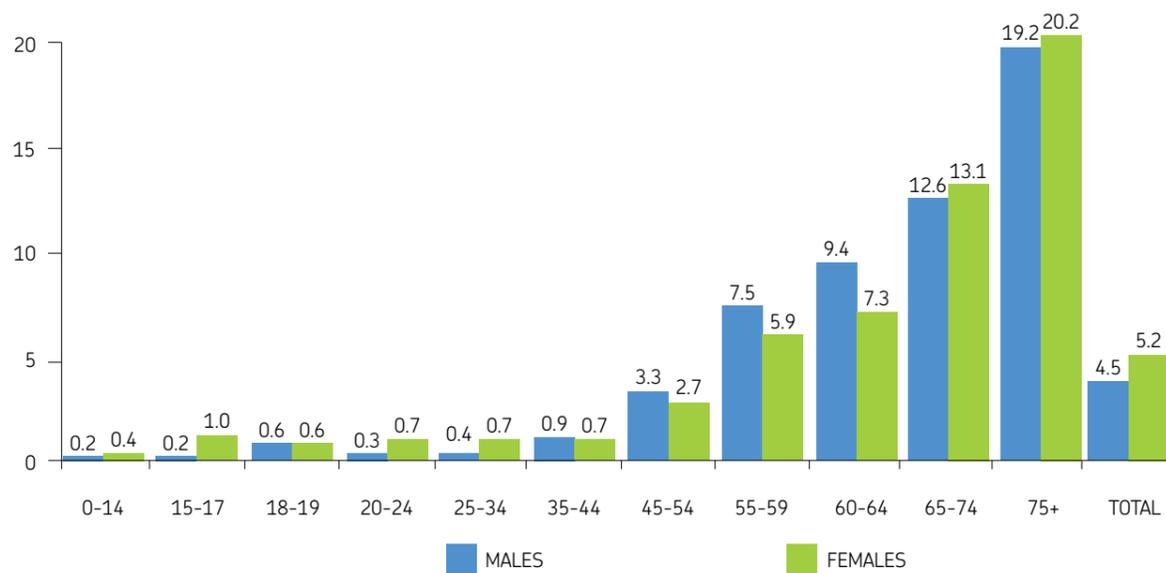
Source: The European House–Ambrosetti elaboration of STAT/ISS data, 2010.

Economic and social impact

Numerous international studies that estimate the economic costs associated with diabetes show a very high impact.

For example, according to the International Diabetes Federation in 2007, $232 billion were spent worldwide in the treatment and prevention of diabetes and its complications. This expenditure will grow to at least $302 billion in 2025.

A recent study by the American Diabetes Association[12] has estimated that in 2007, the U.S. spent $174 billion to care for people with diabetes, a figure which includes $116 billion for direct medical costs and $58 billion calculated as lost productivity of the patients and family members involved in their care. American diabetic patients sustain, on average, costs of over $11,400 per year, including $6,650 directly attributable to diabetes.

As far as Italy is concerned, it has been estimated that the treatment of diabetes and all its associated complications (renal failure, cardiorespiratory failure, neuropathic and vascular lesions of the lower extremities) accounts for 7% of the national public health spending, or about €7.7 billion per year.

The annual average per capita cost of a diabetic patient is around €2,600, of which hospital costs account for over half (54%) of the total costs, while the drugs prescribed to patients with diabetes account for about 16%. In Italy, it is estimated that over 75,000 hospitalizations are related to diabetes and its complications (stroke, myocardial infarction, renal failure, amputation of lower limbs). In addition, if there are complications, the cost of health care delivered to a patient with diabetes increases three to four times.

THE ECONOMIC AND SOCIAL IMPACT OF THE COSTS ASSOCIATED WITH DIABETES ARE VERY HIGH

THE AMERICAN DIABETES ASSOCIATION HAS ESTIMATED THAT IN 2007, THE UNITED STATES SPENT $174 BILLION TO CARE FOR PEOPLE WITH DIABETES IT HAS BEEN ESTIMATED THAT ITALY WILL SPEND ABOUT €7.7 BILLION PER YEAR FOR THE CARE AND TREATMENT OF DIABETICS

2.2.3 Tumors

Tumors, or cancer, the second leading cause of death in the world, both in Europe and in Italy, is a constantly growing pathology, even though we have observed a reversal of the trend since 2005 in the case of men and a slight slowdown of growth in women. Since these are diseases that mostly affect the elderly, the longer life expectancy of individuals plays an important role in their growing diffusion.

In addition to the demographic factor, the frequency of the disease is generally higher in developed countries; but it is only in the most advanced and richest societies, where significant resources are invested for the health of the population, that the possibility exists of reducing the risk and prolonging the life expectancy of the people who are affected by this disease.

Figure 2.20 shows that there has been a reduction in recent years in the number of deaths caused by cancer. Today, in fact, in most economically advanced countries, more than 50% of people who have been diagnosed with cancer can resume their lives after the recovery or stabilization of their clinical picture.

In contrast, in low and middle income countries, the risk of death from cancer is much higher. According to the World Health Organization, in 2007 there were 7.9 million deaths worldwide attributed to cancers[13]: three quarters of these were located in countries with low average incomes.[14] One out of every 8 deaths in the world is due to cancer, which causes more deaths than AIDS, tuberculosis and malaria combined.

It is estimated that in Italy at the end of this decade, nearly 2 million people will have been diagnosed with cancer in their lifetime, including approximately 400,000 patients who were diagnosed less than two years previously, and upon whom a more intense demand for medical care is focused, as well as 700 thousand who became ill more than 10

IN ADDITION TO THE DEMOGRAPHIC FACTOR, THE FREQUENCY OF THE DISEASE IS GENERALLY HIGHER IN DEVELOPED COUNTRIES

IN RECENT YEARS, IN ADVANCED COUNTRIES, THERE HAS BEEN A REDUCTION IN THE NUMBER OF DEATHS CAUSED BY CANCER

IN ITALY AT THE END OF THIS DECADE, NEARLY 2 MILLION PEOPLE WILL HAVE BEEN DIAGNOSED WITH CANCER

years earlier and who are potentially healed or suffering from physical, psychological or social consequences. These numbers will increase over the coming decades.[15]

Figure 2.20. **Evolution of the absolute mortality/100,000 inhabitants from cancer in OECD countries**
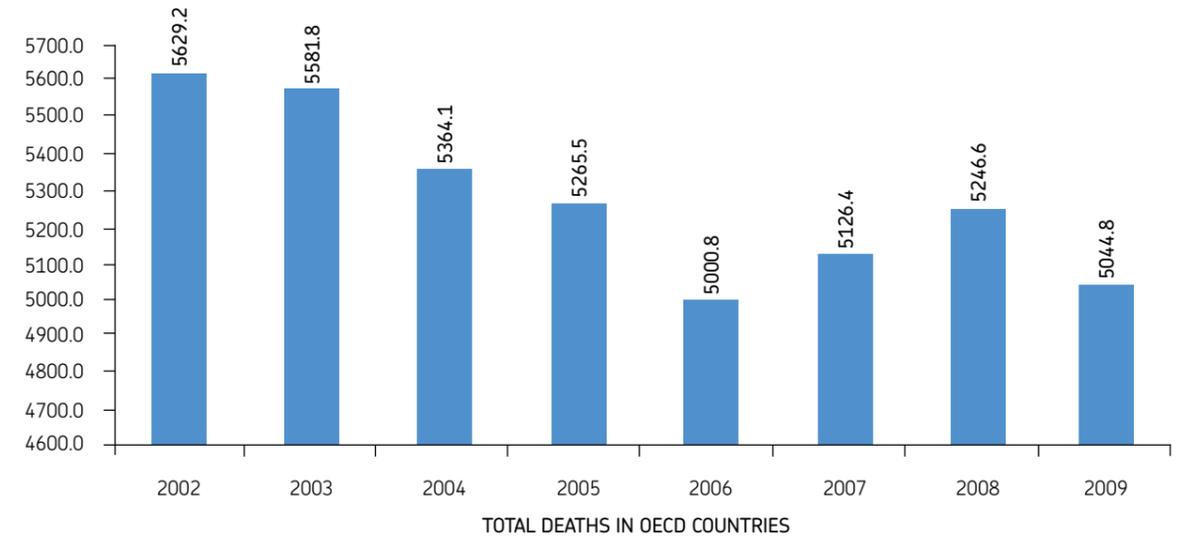
Source: The European House–Ambrosetti elaboration of OECD, data, 2010.

Economic and social impact

The economic impact of cancer is very high and can be measured through an assessment of direct medical costs (treatment, hospitalization, rehabilitation, etc.) and indirect costs related to lost productivity from lost workdays due to illness (indirect costs of morbidity). The social cost is the loss of jobs and premature death (indirect costs of mortality).

The unavailability of consistent data makes it impossible to estimate the overall economic impact of cancer. However, studies and statistics collected in some countries allow for an understanding of the enormity of the economic impact of this disease.

In the U.S., for example, the National Institute of Health estimates that the economic impact of cancer in 2008 amounted to $228.1 billion per year, including both health care costs and the lost productivity of those who were sick.[16] In particular, direct medical costs amounted to $93.2 billion, the indirect costs of illness to $18.8 billion and the indirect costs of mortality totaled $116.1 billion. As can be seen from Figure 2.21, in recent years, the total economic costs have grown steadily, particularly those related to direct medical costs (in 1963, the value of this entry reached $1.3 billion, in 1980, it had risen to 13 billion dollars, in 1990 it rose to $27.5 billion, in 2000 it was $55 billion, eventually reaching $93 billion in 2008). Concerning Italy, the spending on direct healthcare costs was estimated to be €6.7 billion in 2004, 6.6% of the total health expenditure.

Finally, the care of cancer patients in the terminal phase has very consistent physical, mental, social and economic impacts on members of the family. According to a survey

THE ECONOMIC IMPACT OF CANCER CAN BE MEASURED IN DIRECT AND INDIRECT HEALTH CARE COSTS, WHILE THE SOCIAL COST IS THE LOSS OF ONE'S JOB OR PREMATURE DEATH
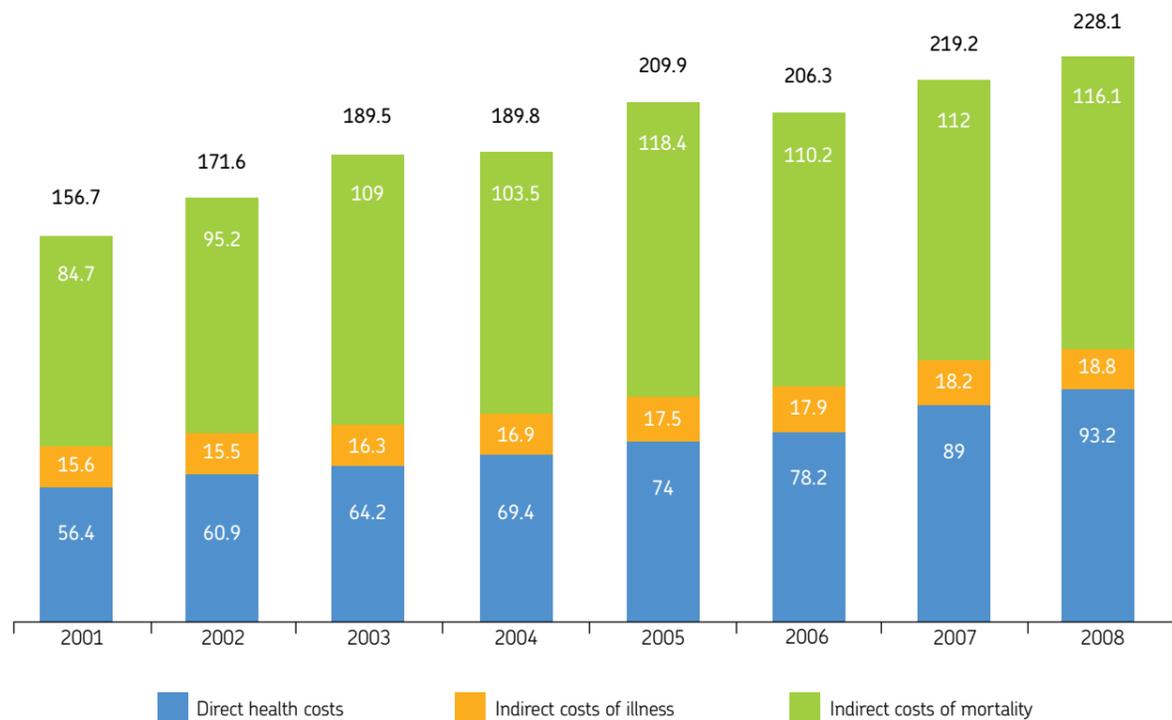
IN THE UNITED STATES, FOR EXAMPLE, THE NATIONAL INSTITUTE OF HEALTH ESTIMATES THAT THE ECONOMIC IMPACT OF CANCER IN 2008 AMOUNTED TO $228.1 BILLION PER YEAR

Figure 2.21. **Progression of the economic impact of cancer in the U.S. (2001–2008, billions of dollars)**

Direct health costs   Indirect costs of illness   Indirect costs of mortality

Source: The European House–Ambrosetti elaboration of data from the American Cancer Society, Cancer Facts&Figures, 2009 and previous editions.

conducted in Italy by the ISDOC (Italian Survey of the Dying Of Cancer),[17] every year, in about 40,000 Italian families, one component must reduce or leave their job to care for a sick family member.

According to the results of a recent survey conducted at the Polyclinic Umberto I in Rome,[18] commitment to helping a cancer patient by a family member often leads to serious repercussions on the working life of the latter:

- 72% of family members caring for a cancer patient claim to have had serious repercussions on their working lives, and of these: 38% suffered losses due to lost earnings during the hospital stay of between 700 and €1,000 per month, while 25% complained of losses even higher than €1,200;
- 13% were forced to take a leave of absence;
- 22% had to leave their job

2.2.4 Cardiovascular diseases

Cardiovascular system diseases[19] are the leading cause of death in all developed countries. Often disabling diseases, their diffusion is likely to increase with the progressive increase in life expectancy.

The main established risk factors are mostly related to inappropriate lifestyles – tobacco smoking, little physical activity, high levels of cholesterol and high blood pressure, type 2 diabetes, abdominal obesity – and are in part attributable to improper nutrition. The simultaneous presence of two or more of these factors multiplies the risk of having ischemic heart disease and cardiovascular accidents.

The World Health Organization data[20] indicates that, in 2008, there were 17.3 million deaths worldwide from cardiovascular disease, 30% of total deaths. Of these, 7.2 million were due to heart disease and 6.1 million due to strokes.

While it was once thought that cardiovascular disease only affected industrialized nations, today 80% of these deaths occur in developing countries or those with an emerging economy.

Diseases of the heart and circulatory system are the leading cause of death in Europe, where it is estimated that they cause more than 4.3 million deaths each year. Almost half (48%) of all deaths that occur are due to cardiovascular disease (54% in females and 43% in males). Slightly less than half of these cases are due to myocardial disease and one-third to strokes.

Although the number of deaths is still very high, there has been a drop, compared to previous years. In particular, between 1995 and 2005 there was a 9.6% decrease in the number of deaths in absolute terms, while the standardized morality rate[21] dropped 26.4%.

THE DIFFUSION OF CARDIOVASCULAR DISEASE WILL INCREASE WITH THE PROGRESSIVE INCREASE IN LIFE EXPECTANCY

THE WORLD HEALTH ORGANIZATION ESTIMATES THAT THERE WERE 17.3 MILLION DEATHS WORLDWIDE FROM CARDIOVASCULAR DISEASE IN 2008

Figure 2.22. **Share of deaths caused by cardiovascular disease in Europe (2008)**

Stroke 13%   Coronary diseases 22%
Other cardiovascular diseases 18%
Other diseases 47%
MALE POPULATION

Coronary diseases 15%   Stroke 12%
Other cardiovascular diseases 18%
Other diseases 55%
FEMALE POPULATION
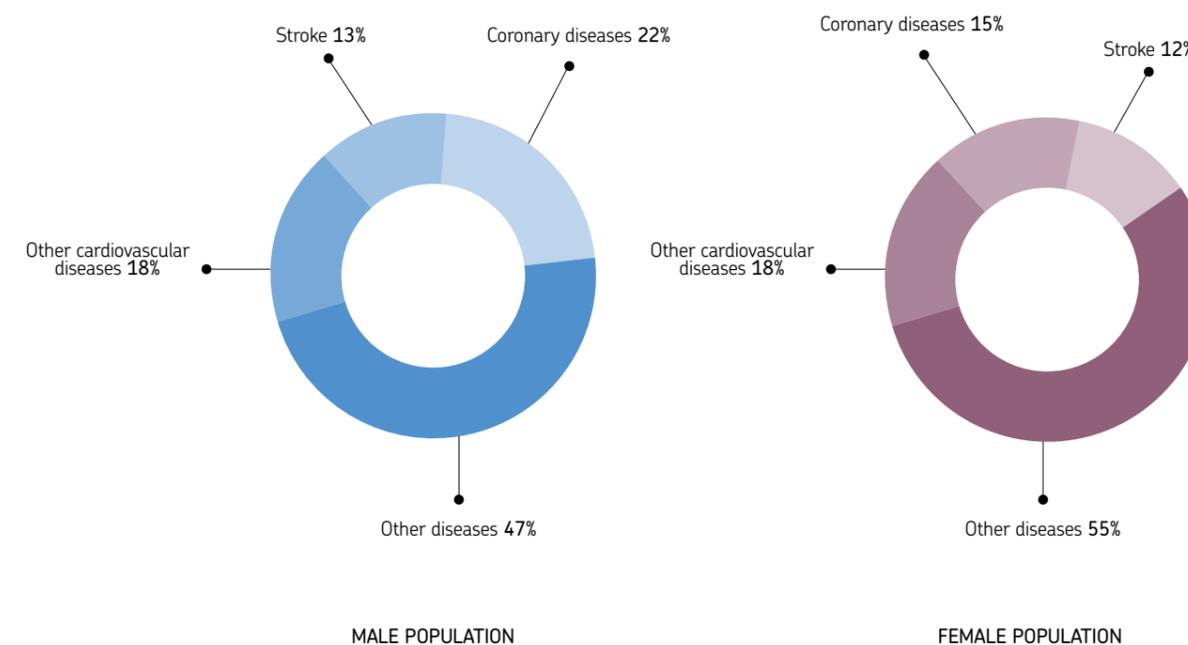
Source: The European House–Ambrosetti elaboration of data from *European Cardiovascular Disease*, 2008.

Figure 2.23. Trends in mortality from stroke and ischemic heart disease in OECD countries between 1980 and 2006

Year	Ischemic heart disease	Stroke
1980	171.8	122.5
1981	170.3	118.6
1982	166.8	113.5
1983	165.2	112.8
1984	162.0	108.6
1985	162.6	108.1
1986	157.5	104.7
1987	154.3	99.6
1988	150.5	96.4
1989	147.6	92.9
1990	144.3	91.8
1991	141.4	89.4
1992	138.3	86.9
1993	137.0	86.2
1994	130.3	82.8
1995	128.9	81.2
1996	123.6	77.7
1997	118.7	73.8
1998	115.4	73.0
1999	114.6	72.1
2000	107.9	69.3
2001	103.2	66.5
2002	100.7	64.8
2003	98.1	62.5
2004	92.5	57.7
2005	89.7	54.2
2006	86.9	52.3

Trends in mortality from ischemic heart disease in OECD countries
trends in mortality caused by stroke in OECD countries

Source: The European House-Ambrosetti elaboration of OECD, data, 2008.

As for the near future, however, estimates derived from a report on demographic changes and Male population Female population cardiovascular disease between 1950 and 2050 indicate that mortality from cardiovascular disease in the U.S. could increase in the period between 2000 and 2030.[22] This recent analysis suggests the need to concentrate on a strong preventive intervention at the beginning of this century.

Economic and social impact

The treatment of cardiovascular disease implies a relatively high average of medical costs, particularly due to the hospitalization of patients in the acute phase of illness, medication, the phase of rehabilitation and home care.

In addition, these conditions will generally lead to the patient's chronic condition and are a major cause of long-term illness and the abandonment of work. These diseases, in fact, materially affect the quality of life of the patients and often involve a reduction in work productivity and the ability to produce income by the patients themselves, as well as by members of their family.

Below are the results of some recent studies that show the high financial cost and social impact of the major cardiovascular diseases at an international level.

The most recent estimates of the total cost of cardiovascular disease in the U.S. indicate an impact of $286.6 billion, with regard to the year 2010. This value includes both direct medical costs (hospital services, drugs, home care, etc.), and a calculation of the indirect costs, such as loss of work productivity caused by illness or the premature death of patients.

CARDIOVASCULAR DISEASES AFFECT THE QUALITY OF LIFE OF THE PATIENTS AND OFTEN INVOLVE A REDUCTION IN WORK PRODUCTIVITY AND THE ABILITY TO PRODUCE INCOME

THE MOST RECENT ESTIMATES OF THE TOTAL COST OF CARDIOVASCULAR DISEASE IN THE UNITED STATES INDICATE AN IMPACT OF $286.6 BILLION, WITH REGARD TO THE YEAR 2010

The spreading of these diseases has serious economic and social repercussions not only in developed countries, but also in developing countries like China. According to recent estimates by the World Health Organization, the cumulative impact of heart disease, stroke and diabetes in ten years (between 2006 and 2015) will lead China to a loss of national income amounting to $558 billion.

The total economic impact of cardiovascular disease in Europe in 2006 amounted to about €192 billion,[23] considered as an average total cost per capita of €391. In particular, the costs for coronary heart disease amounted to €49 billion per year (about one quarter of the total), and the costs for strokes at €38 billion (about one-fifth of the total). 57% of the total economic impact is due to direct medical costs, and 43% to indirect costs due to lost productivity and other non-health costs. In particular, spending on health amounts to just under €110 billion, equivalent to 10% of the total health expenditure.

The total costs of cardiovascular disease in Italy in 2006 have been calculated at around €21.8 billion.[24] Of these, 63% (€13.8 billion) covers the direct costs incurred by the health system, including, in particular, the costs of hospitalization and drugs. However, 37% of the total economic impact of cardiovascular disease is due to the indirect costs of the lost productivity of patients of working age due to the disease (the costs of illness, amounting to €1.4 billion) or death (mortality costs, amounting to €2.6 billion) and other informal costs for the care of patients[25] (€4 billion), for a total of about €8 billion.

SERIOUS ECONOMIC AND SOCIAL REPERCUSSIONS ARE DUE TO THE SPREADING OF THESE DISEASES

IN ITALY IN 2006, THE TOTAL COSTS OF CARDIOVASCULAR DISEASES WERE CALCULATED AT AROUND €21.8 BILLION

David Alan Harvey/National Geographic Stock

2.2.5 Dementia and neurodegenerative diseases

Dementia is a condition that affects 1 to 5% of the population over 65 years of age, with a revalence that then doubles every four years, reaching an average of about 30% at around 80 years of age. Recent statistics show an increasing spread of this condition among individuals under 65 years of age (between 2% and 10% of the total cases).

Dementia refers generically to a state of chronic and progressive dysfunction of the brain functions, leading to a decline in the cognitive abilities of the person. The generic definition of "dementia" includes several diseases, some classified as "primary" dementia (such as Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia) and others that, instead, are called "secondary," in that they result from other conditions such as, for example, dementia from AIDS.

According to the Global Burden of Disease Report, dementia forces humans to live out 11.9% of their years in a chronic disabling condition and lose 1.1% of their life. The 10/66 Dementia Research Group completed a study on the population in Latin America, India and China and found that dementia is the leading cause of dependency (need for treatment) among older people.

Among the diseases that cause dementia, some common risk factors for cardiovascular disease can be identified. The proof of a causal relationship between cardiovascular risk factors and the incidence of dementia such as Alzheimer's is becoming increasingly evident. Patients with high cardiovascular risk (hypertension, diabetes, high cholesterol and smoking) are often more likely to incur neurodegenerative diseases.

DEMENTIA IS THE LEADING CAUSE OF DEPENDENCY (NEED FOR TREATMENT) AMONG OLDER PEOPLE

THE PROOF OF A CAUSAL RELATIONSHIP BETWEEN CARDIOVASCULAR RISK FACTORS AND THE INCIDENCE OF DEMENTIA IS BECOMING INCREASINGLY EVIDENT

51

Figure 2.24. **Prevalence of Alzheimer's disease by age groups (2009)**
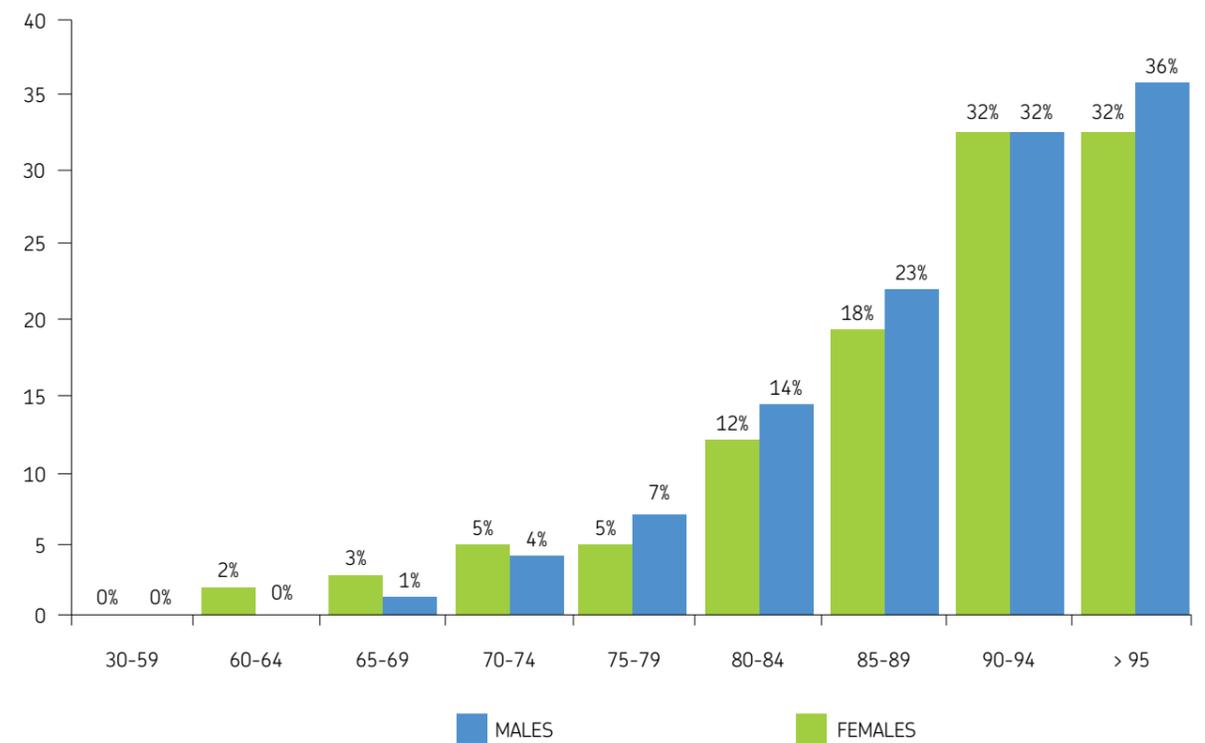
Source: The European House-Ambrosetti elaboration of the EURODEM study.

Economic and social impact

The worldwide cost of dementia, estimated for 2010, amounted to $604 billion, 70% of which was found in Western Europe and North America.[26] These costs represent about 1% of the world GDP and range from 0.24% in low-income countries, to 0.35% of countries in medium-low income, to 0.50% in those with medium-high incomes, and up to 1.24% of high-income countries. In England, the social cost of dementia (17 billion pounds) exceeds the amount spent with regard to strokes, heart disease and cancer.

Even though only 38% of people with dementia live in high-income countries, 72% of the costs result from these countries. In the poorest countries, a fundamental part of the assistance is offered informally by family members, since they lack structured and accessible health services.

Today, in Italy, it is estimated that there are 2 million people with dementia, 63% of whom are over 80 years of age. Costs are high regarding health care and social assistance both for the patients and their families. If the number of Italians suffering from dementia is multiplied by the average annual cost per patient, an estimation of the total annual cost of dementia in Italy is reached: about €50 billion (€10 billion for the direct costs and €40 billion for indirect costs).

2.2.6 Osteoporosis

Osteoporosis is a disease characterized by decreased bone mass and micro-architectural deterioration of bone tissue, causing increased fragility and consequently increased risk of fractures,[27] most of which occur in the areas of the wrist, vertebrae and proximal femur.

This is a global problem, with such steady growth that the World Health Organization has identified it as a health priority worldwide. It is predicted that the incidence of osteoporotic fractures is expected to increase from one every 8.1 minutes in 2001 to one every 3.7 minutes in 2021.[28]

IT IS ESTIMATED THAT OSTEOPOROSIS AFFECTS 150 MILLION PEOPLE WORLDWIDE

It is estimated that osteoporosis affects 150 million people worldwide, over 75 million of whom are in Europe, Japan and the U.S. Most of them have a 15% probability of suffering a fractured wrist, femur or vertebra, a percentage which is very close to that of being affected by coronary disease. In Europe, one out of three women and one out of five men over the age of 50 have experienced an osteoporotic fracture in their lifetime, while in the U.S., it is estimated that although 10 million people are affected by osteoporosis, approximately 34 million Americans have a bone mass that puts them at high risk of developing this disease.

OSTEOPOROSIS IS ONE OF THE MOST COMMON CHRONIC DISEASES ASSOCIATED WITH AGING, AND IT MAINLY AFFECTS WOMEN

In Italy, too, osteoporosis is one of the most common chronic diseases associated with aging (7%, following the 16% of hypertension and 17.3% of arthrosis/arthritis) and shows marked gender differences because, in Italy, it affects 3.9 million women and 840,000 men.[29] In the female population, it affects 15% of females in the 50-59 age group, more than 30% of those aged between 60-69 and 45% of the group aged 70-79.

AGING AND THE CONSEQUENT DEGENERATION OF BONE TISSUE INVOLVES A POSSIBLE "DOMINO EFFECT"

Aging and the consequent degeneration of bone tissue involves a possible "domino effect," or an acceleration in the frequency of the occurrence of new fractures and an increase in their seriousness. The presence of even a single vertebral deformity, for example, triggers a dangerous vicious circle. In fact, the risk of further osteoporotic fractures is increased five-fold.[30]

Figure 2.25. **Number of women with osteoporosis in Italy in 2006, divided into age groups**

3,9 MILLION WOMEN WITH OSTEOPOROSIS

80-89 10%
60-69 22%
50-59 15%
70-79 45%
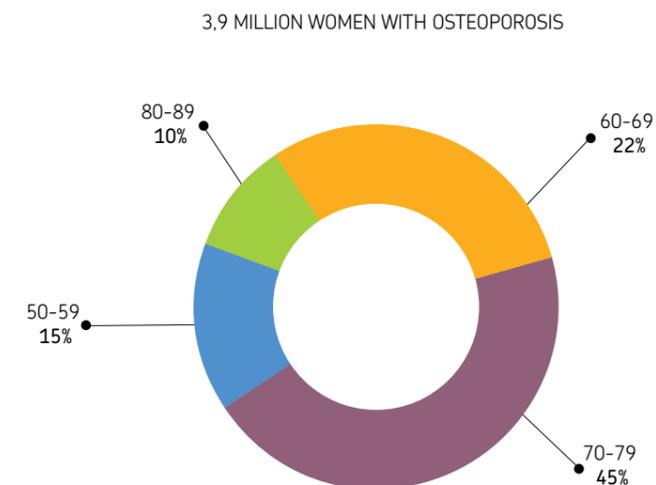
Source: The European House–Ambrosetti elaboration of ESOPO data.

Economic and social impact

The economic burden of osteoporosis is comparable to that of major chronic diseases but, in women older than 45, osteoporosis causes a greater number of hospitalizations compared to other diseases, including diabetes, stroke and breast cancer.

THE ECONOMIC BURDEN OF OSTEOPOROSIS IS COMPARABLE TO THAT OF MAJOR CHRONIC DISEASES BUT, IN WOMEN OLDER THAN 45, IT CAUSES A GREATER NUMBER OF HOSPITALIZATIONS

Despite increased awareness of the disease, it is expected that the number of osteoporotic fractures is likely to increase, hand in hand with the aging European population, going from a cost of €31.7 billion in 2000 to about €76.7 billion in 2050. This data emerged from a recent study by the International Osteoporosis Foundation and represents the amount spent each year in Italy, France, Germany, Sweden, the United Kingdom and Spain treating fractures caused by osteoporosis.[31]

Hip fractures make up 56% of the total costs, vertebral fractures account for 5%, wrist fractures account for 2%, while a combined group of other fractures accounts for 37% of the total.

THE RISK OF FURTHER FRACTURES IN PEOPLE WHO HAVE SUFFERED A PREVIOUS ONE ESTABLISHES THE NEED FOR NEW OSTEOPOROTIC THERAPIES, THUS, HOWEVER, INCREASING THE ECONOMIC BURDEN

As mentioned previously, the risk of further fractures in people who have previously undergone femoral or vertebral fractures establishes the need for new osteoporotic therapies, including those that may be effective throughout the entire skeletal system and not just on the hip and vertebrae, thus, however, increasing the economic burden associated with osteoporosis.

Fractures of the femur, in particular, although not the most common of osteoporotic fractures, can lead to high costs because patients require a long hospital stay. These fractures are a major cause of infirmity, disability and premature death in elderly people. Mortality is about 20% within one year from the fracture, motor disability – 30% of which is permanent, 40% of which is characterized by the inability to walk independently - affects more than half of the patients in the year following the fracture, and only 30-40% of these people resume activities of independent daily life.[32]

According to what has emerged from the study by the International Osteoporosis Foundation, the majority of costs are addressed in the first year following the fracture,

Figure 2.26. **Consequences of a hip fracture one year after the event**

NUMBER OF PATIENTS %
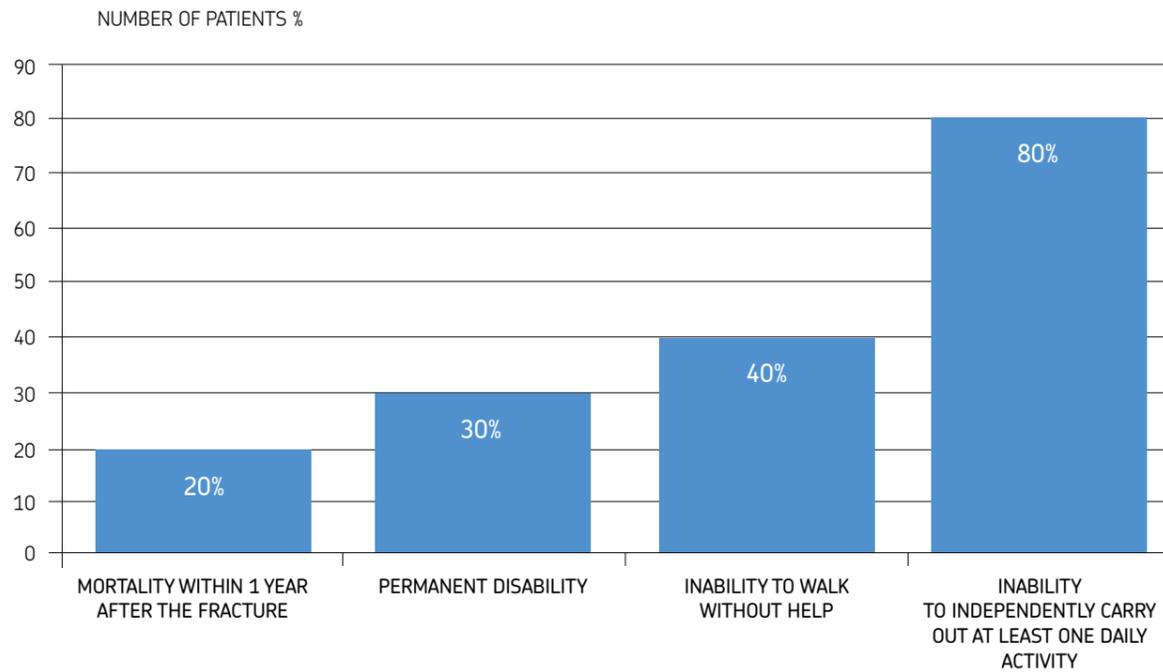
Source: The European House-Ambrosetti elaboration of data from Cooper, C., in "American Journal of Medicine," 1997.

while, conversely, the cost of prevention and drug treatment are a marginal part of the total cost.

In Europe, the healthcare costs incurred in the first year after a fracture of the femur were assessed as amounting to €14.7 billion. This amount reaches 25 billion if all osteoporotic fractures are taken into account.

The country that sustains the highest costs is Germany, with €9.4 billion, followed by Italy, with €6.7 billion, and the United Kingdom, with 5.8 billion.

In Europe, 97% of the lumbar vertebral fractures and 74% of those of the chest result in days of limited activity. The economic burden of fractures of the spine is due, instead, to the cost of outpatient care, nursing and the loss of work days.

THE COUNTRY THAT SUSTAINS THE HIGHEST COSTS IS GERMANY, FOLLOWED BY ITALY AND THE UNITED KINGDOM

2.3 THE PREVENTION OF OBESITY AS A KEY DETERMINANT OF LONGEVITY

The scientific literature has now found that much of the onset of chronic diseases is due to lifestyle.

In particular, the risk factors considered to be the most relevant are: cigarette smoking, obesity, insufficient exercise and an unbalanced diet. It has been well established, in fact, that those who lead a healthy life do not smoke, drink alcohol in moderation and eat enough fruit and vegetables, thereby reducing the chance of incurring chronic diseases by a fourth, as compared to individuals with the wrong kind of lifestyle.

Chronic diseases, in turn, have a significant impact on longevity, since they have been identified as the main cause of the reduction of years lived in good health.

In particular, the mortality rate increases dramatically when individuals exceed the threshold generally recognized as being "overweight."[33] The lifetime of an obese person is actually, on average, 8-10 years shorter than that of a person of normal weight (there is also similar data for smokers). An overweight person of average height has a 30% higher risk of death for every 15 kg of excess weight. In addition to physical problems, obese people also encounter discriminatory behavior. In the work market, an obese person is considered less productive than a person of normal weight because of higher costs or compensation for medical care and the greater number of days of absence from work. Inevitably, because of lower productivity, they are penalized in terms of pay, some estimates speak of -18%. Problems in the workplace, as well as representing a cost to the families, also have an impact on the quality of life by helping to create a situation of professional and personal dissatisfaction.

The rates of overweight conditions and obesity vary greatly among OECD countries. However, as we mentioned earlier, their generalized and constant increase has been witnessed over the past thirty years, caused by an increasingly sedentary lifestyle and the proliferation of unbalanced eating patterns.

The phenomenon, although widespread, appears relatively more concentrated in the female gender. Globally, in fact, the obesity rate tends to be higher in women than in men, and this is also found in OECD countries. In addition, various studies show some disparity between the rate of obesity in the female populations of rich and poor countries, while the data on men is quite uniform.

It does not appear easy to accurately estimate the impact of obesity on mortality. However, a famous study by Olshansky (2005),[34] published in one of the most important medical journals worldwide, estimated that the rise in obesity will lead to a revision of the estimates of life expectancy in the U.S. in the first half of the 21st century.

The UK Department of Health has estimated that, on the other hand, if the current

WHOEVER LEADS A HEALTHY LIFE DOES NOT SMOKE, DRINKS ALCOHOL IN MODERATION AND EATS ENOUGH FRUIT AND VEGETABLES, THEREBY REDUCING THE CHANCE OF INCURRING CHRONIC DISEASES BY ONE-FOURTH

IN PARTICULAR, THE MORTALITY RATE INCREASES DRAMATICALLY WHEN INDIVIDUALS EXCEED THE THRESHOLD GENERALLY RECOGNIZED AS BEING "OVERWEIGHT"

THE INCREASE IN OBESITY WILL LEAD TO A REVISION OF THE ESTIMATES OF LIFE EXPECTANCY IN THE UNITED STATES IN THE FIRST HALF OF THIS CENTURY

growth level of obesity is maintained, life expectancy by 2050 will be reduced by at least five years.

The estimates are more alarming than ever. And they are even more so if the number of years of life lost due to obesity are added to the years of life that individuals affected by this disease (and those connected to it) spend – and will increasingly spend in the future – in a condition of poor health. Moreover, in general, the progressive worsening of the average living conditions makes the data regarding the direct impact on the life span even more alarming.

The BCFN, during its two-year's worth of work on the relationship between diet and health, proposed several measures concerning this query. But the problem and the attempt at finding a solution have now been recognized internationally at the highest institutional levels.

IS IT POSSIBLE TO TAKE ACTION TO REVERSE THESE TRENDS AND ENSURE THE ACHIEVEMENT OF A LONG LIFE SPENT IN "WELL-BEING"?

National governments, especially in OECD countries, have designed and implemented several programs to improve diet and promote physical activity, starting from the earliest years of age, to prevent the risk of obesity and mitigate its devastating effects. The OECD and the World Health Organization have identified three main areas of interest and nine possible actions, which are considered successful. Finally, they collected data and factual evidence in order to estimate the prospective impact on longevity.

EDUCATION INTERVENTIONS AND HEALTH PROMOTION	INTERVENTIONS IN PRIMARY CARE	FISCAL MEASURES AND REGULATIONS FOR THE FOOD INDUSTRY	INTEGRATED MEASURES
1. Programs of prevention/education in schools 2. Programs of prevention/education in the workplace 3. Information campaigns in the media	4. Counseling on physical activity 5. Counseling on food	6. Fiscal measure on the prices of fruit, vegetables and food with high-fat content 7. Regulations on advertising related to food 8. Self-regulation of the food industry on advertising related to food 9. Interventions to improve the labeling of food	10. Combined Strategy (of the nine preceding points)

The analysis conducted shows that the activity of care and nutritional advice is by far the most effective activity for the prevention of chronic diseases, resulting in a major impact in terms of years of life earned, on average.

Some interventions, such as those regarding adults, are able to have a substantially constant impact in the long term, but generate relatively minor benefits if they are considered in terms of "value" (even if achievable in the short-term). In addition, and perhaps not surprisingly, we found that interventions that focus on at-risk individuals are able to generate even more evident and immediate results in terms of longevity.

Figure 2.27. **Life-years gained due to prevention measures regarding mortality and ill health**
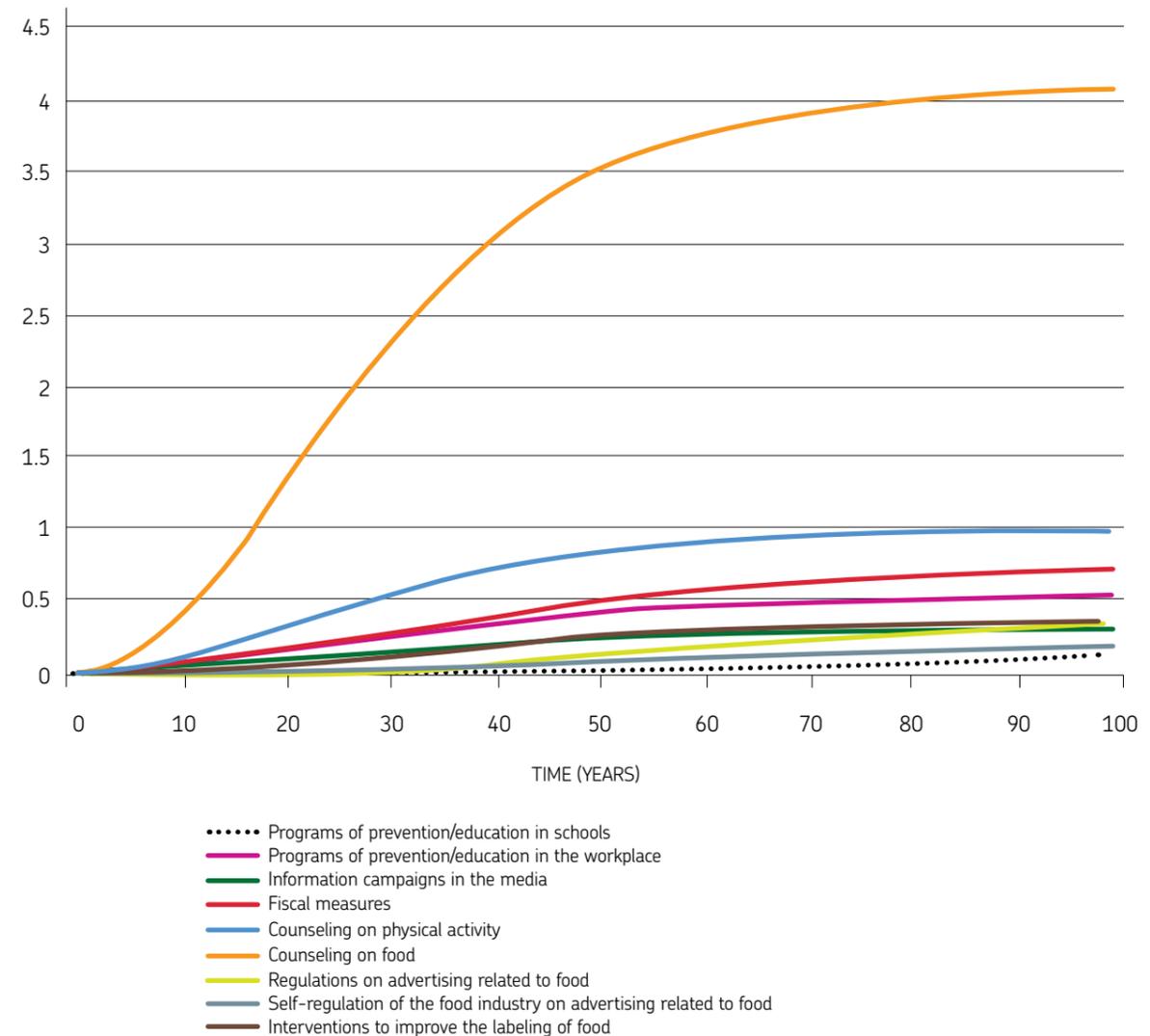
Source: The European House–Ambrosetti elaboration of data from CDP, Model-based analysis relying on input data from multiple sources, listed in Table A.2 in Annex A.

Ultimately it seems essential to focus on the links between eating habits, lifestyle and the onset of major chronic diseases, which are very often "mediated" through the influence of being overweight and obese. Understanding which diet appears to prevent the occurrence of obesity (and, therefore, the onset of related diseases) is crucial for identifying what leverage is in our possession to influence the aging process and ensure the achievement of a long life lived in good health.

The analysis of these links and dietary choices that are "favorable" for longevity will be the subject of the next chapter.

UNDERSTANDING WHICH DIET APPEARS TO PREVENT THE OCCURRENCE OF OBESITY IS CRUCIAL FOR INFLUENCING THE AGING PROCESSES, ACHIEVING LONGEVITY AND LIVING IN GOOD HEALTH

3. SOME KEY DISEASES WITH REGARD TO LONGEVITY AND THE ROLE OF FOOD

3.1 SUMMARY OF THE RELATIONSHIP BETWEEN LIFESTYLES AND DIET, DIABETES AND LONGEVITY

I n the previous chapters, it was shown that, compared with an increase in life expectancy and the dramatic increase in the spreading of major chronic diseases (starting with obesity), it is likely that – in the near future – humanity, for the first time in the modern age, will experience a significantly longer old age that is characterized by a non-optimal quality of life.

Therefore, it is necessary, more than ever, to identify lifestyles and diets that can prolong the disease-free period of life, while at the same time lengthening life.

If, as mentioned, the link between lifestyles and healthy longevity very often appears through the probability of the occurrence of chronic diseases – which can accelerate the aging process –, then it is necessary to thoroughly investigate the link between diet, lifestyles and the development of these diseases, in order to identify correct eating habits and lifestyles.

Diet, as amply demonstrated by the work carried out in 2009-2010 by the BCFN on this issue, is one of the key factors that can influence whether people will be impacted by major chronic diseases – and how severe that impact will be.

In 2009 – in particular – the BCFN carried out an in-depth analysis of the relationship between diet and health with regard to key chronic diseases, such as diabetes, cancer and cardiovascular diseases. In the document Food and Health, a review was made of the scientific evidence and the analyses conducted concerning the relationship between diet and these diseases, investigating the role of the major macro and micro nutrients.

This review has been accompanied by an extensive bibliography. For further details on the main findings in international literature on the relationship between diet and the prevention of these chronic diseases, see the document *Food and Health* (2009).

Along with the diseases already discussed previously, we have conducted an in-depth investigation of the link between lifestyles and food and the probability of the onset of diseases like neurodegenerative diseases and osteoporosis that are particularly associated with aging. For these diseases, a more thorough and detailed analysis has been carried out, with explicit references to the international scientific literature.

T he nutritional approach is widely recognized as an essential tool for preventing and treating type 2 diabetes and for preventing and/or mitigating the development and the severity of diseases/complications directly related to the diabetes itself. Genetic predisposition appears to play a significant role in the onset of type 2 diabetes (for a complete treatment of diabetes, types 1 and 2, refer to the cited document *Food and Health*).

However, the current increase in the incidence of this disease is, according to all the major international scientific associations, strongly due to the changes which have affected the lifestyle of the world's population, characterized on average by an increased intake of calories through a diet that is not always correct and a reduction of physical activity.

Numerous studies have demonstrated the positive potential, in terms of reduction of the risk of type 2 diabetes and the aggravation of the disease itself, of a moderate reduction in body weight. The containment of abdominal adiposity[1] appears to be of particular importance for the prevention of type 2 diabetes and for the improvement of some risk factors associated with it. Many studies have shown that it is a more decisive factor than the general body mass index in the risk of type 2 diabetes, which is also closely related to insulin resistance, a central element in the pathology of diabetes.

Since being overweight or obese appear to have many negative effects in relation to factors linked to diabetes (mainly insulin resistance), programs aimed at changing lifestyles – in the direction of weight reduction and increased physical activity – are able to positively affect the probability of contracting type 2 diabetes.

A 5-7% reduction of body weight, combined with regular physical activity for two and a half hours a week and a nutritional strategy that includes reducing the intake of fat and calories, is able to significantly reduce (~60%) the risk of type 2 diabetes. Such an impact is extremely relevant in light of the spreading of this disease worldwide, as seen in the previous chapter.

Given these relationships, it is evident that overweight conditions and obesity, especially abdominal, are factors that have a negative impact on life expectancy and contribute to an increased risk of developing type 2 diabetes.

The concentration of glucose in the blood after eating appears to be central, both for people with diabetes and for individuals at risk. The quantity, quality and origin of carbohydrates from food are, therefore, of fundamental importance. Carbohydrates (sugars, starches, fibers), fat and protein should, in different amounts and ways, be part of a balanced diet.

There are several variables that appear to influence the effect of foods containing carbohydrates on blood sugar levels: from the specific type of food eaten, to the type of starch employed (amylose or amylopectin), the types of sugar (glucose, fructose, sucrose,

lactose), the degree of working and processing of the food, and the method of its preparation. However, numerous studies have highlighted the general importance of the total amount of carbohydrates ingested, more so than for the type or source of the latter.

For some time now, the so-called "glycemic index"[2] has been used to measure the postprandial (after-dining) effect of the consumption of a constant amount of different types of foods, mostly containing carbohydrates. Although there are differences regarding this indicator, some studies have shown that diets characterized by an overall low glycemic index are able to reduce the risk of type 2 diabetes and, in those who are already diabetic, their blood sugar levels.

It can be seen from the results how diets with a high glycemic index can have a negative impact on aging, in the face of the increased likelihood of developing type 2 diabetes.

Numerous tests have emphasized the positive effects of the consumption of fiber, which can be found in many foods, including legumes, whole grains and some varieties of fruits and vegetables.

Some studies have shown that diets characterized by an increased intake of whole grains, fruits and vegetables are able to reduce the risk of developing the type 2 diabetic pathology of individuals with impaired glucose tolerance. The consumption of foods that are high in fiber is also capable of promoting the reduction and/or containment of the body mass index. Therefore, the intake of whole grains, fruits and vegetables is able to positively influence the probability of reaching the last years of life while still healthy, reducing the probability associated with the onset of type 2 diabetes.

With regard to simple sugars, numerous clinical studies have shown that appropriate amounts of sucrose in the diet do not lead to an increase in the blood sugar levels of the individuals analyzed, with respect to similar amounts of starch; therefore, a direct negative relationship between consumption of sucrose and the probability of incurring the disease of diabetes is not indicated.

There is clearly an indirect relationship, associated with being overweight and obesity, conditions that can be facilitated by an intake of sucrose doses that are not balanced.

In conclusion, there seems to be sufficient scientific evidence to support an indication of a general nature: it is absolutely essential – in the diet of every individual – that there be an adequate amount of carbohydrates, especially from whole grains, fiber, fruits and vegetables, which has a positive impact in terms of longevity in good health.

In general, it is widely accepted that the quantity and quality of fatty acids ingested from food have a particularly significant influence on many risk factors for diabetic disease (and those linked with it, mainly cardiovascular diseases).

Numerous tests have revealed how a high-calorie, daily total intake attributable to ingesting fatty foods (roughly, greater than 30-35%) poses a great risk for the individual regarding weight gain, impaired insulin sensitivity and a significant increase in LDL cholesterol values in the blood.

Observational studies have shown the existence of a significant correlation between high levels of fat intake and the probability of both the development of glucose intolerance and of the passage of such intolerance effectively into a type 2 diabetic disease.

In particular, numerous tests have shown that a higher intake of saturated fatty acids is associated with a higher risk of glucose intolerance and the observation of higher levels of insulin and fasting glucose. Replacing saturated fats with unsaturated fatty acids can generate benefits on insulin sensitivity and postprandial lipid levels and improve glucose tolerance. In relation to the n-3 (α-linoleic) long-chain type of polyunsaturated fatty acids, some studies have found a positive relationship between an increase in their ingestion (for example, through fish) and improved insulin sensitivity.

Despite extensive evidence that quite clearly shows the positive potential within the diet of the intake of n-3 and n-6 fatty acids, existing evidence does not prove sufficient for achieving a precise definition, aimed at prevention, of the optimal ratio of n-3 and n-6 fatty acids in the diet.

Many studies have shown that a diet characterized by a high content of trans fatty acids is able to increase the risk of type 2 diabetes.

At present there is not sufficient scientific evidence supporting the existence of long-lasting benefits in terms of the prevention and cure of diabetes resulting from the adoption of a diet characterized by higher intakes of protein than those found on average in the empirical analysis and deemed adequate to obtain the proper amount of protein (15-20% of total caloric intake). The issue must be studied further.[3]

In general terms, in relation to the reduction of protein deriving from the diet, it is useful to remember that patients with diabetes (or a high risk of diabetes) often have an increased protein turnover (essentially identified in the ratio of proteins used – or eliminated, in the case of diabetic nephropathy – and proteins ingested). An excessive reduction of the total protein intake for such individuals, therefore, does not appear to be positive.

The diabetic pathology often appears to be associated with deficiencies of the presence of micronutrients in the body, highlighting the importance for patients with diabetes, or at risk of diabetes, of a balanced diet that contains adequate amounts of vitamins and minerals. However, today there appears to be sufficient scientific evidence (as also mentioned by the WHO) to identify unique relationships between the intake of specific amounts of vitamins and minerals and the probability of the occurrence of diabetes and related diseases.

A moderate consumption of alcohol appears to be able to have a potentially positive effect on insulin sensitivity, on increasing levels of HDL cholesterol in the blood and a reduction in indices of coagulation and lipid oxidation. However, as also mentioned by the WHO, the available evidence does not allow the indication of a moderate consumption of alcohol as a value for the prevention of the type 2 diabetic condition. Therefore, considering the scientific evidence produced to date, there does not appear to be conclusive data regarding the most appropriate level of alcohol consumption for individuals with diabetes or highly at risk, so the recommendation provided by all major international scientific associations appears to be similar to that given with regard to the general population.

3.2 SUMMARY OF THE RELATIONSHIP BETWEEN LIFESTYLES AND DIET, CANCER AND LONGEVITY

Cancer can be caused by a multitude of factors, including incorrect lifestyle and eating habits. One of the most important non-food factors is tobacco smoke, which increases the normal risk of contracting lung cancer by about 30 times. Tobacco use is responsible for 80% of the cases in developed countries and is the most common type of cancer worldwide. Tobacco smoke is also a major risk factor for cancer of the mouth, larynx and esophagus.

In view of these reports, it is evident that tobacco smoke, and its effects on the body, is a factor that significantly impacts on the life expectancy of individuals.

With reference to the type of diet that is adopted, some studies have estimated that the adoption of an unhealthy diet is a factor in 30% of the incidence of tumors, the second factor after tobacco smoke.

The International Agency for Research on Cancer has designated that being overweight and physical inactivity account for factors affecting between 20% and 35% of the cases of the onset of breast, colon, kidney and esophagus cancers.

Protracted situations, as well as temporary ones, of obesity and overweight conditions are factors that increase the risk of the occurrence of various types of cancers, especially colorectal cancer.

Numerous studies have confirmed that the onset of this type of cancer depends very strongly on the type of food that is eaten. For example, in the United States, where the percentage of overweight and obese people is very high, colorectal cancer is the second leading cause of death from cancer.

Other studies have found relationships between overweight conditions and obesity and cancers of the oral cavity (esophageal adenocarcinoma), pancreatic cancer and breast cancer, endometrial tumors and kidney cancer.

Thus, as shown in the case of diabetes, there is confirmation of the importance of maintaining a healthy weight to prevent the onset of cancer and, therefore, to increase life expectancy in good health.

Concerning the consumption of alcohol, it has clearly emerged from studies that the consumption of alcoholic beverages is the main dietary risk factor for cancer of the mouth, larynx and esophagus. If tobacco smoke is added to the consumption of alcohol, that accounts for over 75% of all tumors in the oral cavity.

Scientific-medical studies have shown that excessive consumption of alcohol represents a risk factor for the occurrence of liver tumors, probably through the development of liver cirrhosis.

Alcohol consumption is a cause of an increased risk of breast cancer and colon/rectum cancer. The results, therefore, show that the consumption of alcohol has a negative impact on aging, in view of the probability of developing cancer. Conversely, the International

THE ADOPTION OF AN UNHEALTHY DIET IS A FACTOR IN 30% OF THE INCIDENCE OF TUMORS; THE SECOND FACTOR AFTER TOBACCO SMOKE

MAINTAINING A HEALTHY WEIGHT TO PREVENT THE ONSET OF CANCER AND, THEREFORE, TO INCREASE LIFE EXPECTANCY IN GOOD HEALTH

CONSUMPTION OF ALCOHOL HAS A NEGATIVE IMPACT ON AGING, DUE TO AN INCREASE IN THE PROBABILITY OF THE OCCURRENCE OF CANCER

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Agency for Research on Cancer showed that 60% of oral cavity cancers are probably related to a shortage of micronutrients due to a diet which is deficient in fruits and vegetables. The lack of consumption of fruits and vegetables is recognized as a cause of an increased risk of developing colorectal cancer, although some studies have yielded conflicting results.

In general, the results of scientific medical studies indicate that regular consumption of fruits, vegetables and fiber in the diet helps reduce the risk of developing cancer of the oral cavity, and stomach, colorectal, endometrial and lung cancers, although in some cases the correspondence of cause and effect is not clearly defined for factors of bias (e.g., people who smoke, the first risk factor for lung cancer, on average consume fewer fruits and vegetables than non-smokers).

Confirmed, once again, is the relationship between a proper diet consisting of fruits, vegetables and fiber, and reducing the likelihood of developing cancer and the consequent increase in life expectancy in good health.

The international medical-scientific community agrees that some aspects of the Western diet, and more specifically the high consumption of meat, salami and sausages, have positive associations with the factors that increase the risk of the onset of cancer.

In numerous meta-analysis studies, it has emerged how the high consumption of preserved meats and a diet characterized by a high concentrations of fats increases the risk of the onset of colorectal cancers. Other studies have observed positive associations, however, between the consumption of poultry (white meat) and fish with tumors of the colon and rectum.

With regard to eating habits, moreover, the high consumption of salt and foods preserved with salt also appears to be a factor in the increased risk of cancer.

Studies conducted internationally and in Asia noted that nose-throat cancer is especially common in East-Asia. This condition has been associated with a high consumption of salted fish (according to Chinese tradition), especially during childhood. Other studies have found that the increase in the risk of stomach cancer is associated with a high intake of foods preserved with salt, cured meats and pickled foods.

By analyzing the relationship between specific micronutrients and the increased onset of cancer, it has emerged that a high intake of folate reduces the risk of the onset of colorectal cancers. In this sense, some studies carried out on vitamin D found that the intake of the latter can prevent the onset of cancer of the colon and rectum.

In general, we underline that medical-scientific studies on the identification of the causes and factors in determining the onset of certain types of cancer have produced controversial results and are often in disagreement with one another, for example, as in the case of the relationship between lung cancer and the intake of beta carotene.

Finally, other studies on high calcium intake have shown that there is an increased risk of developing aggressive prostate cancers, and it has emerged that lycopene, a substance found in tomatoes, is a protective factor against prostate cancer.

Another factor that triggers cancer of the esophagus is the consumption of hot food and drinks, a factor that can influence the increased risk of developing cancers of the oral cavity.

In conclusion, as emerged from the studies analyzed, the number of cancers detected in a population and its percentage rate varies with the type of diet that is adopted, but is mostly due to the eating habits of the individuals.

The International Agency for Research on Cancer has indicated that physical inactivity, combined with an overweight condition, is a factor that can affect between 20% and 35% of the cases of the onset of breast, colon-rectum, kidney and esophagus cancers.

Specific studies have indicated that regular physical activity is associated with a signifi-

REGULAR CONSUMPTION OF FRUITS, VEGETABLES AND FIBER IN THE DIET HELPS REDUCE THE RISK OF TUMORS

A HIGH INTAKE OF FOLATE AND VITAMIN D REDUCES THE RISK OF THE ONSET OF COLORECTAL CANCER

THE NUMBER OF CANCERS DETECTED IN A POPULATION AND ITS PERCENTAGE RATE VARIES WITH THE TYPE OF DIET THAT IS ADOPTED, BUT IS MOSTLY DUE TO THE EATING HABITS OF THE INDIVIDUALS

cant reduction of the occurrence of cancer. Consequently, regular physical activity helps the individual to stay healthy and prevents the onset of the main forms of cancer, with a positive impact on longevity in the long run.

Joel Sartore//National Geographic Stock

3.3 SUMMARY OF THE RELATIONSHIP BETWEEN LIFESTYLE AND DIET, CARDIOVASCULAR DISEASE AND LONGEVITY

The changes that have occurred in the structure of the population and that have led to a steady increase in the average life expectancy and, therefore, of people belonging to the oldest age group, make the diseases typical of this phase of life more evident. Among these diseases, with a latency period longer than that of infectious diseases, are the cardiovascular diseases, which, besides being linked to various environmental factors, are highly dependent on dietary habits, lifestyle and behavior prior to the manifestation of the disease: smoking, alcohol abuse, sedentary lifestyle, etc. It should also be noted that the presence of two or more factors multiplies the risk of cardiovascular disease, as the World Health Organization has also pointed out.

The relationship between lifestyles and proper nutrition, and cardiovascular disease has been demonstrated by numerous studies (one of these, which gained a following, was the North Karelia Project, conducted in 1972 among residents of the Finnish provinces).[4]

Further studies conducted by leading scientific societies emphasized that eating behavior and personal habits can help reduce the risk of cardiovascular disease, especially in old age. Specifically, the main evidence of the international literature on the relationship between diet and cardiovascular disease emphasizes the following behaviors as useful aids for cardiovascular disease prevention: a low consumption of animal fats, cholesterol and hydrogenated fat food, a daily consumption of fruits and vegetables, a strong reduction of salt, the consumption of fish at least two or three times a week, adequate physical exercise and a moderate consumption of alcohol.

The scientific evidence available in the literature clearly shows the protective effect on cardiovascular risk of a significant reduction not only of foods containing saturated fat and cholesterol (which increase both the total amount of cholesterol and the amount of LDL cholesterol, known as "bad" cholesterol), but also those containing trans fatty acids (fatty acids with special structural isomerism, capable not only of increasing LDL cholesterol with an atherogenic effect but also of lowering HDL cholesterol with an anti-atherogenic property).

One of the most effective solutions for reducing the risk of coronary heart disease in order to promote "healthy aging" is, therefore, to replace saturated fats with unsaturated fats (monounsaturated and polyunsaturated) such as, for example, oleic acid, an emblem of the Mediterranean diet.

Of particular importance are the effects produced by an increase in the daily consumption of fruits and vegetables, in addition to a reduction of fatty foods, as assessed by the Department for Human Health in the U.S. study called *Dietary Approaches to Stop Hypertension* (DASH). The results show that such a diet has beneficial effects in reducing blood pressure, in addition to those on lipids and glucose, with significant benefits for the overall profile of cardiovascular risk.

Instead, with reference to omega-3, docosahexaenoic acid and eicosapentaenoic acid found in fish, their benefits have been well established in relation to the regulation of blood pressure, cardiac functions, endothelial function and vascular reactivity; these are valuable allies of a diet that favors healthy aging. Despite extensive evidence, the available data does not yet appear sufficient to define an optimal ratio of n-3/n-6 acids.

Regarding the consumption of fish, a systematic review of studies found in the literature has shown that the regular consumption of fish (at least twice a week) results in significant benefits for the prevention of cardiovascular disease in high-risk individuals. An average consumption of 40-60 grams of fish per day would lead to a 50% reduction of deaths from cardiovascular disease in individuals who are recovering from a previous heart attack.

With regard to alcohol, instead, some meta-analyses suggest that a low/moderate alcohol consumption is associated with a lower risk of developing cardiovascular disease. However, these are observational studies and the observed relation is not necessarily proof of a causal link; on the other hand, it is known that alcohol can lead to addiction and its high consumption is the cause of many illnesses, including cardiovascular disease. This has induced us to recommend a moderate consumption of beer, wine or spirits for those who are regular consumers but not to recommend the use of alcohol to people who do not normally ingest it.

Among the factors that significantly increase the risk of cardiovascular disease there is definitely that of a high intake of sodium. It is directly linked to high blood pressure, which in turn correlates to the risk of developing heart disease, ischemic and hemorrhagic stroke, with a significant impact on the average life expectancy. It is estimated that an average 50% reduction in the use of salt would produce a 50% reduction in the number of people undergoing antihypertensive therapy, a 22% reduction in deaths from stroke and a 16% reduction in the number of deaths from cardiovascular disease.

All studies agree that, even though cardiovascular disease occurs more frequently in middle age or older, the risk factors that cause them are linked in large part to behavior learned during childhood and youth, and carried on into adulthood.

For example, overweight conditions affect 18 million children under the age of 5, while 14% of students aged between 13 and 15 smoke cigarettes regularly.

Physical exercise, however, one of the most important factors that the studies correlate inversely to the onset of cardiovascular disease (especially coronary), decreases significantly during adolescence (after 10 years of age), especially in girls; moreover, with maturity and advanced age, it departs even further from the values suggested for the prevention of these diseases (30 minutes a day almost every day of the week).

The adoption from childhood of a diet with high concentrations of fats, dairy products and meat rich in fat, in particular, appears to be one of the most important risk factors for developing cardiovascular disease later on in life, in that it contributes to the increase of cholesterol in the blood and tissues.

It emerges from the evidence that saturated fatty acids increase both the total amount of cholesterol and the amount of LDL cholesterol (known as "bad" cholesterol).

One of the most effective solutions for reducing the risk of heart disease in order to promote "healthy aging" is to replace saturated fats with unsaturated fats (monounsaturated and polyunsaturated) such as oleic acid.

Numerous studies and clinical tests have shown that the replacement of saturated fat and trans fats with unsaturated vegetable oils and polyunsaturated fats significantly lowers the risk of heart disease, thus confirming the existence of a relationship between diets containing high amounts of trans fatty acids (unsaturated fat with a par-

ticular structural isomerism, the most harmful to the cardiovascular system in that the ratio worsens cardiovascular risk), coronary disease and atherosclerosis.

Conversely, a diet rich in fiber and whole grains can help reduce the risk of developing cardiovascular disease, effectively intervening on lengthening the years of healthy life and the duration of life itself. These findings have emerged in particular from studies conducted in different countries, which have shown that fiber in the diet can help to reduce the concentration of low density lipoprotein (LDL).

Also with reference to the flavonoids, polyphenolic compounds which are secondary metabolites of plants, mainly water-soluble and present in vegetables, tea, onions and fruit, the results of many studies have indicated that there is an inverse relationship between a diet enriched with flavonoids and cardiovascular disease.

The scientific evidence is rather discordant in relation to the role played by antioxidants (glutathione, vitamin C and vitamin E) in reducing the risk of developing cardiovascular disease, although it has been established that these very same agents could prevent the onset of other diseases related to aging, such as osteoporosis, by intervening in the long-term health of the bones.

Finally, different epidemiological studies have shown that the frequent consumption of nuts (walnuts, peanuts, almonds, etc.) is associated with a reduced risk of developing cardiovascular disease, since they are characterized by a high concentration of fatty acids, yet have a low concentration of saturated fats. Because of their high energy content, the inclusion of this group of foods should be balanced with the individual caloric needs.

Michael Melford/National Geographic Stock

3.4 SUMMARY OF THE RELATIONSHIP BETWEEN LIFESTYLES AND DIET, NEURODEGENERATIVE DISEASES AND LONGEVITY

The increase in the average life expectancy of typical Western society has led to the emergence of major public health issues because of the social burden of chronic disabling diseases, determined by aging itself. Among these, chronic regressive brain diseases are by far the most painful for the patient and family members, and the most costly to society.

Dementias, such as neurodegenerative diseases, are primary disorders that tend to have their onset or worsening with the advancement of age.

Aside from the clinical picture, today we can see that the damage is the result of an interaction between a genetic predisposition and environmental factors. These may include lifestyle, nutrition, infectious agents and environmental toxins.

As shown by a study[5] conducted in the late '80s, in the analysis of various endogenous and exogenous protective factors in the serum of patients with a dementia of the Alzheimer or vascular types, significant decreases were found in their levels of vitamin E, C, carotenoids, zinc and albumin. How much this reflects an incorrect diet or is a direct influence of the disease on a biochemical factor, however, is still under discussion.

As shown in more detail further on, the use of antioxidants to prevent neuronal damage or in trying to slow down any signs of neurological degeneration is still being studied, both experimentally and clinically.

Some experiments[6] have exhibited particular aspects of the oxidative reactions in the brain of patients with Alzheimer's disease. Some antioxidants such as vitamin E – contained in the seeds in general, in some grains, fruits and raw vegetable oils – appear to have beneficial effects in the case of Alzheimer's dementia, as they seem to be able to protect cultured neurons against the toxicity of β-amyloid,[7] and also against the oxidative stress produced by other important factors for the disease.

As for Parkinson's disease, on a small sample of participants, it was found[8] that an association of vitamin E, beta carotene, vitamin C and flavonoids - natural chemical compounds widely found in many kinds of fruit (citrus fruits, apples, apricots, etc.), vegetables (cabbage, broccoli, spinach, tomatoes, fennel, onions, etc.), as well as some beverages (red wine, tea, fruit juice) – can protect against the onset of the disease.[9]

Although some studies have criticized the involvement of metals in the evolution of several neurodegenerative diseases,[10] there is a lot of evidence, however, showing that ionic imbalances may be at least partly responsible for the neuronal damage.

There is proof[11] that the dementias are associated with a deficiency of magnesium (contained in many foods such as cereals, walnuts, almonds, peanuts, buckwheat, cocoa, wheat germ, lentils, green vegetables, and also meat and starchy foods), which has a known protective action in the brain. This could be caused either by a low dietary intake

THE INCREASE IN THE AVERAGE LIFE EXPECTANCY OF TYPICAL WESTERN SOCIETY HAS LED TO THE EMERGENCE OF MAJOR PUBLIC HEALTH ISSUES BECAUSE OF THE SOCIAL BURDEN OF CHRONIC DISABLING DISEASES, DETERMINED BY AGING ITSELF

CONCERNING THE DIET, IN PARTICULAR, THE RELATIONSHIP BETWEEN NUTRIENT DEFICIENCY AND DEMENTIA HAS BEEN HIGHLIGHTED FOR SOME TIME

SOME EXPERIMENTS HAVE EXHIBITED PARTICULAR ASPECTS OF THE OXIDATIVE REACTIONS IN THE BRAIN OF PATIENTS WITH ALZHEIMER'S DISEASE

THERE IS PROOF THAT THE DEMENTIAS ARE ASSOCIATED WITH MAGNESIUM DEFICIENCY, WHICH HAS A KNOWN PROTECTIVE ACTION IN THE BRAIN

of the mineral or to a poor ability of the body to physiologically retain it. There are also factors that put dementias like Alzheimer's and vascular ones into relation. Hypercholesterolemia, already known as a risk factor for atherosclerotic disease, may, in fact, be a causal factor in the development of dementia of the Alzheimer type.

Studies on cholesterol levels[12 13] and the relationship between saturated fatty acids/polyunsaturated acids in the diet[14] established the involvement of fat metabolism in neurodegeneration, noting that a high consumption of saturated fats and cholesterol increased the risk of cardiovascular disease, which is definitely associated with the development of dementia. For this reason, a diet high in fish is inversely correlated to the incidence of dementia in general and to Alzheimer's disease in particular.

Instead, high-calorie diets[15] that are rich in cholesterol and saturated fat and low in fiber, vegetables and fruit[16] play a role both in the formation of plaques of β-amiloide[17] and in causing oxidative damage to neurons.[18 19] This is also corroborated by data showing a reduced risk of Alzheimer's disease through the use of drugs that lower the level of lipids in the body[20 21] and by the preliminary results of a study that showed a lower risk of developing neurodegenerative disease among subjects who consume fruits and vegetables and foods rich in bioactive components with high antioxidant activity, rather than meat.[22]

These products that are rich in active components belong to the category of "nutraceutical" products that help the body exert a protective/preventative effect against a number of biochemical markers (such as cholesterol) which are linked or related to chronic degenerative diseases. These kinds of products can be a useful complement or they can strengthen dietary patterns that already provide the correct consumption of foods that are naturally rich in these compounds, such as many types of fruits and vegetables.[23]

A study conducted in 2004, and presented in Philadelphia at the "Ninth Annual Conference on Alzheimer's Disease and Related Disorders" by Harvard researchers, studied the role played by fruits and vegetables in Alzheimer's disease, through the assessment of the dietary intake of these foods on the part of 13,000 women between 1984 and 1995, and the correlation of these values with the results obtained in tests of cognitive function conducted between 1995 and 2003, when the women were in their eighth decade of life. The study thus showed how older women who had consumed more vegetables rich in folate and antioxidants (carotenoids and vitamin C), as in the case of green leafy and cruciferous vegetables (such as cabbage, broccoli, watercress, turnip, radish), showed less cognitive decline than the other women with a low intake of these vegetables.[24]

The scientific opinion that diet can help reduce the risk of neurodegenerative disorders, because foods may represent an important source of compounds with neuroprotective activity, is also confirmed by epidemiological and experimental studies relating to active components belonging to the class of polyphenols (such as those of green tea), which showed that they can cross the bloodbrain barrier, thus limiting age-related cognitive decline and acting as neuroprotectors in models of Parkinson's disease and ischemia/reperfusion damage.[25 26]

A growing scientific interest is also devoted to the role of homocysteine,[27] whose increased levels, however, seem to be an independent risk factor for Alzheimer's disease, as well as being a risk factor for vascular disease of the central nervous system (another common cause of dementia).[28 29] Although there are hereditary forms, acquired hyperhomocysteinemia is usually the result of low levels of vitamin B12, vitamin B6 and folate, which are necessary for its metabolism.

Good sources of folate, therefore, include legumes, orange juice, asparagus, walnuts and leafy green vegetables such as spinach; sources of vitamin B6 include whole grains, soy-based foods, peanuts, walnuts, bananas and avocados; sources of vitamin B12 are usually

HIGH-CALORIE DIETS RICH IN CHOLESTEROL AND SATURATED FAT AND LOW IN FIBER, VEGETABLES AND FRUIT PLAY A ROLE BOTH IN THE FORMATION OF PLAQUES OF β-AMILOIDE AND IN CAUSING OXIDATIVE DAMAGE TO NEURONS

THE SCIENTIFIC OPINION THAT DIET CAN HELP REDUCE THE RISK OF NEURODEGENERATIVE DISORDERS IS ALSO CONFIRMED IN EPIDEMIOLOGICAL AND EXPERIMENTAL STUDIES

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foods and products of animal origin or other alternatives such as cereals and fortified soy milk or vitamin supplements.

Also, controlling the intake of calories in the diet[30] would seem to have a role in the prevention of neurodegenerative diseases like Alzheimer's. For example, some populations in China and Japan have low average daily caloric intakes (1600-2000 calories a day) and a lower incidence of Alzheimer's disease, compared to people in the U.S. or Western Europe, whose diet typically has a content higher than 2000 calories a day.[31]

This observation is corroborated by a study in 2002 of elderly American patients who were followed for an average period of four years. The results showed that the risk of developing Alzheimer's disease was greater in patients with an increased consumption of calories, than in those whose diet was characterized by a moderate intake of caloric energy.[32]

To summarize, although studies regarding the relationship between diet and neurodegenerative diseases have revealed rather nuanced direct links between diet and neurodegeneration processes, it should be noted, however, how such dietary habits may help define the risk profile of an individual, along with other biological and behavioral components that affect their state of health.

The results obtained from studies carried out and those underway will help to identify the foods and their key components for the development of new preventive/protective strategies against debilitating diseases, such as neurodegenerative disorders. At a time when the average life span is lengthening and the prevalence and incidence of neurodegenerative diseases are increasing, the need for new strategies for preventive/therapeutic measures that protect individuals from diseases associated with aging, no matter the cause, is more urgent than ever.

CONTROLLING THE INTAKE OF CALORIES IN THE DIET WOULD SEEM TO HAVE A ROLE IN THE PREVENTION OF NEURODEGENERATIVE DISEASES LIKE ALZHEIMER'S

DIETARY HABITS MAY HELP DEFINE THE RISK PROFILE OF AN INDIVIDUAL
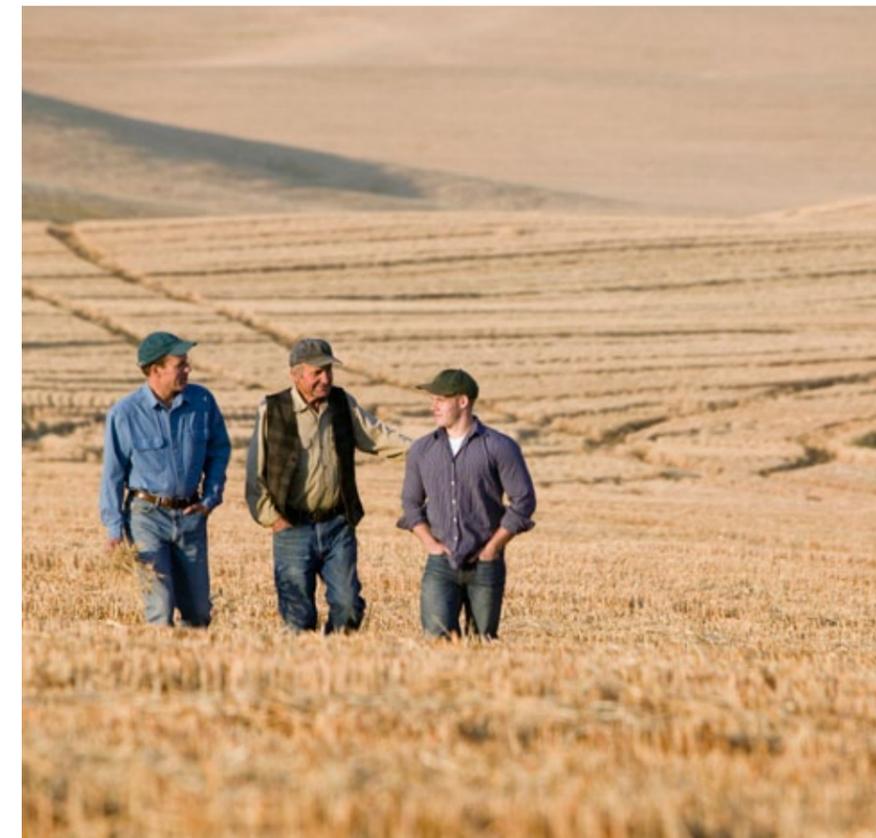
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The Mediterranean diet for countering the onset of Alzheimer's disease

As already stated, there are many international studies which show that the correction of some dietary habits contribute to obtaining good results in terms of protection from neurodegenerative (and cardiovascular) diseases.

A study published in 2008 in the "British Medical Journal,"[33] and based on the analysis of information from seven different studies conducted over the past two years around the world (on a total of over two million people), focused on the benefits generated by the so-called "Mediterranean diet model" in order to determine the extent, already amply demonstrated when dealing with cardiovascular diseases, and the protection generated by such a diet with regard to neurodegenerative diseases as well.

Developing a specific score of adherence to the Mediterranean diet, research has highlighted that an increase of just two points in one's score, in fact, will result in a significant gain in terms of protection against major chronic diseases, such as cardiovascular disease, neurodegenerative diseases, as well as Alzheimer's, Parkinson's and dementia. Increasing, albeit slightly, one's adherence to the dietary habits of the Mediterranean area would ensure a reduction in cardiovascular disease and tumors of 10 and 6%, respectively, and reduce the risk of developing neurodegenerative diseases by 13%.

Orienting one's diet, above all, to a consumption of fruits and vegetables, cereals and legumes, fish and olive oil would delay the onset of Alzheimer's to such an extent that, even though 30% of the population runs the risk of developing the disease, the adherence to a Mediterranean diet would be sufficient for delaying the first appearance of the symptoms by ten years, leading to a 90% reduction of the number of those affected.

Jim Richardson/National Geographic Stock

3.5 SUMMARY OF THE RELATIONSHIP BETWEEN LIFESTYLES AND DIET, OSTEOPOROSIS AND LONGEVITY

The role of nutrition is very important in preventing/delaying the onset of certain diseases and for maintaining health, particularly with respect to the elderly, who constitute a more vulnerable category when considering the risk of malnutrition to which they are exposed because of the frequent monotony of their diet, which leads to a nutritional deficiency.

As stressed by the World Health Organization[34] in its report *Keep fit for life: Meeting the nutritional needs of older persons*, the aging process has consequences on the nutritional needs of older people on two levels:

- energy needs per kilogram of body weight decreases with age, which reduces the intake requirements of some nutrients; and
- an increase in nutritional requirements for other essential nutrients.

The factors related to diet, compounded by changes that occur naturally with the aging process, also appear to be linked to the manifestation of many diseases associated with aging, such as osteoporosis.

Although the specific link between osteoporosis and nutrition revealed by studies of this disease is relatively moderate, the presence in some foods of specific micronutrients, and particularly calcium and vitamin D,[35][36] can help prevent osteoporosis thanks to their effective protection of the bones.

THE AGING PROCESS HAS CONSEQUENCES ON THE NUTRITIONAL NEEDS OF OLDER PEOPLE ON TWO LEVELS

THE PRESENCE OF CALCIUM AND VITAMIN D CAN HELP PREVENT OSTEOPOROSIS

Figure 3.1. *Keep fit for life. Meeting the nutritional needs of older persons*

EVIDENCE	DECREASED RISK	NO RELATIONSHIP	INCREASED RISK
CONVINCING Older people[a]	Vitamina D Calcium Physical activity		High alcohol intake Low body weight
PROBABLE Older people		Fluoride[b]	
POSSIBLE	Fruits and vegetables[c] Moderate alcohol intake Soy products	Phosphorus	High sodium intake Low protein intake (in older people) High protein intaake

[a] In populations with high fraccture incidence only. Aplies to men and women older than 50-60 years, with a low calcium intke and/or poor vitamin D status. [b] At levels used to fluoridate water supplies. High fluoride intake causes fluorosis and may also alter bone matrix. [c] Several components of fruits and vegetables are associated with a decreased risk at levels of intake within the normal range of consumption (e.g. alkalinity, vitamin K, phytoestrogens, potassium, magnesium, boron). Vitamin C deficiency (scurvy) results in osteopenic bone disease.

Source: World Health Organisation, 2002.

The previous table summarizes the main links established between the intake of specific micronutrients (calcium and vitamin D) and the prevention of osteoporosis (particularly highlighting the existence of benefits generated in the elderly), such as eating behavior responsible for the increased risk of developing osteoporotic diseases.

Considering that the growth of the skeleton is complete around 20-30 years of age, after which, in both sexes, the loss of bone mass begins – and is accelerated in women by menopause – nutritional factors, such as calcium and vitamin D intake and exercise, have many effects in regard to the bone loss associated with age and muscle strength.

Good nutrition, in terms of a balanced diet and adequate caloric intake, is essential for the normal growth and development of all tissues, including bone. Therefore, assessment of the nutritional status and an appropriate food history are milestones in the evaluation of the risk profile for osteoporosis.

Recent studies, such as the one conducted by a team of researchers from Europe and the U.S. in 2010 and published in the "British Medical Journal," [37] have shown that the daily intake of vitamin D is associated with calcium and reduces the risk of fractures by up to 8%, thereby constituting an essential tool for the success of any treatment for osteoporosis.

Calcium is the most important mineral in our body: 99% of it is found in bones and teeth, while only 1% is found in body fluids. The metabolism of calcium is closely related to that of phosphorus. In the skeleton, great quantities of calcium and phosphorus are present in the form of hydroxyapatite crystals, attached to collagen fibers. The deposition of these crystals and their orientation are partially regulated by the mechanical stress that the skeleton receives; for this reason, an extended period of bed rest or physical inactivity increases progressive bone demineralization and can lead to osteoporosis.

The physiological process of mineralization of the bone architecture also usually decreases with age, which affects the manifestation of osteoporosis, especially in women after menopause, due to the reduction in estrogen levels.

However, it is possible that this disease is also present due to the long-term intake of drugs (such as steroids and anticonvulsants) and diseases related to a malfunctioning of the thyroid.

THE GROWTH OF THE SKELETON IS COMPLETE AROUND 20-30 YEARS OF AGE, AFTER WHICH THE LOSS OF BONE MASS BEGINS

THE DAILY INTAKE OF VITAMIN D IS ASSOCIATED WITH CALCIUM AND REDUCES THE RISK OF FRACTURES BY UP TO 8%

CALCIUM IS THE MOST IMPORTANT MINERAL IN OUR BODY, ITS METABOLISM IS CLOSELY RELATED TO THAT OF PHOSPHORUS

IT IS POSSIBLE THAT OSTEOPOROSIS IS ALSO DUE TO THE LONG-TERM INTAKE OF DRUGS

Figure 3.2. **Levels of daily intake of calcium at different ages recommended by the European Union**

RECOMMENDED DIETARY CALCIUM INTAKES

	POPULATION	AGE (YEARS)	INTAKE (MG/DAY)
Europea Community		6–11 months	400
		1–3 years	400
		4–6	450
		7–10	550
	Male adolescents	11–17	1000
	Female adolescents	11–17	800
	Adults (both sexes)	PRI	700
		AR	550
		LTI	400
	Pregnant females		700
	Lactating females		1200

* PRI, "Population reference intake" (intake sufficient for practically all healthy people in a population); AR, average requirements; LTI, lowest threshold limit (intake below which, based on current knowledge, almost all individuals will be unlikely to maintain metabolic integrity according to criterion chosen).

Source: World Health Organization, *Prevention and Management of Osteoporosis,* 2003.

So, although the onset of the disease cannot be exclusively attributed to calcium – but rather, is due to the combination of environmental, genetic and nutritional factors –, its importance, particularly in the prevention of osteoporosis, is therefore fundamental when considering that, in all age groups, the dose taken each day is actually lower than what has been recommended.[39]

Although the main recommendations for those between the ages of 11 and 17[40] [41] regarding the recommended daily dose of calcium indicate values between 800 mg (in Europe)[42] and 1,000 mg (in the U.S.)[43] for females and 1,000 mg (in Europe) and 1,300 mg (in the U.S.) for males, in Italy, at least 70% of all female adolescents and 60% of male adolescents are taking doses below those that have been recommended.[44]

In adults, the calcium intake should be around 700 mg (in Europe) – 1,000 mg (U.S.) a day, but only 50-60% of the population seems to actually comply with these suggestions. Finally, as can be seen in Figure 3.3, in women of postmenopausal age (women aged between 51 and 70 years of age), the recommendations of the Institute of Medicine advise a calcium intake of around 1,200 mg in the absence of estrogen therapy, while in the case of such therapy, the recommended requirement is equal to that of men over the age of 50 years (1,000 mg).

From a nutritional standpoint, in order to prevent osteoporosis, it is necessary to avoid the loss of calcium, which is mainly due to factors such as the excessive consumption of

Figure 3.3. **Recommended daily intake levels of calcium and vitamin D at different ages**

Life Stage Group	CALCIUM			VITAMIN D		
	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)
Infants 0 to 6 months	--	--	1000	--	--	1000
Infants 6 to 12 months	--	--	1500	--	--	1500
1–3 years old	500	700	2500	400	600	2500
4–8 years old	800	1000	2500	400	600	3000
9–13 years old	1100	1300	3000	400	600	4000
14–18 years old	1100	1300	3000	400	600	4000
19–30 years old	800	1000	2500	400	600	4000
31–50 years old	800	1000	2500	400	600	4000
51–70 years old males	800	1000	2000	400	600	4000
51–70 years old females	1000	1200	2000	400	600	4000
>70 years old	1000	1200	2000	400	800	4000
14–18 years old pregnant/lactating	1100	1300	3000	400	600	4000
19–50 years old pregnant/lactating	800	1000	2500	400	600	4000

Source: Food and Nutrition Board, Institute of Medecine, *Dietary Reference Intaes for Calcium and Vitamin D*, 2010.

animal protein, excessive consumption of sodium chloride in the diet, excessive alcohol consumption, smoking and being overweight.[45]

Retrospective studies[46] [47] [48] have shown that individuals who consumed milk regularly during their childhood present a higher bone mass in adulthood than those who did not follow such a lifestyle.

This prospect is even more relevant when one considers that at the level of the general population, a 10% increase of the bone mass peak could halve the risk of fractures in adult life. Also, physical activity, particularly antigravity activities such as walking, running and dancing, is a powerful incentive for maintaining or increasing bone mass: the weight of the body, in fact, positively stimulates calcification, resulting in increased bone density. For this reason, the regular practice of physical activity during adolescence/youth helps the maximum development of the bone mineral, averting the risk of osteoporosis later in old age.

Although milk and dairy products, as well as mineral waters rich in calcium and low in sodium and nitrate are examples of good sources of calcium, it should be noted that the individual variability in absorption of calcium is very broad and is influenced by the levels of vitamin D, the lack of which can lead to rickets in children and osteomalacia in adults, both of which are characterized by defective bone mineralization. Also, during adolescence, when milk consumption decreases, the intake of vitamin D may be inadequate and this can adversely affect calcium absorption.

The lack of vitamin D[49] is also very common in the elderly population, partly due to their low income, but also partly due to a decreased intestinal absorption, decreased skin synthesis and a reduced conversion of the more active form of the vitamin.

Vitamin D[50] is a fat-soluble vitamin in the body found in the form of:
- *Cholecalciferol* (D3), synthesized in animal organisms and present in greater quantities in fish oil and egg yolk; and
- *Ergocalciferol* (D2), deriving from plants and yeast.

Vitamin D exerts its functions by increasing the absorption of calcium and phosphorus in the intestine, and the absorption of calcium in the kidneys, while preserving normal bone mineralization by maintaining the levels of calcium and phosphorus. Since most vitamin D is synthesized independently by the skin through exposure to the sun, dietary recommendations on its administration for adults cannot be made. However, in cases of increased demand or reduced synthesis, such as in the elderly, especially if they are not exposed to the sun, it is recommended to intervene through dietary supplementation of about 10 μ g/day of vitamin D.[51]

Foods with the highest content of this vitamin are liver, fish oils (especially cod liver oil), fatty fish like salmon and sardines, milk and dairy products (especially butter) and eggs.

Several studies[52] [53] have shown that other micronutrients, in addition to calcium and vitamin D, can also prevent the onset of osteoporosis by intervening in the long-term health of the bones.

These are the main antioxidants, substances that can neutralize free radicals and protect the body from damage to cellular structures such as the plasma membrane and DNA, accelerating the processes of cellular aging, depressing the immune system, favoring the onset of heart disease, cancers and diabetes, and weakening the bones.

Our body is able to monitor the activity of free radicals by special endogenous antioxidants (synthesized autonomously): enzymes such as catalase or reduced glutathione, exogenous nonenzymatic substances (found in foods), with antioxidant properties such as vitamin E, vitamin C, carotenoids, polyphenols and anthocyanins.

In conclusion, as already expected, the studies conducted have found a moderate link between diet and the prevention of osteoporosis and agree on highlighting that prevention

IN ORDER TO PREVENT
OSTEOPOROSIS, IT IS
NECESSARY TO AVOID
THE LOSS OF CALCIUM

PHYSICAL ACTIVITY IS A
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THE INDIVIDUAL
VARIABILITY IN
ABSORPTION OF
CALCIUM IS VERY
BROAD AND IS
INFLUENCED BY THE
LEVELS OF VITAMIN D

VITAMIN D IS A FAT-
SOLUBLE VITAMIN IN
THE BODY FOUND
IN THE FORM OF
CHOLECALCIFEROL
AND ERGOCALCIFEROL

THE MAIN ANTIOXIDANTS,
TOGETHER WITH CALCIUM
AND VITAMIN D, CAN
PREVENT THE ONSET OF
OSTEOPOROSIS

should begin at an early age, when the calcium intake through food is absorbed by the body and contributes effectively to the consolidation of bone density.

In adulthood and, finally, in old age, the slowing of osteoporosis disease cannot be separated from the adoption of a proper diet – characterized by a reduction of the ingestion of salt, an increased consumption of fruits and vegetables, consuming a minimum dose of 400/500 mg of calcium and the elimination of alcoholic beverages – as well as a healthy lifestyle characterized by moderate physical activity, maintaining a balanced body weight, and the elimination of smoking.

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3.6 CONCLUDING REMARKS

As revealed in the course of this chapter, the role of nutrition and lifestyle appears to be quite relevant in preventing/delaying the onset of diabetics, cancer, and cardiovascular, neurodegenerative and osteoporotic diseases in the elderly and in keeping them in good health.

Thus, there is a sort of "puzzle" of aspects upon which to act in order to establish a comprehensive regime of proper nutrition for longevity, identifying the correct and "workable" mix of eating habits and lifestyle: the attention paid to the caloric intake should be associated with the attention given to the caloric intake of different macronutrients (carbohydrates, fats and proteins) and micronutrients (such as the phytochemicals); such behavior should always be combined with regular physical exercise.

In this regard, studies of significant interest and reputation were conducted on the diet found in the region of Okinawa in southern Japan. Willcox *et al.*[54] have analyzed the residents of that region, who are famous for their high average life expectancy, thanks to the presence of a significant number of centenarians and the low risk involved in relation to the onset of diseases associated with old age.

Based on the studies conducted, it is believed that these peculiar features of "longevity" are strongly correlated with the particular local diet, which is low in calories yet highly nutritional, with a high presence of phytonutrients, including – mainly – antioxidants and flavonoids. It consists of a particularly high consumption of fruits and vegetables and is very limited as to meat, refined grains, saturated fat, sugar, salt and high-fat dairy products. One of the distinctive features of the traditional diet is the high consumption of sweet potatoes and green leafy vegetables, foods that are low in calories but very rich in antioxidants.

As reported by Willcox *et al.*, this diet is similar – in many regards – to the Mediterranean diet. Many features that the Mediterranean diet and the traditional diet of Okinawa have in common – such as low levels of saturated fats, a high intake of antioxidants, and low glycemic index – contribute to placing them among the very best diets in relation to the promotion and protection of health and longevity. All these elements contribute to significantly reducing the risk of developing cardiovascular disease, cancer, diabetes and other chronic diseases.

As a whole, the Mediterranean diet is one of the most balanced diets, allowing – in an intake of about 2000 calories a day – for an ingestion of all the essential macro and micro nutrients. The Mediterranean diet, therefore, appears capable of generating significant longevity benefits without running the risk incurred from excessive dietary imbalances (from both a medical point of view and a social point of view, and the overall well-being of the person).

THE MOLECULAR, METABOLIC AND HORMONAL CHANGES PLAY A CENTRAL ROLE IN THE ONSET OF DIABETES, CARDIOVASCULAR DISEASE AND CANCER

STUDIES WERE CONDUCTED ON THE DIET FOUND IN THE REGION OF OKINAWA IN SOUTHERN JAPAN, WHOSE RESIDENTS ARE FAMOUS FOR THEIR HIGH AVERAGE LIFE EXPECTANCY

MANY FEATURES THAT THE MEDITERRANEAN DIET AND THE TRADITIONAL DIET OF OKINAWA HAVE IN COMMON CONTRIBUTE TO PLACING THEM AMONG THE VERY BEST DIETS IN RELATION TO THE PROMOTION AND PROTECTION OF HEALTH AND LONGEVITY

4. INFLAMMATORY STATES AND CALORIE REDUCTION: TWO AREAS OF CROSS RESEARCH

4. INFLAMMATORY STATES AND CALORIE REDUCTION: TWO AREAS OF CROSS RESEARCH

After examining many studies on the correlation between healthy lifestyles, nutrition and preventive effects (favorable or otherwise) on the emergence of the most common non-communicable diseases, in this chapter we introduce two areas of recent research that in the near future will give us further evidence and open up new scenarios for understanding the possibility of living for a long time in good health.

The first area of research relates to the states of inflammation in our cells that, based on modern theories, seem to be at the root of many non-communicable diseases, or as states of progressive cellular inflammation which then develop into full-blown diseases.

On the basis of this hypothesis, there begin to be numerous observations regarding the interactions between individual genetics, the environment and eating habits: indeed, if it has long been known how environmental factors, such as different pollutants, have pro-inflammatory effects, the first evidence is emerging on how the model of the diet adopted can also greatly influence an inflammatory state and, thus, affect the health of the individual, contributing to the aging processes and, consequently, their life expectancy.

The second area of research involves the study of the effects on the physiological parameters and biochemical processes of the body through a nutritional approach, which requires the reduction of caloric intake, along with the proper intake of all the nutrients which are qualitatively and quantitatively necessary for a positive influence on lengthening one's life in optimal health.

The role played in the aging process, as much by inflammatory states as by eating habits acting to slow these states down, seems to be made up of two main cross-cutting and innovative areas of research on the determinants of healthy longevity. It will probably be possible to understand much more about the key elements that can influence aging from further, in-depth research on inflammation. In parallel, significant indications – also practical – about the optimal diet for health and longevity can be identified by experiments involving the introduction of the proper systems of caloric restriction in humans.

In the light of the innovativeness of these issues and the centrality that they appear to have in understanding the molecular and biological basis of longevity, the BCFN has chosen to create – thanks to the support of experts of international renown[1] – a review of the evidence that has emerged from major international studies on the subject, trying to highlight the existing and/or potential links, including inflammatory conditions, dietary choices and aging.

BASED ON MODERN THEORIES, STATES OF PROGRESSIVE CELLULAR INFLAMMATION DEVELOP INTO FULL-BLOWN DISEASES

THE REDUCTION OF CALORIE INTAKE HAS A POSITIVE INFLUENCE ON LENGTHENING ONE'S LIFE IN OPTIMAL HEALTH

THE BCFN HAS CHOSEN TO CREATE A REVIEW OF THE EVIDENCE THAT HAS EMERGED FROM MAJOR INTERNATIONAL STUDIES ON THE SUBJECT, TRYING TO HIGHLIGHT THE EXISTING AND/OR POTENTIAL LINKS

4.1 INFLAMMATORY STATES AND LONGEVITY

4.1.1 Introduction

Human history is characterized by a progressive increase in life expectancy, which now exceeds 70 years of age in many countries.

At the cellular level, there are several critical mechanisms that help repair the microscopic damage and that depend on genetic factors, but also on factors related to the type of alimentation (diets that promote inflammation, malnutrition, excessive portions, etc.), lifestyles (smoking, stress, sedentary lifestyle) and external environmental factors (pollution).

Our survival and our potential longevity are related to the ability of the cells and molecular mechanisms of defense in our bodies to continuously perform these roles of protection and reparation. These cells, however, can exhaust their ability to replicate and, therefore, their potential for more or less quick repair throughout life. In other words, it is as if the repair potential that each individual has upon birth can be drained, more or less quickly, depending on the variables mentioned above.

The exhaustion of the ability to reproduce the "consumed" cells in the healing processes leads to the progressive overwhelming of inflammatory and degenerative phenomena, such as atherosclerosis. Some chronic degenerative diseases may result from a progressive inability to cope with situations of continuous inflammation and the progressive failure of the repair processes (neurodegenerative diseases). Other diseases and health conditions, such as diabetes and obesity, instead produce an inflammation of the blood and tissues capable of generating a more intense use of reparative processes, therefore also influencing their premature exhaustion over time, which results in a shortening of life expectancy.

The BCFN's interest in this issue is related to the fact that it seems to emerge more and more clearly from some recent studies that the factors related to nutrition and the type of diet adopted appear to be critical factors that can influence the speed with which people "consume" their repair processes over time and, consequently, their longevity and life without chronic degenerative diseases.

In this context, recent scientific studies have highlighted the link between the different chronic diseases and the state of "silent" inflammation generated by the adoption of inappropriate dietary patterns. These studies show that the type of eating pattern can positively or negatively affect the body's inflammatory responses. This level of inflammation would be considered "low," i.e., causing less pain and, therefore, "silent." The prolonged presence of such a level of silent inflammation, resulting in a faster consumption of the body's repair processes, ultimately has an impact on the emergence of chronic diseases and, therefore, on longevity and the quality of life of the population.

With regard to chronic diseases, it should be noted that the studies found in scientific lit-

SURVIVAL AND POTENTIAL LONGEVITY ARE RELATED TO THE ABILITY OF THE CELLS AND MOLECULAR MECHANISMS OF DEFENSE

THE EXHAUSTION OF THE ABILITY TO REPRODUCE THE "CONSUMED" CELLS IN THE HEALING PROCESSES LEADS TO THE PROGRESSIVE OVERWHELMING OF INFLAMMATORY AND DEGENERATIVE PHENOMENA

BASED ON RECENT SCIENTIFIC STUDIES, THE LINK BETWEEN THE DIFFERENT CHRONIC DISEASES AND THE STATE OF "SILENT" INFLAMMATION GENERATED BY THE ADOPTION OF INAPPROPRIATE DIETARY PATTERNS HAS BEEN HIGHLIGHTED

erature made with reference to several predisposing factors for chronic diseases, and in particular cardiovascular diseases, have shown a great inter-individual variability in the event of the illness and age when it occurs, even in subjects with the same risk profile.

One hypothesis that has arisen to explain this phenomenon is that the individual variability in disease risk may be related to changes in the aging process. In this context, telomeres, the terminal region of chromosomes, might represent a marker of the biological age, that is to say, aging.

In other words, telomeres can be viewed as "biological clocks" in which, following the cell reproduction which happens in particular in the aforementioned repair processes, their length is progressively reduced until they can no longer carry out their protective function for the chromosomes. Thus, the cells are no longer able to reproduce successfully, grow old and die.

Specifically, the telomere is the terminal region of chromosomes, hence, as the name suggests, it is composed of highly repeated DNA and has a decisive role in avoiding the loss of information during the duplication of the chromosomes. The polymerase DNA is indeed able to replicate the chromosome to its termination and, therefore, if it were not for telomeres, which are shortened with each replication, this process would lead to a significant loss of genetic information in any event.

In humans, the repeated sequence in the telomeres is composed of six TTAGGG nucleotides,[2] repeated for a length ranging from 3 to 20 kilo bases. There are an additional 100-300 kilo bases of telomere-associated repetitions, which are arranged between the telomere and the rest of the chromosome.

The telomeres are extended by the telomerase enzyme, whose task is to avert this fate by always synthesizing (i.e., duplicating) new telomeric sequences. Unfortunately, in somatic cells, telomerase activity tends to disappear, and this seems to cause the phenomenon of the shortening of the ends of chromosomes which appear to be related to aging.

In other words, the process is as follows: each time a cell duplicates itself, it transmits a sequence of telomeres; when all its sequences are used up, it dies.

In summary, and in this context, studies on telomeres show that there is a relationship between telomere length and the onset of chronic diseases. Furthermore, in the most direct route, some studies have emerged showing that cellular inflammation (including "silent") is one of the bases of interpretation concerning the origin of several chronic diseases.

Although it was well known in the past that wounds or microbial attacks were due to inflammatory responses of the organism, for some years now, studies have emerged that also indicate that dietary patterns can have a positive or negative influence on these inflammatory responses. The molecular and metabolic bases are very complex, and studies have not yet provided exhaustive answers in this regard, above all, because the level of the resulting inflammation would be "low," that is, causing less pain, and the markers that would signal this "silent" level are not always clear (for example, reactivity to protein C).

These levels of inflammation, which are also caused by the type of dietary pattern adopted, involve "repair actions" of the body, with telomeres playing a primary role. As mentioned previously, the more the telomeres are called upon for repairs, the shorter the telomeres get until they are exhausted and no longer capable of carrying out their protective function. As discussed in the BCFN papers of years past,[3] there is a strong relationship between the eating patterns and lifestyle adopted and the onset of chronic diseases. So the matter of telomeres is important both with regard to their relationship with chronic diseases and with reference to inflammation generated by the adoption of an incorrect diet, which in turn is related to chronic diseases. It has been shown[4] that diabetes, obesity, high blood pressure and cardiovascular diseases are linked to one's lifestyle.

Furthermore, prolonged exposure to inflammation is common to many diseases, such as obesity, type 2 diabetes, cardiovascular disease and neurodegenerative problems, that have a consistent impact both on life in an absolute sense and on life expectancy in good health, i.e., the years of life free from disability. The adoption of an incorrect diet, diabetes and obesity generate a constant situation of inflammation in the body which, contrary to what one might think, is not a protective response of short duration, but instead may accompany individuals for a long time, with a significant "consumption" of the repair processes and damage in terms of longevity.

4.1.2 The relationship between telomere length and aging

As we discussed earlier, telomeres have the function of "protection" of the chromosomes in cell duplication; their goal is to prevent the degradation of the chromosome, undergoing degradation themselves, i.e., shortening.[5]

Already in 1961, Hayflick discovered that this degradation of telomeric DNA leads to a point where the cell can no longer divide, which coincides with the point of the maximum shortening of telomeres.[6] The presence of a limit to the number of cell divisions (mitosis) due to the shortening of telomeres, which Hayflick identified, led to the hypothesis of a maximum number of mitotic telomeres, which was, in fact, called the Hayflick limit.

At this point, the cells reach replicative senescence, which corresponds to the time when they are unable to replicate further, thus leading to the various changes/phenomena that are associated with aging (skin wrinkles, delayed wound healing, an unready immune system response that leaves the field open to age-related diseases, such as cancer, etc.).

With the objective of demonstrating the relationship between the shortening telomeres and the different phenomena related to aging, some researchers have used fibroblast cells as an experimental tool. The fibroblasts (connective tissue cells) are ideal for aging studies, as they are characterized by four stages of development and have a finite replicative capacity. The first two phases are characterized by the growth, development and proliferation of cells, whereas in the third stage, there is a reduction of the ability of the cells to replicate, and many cells start to die.

Finally, in the fourth phase, the old cells have completely lost the ability to replicate and do not respond to growth factors.

This study, conducted with human fibroblasts from donors in different age groups, has shown a relationship between age and telomere length. Specifically, there was a statistically significant inverse relationship between donor age and telomere length; that is to say, the older the person, the shorter the length of the DNA.[7]

However, with reference to the Hayflick limit, its correlation with senescence was proven later, in 1998, and after the study on fibroblasts, when the Geron Corporation[8] developed techniques that could extend telomeres, which brought about a significant slowing of cell senescence.

Since the late nineties, many scholars and supporters of the technology for extending the duration of life have focused their attention on the role of telomeres in senescence and on the possibility of their extension. At the theoretical level, through the induction of telomerase, temporarily (by drugs) or permanently, it would be possible to lengthen the telomeres. This approach, however, has not been confirmed by independent studies on humans, despite the fact that some medical and scientific research is developing drugs that activate these processes in humans.

A study[9] conducted on the nematode worm, *Caenorhabditis elegans*,[10] indicated that the extension of telomeres can prolong the life of this category of worms. Two groups of worms were studied, whose only difference was in the length of telomeres. The kind of worm with longer telomeres, or more specifically, modified ones, on average showed a 20% greater life expectancy compared to the kind with unmodified telomeres.

Another contrasting figure emerges from the studies conducted with reference to the impact on the life expectancy of cloned animals. Kubota[11] carried out a study on a 17-year-old bull, taking some of its cells and allowing them to divide. Creating clones of cells taken at different stages of development, he showed that the older cells with shorter telomeres were found to be the most efficient. This study revealed that the telomeres are a cellular clock, but their length does not appear to be a determining factor (or the only one) of the aging process.

There are studies along these lines, such as those by Blackburn,[12] showing that telomeres, taken individually, would not be an index of replicative cell potential and, therefore, would not be so relevant as an indicator for cellular aging. Consider, for example, as studies conducted by Steiner[13] and Kakou[14] have shown, that among primates, human beings have the highest life expectancy and the shortest telomeres.

Studies on human beings have led to conflicting results. Studies by Tabuko,[15] Serra[16] and Renault[17] showed that in humans, there is either a weak relationship or none at all between age and telomere length, while on the opposite side, Franceschini[18] has reported the presence of long telomeres in the cells of centenarians.

With regard to mortality (and not to aging), some studies by Cawthon[19] investigated the relationship between telomere length and mortality in humans. The in-depth study tested the association between telomere length and death in 143 Utah residents between 60 and 97 years of age. For each additional year of age, the study showed a loss of telomeric sequence and there were no significant differences between men and women in the rate of decrease in telomere length. The percentage loss was comparable, but the female telomeres were 3.5 percent longer than the male telomeres. In other words, women and men lose the same amount of telomere length, it is just that women have longer telomeres to start with.

The study showed that the people characterized by a shorter length of telomeres had a mortality rate twice that of those with telomeres of greater length. The average loss of survival was 4.8 years for women and 4 years for men.

In short, Cawthon showed that telomere length is a significantly predictive factor of mortality in people between 60 and 74 years of age and is moderately predictive in people aged 75 or older.

4.1.3 The relationship between telomere length and disease

The degradation of telomeric DNA is not only linked to aging, but also plays an important role in a multitude of diseases. For example, degradation of telomeres is associated with certain genetic diseases such as Down Syndrome and aplastic anemia, or genetic mutations that are able to influence their structure and replication process.

As demonstrated by Harley,[20] chronic stress can also lead to a shortening of telomeres, causing classic syndromes of advanced age. Studies in this field have shown that people with shorter telomeres than the average of the population are more susceptible to heart disease and stroke, and this coincides with the fact that elderly people with shorter telomeres have a greater chance of developing these conditions.[21] It has emerged from these studies that, by blocking cell division, telomere shortening can cause damage to the pro-

liferative tissue of individuals and prevent the renewal of the tissue in the lungs, causing an increased risk of pulmonary fibrosis, or scarring of the fibrous connective tissue, with effects on respiration.

Again with reference to situations of stress, a recent study by Drury[22] revealed how stress can cause the shortening of telomeres even in children. His research involved 136 orphans between the ages of 6 and 30 months, who participated in a project launched in the U.S. in 2000 that was designed to monitor the health and development of children in orphanages. In the period of observation, half of the orphans continued to live in an orphanage, while the other half was entrusted to a foster family. From the analysis of the telomeres of the children, performed between their sixth and tenth years of age, it emerged that the longer the children had lived in an orphanage, the shorter their telomeres were. The results of the study have opened a new path of research with the aim of understanding whether, in addition to being a marker of aging, telomere length can also be used as a marker for all factors commonly referred to as "adverse experiences."

Other studies conducted by Brouilette[23] on patients subjected to coronary artery disease have shown that they have a shorter telomere length than patients with normal coronary arteries. This diversity can also be seen in patients who have had a heart attack before the age of 50, as compared to subjects with no history of heart attack.

In the same study, the authors also report the correlation between telomere length[24] and the risk of developing coronary heart disease. Specifically compared were the lengths of telomeres in 484 men who developed a coronary event, with the telomere lengths of 1,058 men who did not develop any such event, also considering the benefits of the use of statin.[25] From the study results, the authors concluded that, in men at high risk of developing coronary heart disease, the telomere length in cells of the leukocyte series is predictive of coronary events in middle age and identifies people who may benefit from the use of statins.

The main issues that emerge from the study suggest that short telomeres reflect a functional modification of cells, for example, senescent lymphocytes that produce increased amounts of inflammatory cytokines (chemical mediators for the initiation and modulation of the inflammatory process).

The decrease in telomere length could, instead, limit the reparation capacity of the endothelium and, thus, worsen the trend of the atherosclerotic process. Alternatively, the reduced length of telomeres may indicate an accumulation of various oxidative stresses.

Later on, Brouilette[26] once again carried out an in-depth investigation on the relationship between telomere length and coronary heart disease, showing that inheriting shorter telomeres increases the probability of incurring cardiovascular disease. The study results confirmed this hypothesis, namely that the reduced length of telomeres is one of the main anomalies that explains the pathogenesis of cardiovascular disease.

With reference to diabetes, a recent study by Sampson[27] found that the telomere length of monocytes in patients with type 2 diabetes is significantly lower than in healthy subjects. Obesity, diabetes, high blood pressure and cardiovascular disease are positively related to the adoption of incorrect diets and unhealthy lifestyles.

With reference to the latter, studies by Valdes[28] analyzed the relationship between lifestyle and telomere length, verifying the correctness of the hypothesis that an increase in body mass index (BMI) and cigarette smoking may be associated with reduced telomere length in white blood cells.

The in-depth study involved 1,122 caucasian women in the UK between 18 and 76, including 119 with BMI greater than 30, equivalent to 11%, and 85 with BMI less than 20, equivalent to 8%. None of them presented a clinical picture of diabetes, 47%of them had never smoked, 33% of them were ex-smokers, 18% was made up of active smokers and the

remaining 2% gave no information on the matter. The authors have shown that telomere length decreases with age at an average of 27 base pairs per year. The telomeres of obese women are shorter by 240 base pairs than those of lean women. With regard to cigarette smoking, however, each pack of cigarettes smoked per year is equivalent to a further loss in telomere length of 5 base pairs. The results have strongly highlighted that obesity and cigarette smoking accelerate the aging process.

Vogel[29] showed that meals high in fat and sugars increase the level of inflammation. Even a single high-fat meal increases the circulating micro-particles, which are an index of endothelial dysfunction. In general, the evidence leads to underlining how meals that are high in fat and sugar produce vascular dysfunction by an increase in oxidative stress.

In addition, a very recent study conducted by Lynn,[30] performed on nearly 2,500 individuals, showed that telomere length in leukocytes is significantly associated with level of physical activity.

This association remains significant even when age, sex, BMI, tobacco smoking and socioeconomic status vary. The findings show that a sedentary lifestyle, in addition to tobacco smoking and body mass index, has a significant impact on telomere length in white blood cells and can accelerate the aging process.

Telomere length in leukocytes is also a factor to be correlated with bone density and, therefore, is able to explain osteoporosis in women.[31] This result was found in a study by the International Osteoporosis Foundation, conducted on 2,150 women, which showed that telomere length in leukocytes can be used as an indicator of the level of aging of the bones.

4.1.4 Concluding remarks

The increasing attention given to telomeres by the general public has just been in recent years, that is to say, since researchers began to associate them with the aging process. Aging is a complex phenomenon of degeneration of the body's vital capacity, which even in the absence of disease, leads to death. Therefore, despite some misconceptions and prejudices, aging is not necessarily associated with disease and more or less disabling ailments, since its effects, in terms of decreased psychomotor performance, can be observed even in perfectly healthy individuals. Generally, studies carried out on telomeres show that there is a relationship between telomere length and the onset of chronic diseases, which, in turn, are linked to lifestyle and diet.

In the most direct route, some studies are emerging that also show how dietary patterns can positively or negatively affect the body's inflammatory responses. The level of inflammation resulting from the adoption of poor eating habits would be "low," i.e., causing little pain. According to the literature, there are not always clear indicators that would signal such a "silent" level.

The "silent" cellular inflammation, then, becomes a basis of interpretation of the origin of several chronic diseases, in that these levels of inflammation, caused by the type of dietary pattern adopted, imply "repair actions" of the body in which telomeres play a primary role. As mentioned previously, the greater the frequency and intensity with which the telomeres are called upon for repairs, the greater the speed with which they shorten until they are exhausted.

The diet adopted by individuals in a population becomes an important factor in the treatment of inflammation produced by situations of obesity,[32] diabetes and cardiovascular diseases.

A good example of this is the one relating to the average length of telomeres in the two dietary models under comparison: American eating habits and the Mediterranean diet. The figure below is a working hypothesis by Professor Camillo Ricordi.

IT IS ASSUMED THAT
THE LEVEL OF "SILENT"
INFLAMMATION GENERATED
BY THE EATING HABITS OF
THE AMERICAN
PEOPLE COULD LEAD
TO A GREATER USE OF
REPARATIVE PROCESSES
AND, THEREFORE, TO A
FASTER SHORTENING OF
THE TELOMERES

As can be seen, the level of "silent" inflammation generated by the eating habits of the American people suggests that it could lead to a greater use of reparative processes and, therefore, to a faster shortening of the telomeres compared to individuals who have adopted a Mediterranean diet. Prolonged exposure to a level of "silent" inflammation does not produce immediate effects, but in the long term leads to significant and important effects on telomere length and, ultimately, the level of aging of the organism and life expectancy in good health.

In this context, the advances that genetics is making have given rise to enthusiasm about the study of anti-aging strategies and the implementation of gene or drug therapies.

The interest on the subject is so great that by the end of this year, Life Length[33] will have come out with a test for discovering the status of one's telomeres.

However, it should be noted that:

- the results of the research and studies are not yet fully consolidated and do not lead to conclusive or statistically significant evidence with respect to the generality of individuals;
- a distinction should be made between experiments and studies on cells and on animals, and experiments on human beings. The generalization of the positive outcomes on specific cells or animals is not to be taken for granted with regard to the human species;
- it is opportune to distinguish between partial results (i.e., obtained on a specific part of the body) and total results. In fact, prolonging the effectiveness of an organ does not necessarily increase the longevity of the organism, just as cellular immortality does not mean human immortality;
- we are in a highly complex situation concerning the simultaneous interaction of several factors, and the matter under question is currently at the very frontier of research. Therefore, the different hypotheses and partial results achieved are likely to be refuted more organically or confuted in the near future.

It seems to emerge from studies that telomere length is correlated to biological age only in old age. If you consider a person who is 30 years old, the length of their telomeres does not say anything about how and when they will grow old, because what matters is the speed at which telomeres shorten, and this depends in large part on the lifestyle adopted.

Figure 4.1. **Impact of diet on the length of telomeres**
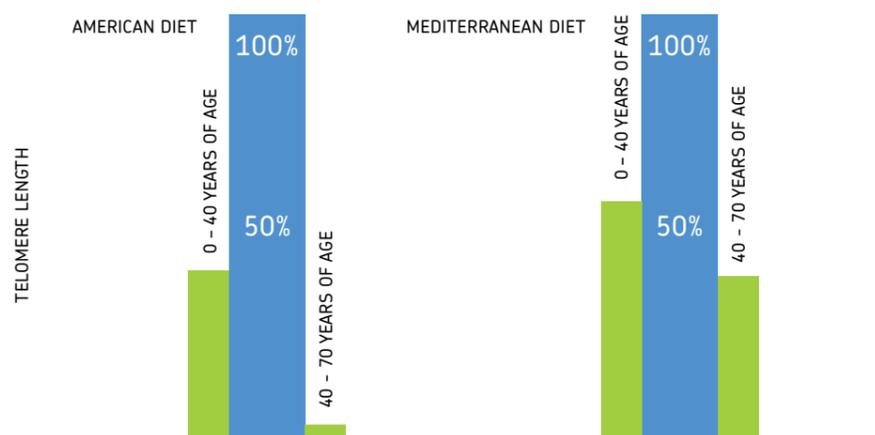
Source: Ricordi C., presentation first Advisor Board – BCFN, 17 February 2011.

Concerning all this evidence, any test must be evaluated carefully. In fact, it seems to emerge from studies that telomere length is correlated to biological age only in old age. In other words, if you consider a 30 year-old person, the length of their telomeres does not say anything about how and when they will grow old, because what matters is the speed at which telomeres shorten, and as seen from the analysis of the studies, this depends in large part on the lifestyle adopted.

In addition, if it is true that people born with telomeres that are shorter than normal ones, are born "older" than normal, it is yet to be proven that those who have longer telomeres will live longer.

In conclusion, it should be noted that it is not true that the telomere length represents an absolute indicator of aging of the individual and, thus, of their life expectancy, but is only an indicator of biological age where the correct parameter to consider is the rate at which the telomeres shorten, rather than their absolute length.

IT SEEMS TO EMERGE
FROM STUDIES THAT
TELOMERE LENGTH
IS CORRELATED TO
BIOLOGICAL AGE ONLY IN
OLD AGE. THE SPEED AT
WICH TELOMERS SHORTEN
DEPENDS IN LARGE
PART ON THE LIFESTYLE
ADOPTED

David Alan Harvey/National Geographic Stock

4.2 CALORIC RESTRICTION

AGING IS THE RESULT
OF THE GRADUAL
ACCUMULATION OF
DAMAGE TO DNA,
CYTOPLASMIC PROTEINS,
CELLULAR ORGANELLES
AND ORGANS

As mentioned at the beginning of this document,[34] aging is the result of the gradual accumulation of damage to DNA, cytoplasmic proteins, cellular organelles and organs. This damage accumulates because the systems devoted to the reparation or removal of the damage do not work perfectly and fail to completely remove the damage that, thus, accumulates over time.
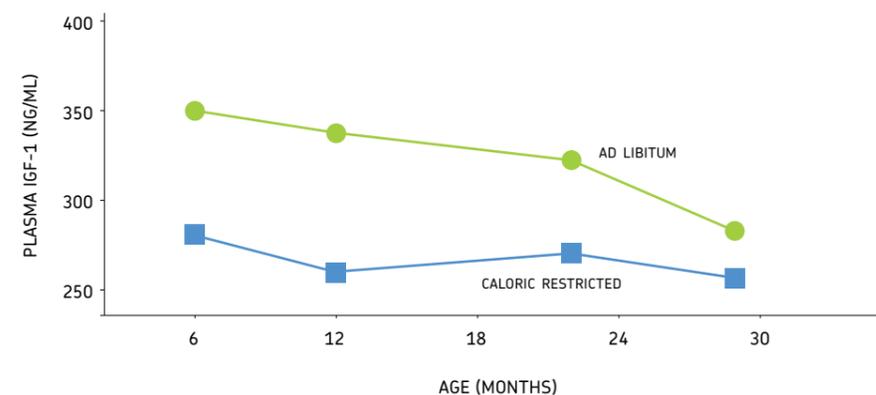
As mentioned in the introduction, there is no intervention to date to prevent, stop or reverse the aging processes of the organism, but rather, there are dietary, genetic and pharmacological interventions that have been shown to slow aging and increase the lifespan in experiments on animals.[35]

In light of the different research conducted – and ongoing – with regard to the influence of the diet on health, and on the basis of evidence gathered by specific studies on calorie restriction – which have had a particularly strong acceleration over the past 10 years – we can say that caloric restriction without malnutrition (i.e., its reduction in energy intake up to a limit of 50%, but along with an adequate intake of vitamins and minerals) is one of the most powerful interventions for slowing aging and for increasing the lifespan in many kinds of animals (such as worms, fruit flies, yeast, mice, rats and dogs).[36]

CALORIC RESTRICTION
WITHOUT MALNUTRITION
IS ONE OF THE
MOST POWERFUL
INTERVENTIONS FOR
SLOWING AGING
AND FOR INCREASING
THE LIFESPAN

The extension of the lifespan mediated by caloric restriction is greater if the reduction in food intake in mice is initiated immediately after weaning, but a significant increase in the maximum lifespan can be observed even when calorie restriction is initiated in adult animals (12 months of age, which is roughly equivalent to 50 years of age in a human).[37]

Hundreds of studies on experiments with animals have shown that caloric restriction prevents or slows the onset of most chronic diseases associated with aging and extends the lifespan up to a maximum of 50%.[38] For example, caloric restriction drastically reduces (up to a maximum of 60% less) the risk of developing cancer (which is the leading cause of death in rodents).[39]

ABOUT 28% OF THE
RODENTS UNDER CALORIC
RESTRICTION DIE A
NATURAL DEATH IN OLD
AGE WITHOUT SIGNIFICANT
PATHOLOGIC LESIONS,
WHEREAS ONLY 6% OF
THE RODENTS EATING AD
LIBITUM DIE WITHOUT ANY
PATHOLOGY

Finally, as evidenced by studies carried out by Shimokawa et al. (1993),[40] about 28% of the rodents under caloric restriction die a natural death in old age without significant pathologic lesions, whereas only 6% of the rodents eating ad libitum (at free will) die without any pathology. This data suggests that in mammals, aging is not inevitably associated with the onset of chronic diseases, and that it is possible to live a long life without incurring disease. Many studies are currently underway to understand the metabolic and molecular mechanisms underlying this phenomenon.

4.2.1 What are the mechanisms by which caloric restriction slows the aging process?

THE MECHANISMS
UNDERLYING THE
ANTI-AGING EFFECT OF
CALORIC RESTRICTION
ARE COMPLEX AND NOT
FULLY UNDERSTOOD

The mechanisms underlying the anti-aging effect of caloric restriction are complex and not fully understood. From numerous studies in progress, however, it seems that the reduction of growth factors (such as IGF-1, insulin) and of the activity of the signaling pathways of insulin/IGF-1 ("nutrient-sensing pathways"), the reduction of inflammation, protection against oxidative stress and other changes in the metabolic and neuroendocrine structure are the main factors that promote health and longevity in animals experiencing caloric restriction.41 In animals used in experiments, for example, caloric restriction reduced plasma levels of IGF-1 by 30-40%.[42] Caloric restriction also reduces the levels of sex hormones, increases the body's ability to repair DNAdamage, increases the removal of damaged proteins and cellular organelles (autophagy), increases stress resistance mechanisms, makes glucose metabolism more efficient, and slows the immunological decline that occurs with aging.

In general terms, in the presence of a reduction in calorie intake (but with an adequate and proper intake of nutrients), the body slows down the aging process and upgrades the systems for repairing damage. Nature, in a sense, is put into a state of "standby" and "protection" if itperceives a lack of nourishment.

IN THE PRESENCE OF A
REDUCTION IN CALORIE
INTAKE THE BODY
SLOWS DOWN THE AGING
PROCESS AND UPGRADES
THE SYSTEMS FOR
REPAIRING DAMAGE

This hypothesis was confirmed recently by several studies using different genetic models of longevity. In fact, in mice in which, by using sophisticated methods of genetic engineering, levels of growth factors (i.e., GH, IGF-1, insulin) and/or nutrient-signaling pathways, through which these factors act (PI3k/AKT/mTOR/p66shc) have been reduced,[43] the lifespan has lengthened considerably.[44] Some scientific studies have identified, in particular, a negative relationship between the level of growth hormones and IGF-1 and longevity. Yuan et al. (2009), for example, found that the reduction of circulating levels of IGF-1 is associated with a significant increase in the average lifespan in the mice used in the experiments.[45]

In addition, Ikeno et al. (2003 and 2006) and Vergara et al. (2004) showed that 25% of the Ames and Snell dwarf mice that are genetically deficient in growth hormone (living up to 50% more than the control population and that have very low levels of IGF-1) die without any evidence of pathological lesions at autopsy, compared to a percentage between 0 and 7% found in normal mice. In addition, approximately 50% of the mice in which the growth hormone receptor had been silenced and which, therefore, had low circulating levels of IGF-1 (these GHR-KO mice live up to 50% more than those of normal control), died without any pathology found at autopsy.[46]

Figure 4.2. **Link between caloric restriction and IGF-1 levels**

Source: Breese CR. et al., 1991.

4.2.2 What is the role of fat mass in mediating the anti–aging effects of caloric restriction in animals used in experiments?

Some authors mistakenly believe that the reduction of fat mass in animals under calorie restriction is the determining factor in slowing the aging process and reducing the incidence of cancer. The experimental evidence does not support these conclusions. In fact, only the average lifetime, not the maximum one, is increased in the animals used in the experiments, which maintain low body fat through a regular regimen of physical activity. Instead, the maximum life increases by 30% in the sedentary animals used in experiments that were subjected to a regime of caloric restriction to maintain a body weight equal to that of animals that got exercise.[47] This experimental data suggests that both physical activity and caloric restriction are able to counteract the excessive accumulation of fat and the deleterious metabolic consequences associated with it, prolonging the lifespan. However, only the chronic reduction in calorie intake can slow down the inherent aging process in the body and prevent diseases that are fat-independent.

Figure 4.3. **Caloric restriction and longevity (the evidence in mice)**
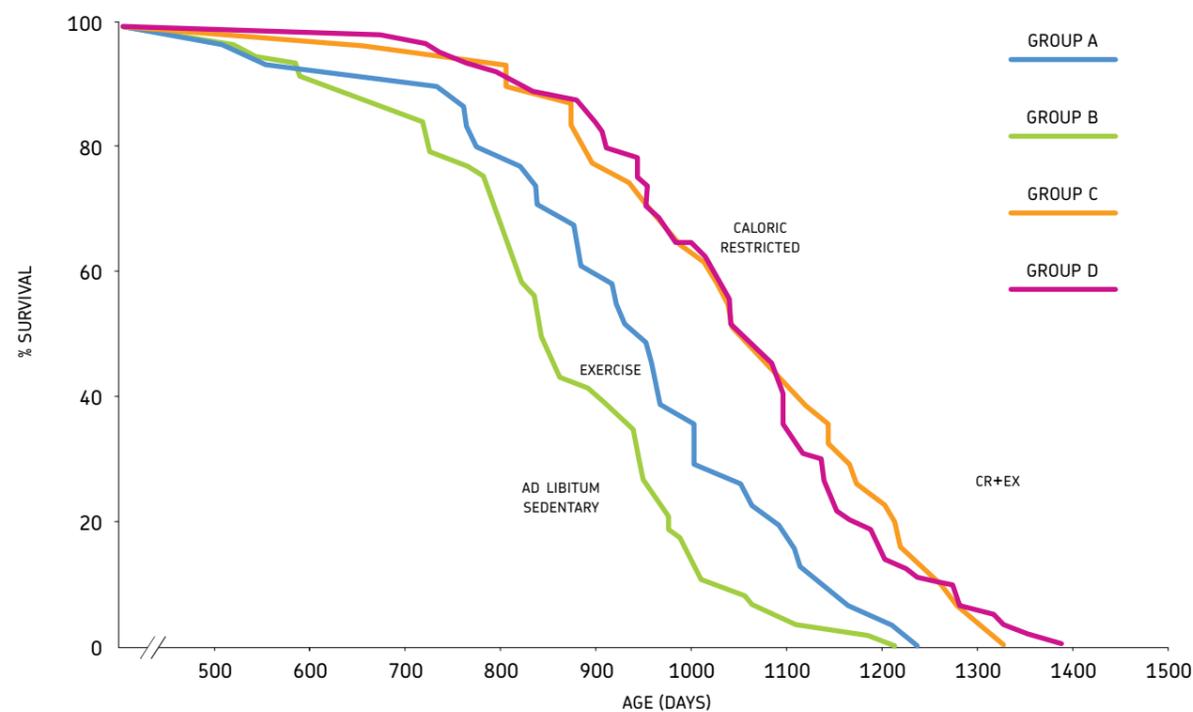
Source: Holloszy, J.O., 1997.

4.2.3 What are the effects of caloric restriction without malnutrition in non–human primates?

The research on caloric restriction in nonhuman primates began, significantly, in the Eighties. In 1984, the National Institute on Aging launched the first large controlled study of caloric restriction in primates.
From the results of these and other studies conducted at the University of Wisconsin, already at the beginning of the Nineties, it was deduced that the primates subjected to caloric restriction schemes showed a slower decline in circulating levels of the dehydroepiandrosterone sulfate steroid hormone produced by the adrenal glands, lower plasma concentrations of glucose, insulin, cholesterol and triglycerides, lower systolic and diastolic pressure, less stiffness of the arterial walls and increased insulin sensitivity and levels of HDL-cholesterol.[48]

A recent study published in "Science" by the Weindruch group[49] has finally revealed that a 30% reduction in food intake for 20 years in monkeys is capable of reducing disease and mortality from cancer and cardiovascular disease by 50%. The monkeys with a caloric restriction were also completely protected against obesity and mellitus diabetes. In this study, the researchers also demonstrated a significantly slower atrophy of certain areas of the brain in the monkeys with the caloric restriction than in those who ate ad libitum. However, the study is still ongoing, and it will take another 10 years to determine if the monkeys with caloric restriction will live longer.

4.2.4 What are the effects of caloric restriction without malnutrition in humans?

It is not yet known whether a regimen of caloric restriction with an adequate intake of all essential micronutrients is able to slow aging in humans. However, studies conducted on a group of individuals who, for about 8 years, voluntarily submitted to a regime of calorie restriction with optimal nutrition (consuming at least 100% of recommended levels for each nutrient), have shown significant reductions in major cardiovascular risk factors, as well as in inflammation, blood pressure, insulin, glucose, intimal thickness of the carotid arteries, and some hormones and growth factors.[50]

This data suggests that the risk of developing mellitus diabetes, myocardial infarction, stroke and heart failure, diseases that account for 40% of the causes of death in western countries, is extremely low. In addition, a recent echocardiographic study showed that caloric restriction with optimal nutrition can slow the physiological deterioration of diastolic function, a well-known marker of aging of the heart.[51]

Caloric restriction in humans reduces many of the metabolic and hormonal factors that are associated with an increased risk of developing cancer Moreover, caloric restriction in humans reduces many of the metabolic and hormonal factors that are associated with an increased risk of developing cancer,[52] as well as obesity, hyper-insulin, inflammation, oxidative stress and elevated levels of testosterone and estrogen.

Nevertheless, there are differences between humans and rodents. In rodents, caloric restriction causes a 20-40% reduction in circulating levels of IGF-1, regardless of the level of protein ingested in the diet. This reduction, however, has not been found in humans. Fontana et al. (2008)[53] did not find a decrease in circulating levels of IGF-1 in humans, neither as a result of a regime of calorie restriction lasting for one year (in a randomized clinical trial) nor in an observational study of chronic long-term calorie restriction. Instead, these studies suggest that the reduction of the protein in humans is more important than the reduction of the caloric intake for reducing the circulation levels of IGF-1. In fact, in a group of vegans with a protein intake in their diet that is close to that recommended in the food guidelines (equal to 0.8 g / kg / day), the IGF-1 levels were lower and in line with those considered to be optimal for the prevention of some of the most frequent forms of cancer, such as breast, colon and prostate cancer.[54] In this sense, a moderate protein restriction that lowers the levels of IGF-1 could be an important nutritional strategy to prevent the onset of tumors and to slow the aging process.

Figure 4.4. **Protein and calorie restriction: effect on IGF-1 in humans**
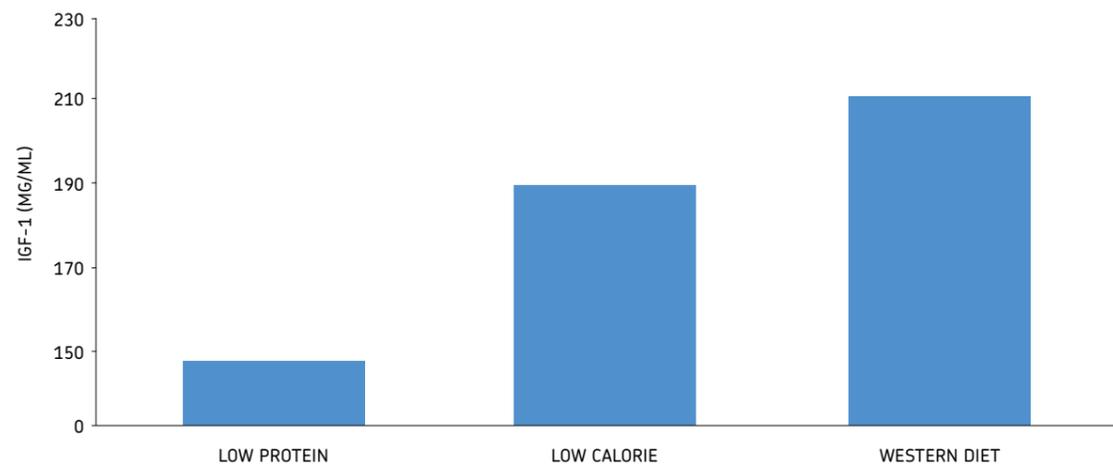
Source: Fontana *et al.*, 2008.

EXCESSIVE CALORIC RESTRICTION CAN LEAD TO SERIOUS DAMAGE TO HEALTH

Alongside the many positive effects found by studies conducted so far, it is necessary, however, to stress that excessive caloric restriction can, in turn, lead to serious damage to health, such as osteoporosis, sarcopenia, immune deficiency, anemia, decreased body temperature and sensitivity to cold, decreased libido, infertility and amenorrhea.
Fontana *et al.* (2007)[55] very effectively and clearly summed up the main health impacts – positive and negative – adjustable to the varying food intake.

Figure 4.5. **Relation between caloric intake, health and aging**
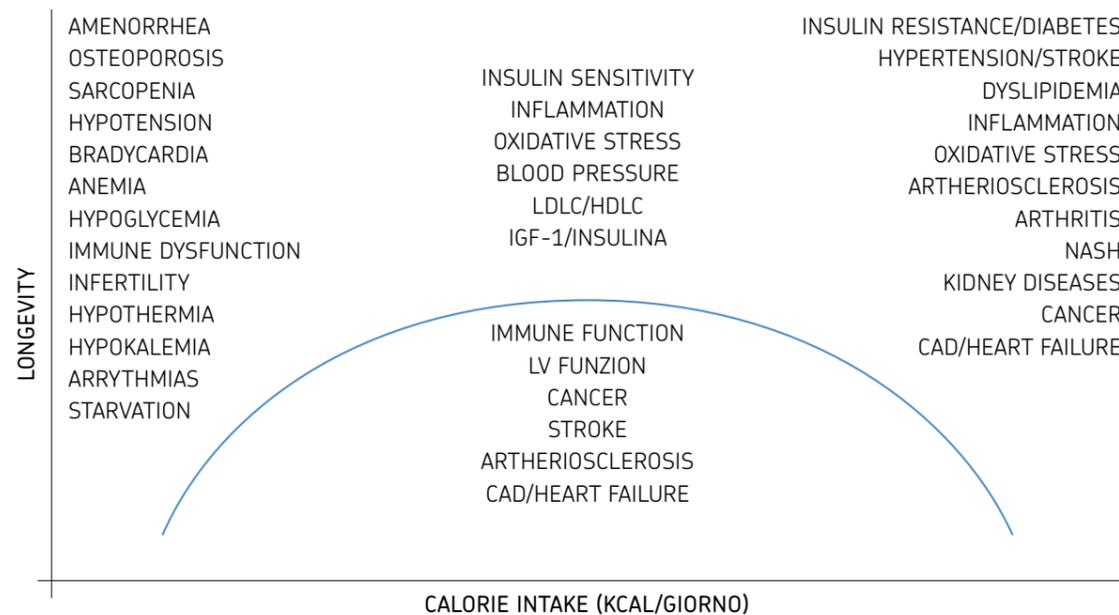
Source: Fontana *et al.*, *JAMA*, 2007.

4.3 CONCLUDING REMARKS

The demonstration that the average and maximum longevity of rodents is substantially extended by conditions of caloric restriction has been shown - as we have seen - in numerous studies, showing that the incidence of a wide range of diseases (virtually all types of cancer, cardiovascular diseases, diabetes, kidney disorders, autoimmune disorders, degeneration of the eyes, and others) is significantly reduced in animals subjected to caloric restriction. The maximum longevity of humans is about 120 years, while that of mice is about 39 months. The application of regimens of caloric restriction allows for extending the maximum longevity of the mice from 39 months to 56 months, a proportion that – in human terms – would correspond to 158 years. In addition, the longest-living mice are more youthful in appearance, in their mental and physical abilities and demonstrate superior resistance to stress and disease.

So will caloric restriction also be able to retard aging in non-human primates and humans? Studies are in progress, but for now the scientific evidence does not allow us to recommend caloric restriction in people who have a normal weight (BMI <25 kg/m^2). However, in overweight and obese people (BMI> 25 kg/m^2) a regimen of caloric restriction is highly recommended. In fact, the scientific evidence is sufficient to show that a weight reduction of 5-10% improves the metabolic/ hormonal picture and significantly reduces the risk of tumors and heart disease/metabolic risk in obese subjects. The loss of weight and abdominal fat will lead to a reduction of levels of blood pressure, blood glucose, triglycerides, total cholesterol and LDL, the markers of inflammation, and will increase insulin sensitivity and HDL cholesterol levels. Furthermore, weight loss will cause an improvement of the hormonal profile, with reduced levels of insulin, leptin, testosterone, estradiol, inflammatory cytokines, and the risk of cancer.

For people who have a normal weight, however, it is advisable to maintain a healthy weight and avoid the accumulation of fat in the abdomen (= increase in waist circumference) through a mildly low-calorie diet that is rich in all nutrients (vitamins and minerals), and a regular exercise regimen.

According to the latest definitions of the International Diabetes Federation for Europeans, the values of normality for the circumference of the waist should be <80 cm for women and <94 cm for men.[56] It is possible that a more drastic reduction in energy intake could have additional effects in slowing the aging process in humans. However, there is still no scientific data demonstrating an effect on monkeys and humans of caloric restriction increasing lifetime to the maximum limit. In addition, no data is available yet concerning the optimal level of calories to eat to slow the aging process; age, gender, genetic background and the level of physical activity all greatly affect the amount of calories that must be eaten to promote longevity.

FOR NOW, THE SCIENTIFIC EVIDENCE DOES NOT ALLOW US TO RECOMMEND CALORIC RESTRICTION IN PEOPLE WHO HAVE A NORMAL WEIGHT. HOWEVER, IN OVERWEIGHT AND OBESE PEOPLE (BMI> 25 KG/M2) A REGIMEN OF CALORIE RESTRICTION IS HIGHLY RECOMMENDED

5. CONCLUSIONS AND PROPOSALS

This paper ideally concludes a course of action that began with our position papers, Food and Health and Nutrition, in 2009, and Healthy Growth in Children, in 2010. The intention of the first paper was to highlight and substantiate the link, now accepted by the scientific community, between good nutrition and the prevention of the most common noncommunicable diseases (cancer, cardiovascular disease, diabetes). The "good news" with which the paper concluded was the existence of a rather small group of correct choices regarding nutrition and behavior (physical activity, renunciation of smoking, moderate alcohol intake), which, if followed, provide a cross-protection against major non-communicable diseases. In summary, according to what emerges from scientific literature, preventing disease through diet is feasible, inasmuch as it requires food choices that are easy to understand and adopt.

The second study conducted in the following year addressed the issue of proper nutrition for children, in light of concerns related to the metabolic processes of growth. This document originated from the desire to understand and represent the degree of scientific knowledge acquired regarding the link between proper nutrition and longevity, where by "longevity" we mean longer life expectancy in good health.

It is not so much a matter of living longer, but rather of living better, longer.

The first important fact to emerge from studies is that the aging process begins early in life. Inside the body, the process of cell regeneration is constantly active and the fact that cellular repair mechanisms need to be maintained in good working order throughout our entire life span affects the overall expectancy and quality of life. Once again, a significant relationship emerges: a healthy diet – according to some of today's most reliable scientific theories – has an influence on many processes that affect aging and the cellular process of inflammation, in addition to evident links to the prevention of the aforementioned diseases, which are crucial factors in accelerating the aging process.

Eat well today to live better today, one might say. Not only that, but we should add: eat well today to live better and longer tomorrow as well.

In our previous publications in the field of nutrition and health, we identified some guidelines that can be summarized in three key concepts: learn, inform, act. The work conducted on longevity now allows us to integrate and further enrich the picture of our findings and possible future courses of action. Below, we offer what we believe are the most important actions.

Promoting further in-depth studies on the available scientific knowledge of the relationship between diet and health

We understand the mechanisms that underlie the human metabolism better today. Over the past decade, parallel to the growing knowledge of genetics and molecular biology, the mechanisms that underlie and regulate the course of aging have started to be better understood and verified. But much more needs to be done and the evidence in this paper represents only the tip of the iceberg. This field of research is indeed still very recent and constantly changing.

The research areas we have proposed are the most promising "frontier" areas, which in the coming years will allow us to grow a deeper understanding of the interaction between food and the mechanisms of aging. Therefore, what we consider to be crucial are:

- further *studies on the mechanisms of aging and cell repair*. We know, in fact, that the incidence of non-communicable diseases is related to the health (degree of inflammation) of some cells in our body. In particular, the study of pro-inflammatory and inflammatory states may be one of the most promising areas of research, in light of their many connections with the diseases under consideration, diabetes in particular.

- *more in-depth study of the gene-nutrient-disease relationships in order to specifically and systematically understand the mechanisms of interaction between different nutrients and genes* that from time to time play important roles in preventing or causing various diseases;

- *promoting systematic research on the topic of calorie restriction*: this approach has undoubtedly produced a fair amount of interesting evidence in animal models and its "transfer" onto a human level, both of which require additional confirmation and/or new evidence as well as how applicable it can be in daily life;

- *encouraging further studies of these dietary models that, for various reasons, have already provided very important evidence in the prevention of chronic diseases and healthy aging*. The Mediterranean diet – due to its confirmed preventive action on various diseases - and the "Okinawa" model – for its relationship to longevity – should be further investigated in relation to their potential positive effects on our entire lifespan.[1]

Facilitating the dissemination of correct nutrition information to educate and promote the adoption of appropriate eating habits and lifestyles

Through the work carried out over the past three years, we have found that there was a high degree of convergence in terms of operational guidelines for an adequate diet, capable of being a form of prevention against all the major chronic diseases, regardless of the disease examined. In other words, there are styles of living and eating that, simultaneously and in parallel, are capable of minimizing the risk of cancer, cardiovascular disease, diabetes, osteoporosis and neurodegenerative diseases, as well as eating disorders such as overweight conditions and obesity.[2]

These same lifestyles are also the best insurance for an adulthood and advanced age that can be lived in good health.

It is, therefore, possible (and necessary) to help people choose and implement a proper way of eating, since the basic characteristics of a proper diet are known.

Governments, scientific societies, medical professionals and private companies need to make an intense effort in communicating, so that individuals can grow their awareness of the importance of eating habits and a greater knowledge of the topic overall.

This objective can be achieved through focused educational action concerning today's

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youth that promotes long-lasting and healthy development, capable of guaranteeing true progress in each country and, at the same time, a reduction in public spending.

To achieve this end, the role of information technology appears to be important, because the development of systems and authoritative institutional application tools that are easily accessible can help people to adopt behavior with regard to their eating habits and physical activity that can gradually correct them.[3]

Finally, we believe that the further development of food products and solutions consistent with the adoption of a diet which is "healthy," yet able to meet the needs and tastes of the people, could be a possible way to redefine the value of food and turn it into "a unique, enjoyable daily habit for feeling good for a long time."

Structuring policies and social and health interventions

We need to find new and more effective ways of transmitting scientific knowledge in the field of nutrition and health so that it can be translated into concrete actions, in the direction of broad and multifarious projects that can have a real impact on people's behavior.

It is a challenge that must be addressed in an integrated manner by all the parties involved, according to a logical system and which, in this sense, concerns not only public institutions – which are certainly at the forefront on this side –, but also other subjects, including private companies and doctors. Such rationale for joint action should also be applied to scientific research, both private and public.

In particular, the agri-food industry should seek to implement strategies and operational plans consistent with the guidelines identified for proper nutrition, to encourage the possibility of conducting scientific, nutritional and technological research, and to work constructively on several important issues of concern (for example, the progressive improvement of the nutritional profiles, the definition of foods with specific functionality, improved nutritional density of products, etc.).

We do not want to reiterate the directions for improving the entire complex of measures aimed at the dissemination of correct eating habits and lifestyles, which we have already proposed in several other instances.[4] We would simply like to remind readers that the dietary recommendations and lifestyles provided must be practical and feasible in the actual circumstances of people's lives, and that the intervention plans formulated in the field of nutrition and health must be defined according to a "structural" standpoint which aims to influence behavior in a sustainable manner over time.

FOCUSED EDUCATIONAL ACTION DIRECTED AT TODAY'S YOUTH

REDEFINE THE VALUE OF FOOD AND TURN IT INTO A UNIQUE, ENJOYABLE DAILY HABIT FOR FEELING GOOD FOR A LONG TIME

CONCRETE ACTIONS THAT CAN HAVE A REAL IMPACT ON PEOPLE'S BEHAVIOR

A CHALLENGE THAT CONCERNS NOT ONLY PUBLIC INSTITUTIONS BUT ALSO OTHER SUBJECTS SUCH AS PRIVATE COMPANIES AND DOCTORS

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CHAPTER 2

1. *Italy in 2030: The Future Demographic*, Euromonitor International, 2010.

2. Europe, United States, Australia, Japan.

3. The first stage is called "antique" and is characterized by high birth rates offset by high mortality rates. In fact, in traditional societies structured on the basis of family, the birth rate was encouraged by popular sentiment and religion. To survive, society and the family needed a high number of "work hands" and people. The natural balance (i.e., the difference between births and deaths) was close to zero and population growth was slow because of epidemics, wars and famines. The second stage is that of transition, in which, thanks to the improvement of living conditions (increase of agricultural production and food resources, introduction of vaccination and the affirmation of improved sanitation in general) mortality is reduced, while the birth rate is still high. In the third stage, the birth rate goes down again to match that of the mortality rate. It reaches the level of zero growth and some countries may record negative balances.

4. Benin, Burkina Faso, Burundi, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Rwanda, São Tomé and Príncipe, Senegal, Sierra Leone, Somalia, Sudan, Togo, Tanzania, Uganda, Zambia, Afghanistan, Bangladesh, Bhutan, Cambodia, East Timor, Laos, Myanmar, Nepal, Yemen, Kiribati, Samoa, Solomon Islands, Tuvalu, Vanuatu, Haiti.

5. The average number of years a human being can aspire to live.

6. Population Health Metrics, 2011.

7. *The future of Pensions and Healthcare in a Rapidity Aging World*, World Economic Forum, 2010.

8. *The future of Pensions and Healthcare in a Rapidity Aging World*, Conclusions, Facts and Projections," World Economic Forum, 2010.

9. *The future of Pensions and Healthcare in a Rapidly Aging World*, World Economic Forum, 2010.

10. An individual is considered to be obese if the body mass index (BMI) is greater than 30.

11. The rough rate is the ratio between the number of cases where the disease under study is found and the reference population, i.e., the rate without further corrections. The standardized rate is a system of adjustment of a rate that allows for comparison of the populations that have different distributions among them, such as age.

12. American Diabetes Association, *Economic Costs of Diabetes in the U.S. in 2007*, in "Diabetes Care," Vol. 31, 3, March 2008.

13. World Bank Organization, *Fact Sheet 297*, February 2009.

14. The cancers that cause the greatest number of deaths worldwide are lung cancer (1.3 million deaths per year), stomach cancer (803 thousand deaths per year), colorectal cancer (639 thousand deaths per year), liver cancer (610 thousand deaths per year) and breast cancer (519 thousand deaths per year).

15. *Health Watch Report 2008. Health status and quality of care in the Italian regions*, Sacred Heart Catholic University, Rome, 2008.

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17. ISDOC Study Group, *Actual and Preferred Place of Death of Cancer Patients. Results from the Italian Survey of the Dying of Cancer (ISDOC)*, in the "Journal of Epidemiology and Community Health," 2006.

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19. For example, stroke, hypertension, thrombosis, aneurysm, stroke, etc.

20. World Health Organization, *Causes of Specific Mortality, Global Burden Disease*.

21. The standardized rate permits a comparison between different periods regardless of the age distribution of the population in different periods. This is an "artificial" indicator that does not correspond exactly to the real value, but which is suitable for comparing the values of mortality between the different periods as to the age structure.

22. Foot, D., R. Lewis, T. Pearson, G. Beller, *Demographics and cardiology, 1950–2050*, in "Journal of the American College of Cardiology," Vol. 35, 5, 2000.

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24. British Heart Foundation, *European Cardiovascular Disease Statistics 2008*; *Health Promo-*

tion Research Group, University of Oxford; *Health Economics Research Centre, Department of Public Health*, University of Oxford, 2009.

25. These are mainly the hours of care received by patients with coronary or cerebrovascular diseases by people without salaries.

26. *World Alzheimer Report, 2010.*

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CHAPTER 3

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CHAPTER 4

1. For their significant contribution to the preparation of this chapter, we particularly wish to thank Professor Camillo Ricordi (*Professor of Surgery, Medicine, Biomedical Engineering, Microbiology and Immunology, University of Miami, USA*), Professor Gabriele Riccardi (*Professor of Endocrinology and Metabolic Pathologies, University of Naples "Federico II"; President-elect of the Italian Society of Diabetology – SID*) and Professor Luigi Fontana (*Director of the Department of Nutrition and Aging, National Institute of Health, Rome, Italy; Research Associate Professor, Division of Geriatrics and Nutritional Science, Center for Human Nutrition, Washington University Medical School, St. Louis, MO, USA*).

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CHAPTER 5

1. For a further discussion on this subject, please refer to section 3.6 of this document.

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tally friendly." The scientific evidence in the fields of *water management* and *climate change* (see the position paper *Water Management* and *Climate Change, Agriculture and Food*) demonstrates how the environmental implications of production decisions related to dietary styles are very important, both positively and negatively. In the second position paper mentioned, we made an environmental pyramid associated with the well-known food pyramid, demonstrating how a healthy and balanced diet is characterized by its low environmental impact, measured in terms of the overall footprint.

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