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POSITION PAPER

The Mediterranean diet from past to future: Key concepts from the second "Ancel Keys" International Seminar

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Abstract The year 2020 celebrated the tenth anniversary of the recognition of the Mediterranean Diet as Intangible Cultural Heritage of Humanity by the UNESCO Intergovernmental Committee. This event represented a milestone in the history of nutrition, as the Mediterranean diet was the first traditional food practice to receive such award. Since then, a lot has been discussed not only on the beneficial aspects of the Mediterranean diet, but also on its complex role as a lifestyle model that includes a set of skills, knowledge and intercultural dialogue. This process ended up with the recognition in 2019 of Mediterranean diet as a possibly universal model of healthy diet from the EAT-Lancet Commission. These concepts were widely debated at the 2019 "Ancel Keys" International Seminar, held in Ascea (Italy) (for more information see: www.mediterraneandietseminar.org) with the aim to stimulate interest and awareness of a young group of participants on the current problems inherent to the effective implementation of the Mediterranean diet. The present article collects the contributions of several lecturers at the Seminar on key issues such as methodological and experimental approach, sustainability, molecular aspects in disease prevention, future exploitation, without neglecting a historical view of the Seven Countries Study. From the Seminar conclusions emerged a still vibrant and modern role of Mediterranean diet. The years to come will see national and international

Abbreviations: ALA, α-linoleic acid; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular diseases; DHA, docosahexaenoic; EFSA, European Food Safety Authority; EPA, eicosapentaenoic; ER, endoplasmic reticulum; EVOO, extra-virgin olive oil; FAO, Food and Agriculture Organization of the United Nations; GDA, Guideline Daily Amount; GHGE, greenhouse gas emissions; ICAM-1, Intercellular Adhesion Molecule-1; IL-6, interleukin-6; MAI, Mediterranean Adequacy Index; MUFA, monounsaturated fatty acids; NLRP3, NOD- LRR- and pyrin domain-containing 3; PREDIMED, PREvención con DIeta MEDiterránea; PUFA, Polyunsaturated fatty acids; RCT, randomized controlled trials; RDA, Recommended Daily Allowance; ROS, reactive oxygen species; VCAM-1, Vascular Cell Adhesion Molecule-1.

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efforts to reduce the barriers that limit adherence to Mediterranean diet in order to plan for multi-factorial and targeted interventions that would guide our populations to a sustainable healthy living.

Introduction

From a strictly nutritional point of view, the Mediterranean diet refers to the dietary habits of populations dwelling in the lands surrounding the Mediterranean sea. Mediterranean diet, as defined during the half of the 20th century, consists in a dietary regime characterized by a high consumption of plant products and moderate to low amounts of fish, meat and dairy products, added sugars and wine taken with meals [1].

On the basis of ecological, prospective and more recently intervention trials, this dietary pattern is recognized to be associated with lower incidence and lower death rates from cardiovascular diseases and cancer [2]. Moreover, the Mediterranean diet has the potential to have a low environmental impact in terms of use of soil, energy requirement, water consumption and greenhouse gas emissions [3]. Due to its respect for biodiversity, the natural geophysical characteristics and the gastronomic traditions of the territory, the Mediterranean diet was awarded in 2009 by the UNESCO “intangible heritage of mankind” [4].

However, in spite of the recognized benefits for the human health and for the planet life, it is nowadays largely recognized by all the leading experts that the eating habits of the “Mediterranean” populations have been gradually shifting away in the last fifty years from the traditional model due to a growing consumption of animal products with reduction in the use of plant products, with the resulting higher intake of saturated fats and animal protein in place of plant protein and fat, wholegrain cereals and dietary fiber [5]. These negative changes are further associated with excess salt and added sugar intake (the latter largely in the form of sweetened beverages) as well as with increased consumption of alcoholic beverages, a progressively more sedentary lifestyle and the subsequent increase in the prevalence of obesity.

With this background in mind, the Italian Society of Human Nutrition, in collaboration with Federico II University of Naples, the University of Salerno, the Institute of Food Sciences of the Italian National Research Council, the Neuromed Mediterranean Neurological Institute (Pozzilli), the Alario Foundation and the Association for the Mediterranean Diet and Lifestyle Ancel Keys - Pioppi, organised in Ascea Marina (the ancient town of Velia) in 2017 and 2019 the “Ancel Keys” International Seminar (see www.mediterraneandietseminar.org/ for more information), with the objective to provide young scholars an opportunity to learn from some of the most prominent experts in the field of Mediterranean diet. In details, this one-week residential seminar aimed at: 1) providing young researchers and health professionals in the broad nutritional field the basic instruments to mature full knowledge and awareness of the problems inherent to the implementation of a modern effective Mediterranean-like dietary pattern; 2) helping generate an international young investigators and field workers network highly qualified to take action and develop synergic initiatives for the revitalization and diffusion of the Mediterranean diet worldwide.

This paper summarises the main outcomes of a selection of individual presentations held in the 2019 edition of the Seminar as well as an overall review of the event.

Historical introduction to the Seven Countries Study: an upgrade on diet, 50-year coronary heart disease and all-cause mortality

The Seven Countries Study was the first to examine systematically the relation among diet, lifestyle, risk factors and rates of coronary heart disease (CHD) and all-cause mortality in contrasting populations. Ancel Keys started and coordinated the program in seven countries: the United States, Finland, The Netherlands, Italy, former Yugoslavia, Greece, and Japan. At the baseline survey 16 cohorts consisting of 12,763 middle-aged men were examined in 1958−1964. The average population intake of saturated fat and sucrose was positively related to 50-year CHD mortality rates, while a negative correlation was observed for starch. . Traditional Mediterranean and Japanese diets were rich in plant foods, low in animal foods, hard fats and sweet products and were also inversely associated with long-term CHD mortality rates [6].

In 1960 Kastelli, a village in central Crete, had a traditional Mediterranean diet. The resident middle-aged farmers were physically active and their diet was rich in whole-grain bread, legumes, vegetables, fruit, olive oil, low in fish, meat and added sugars [7]. Forty years later the remaining elderly Cretan men had still a similar Mediterranean diet. However, a nutrition transition had occurred on the island of Crete between 1960 and 2005 [8]. The Cretan farmers in the valley of Messara in Southern Crete ate less bread, vegetables, fruit, and olive oil and conversely much more meat; an increase in sedentariness was also observed as compared with 1960. Mean body weight was 63 kg in 1960 and 83 kg in 2005. The

prevalence of obesity (BMI >30 kg/m2) was 2% in 1960 and 41% in 2005. This shows that the traditional Cretan Mediterranean diet was already exchanged for a Western diet within 45 years and the island has now one of the highest levels of obesity in the World and a high risk of CHD and all-cause mortality.

The Mediterranean sea borders on as many as 18 countries: the area differs markedly in geography, economic status, health, lifestyle and diet. This rules out the existence of "the" Mediterranean diet. In general terms, however, the Mediterranean diet is defined as the diet "which is usual for people from countries whose coasts are washed by this sea, and is moderate in cereal products, fish, legumes, olive oil, fruit and vegetables in combination with little meat and wine [9]". The main characteristics of this diet is plant-food based, with olive oil as the principal source of fat. In 1960 the diet of the middle-aged farmers in the village of Montegiorgio, close to Ancona, central Italy was high in white bread, moderate in olive oil and meat, but relatively low in fruit and vegetables [10]. Between 1965 and 1991 the ageing Montegiorgio farmers showed a three-fold increase in the consumption of fruit and vegetables and a lower intake of wine. This suggests that the adhesion to Mediterranean diet in Montegorgio improved [11].

In the 1960s, there were substantial variations in Mediterranean dietary patterns. An example of a food pattern score was the Mediterranean Adequacy Index (MAI) based on 15 food groups all expressed as gram per 1000 kcal [12]. The numerator of the score included foods typical of the traditional Mediterranean diet while the denominator included non-typical foods. The typical Mediterranean foods were: bread, cereals, legumes, potatoes, vegetables, fruit, fish, olive oil and wine, and the non-typical foods: high-fat milk, cheese, eggs, meat, hard fats and sweet products. High scores for the MAI indicated better adhesion to the "traditional Mediterranean diet". In the Seven Countries Study the MAI food pattern score at baseline was strongly inversely correlated to 50-year CHD mortality ($r = -0.91$) [6]. Improvements could be made in the Mediterranean dietary patterns in different countries, for instance replacing refined bread and cereals by wholegrain foods in Italy, unfiltered by filtered coffee in Italy and Greece and a lower amount of added sugar and wine intake in Italy [13]. On Crete, a nutritional transition took place from a traditional Mediterranean diet and a physically active pattern in 1960 to a Western diet with physical inactivity in 2005. Remedies for the transition could be attractive Mediterranean eating and physically activity patterns.

Mediterranean Diet: a practical approach

A practical approach to human nutrition

A large body of evidence shows that healthy eating patterns and regular physical activity can help people achieve and maintain good health and reduce the risk of chronic diseases. European and US Dietary Guidelines reflect this evidence through their recommendations that are aimed to help the general population to consume a healthy, nutritionally adequate diet [14,15]. This eating pattern is largely concordant with nutritional guidelines highlighting that it is necessary to combine healthy choices from across all food groups, to pay attention to calorie limits, to reduce the daily intake of saturated fats (<10% of calories), added sugars (<10% of calories) and sodium (<2300 mg), and to avoid trans fats as possible. In the traditional Mediterranean diet alcohol (mostly wine) is consumed in moderation and in general does not exceed the recommended limits of one drink per day for women and two drinks per day for men. However, appropriate food choices are not the only pillar of a healthy behavior; refraining from smoking and practicing regularly physical activity are also very important. In this respect Physical Activity Guidelines are particularly relevant in order to achieve and maintain a healthy body weight [16] since the relationship between diet and physical activity contributes to energy balance and has to be taken into consideration for body weight management.

However, despite what is recommended by evidence-based nutritional guidelines, more than 80% of the population even in Mediterranean countries eat less than the recommended amount of vegetables, about 70% eat more saturated fat, sodium, and added sugars than what is recommended and only 5% adhere to the recommended consumption of whole grain cereals [17]. This suggests that there is a gap between what we know to be the healthy eating pattern and its adoption by the population. Therefore, in order to promote a better implementation of appropriate eating choices it is important to translate general principles into practical lifestyle habits. This can be achieved by 1) evaluating the adherence to the current Dietary Guidelines to pinpoint the most critical pitfalls in order to implement tailored proposals for changes of food habits, and 2) teaching the best use of nutritional information reported on food packaging as a tool to promote healthy food choices.

The adherence to the current Dietary Guidelines can be evaluated by a semi-quantitative food frequency questionnaire recalling all foods and drinks consumed in the previous week at breakfast, snacks, lunch and dinner. Then, the consumption of each food can be categorized in food groups in order to evaluate the degree of agreement with current dietary guidelines. When the frequency of consumption is not in line with guideline recommendations, specific advice can be given in order to improve the adherence to the recommended intake. In addition, the nutritional profile of each food group can be utilized to calculate how the frequency of intake of any specific food can contribute to the adherence to guidelines. Regarding the food nutritional labels, they may help people to buy foods and drinks at the supermarket taking into account their nutritional value and deciding the frequency and the portion size of each food choice according to their macro and micro nutrient composition as well as their energy content. This could help people to implement nutritional recommendations in the real-life [18]. Labels provide

nutritional information about: energy, fat (saturated fat as optional), carbohydrate, added sugars, protein, and salt content per 100 g of product and sometimes per portion. Some labels provide further optional information, i.e. fiber content, other fats, vitamins and minerals. Other labels can provide information on how a particular food or drink product fits into people recommended diet and indicate the reference intakes for serving size of each product in relation to specific nutrients expressed as Recommended Daily Allowance (RDA) or as Guideline Daily Amount (GDA) for an adult consuming 2000 kcal/day.

Another important educational approach is the explanation of the exact meaning of some expressions reported on the food labels such as the "nutrition facts" showing what nutrients contained in the food need to be limited (i.e. saturated fat) or to be increased (i.e. fiber) or the "Nutritional Claims" providing information about beneficial nutritional properties of a given food due to its reduced or increased content/absence of specific nutrients (i.e., low sodium; gluten free; without sugar).

The low adherence to Dietary Guidelines observed in most populations of the world suggests the need to develop further implementation strategies that take into account people's cultural, social and economic level by an integrated, multidisciplinary, and comprehensive approach, involving a complementary range of actions, and working at an individual, community, environmental and policy level. The contribution of socio-psychological strategies to promote a Mediterranean style diet should be also considered [19]. A study by Vitale et al. [20] investigating the effectiveness and long-term impact on the composition of the habitual diet of a nutritional intervention program based on the promotion at a worksite canteen of healthy food-choices resembling the traditional Mediterranean diet showed that promotion of this type of diet facilitates the adherence of people to the nutritional intervention program and is effective to modify the dietary habits in a beneficial way and to keep these changes in the long-term [20]. A plausible explanation of this success is the fact that the traditional Mediterranean diet has a strong cultural and gastronomic background that facilitates its use as a tool for healthy food choices: these can be valued by people not only for their benefits on nutrition and health but also for their taste and palatability. This type of approach represents an example of how it is possible to implement dietary guidelines for a healthy eating that could be extended to other working sites as well as to school canteens and families.

Tips to design an observational study in nutritional epidemiology

Nutritional epidemiology is the study of the nutritional determinants of disease in human populations. To provide the best possible evidence on the role of nutrition in maintaining health or predisposing to illness, a good study needs the following: a) a clear research question; b) the most suitable study design; c) well-standardized and validated methods. Indeed, poorly designed studies are a waste of time and money and are also unethical. There are several limitations that need to be taken into account when dealing with nutrition studies. Among the main criticisms to observational studies, we acknowledge the following: a) lack of precision and specificity in dietary assessment; b) difficulty in determining whether the observed associations are causal; c) many kinds of bias; d) biological measures of nutrient may not accurately and reliably reflect dietary intake; e) non-nutrient characteristics to be considered.

Observational studies may have a retrospective (e.g. ecological studies) or prospective design (longitudinal cohort studies). However, ecological studies are not only retrospective. The Seven Countries Study is an example of a prospective ecological study based on 16 cohorts (population level) and 16 longitudinal prospective cohorts (individual level). Nutritional epidemiology also relies on experimental designs such as clinical trials. Each study type has its own strengths and limitations.

Notwithstanding its intrinsic limitations due to the extremely complex nature of diet, nutritional epidemiology has largely added to the understanding of the etiology of many diseases, contributing to improvement of public health. The Mediterranean diet is now facing a global challenge as the global industrial food system is emerging and contributing to a worldwide transition towards new eating models. Indeed, traditional nutritional epidemiology still relies on the use of tools, which were not designed to distinguish foods based on industrial processing, nor on the type of farming (e.g. organically/conventionally grown).

Current assessments of Mediterranean diet, as well as of other healthy dietary patterns, are based on principles of traditional nutritional epidemiology, which appear to be insufficient to keep up with a rapidly evolving food system.

A traditional Mediterranean diet is indeed not just a sum of foods, but a complex model characterized by biodiversity, seasonality, local food production and involves a set of skills, knowledge, processing and cooking that altogether represent the cultural basis of this dietary pattern recognized as UNESCO Intangible Cultural Heritage of Humanity [4]. Based on traditional dietary questionnaires, we are not able to distinguish where foods had been grown, transformed, nor which preservatives and pesticides had been used nor how this food has been cooked.

Although the current conventional assessment of Mediterranean diet has been, up to now, able to discriminate populations at different risk [21,22], there is reason to believe that quantity-based assessment, that leave out plenty of crucial features of the Mediterranean diet, is not able to fully account for all the benefits/risks associated with specific dietary patterns, since it neglects the importance of a number of non-nutrient characteristics that are of crucial importance at a time dominated by a monolithic global industrial food system.

Critical issues in nutritional epidemiology

According to the World Health Organisation, a healthy diet is sufficient and balanced in terms of quantity, quality and safety. Without going into the details of the definition, that can be easily found elsewhere [23], it is evident that a large proportion of the world population still consumes "unhealthy" diets, whose impact significantly contributes to the unacceptable burden of about 11 million preventable deaths globally per year [24]. Nutrition research has the potential to contribute to the reduction of this unacceptable burden and can play a fundamental role in informing public health programmes and policies. However, despite the impressive and continuous increase of published papers in nutrition and related disciplines, the translation of the research findings into health policy remains unsatisfactory.

The beneficial (or even detrimental) effects of foods, and of their respective content of biologically active compounds is generally subject to thorough evaluation by means of epidemiological analysis, intervention studies, and basic research on animal or cell-based models. The systematic investigation and rigorous evaluation of the different lines of evidence, using a consistent approach (see for instance Ref. [25]) finally provide the basis for the risk-benefit assessment of food and dietary patterns.

Given the ethical issues and practical hurdles associated with randomised controlled trials, nutritional epidemiology is frequently regarded as the key discipline underpinning food regulations and policymaking. However, it might be argued that the observed associations between nutritional factors and health outcomes might not necessarily reflect a causative link between the two. In that sense, nutritional epidemiology has been criticized on account of inherent difficulties in measuring diet and drawing on observational data to address etiological questions [26]. In particular, exposure assessment is a problematic point in nutritional epidemiology, as it requires extensive methodological know-how in order to obtain reliable results. Recently, Ioannidis suggested that investigations on complex scientific questions have been carried out using flawed methodologies [27]. Approximate/vague phrasing is often used in this type of studies to describe findings that, due to the nature of the experimental design, reflect correlation rather than causality; such correlations often underpin policies and burden-of-disease studies. Unfortunately, such hypothesis-generating evidence is often translated by some health writers and science journalists in dramatic pronouncements such as "Eating red meat causes cancer", "Healthy whole grains help lose weight". Although some authors do acknowledge methodological limitations in their reports, findings get often misinterpreted or misrepresented by popular media, leading to the diffusion of nutritional advice based on inadequate evidence. It is therefore essential that the burgeoning amount of published empirical evidence is systematically reviewed: however, recent meta-analysis based on flawed experimental approaches have led to the re-ignition of debates that were previously considered all but settled [28].

This issue has led to justifiable questions on how feasible and reliable it is to base new policies on nutritional epidemiology studies. Regardless, Giovannucci and colleagues recently argued that, despite the unavoidable methodological flaws, results obtained following this approach are still a valuable indicator on the effect of diet within a population [29]. For example, a solid body of evidence indicates that reduction in dietary sodium, and increase in dietary potassium should lower blood pressure and the risk of stroke [30,31]; thus, leading to a decrease in cardiovascular diseases (CVD) risk. Consistent effects may be also observed by studying complex dietary patterns rather than individual nutrients. As an example, the original report showing that greater adherence to the Mediterranean diet is associated with lower total mortality [32] has been recently confirmed by exhaustive analyses of the literature, suggesting the protective role of the Mediterranean diet on the risk of major chronic diseases (including CVD, diabetes and overall cancer incidence) and total mortality [2].

In order to provide solid and transparent bases for nutritional decision-making, scientific evidence and any methodological flaws underpinning it should be taken into account [33]. To this regard, the so-called "Hill criteria" are still a valuable tool to facilitate the inference of causative links on the base of observational data, therefore providing empirical evidence to inform policymaking [34]. In his seminal 1965 paper, Hill developed a checklist describing the essential conditions necessary to establish a causative link: strength, consistency, temporality, dose–response, plausibility, coherence, and experimental evidence. While this is still a heatedly debated matter, decisions critical to public health should be backed by the existing body of empirical evidence, recognizing its limitation and striving to acquire further and more reliable evidence [35]. Recent EFSA (European Food Safety Authority) guidelines have acknowledged the importance of an evidence-based assessment when the scientific results will be used to inform nutritional policymaking [25].

Likewise, the uncertainty surrounding available evidence should be carefully estimated [36], and any type of evidence that is insufficient, or based on flawed methodological approaches should be recognised as inadequate to base any critical decision-making upon, and the public should be transparently made aware of the pros and cons of all available options.

Assessment of adherence to Mediterranean diet

Mediterranean-style diet is not a specific diet, but rather a collection of eating habits traditionally followed by people in the different countries bordering the Mediterranean sea [37]. It is beyond doubt that there is not a single Mediterranean diet; dietary habits of countries bordering Mediterranean sea vary considerably, and even inside the same country, relevant differences in dietary pattern exist. Therefore, Mediterranean diet should be considered not just a dietary pattern, though an integrated way of living

where foods represent only one of the relevant components along with culture, beliefs, tradition, and pleasure [38]. This complexity explains why a general definition of such dietary pattern is difficult to obtain, as well as the methods of measurements are not easy to evaluate.

For decades, studies have been targeted to the evaluation of single dietary components of the Mediterranean diet in relation to different health outcomes. It seems clear, on the other hand, that such a reductionist approach presents several conceptual and methodological limitations because food components of diet present synergistic and antagonist interactions, and most importantly, because people eat a complex of nutrients and not just isolated foods. Thus, research efforts in this field switched progressively to the evaluation of a score for the adherence to the Mediterranean dietary pattern, rather than to the identification of single nutrients in association with the disease. As a result, an increasing number of studies have been carried out by summing foods considered to be important for health to provide an overall measure of dietary quality, i.e. a quality diet score [39]. A large number of indirect indices have been proposed, with the use of two different approaches. One approach has been based on the composition of predefined quality indices using current nutrition recommendations from the major scientific associations. This method is defined as “theoretically defined dietary adherence method”. The other approach is based on “empirical adherence to dietary patterns” and statistical analyses such as cluster analyses. The first index of adherence to the Mediterranean diet was created by Trichopoulou and colleagues and was based on the daily and/or weekly consumption of some foods defined a priori typical of the Mediterranean diet [32]. Subsequently, other adherence indices were created, specific for different geographical regions, based on guidelines or which consider not only food groups but also nutrients among the various components [39].

Although optimal in epidemiological contexts, the main limitation of the above-mentioned adherence scores is that they are difficult to apply individually. They also do not provide the exact quantification of the food components. For this reason, in 2014, in the framework of the meta-analysis on the Mediterranean diet and health status, a new score of adherence to the Mediterranean diet, applicable on an individual level also in an outpatient setting and based on data in the scientific literature was proposed: the MEDI-LITE questionnaire [40]. The strength of this questionnaire lies in the fact that both the choice of food groups and the reference portions come from the most up-to-date and comprehensive systematic review of the literature in this field. The questionnaire consists of simple and quick questions and allows the user to determine the consumption, in terms of daily and/or weekly quantities, of 9 food groups: fruit, vegetables, cereals, legumes, fish, meat and products based on meat, dairy products, alcohol and olive oil [41]. In the context of the Mediterranean countries that are increasingly moving away from the principles of the Mediterranean diet it seems essential to implement simple tools, possibly integrated with the new technologies, for attracting attention of the general population to preventing diet-related diseases through modifications of lifestyle and dietary habits.

Healthy, sustainable eating patterns: what about the Mediterranean diet?

Poor diet is a leading risk factor for disease worldwide, accounting for a growing burden of cardiovascular disease, type 2 diabetes and various cancers [42]. Food-based dietary guidelines have been defined for the prevention of major lifestyle-related diseases. Current dietary guidelines for westernized societies emphasize a shift from animal source foods to plant-based foods, which includes a reduction in the intake of red and processed meat and higher intakes of vegetables, fruit, whole-grains, legumes, seeds and nuts. Other recommendations include replacement of animal fats with plant oils, and limiting the intake of salt, sugar-sweetened beverages and alcohol. Dietary guidelines aim at improving population health. However, it should be noted that consumers are part of a complex food system, and dietary choices will not only affect health but also our planet's ecosystems.

Modern diets that emphasize animal source foods put a major burden on the environment. Global food production and consumption account for 60% of biodiversity loss and 25% of total greenhouse gas emissions (GHGE), 55% of which is due to animal source foods [43]. Livestock consume one-third of global cereal production and use about 40% of arable land. The Food and Agriculture Organization of the United Nations (FAO) projected that food production will have to increase by 60% in 2050 to satisfy the needs of a growing and richer world population [44]. The consumption of meat is on the rise in many parts of the world, including the Mediterranean countries. There is an urgent need for more sustainable diets, defined by FAO as “those diets with low environmental impacts which contribute to food and nutrition security and to healthy life for present and future generations.” Such diets are “protective and respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable; nutritionally adequate, safe and healthy; while optimizing natural and human resources” [45]. The EAT-Lancet Commission, a multidisciplinary team of scientists from 16 countries, calls for sustainable food systems that produce diets with an optimal amount of calories, a diversity of plant-based foods, low amounts of animal source foods, unsaturated rather than saturated fats, low amounts of refined grains and highly processed foods, doubled amounts of fruit and vegetables, legumes and nuts, and halved amounts of added sugars and red meat [46].

The traditional Mediterranean diet is characterized by high intakes of olive oil, legumes, nuts, cereals, vegetables and fruits, and a moderate to high intake of fish (depending on the region). It includes moderate amounts of dairy, mainly as cheese and yogurt, and small amounts of meat. Wine (if culturally accepted) is consumed with

meals. The Mediterranean diet has major health benefits, including protection against cardiometabolic diseases, various cancers and possibly also mental disorders [47]. It fulfils most nutrient requirements and helps maintain a healthy body weight. Part of the benefit may be attributed to traditional Mediterranean living, including its culinary activities, slow eating, dining with family and friends and regular physical exercise. The Mediterranean diet encourages local and seasonal food production and consumption, thereby minimizing environmental impact and preserving biodiversity. Recent studies proposed the Mediterranean diet among the healthiest and most environmentally friendly diets in the world [48]. This applies, however, to the local context. Exporting the Mediterranean diet to other parts of the world increases its environmental impact, because of transport and storage. A wide variety of healthy, sustainable diets may be identified across the globe, respecting also local food production and sociocultural values.

Even though the healthfulness of the Mediterranean diet is widely acknowledged, further improvements may still be possible. With regard to beverages, tea and filtered coffee could be included and wine consumption may be reduced and the intake of wholegrain foods may be increased. The Mediterranean diet tends to be salty. To illustrate, daily salt intake may exceed 10 g (corresponding to 4000 mg of sodium) in southern Italy [49]. Furthermore, over 55% of Italian adults have high blood pressure, which is often uncontrolled [50]. This is a major public health challenge, given the fact that salt and high blood pressure are leading risk factors for premature mortality [42]. Diets in the Mediterranean area have changed dramatically over the past decades, now including more industrially processed foods and meat. Both for health and sustainability, Mediterranean populations should not abandon their traditional diets. Estimations based on a Spanish cohort showed that GHGE and the use of land, water and fossil energy would decline by 33–72% if the population readopted their traditional diet [51].

As a basis for future food and health policy in Europe, the multidisciplinary SUSFANS project was set up (www.susfans.eu). Within the SUSFANS conceptual framework, the SHARP-model was developed for defining diets in Europe that are environmentally Sustainable, Healthy, Affordable, Reliable and Preferred (by consumers). The SHARP-model uses commonly observed (i.e. preferred) diets as a starting point. Diet scenarios are based on individual-level data from national food consumption surveys in EU countries, including Denmark, Czech Republic, France and Italy [52]. Food intake data are first harmonized according to the FoodEx2 system by the EFSA. Food intakes are then linked to GHGE and land use, using life cycle assessment databases. In the selected EU countries, animal source foods accounted for around two-thirds of diet-related GHGE. Excess calories, a major driver for obesity, also put a substantial burden on the environment. Preliminary data from the SHARP-model show that the Italian diet outperforms other EU diets for health and sustainability. Furthermore, it shows that replacement of beef with other animal source foods (e.g. poultry, dairy, eggs) is an important first step towards more healthy, sustainable diets in Europe. Once achieved, EU consumers could move beyond their current dietary practices, towards more plant-based diets. To this end, the traditional Mediterranean diet can serve as a good example.

The effects of the Mediterranean Diet in disease prevention

Essential fatty acids from the Mediterranean diet: effects on cellular metabolism

The Mediterranean dietary pattern has been shown to have several beneficial effects on diseases associated with chronic inflammation, including insulin resistance/diabetes, cardiovascular diseases, arthritis, cancer and neurodegenerative diseases [2,53–58]. Both fat (oleic acid, omega-3 and omega-6 polyunsaturated fatty acids, PUFAs) and non-fat components (phenolic compounds) of the Mediterranean diet have been shown to exert important anti-inflammatory activities [59,60], Omega-3 PUFAs, in particular have been shown to affect the expression of some pro-inflammatory gene and the activity of immune cells [55,59,60]. Omega-3 PUFAs include the essential long chain polyunsaturated fatty acid α-linolenic acid (ALA), which is the major component of photosynthetic apparatus of plants, and it is an essential fatty acid for humans. ALA represents the starting point for the creation of longer and more desaturated fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA). However, EPA and DHA can be also considered essential fatty acids due to the very slow conversion of ALA in EPA and DHA in human tissues. Therefore, they have to be ingested through diet, predominantly from marine organisms [61,62]. Omega-3 PUFAs may play their beneficial role in the prevention of metabolic disorders through their impact on cell membrane structure [63,64], which in turn may improve inflammatory onset/progression by ameliorating the function of cellular organelles, including mitochondria and endoplasmic reticulum (ER). Mitochondria are considered the powerhouse of the cells, but their dysfunction is linked to oxidative stress with reactive oxygen species (ROS) overproduction. They are highly dynamic organelles undergoing a coordinated cycle of fusion and fission, referred to as “mitochondrial dynamics” [65]. Fusion processes are associated with the optimization of mitochondrial function, whereas fission processes are associated with oxidative stress and removal of damaged mitochondria [66]. Alteration of mitochondrial dynamics and bioenergetics has been shown to be linked to ER stress and inflammatory pathway onset [60]. Saturated fatty acids (typical compounds of Western diet) elicited mitochondrial fragmentation and dysfunction, ROS production, ER stress and inflammatory pathway activation associated with insulin resistance/diabetes and ectopic fat accumulation in liver and skeletal muscle [67,68]. On the other hand, omega-3 PUFAs promoted mitochondrial fusion improving

mitochondrial function and reducing ROS production in liver and skeletal muscle both *in vitro* [69,70], and *in vivo* experiments [71–75]. Omega-3 PUFAs increased mitochondrial content in skeletal muscle by inducing the expression of transcriptional factors involved in mitochondrial biogenesis, and are able to induce an increase in mitochondrial fatty acids oxidation and therefore to prevent or reverse lipid ectopic accumulation and insulin resistance in liver and skeletal muscle [68,71,76]. In addition, omega-3 PUFAs have been also proposed to attenuate ER stress, and to prevent inflammation and metabolic disorders through inhibition of NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome [60,77,78]. A recent review also hypothesized that an adequate omega-3 PUFAs intake may be a valid strategy against coronavirus infection, by protecting against an excessive lung inflammatory response and cytokine overproduction [79].

Further research studies are needed to clarify the effect of omega-3 PUFA on the complex interaction between cell organelles stress and onset of the inflammatory process in the conceptual frame of "metaflammation" and its link to metabolic as well as viral diseases. These studies may be useful to shed light on the positive effect of the Mediterranean dietary pattern and to strengthen the rationale of health promotion campaigns to raise awareness of healthy food choices.

Experimental scientific evidence of the Mediterranean Diet

If the Seven Countries Study represented the first large scale, observational study demonstrating the beneficial effects of Mediterranean diet on health, we had to wait the 21st century for the first large scale, multicentre randomised controlled trial: the PREDIMED (PREvención con DIeta MEDiterránea). The Seven Countries Study established a strong inverse association between MUFA intake (present in olive oil) and overall mortality, especially from CHD [80]. The PREDIMED was designed to compare the effectiveness of the Mediterranean diet compared to a low-fat diet in the primary prevention of CVD in asymptomatic patients at high cardiovascular risk [81]. Before PREDIMED, the Lyon Heart Study in France revealed, in a randomized clinical trial on 605 patients who had had a myocardial infarction, that a Mediterranean-style diet supplemented with margarine enriched with α-linolenic acid was associated with remarkable reductions in CHD event rates and cardiovascular mortality [82]. The primary endpoint of the PREDIMED study was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) in three intervention groups: Mediterranean diet supplemented with EVOO (extra-virgin olive oil), Mediterranean diet supplemented with mixed nuts and a low-fat diet. The study enrolled 8713 men and women (7447 eligible) without predetermined diagnosis of CVD, but with either type 2 diabetes mellitus, or at least three 3 major CVD risk factors (hypertension, high plasma LDL cholesterol, low HDL cholesterol, overweight or obesity, current history of smoking and family history of premature CHD). The trial was stopped after a median follow-up of 4.8 years since an interim analysis showed hazard ratios of 0.70 (95% CI, 0.54–0.92) for the Mediterranean diet supplemented with EVOO and 0.72 (CI, 0.54–0.96) for the Mediterranean diet supplemented with mixed nuts compared to the control group [81]. The study led the authors to assert that "if the entire Spanish population between 55 and 80 years old, about 7,500,000 people, received the PREDIMED Mediterranean diet intervention, we could prevent up to 100,000 heart attacks or strokes, 212,000 cases of diabetes, 75,000 cases of arterial diseases and 87,000 arrhythmias in less than 5 years" (L. Serra-Majem, personal communication; [83]). The PREDIMED study was republished in 2018, after evidencing significant irregularities in the randomization procedures [84,85]. The new publication, that treated PREDIMED as a non-randomised study and excluded not randomized participants, confirmed that Mediterranean diet supplemented with EVOO or nuts was associated with about 30% lower risk of major cardiovascular events over a period of 5 years [86]. The impact of the PREDIMED study was magnified by a large abundant number of qualified scientific articles showing that other pathological conditions can benefit from the supplementation of the Mediterranean diet enriched with EVOO or nuts, such as diabetes [87], atrial fibrillation [88,89], dietary glycemic index [90]; body weight and obesity [91–94], breast cancer [95], age-related cognitive decline [96] (for additional reviews on the positive outcomes of the PREDIMED study, see also [97,98]).

The questions that spontaneously raise are: why and how is Mediterranean diet beneficial from a molecular point of view? How can the different macro- and micronutrients present in the Mediterranean diet contribute to prevent or ameliorate pathological conditions that largely differ from molecular and pathophysiological perspectives? These questions remain open since it is not easy to reproduce in experimental models, that allow molecular dissection, the complex *in vivo* conditions implied by a large intervention study. On the other side, for ethical and practical reasons, human trials cannot always provide the required types of biological samples and in sufficient amount for the molecular analysis. We can often see the description of "the head" and "the tail" of a specific beneficial effect associated with a dietary pattern, but we ignore the molecular aspects. As an example, Mediterranean diet reduces cellular lipid levels and LDL oxidation [99] or lowers the concentrations of VCAM-1, ICAM-1, IL-6 and CRP [100,101], but how? Who does the job? In the case of Mediterranean diet, EVOO has been long indicated as a key food to explain its beneficial effects. In fact, EVOO has particular fatty acid composition elevated in MUFA (oleic acid), and with an ideal quantity of PUFA with a relatively low n-6 PUFA/n-3 PUFA ratio (see paragraph above). However, EVOO also contains minor bioactive compounds, such as phenolic antioxidants. A recent review underlines that the dietary consumption of oleic acid is not only associated with a low risk of atherosclerosis and beneficial

effects on lipoprotein metabolism, but can modulate key mitochondrial and endothelial molecular pathways involved in the prevention and treatment of insulin resistance and diabetes [102]. It remains to be demonstrated in a large RCT if a source of fatty acids similar in composition to EVOO in terms of MUFA and/or n-6 PUFA/n-3 PUFA ratio, such as canola oil, is able to exert beneficial effects comparable to those described by the PREDIMED study. Lights and shadows also characterize the role of bioactive phenolic compounds that in Mediterranean diet primarily derive from coffee, fruits and EVOO (about 11%)). The PREDIMED Study Investigators published several articles demonstrating the beneficial effects of polyphenols in the Mediterranean diet. As an example, greater intake of polyphenols was associated with decreased CVD risk [103] and lower body weight [104]; cognitive performance was improved in elderly subjects at high cardiovascular risk by higher polyphenols intake [105]. In the PREDIMED population, high-risk subjects who reported a high polyphenol intake showed a reduced risk of overall mortality compared to those with lower intakes [106]; an increase in polyphenol intake was associated with decreased inflammatory biomarkers (VCAM-1, IL-6, TNF-α, MCP-1), in agreement with the anti-inflammatory effects of polyphenols [107]. However, considering the very low bioavailability and the high biotransformation at intestinal and tissue level of polyphenols, how can it be, at a molecular level, that the tiny amount of circulating polyphenols exert such a variegate spectrum of biological actions? In addition, the studies cited above are based on the high-vs-low quartile of "total" polyphenols intake, while it is clear that different foods present in the Mediterranean dietary pattern possess a high variability in their phenolic profiles in terms of quantity and quality and, consequently, bioactivity in relation to the different cultivars, time of harvesting and climates. It is oversimplistic to assert that the protective effects of polyphenols in Mediterranean diet can be justified by evoking the tons of cellular and animal studies where they are administered at pharmacological doses.

New approaches are clearly required to investigate in depth the molecular aspect of Mediterranean diet. Lluis Serra-Majem et al. [98] foresight in the metabolomics profile of Mediterranean diet the strategy to discover new biomarkers of nutritional exposure and to dissectout the molecular mechanisms whereby diet positively or negatively affects health and disease. This approach, coupled with the study of gene–diet interaction, could bring to the identification of individuals with greater genetic susceptibility to certain diseases that can specifically benefit (or not) from the administration of the Mediterranean diet [98]. This concept can be further expanded aiming to design new nutritional interventional studies where modification of canonical dietary patterns (e.g., regional habits of traditional Mediterranean diet) are introduced. These studies should target groups of individuals with specific needs (e.g., obese/overweight, aged people prone to cognitive dysfunctions, etc.) and the beneficial outcomes of the experimental diet will be evaluated combining the individual genetic background and health history with their specific "foodome", defined as the precise subset of chemicals to which each individual is exposed with the diet [108]. This approach will help to identify key components present in the daily eating patterns able to ameliorate the health status of the subjects enrolled in the study. Their identification will stimulate the investigation of the molecular mechanisms of action using specific experimental models (e.g., cellular and animal models). As commented below (paragraph 5.1) the described approach can open up a wealth of possibilities towards our own personal nutrition and health needs taking advantage of the dramatic drop in the cost of genome sequencing and the new advanced technologies in food engineering, which are significantly contributing to simplify the availability of personalized meals.

Mediterranean Diet: from past to future

Mediterranean food design and opportunities for health claims

Prepacked and processed foods have a central role in the diet of the population in developed societies. Although their consumption has been criticized and related to increased risk of non-communicable diseases [109], these foods could potentially contribute to the adherence of Mediterranean diet. In fact, they can combine the need for convenience, long shelf life and palatability required by consumers with the raw materials and nutritional principles typical of Mediterranean diet. To meet this aim, such foods should be developed taking into account first the general rules for designing healthy foods and, secondly, the framework of the Health Claim EU regulation.

To date, there is not a generally accepted definition of healthy foods. The notation « healthy foods» is preferred over the one « functional food » for which there is not a legal definition yet. Moreover, South America, Asia and even African countries are interested in functional foods with an intriguing overlap with local traditional healthy foods and this could be the case of typical Mediterranean foods such as EVOO. Healthy traditional foods could be linked to both elements present in healthy food labelling such as "improvement of physiological functions" and "disease prevention".

The healthy food market is characterized by a high rate of failure. Therefore, to realize a successful healthy food, experts having a different background, such as food technologists, nutritionists and medical doctors, should work together following a detailed work plan [110].

The process of healthy foods design is often spoiled by the absence of a clear strategy. The first step of this process is to find a "good idea" and this can be usually screened by focusing on the need of the target. This is usually a specific group within the population having some specific demand and health preference. The idea generation for healthy foods design follows three specific rules: 1) They belong to the respective food category: consumers do not perceive

healthy food as a separate category; 2) They should be as good as the conventional standard; 3) They must fulfil one specific need: one health function or one disease prevention (a little bit of everything usually does not work).

Taking this in mind, it is plenty of technological strategies to design the products with the required characteristics. The simplest one is adding a functional ingredient to a well-known food, checking that there is no degradation of bioactive principle during the processing. Furthermore, the amount of bioactive principle present in a standard portion should be considered: this amount should be sufficient to exert the desired effect without requiring overconsumption of the specific food. Fermentation, non-thermal technologies and controlled release during digestion are commonly used strategies in the design of healthy foods, which go beyond the addition of a functional ingredient and that could be particularly suitable for the combination with Mediterranean diet. For instance, to obtain a polyphenol-rich olive oil, innovative extraction procedures can be adopted [111].

The development of healthy foods should closely follow the Health Claim Regulation [112]. Based on this EU regulation, health claims regulated by the article 13 describe or refer to: (a) the role of a nutrient or other substance in growth, development and body functions, or; (b) psychological and behavioural functions, or (c) slimming or weight control or a reduction in the sense of hunger or an increase in the sense of satiety or (d) reduction of the available energy from the diet. Health claims under the article 14 may refer to the reduction of disease risk (14 (1) (a), implying that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor for the development of a human disease, or to children's development or health (14 (1) (b). Over the years, the messages reported on the pack label drastically increased with the aim to inform consumers about the product characteristics and nutritional qualities. These declarations on the pack affect the consumers' quality product perception and, in turn, their intention to buy. However, the claims cannot be false, ambiguous or misleading for consumers. Only information in conformity with the conditions set out in the Regulation 1924/2006 can be used and, the most important thing, only information scientifically sustained is permitted. Therefore, to be used information needs to be approved and authorized. The EFSA is the authority that reviews the science behind any claim and when approved it is the European Commission that authorizes a claim. Three criteria are mainly considered in an application for authorization of a claim by EFSA [113]. Firstly, the food that will bear the requested claim needs to be well characterized. Accordingly, a claim can be asked for yoghurt, not for dairy foods. Vague claims that are not well defined are not authorized and the claimed effect must be measured using a reliable and suitable outcome variable(s). The outcome variable(s) must be measured *in vivo* in humans by generally accepted methods, and its changes should be associated with evidence of a beneficial physiological effect and could be proposed as part of the mechanisms by which food may exert the claimed effect. The last criterion is the trickiest and it is related to the scientific evidence behind the claim. The application dossier must include the totality of the available scientific data on the claimed effect, including data in favour and data not in favour if any of such a relationship. The most valuable studies are those of intervention carried out on humans with a representative group of subjects and an appropriate control group. In addition, the intake of study food must be realistic, the treatment long enough, the outcomes of the study must reflect directly the claimed effect, the claimed effect must be plausible, the effect needs to be statistically significant and its size biologically relevant.

As reported above, Mediterranean diet is a protective regimen against almost all the non-communicable diseases [114] and prevents several other conditions such as cognitive decline [115], depression, anxiety and psychological distress [116]. However, Mediterranean traditional recipes are time-consuming and are not suitable for people asking for convenient foods, ready-to-eat and ready-to-go. A pragmatic approach to the development of healthy food inspired by the principles of Mediterranean diet should not underestimate that the reasons to buy a food product are based on price and convenience not only on taste and (perceived) healthiness. At the supermarket, consumers perform a quick trade-off among all their needs and, for many of them, the most influencing factors are not the ones we attribute to a certain product.

In this vein, mild technologies such as high pressure combined or not with heating, pulsed electric field and ohmic heating and precise heating (infrared or radiofrequency) could be new strategies for implementing traditional recipes in a modern framework taking also into account the sustainability issue, that is increasingly influencing the consumer behaviour and especially the new generations. Many of the elaborated recipes of the Mediterranean diet but also some of the pillar ingredients are considered suitable for ceremonies but not for the daily consumption by an increasing share of the young generation. Such traditional rethought foods can be made appealing and affordable for these consumers so that they can compete with the fast foods poor in nutrients. In this way, it would be possible to improve the nutritional status of modern consumers. Typical Mediterranean foods and their formulated products could meet the request for bearing a healthy claim since are nutritious and rich in bioactive compounds. Embracing new technologies and the new ideas of personalized food design could be an effective strategy to allow Mediterranean foods to survive the next two thousand years.

On the evolution of the Mediterranean diet

Early descriptions of the Mediterranean diet dating back to 1948 [117] together with the systematic recording of food and nutrient intakes in the region through the Seven Countries Study [118] provide evidence of a plant-based dietary pattern characterised by the liberal use of olive

oil, the consumption of generous amounts of plant foods and a moderate or even low intake of foods of animal origin. The indications on the health-promoting effect of these intakes have primarily derived from observational epidemiological studies [119,120], have subsequently been supported by findings on possible mediators and underlying mechanisms [98] and have recently been confirmed through randomised controlled interventions [86]. Nonetheless, contrary to other, also highly cited, dietary patterns, the Mediterranean diet has not been specified on the basis of analytical evidence for healthy dietary choices. It is rather a natural experiment, a holistic lifestyle that existed in the region for years and was discovered in the second half of the 20th century as an example of a food pattern which not only enhances health and general well-being, but is also adapted to the natural resources and needs of the Mediterranean populations [121].

In the years that followed the discovery of the attributes of the Mediterranean diet, market globalization and worldwide acculturation allowed for larger varieties and higher quantities of food available, which combined with a steadily increasing prosperity lead Mediterraneans away from their traditional eating habits. Publications presenting changes over time in the diet of populations participating in the Seven Countries Study point towards an increase in the intake of processed foods and saturated fat and a decrease in the intake of plant foods and MUFAs [122,123]. Findings are alarming, particularly in relation to the trend-setting younger generations since studies among children, adolescents and young adults in the Mediterranean clearly indicate that large proportions of these populations poorly adhere to their traditional diet [124,125]. Ironically, non-Mediterranean populations have been the major benefactors, since during the same period they have been experiencing a nutrition transition that favours the Mediterranean dietary pattern [126].

Over the years, numerous actions and strategies to promote the Mediterranean diet (or its specific components) have been widely implemented [127]. Populations within and far beyond the Mediterranean region have a generally reasonable understanding of what this diet constitutes of and it is now broadly perceived that the Mediterranean diet promotes health and longevity. Yet a substantial proportion of the population, particularly in the Mediterranean region, encounter difficulties in complying and this is also reflected in the countries' health indices (including obesity rates) [128,129]. Notwithstanding the fact that prevention is not always attractive, other issues such as large portion sizes, limited physical activity and food pricing policies may also be responsible and are therefore worth considering [130,131]. Current efforts at national and international level should shift from a sheer promotion of the Mediterranean diet towards apprehending the barriers that limit adherence in order to plan for multi-factorial and targeted interventions that would guide our populations to a sustainable healthy living.

Toward a modern Mediterranean Diet for the 21st century

In 1975 Ancel and Margaret Keys described the Mediterranean diet in their book *How to eat well and stay well*. The Mediterranean way, as the ordinary food of the common Neapolitans: "*… homemade minestrone, pasta …. always freshly cooked,…bread never served with any kind of spread, …great quantities of vegetables; a modest portion of meat or fish twice a week; always fresh fruit for dessert …. It would be hard to do better than imitate the diet of the common folk of Naples in the early 1950s*" [132]. Today these statements are still valid.

However, numerous changes have been introduced in the last 50 years in modern society: industrialization associated with migration from rural to urban areas; shift toward sedentary work with less daily physical activity; availability of food with consequent modification in proportions of nutrients and total caloric intake; decreased proportion of proteins and fat of vegetable origin compared to those of animal origin, more added sugars especially soft drinks, cookies and less fibres, vitamins and minerals. Caloric imbalance from excess of food and reduction of caloric expenditure are responsible for epidemic of obesity, major CVD and cancers.

There is a need to highlight the weak points of the Mediterranean diet in order to avoid or reduce disadvantages; in particular, to know how many calories are needed per day, what proportion of energy for fats, and of "favourable" fat, such as olive oil, which is high in calories; wine has no nutrients and is high in calories; and finally salt intake [133], of which in adult population no more than 5 g/day of salt are recommended by health authorities. The DASH diet, which is associated with limited sodium consumption (1.5 g or 67 mmol/day) along with low consumption of fat foods, limited red meat, sweets and soft drinks, high intake of fruits and vegetables, whole grains, legumes, low fat dairy products, fish and poultry reduces blood pressure in hypertensive patients and in the general population [134]. This food pattern is close to the Mediterranean diet described by Ancel and Margaret Keys, and we have to come back to it with low salt and moderation in olive oil, alcohol and calories, if we want to claim that the Mediterranean diet we are favouring is good and healthy.

Guidelines suggest the healthy diet is based on no more than 30% of total calories from fat, 50% from carbohydrates and 20% from proteins. Saturated fats should not be more than 7–8% of total energy (quantity characterizing the "reference Italian Mediterranean diet" at the 1960s and populations with longer life expectancy); SFAs less than 10%; cholesterol less than 300 mg/day. This eating pattern, with regular and daily physical activity and avoidance of smoking, enables lifelong maintenance, optimal level of total serum cholesterol, blood pressure, normal weight, and increases the proportion of the population at favourable cardiovascular risk profile [135].

Concluding remarks

The recognition by the UNESCO Intergovernmental Committee, ten years ago, of the Mediterranean Diet as Intangible Cultural Heritage of Humanity [4] marked a milestone in the history of nutrition as the Mediterranean Diet was the first traditional food practice to receive such award. Pollica and the Cilento were indicated as one of the four "emblematic communities" selected by the Committee as the physical places most representative of the Mediterranean style, a choice fully justified by the fact that this place had been for several decades home to Prof. Ancel Keys, the man who in the 1960's gave the 'Mediterranean Diet' its name and who spent his life studying the Mediterranean lifestyle and promoting it worldwide with its seminal books. The other emblematic communities were Soria, in Castilla y Léon in Northern Spain, Koroni, in Greece, and Chefchaouen in Morocco. Later on, Cyprus, Croatia and Portugal were added to this restricted list.

As correctly pointed out in other parts of this report, the Mediterranean diet was recognized not just as a collection of traditional recipes but rather as a complex lifestyle model characterized by biodiversity, seasonality and local food production, involving a set of skills, knowledge, processing and cooking, the sense of hospitality, constructive relationships, intercultural dialogue and respect for diversity. Similar concepts we find in the Document on Sustainable Healthy Diets produced by a Food and Agricultural Organization/WHO Expert Consultation held in Rome last year which referred to diets as being more than a mere combination of foods or the dietary patterns associated with them, but indeed as part of a way of life that is shaped by local social, cultural and economic contexts [136].

The Mediterranean diet in the FAO/WHO document is mentioned as a good example of "territorial" diet, being linked to a specific geography. This vision of Mediterranean diet appearshowever reductionistic since the basic nutritional features that make it the best documented example of healthy diet might be effectively matched by diets typical of far different countries or modelled by other countries (examples might be the New Nordic Diet in the Scandinavian area or even the DASH diet in the United States). And probably the most recent indirect recognition of Mediterranean diet, in its basic nutritional features, as a possibly universal model of healthy diet came also last year from the EAT-Lancet Commission which, in the attempt to define a model of "healthy and sustainable reference diet" for the planet, designed a model strikingly similar to the Mediterranean diet [46].

These concepts were widely debated at the Seminar in the attempt to provide the young participants an opportunity to become aware of the current problems inherent to the effective implementation of the Mediterranean diet and also to help generate an international group of young investigators qualified to take action and develop synergic initiatives for the diffusion of the Mediterranean diet worldwide.

Whereas the Mediterranean diet is widely recognized as being associated with lower incidence and lower death rates of cardiovascular diseases, cancer and other non-communicable diseases, we have however to realistically face the numerous changes occurred in the last 50 years in modern society that have caused the habitual diet of the Mediterranean countries to worsen day after day: global industrialization and commerce, massive urbanization, increase in the cost of plant foods leading to their substitution by less wealthy people with less nutritious but more energy dense lower quality foods, which together with the increased sedentariness has produced a caloric imbalance responsible for the obesity epidemic. In addition to the decline in the quality of diet, the current food systems have contributed to generate social inequalities, with a few actors in the system making unjustified profit while many others, including ethnic minorities and immigrant workers, are more and more impoverished. The Mediterranean countries unfortunately are no exception in this regard.

This negative trend requires a strong commitment on the part of nutritionists, but also of the public health institutions and by the food industry, in a common attempt to rediscover the essence of our traditional diet while taking care of the social distress associated with the modern food production system.

The Seminar has also highlighted the need to pay due attention to technological developments that may help to overcome at least some of the problems that nowadays we face in the application of a healthy diet: new technologies may help modern husbandmen and farmers to produce healthy foods sticking to local traditions but also at a reasonable cost. There is in fact a key question that ought to be answered: what can be done to keep the costs of healthy foods, renowned for their precious taste and for their beneficial nutritional features, accessible to many more people?

Last but not least, the sustainability issue. The Mediterranean diet encourages local and seasonal food production and consumption, thereby minimizing the environmental impact and preserving biodiversity. For these reasons and obviously because it maximizes the consumption of plant foods it is considered not only the healthiest but also the most environmentally friendly traditional diet in the world. Nevertheless, further improvements are necessary and possible. Since exporting the Mediterranean diet as such to other parts of the world would have heavy environmental impact due to transportation and storage, its healthy characteristics might be mimicked everywhere in the world using local foods and local ways of preparation and cooking, while respecting local food production, local cultural values and not requiring movements of foods all over the world.

We are committed to explore this issue in more depth in future editions of the Seminar.

Conflicts of interest

The authors declare no conflict of interest.

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