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Mediterranean Diet and Gene-Mediterranean Diet Interactions in Determining Intermediate Cardiovascular Disease Phenotypes

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1. Introduction

Currently, cardiovascular diseases (CVD) are one of the most important problems in the world. In fact, CVD are the first cause of death all over the world and, according to the World Health Organization (WHO), it is expected to remain so over coming years due to aging population and the increase of prevalence of CVD in countries with fewer resources.

According to European statistics, 2008 for CVD, the leading causes of death in Europe are coronary heart disease and stroke. In Europe, deaths from these diseases are 4.3 million each year. Nearly half (48%) of all deaths are due to CVD (54% of deaths in women and 43% of deaths in men). Regional variations in cardiovascular mortality have been observed both between and within countries in Europe (Sans et al., 1997; Müller et al., 2004). Coronary heart disease mortality patterns showed a clear north-east to south-west gradient in CVD mortality (1990–1992; 45–74 years age-adjusted) with the lowest rates for both men and women in France, Spain, Switzerland, and Italy (Sans et al., 1997). Many factors could be related to the different distribution (eating behaviours, life style, and genetics).

To begin with the development of this chapter it is necessary to consider firstly the health determinants to better understand and focus the aim of this chapter.

The model of health fields proposed by Laframboise in 1973 and developed in Lalonde Report in 1974 (Lalonde 1974) has revolutionized contemporary public health due to the approaching and explaining of the health levels in the populations and therefore, the way of formulating health policies. Marc Lalonde proposed a new "health field" concept that can be broken up into four broad elements: Human biology, Environment, Lifestyle, and Health Care Organization".

Of the four determinants of health, the one which is most susceptible to be modified is lifestyle. Apart from not smoking, the most important lifestyle determinants of good health are what we eat and how active we are. A healthy diet helps to maintain or improve our health. However, as we said before, the CVD are increasing all over the world, and authorities view it as one of the most serious Public Health problems in the 21st century.

CVD are complex and the risk factors that contribute to the development of CVD can be classified into different categories depending on whether they are modified or not (Posner et al., 1991, Haskell et al., 2003) and how they contribute to the development of CVD (Linton et al., 2003). Thus, on the one hand, we have not modifiable factors such as age, sex, family history and genetics. With regard to genetics, we inherit the genetic risk to develop CVD, but this risk can be modulated by other modifiable factors. In this chapter we will deeply discuss the relation between genes and environmental factors (especially diet) in the prevention of CVD (Figure 1).

On the other hand, we also have factors that are susceptible to be modified such as cholesterol concentrations, hypertension, smoking, diabetes, type of diet, obesity, sedentary lifestyle, stress and consumption of oral contraceptives. The more risk factors a person has, the higher risk of developing CVD. Some risk factors can be changed, treated or modified, and some others not. But controlling the largest possible number of risk factors through changes in lifestyle and/or drugs can reduce cardiovascular risk. Among the environmental factors associated with CVD, and as a part of one of the health determinants proposed by Lalonde, diet has a great impact on lipid metabolism, oxidative stress and the development of the atherosclerotic process (Ordovas et al., 2004) (Figure 1). Changes in eating behaviours have contributed to the growing epidemic of chronic diseases. These changes are characterized by an unbalanced diet consisting of food with a high density of energy rich in saturated fatty acids (SAF) as well as a decrease in physical activity. This process is called nutritional transition. Given these facts, researchers are trying to elucidate the best diet to prevent CVD. However, there is a widespread of controversy. Different proposals have been considered such as low-fat diet, diet low in carbohydrates and high in proteins, among others, all promoted by the acquisition of knowledge, fashion or business interests (Ordovas et al., 2004).

Traditionally, the American Heart Association (AHA) has based dietary recommendations for primary care of cardiovascular risk in a low-fat diet (Krauss MR et al, 2000). This diet is also based on reducing all types of fat so that the contribution of total fat calories should be less than 30% (of which SAF are less than 10%) and cholesterol intake less than 300 mg daily. This type of diet causes a decrease in total cholesterol (TC) and LDL-C, and a decrease or not variation in HDL-C and increases or unchanged triglycerides (TG) concentrations (Obarzanek et al., 2001; Lichtensein et al., 2002, Howard et al., 2006). Later on, in 2005, a new version of USDA pyramid in which food groups are presented in vertical and which incorporates the concept that the diet should be tailored to individual needs came up (USDA, 2005).

After the AHA recommendations, other types of diets have been proposed such as diets rich in protein, low carb, Mediterranean diet, etc. Mediterranean diet has attracted the most interest by its great relevance regarding the protective role in primary and secondary care of CVD.

The aim of this chapter is to analyse the role of the Mediterranean diet in determining intermediate CVD phenotypes. We also review one of the most emerging topics currently: the role of gene-Mediterranean diet interactions on CVD.

2. Mediterranean diet

Due to the great incidence of CVD, Mediterranean diet has gained a considerable popularity during the last decades. The Mediterranean area is a sociocultural construction built on the

countries bordering the Mediterranean Sea. Food habits have been consolidated over the centuries and are the result of geographical and climatic factors, as well as cultural, political and religious factors of Mediterranean people. Mediterranean area is identified by characteristics based on agriculture (natural grain, olives, wine and vegetables), fishing and consumption of poultry instead of other meats.

Furthermore, Mediterranean diet includes food and cooking techniques typical of Mediterranean countries which have been gradually abandoned by western patterns.

The Mediterranean diet has been described as a model from a nutritional point of view due to the good balance that provides its food items (micronutrients, vitamins, antioxidants). Nevertheless, as well as the cooking techniques have been abandoned, in the last few years changes in lifestyle have triggered a move away from the recommended intakes in relation to several nutrients. All these changes make it even more difficult to ensure adequate intakes of vitamins and minerals. This problem could affect more to certain risk groups such as women, the elderly, children, gestating and lactating women and ill people. Knowing the extent of this reality it seems worthy to inform people and society in general about the necessary changes in the diet and about the characteristics of the Mediterranean diet which are being lost and should be restored.

2.1 Definition of the Mediterranean diet

The concept of the Mediterranean diet originated from several observational studies in the 1950s, being the most known the Seven Countries Study initiated by Ancel Keys (Ancel Keys 1970). Subsequently, several studies have associated increased longevity, lower mortality and morbidity to Mediterranean diet (Keys et al., 1986; de Lorgeril et al., 1999; Singh et al., 2002; Trichopoulou et al., 2003; Knuops et al., 2004). Taken as a whole, these studies showed that, despite a high fat intake, these populations had low rates of coronary heart disease and other vascular diseases, cancer, inflammatory and degenerative diseases, resulting in a long life expectancy. The Mediterranean dietary pattern was considered to be largely responsible for the good health observed in these regions (Keys et al., 1986). Currently, there is a great number of clinical and epidemiological studies that have shown the benefits of the Mediterranean diet. However, these effects are attributed to the traditional Mediterranean diet and not to the Westernized patterns that nowadays characterize the South European countries (Serra-Majem et al., 2004).

Although there are several variations of the Mediterranean diet, the main characteristics include high consumption (daily consumption) of vegetables, fruit, whole grain cereals and low fat dairy products; weekly consumption of fish, poultry, tree nuts and legumes; relatively low consumption of red meat (approximately twice a month) as well as moderate daily consumption of alcohol (preferably in the form of wine) normally with meals (keys et al., 1986) (Figure 1).

Most of the articles published so far on Mediterranean diet are observational studies. However, there is a lack of intervention studies that demonstrate causal relationship. Although there are few randomized controlled trials of dietary intervention with Mediterranean Diet, we have recently strong data from one large randomize control trial supporting the beneficial effects of Mediterranean diet on CVD prevention (Estruch et al., 2006).

2.2 Principal studies that focus on Mediterranean diet and cardiovascular diseases

In general, there is a predominance of observational studies related to Mediterranean Diet compared to clinical trials in the study of CVD. Thus, most of the studies are cross-sectional studies with a level III of evidence (based on the quality of evidence according to the 2nd edition of the U.S. Task Force (Harris et al., 2001)). The *ATTICA* study is the most remarkable (Pitsavos et al., 2003) and it was conducted on a representative sample of Greek men and women recruited from May 2001 to December 2002 in order to analyze cardiovascular risk factors, establish associations with lifestyle, socioeconomic factors, psychological characteristics, and assess their impact on CVD over a year, five and ten years. Several studies found a positive association between Mediterranean Diet and CVD (Tzima et al., 2007; Panagiotakos et al., 2006; Pitsavos et al., 2007).

Two other large European cohort studies (evidence level II-2) include the Greek cohort within *EPIC* (European Prospective Investigation into Cancer) (Trichopoulou et al., 2003, Slimani et al., 2002). They study the relationship between nutrition and cancer in 519,978 participants from 23 centers located in 20 European countries.

Another cohort study is the *HALE* (Knoops et al., 2004) (Healthy Ageing: Longitudinal Study in Europe). This project analyzed age-related changes and the determinants of healthy aging in terms of mortality and morbidity, and physical, mental, cognitive and social functionality in 13 European countries. Results from this study suggest that a high adherence to Mediterranean diet is associated with a reduction in both overall mortality and cardiovascular mortality.

Regarding intervention studies (level I of scientific evidence), two of the most known studies analyzing Mediterranean Diet are *PREDIMED* study (Prevention with Mediterranean diet) (Estruch et al., 2006) and *Medi-RIVAGE* study (Mediterranean Diet, Cardiovascular Risks and Gene Polymorphism) (Vincent-Baudry et al., 2005).

PREDIMED study is a multicenter, prospective, randomized, controlled trial whose goals are to assess the efficacy and safety of a Mediterranean diet in primary care of CVD. It was designed in 2002 and it is the first long-term clinical trial that recruits high-risk patients (around 7,000 participants from different regions in Spain) to follow a Mediterranean diet supplemented with virgin olive oil (VOO) (1 liter a week) or nuts (30 g per day of which 15 g almonds and 15 g walnuts).

Medi-RIVAGE study is a randomized clinical trial conducted in France on 212 women and men with at least one cardiovascular risk factor. The aims of the study are to evaluate the effect of two types of diet in the prevention of CVD and to investigate biological mechanisms and genetic polymorphisms related to metabolism. On the one hand, they study the traditional Mediterranean diet (35-38% of total energy from fat: 50% monounsaturated fatty acids (MUFA), 25% polyunsaturated fatty acids (PUFA), 25% SFA) and on the other hand, a low fat diet based on the AHA (30% of total energy from fat: 33% MUFA, 33% PUFA, 33% SFA).

With regard to studies that analyze final cardiovascular risk phenotypes, two of the most outstanding studies (level I of scientific evidence) are the Lyon Diet Heart Study and the Indio-Mediterranean Diet Heart study.

The *Lyon Diet Heart Study* (de Lorgeril et al., 1999), a randomized, controlled trial with free-living subjects (half of 600 men and women in France), tested the effectiveness of a Mediterranean-type diet (consistent with the new AHA Dietary Guidelines) on composite measures of the coronary recurrence rate after a first myocardial infarction during 46 months. Subjects in the experimental group were instructed by cardiologists and dietitians to adopt a Mediterranean-type diet. They demonstrated the effectiveness of Mediterranean diet in the secondary care of CVD. However, the intervention group with Mediterranean diet received margarine rich in alpha-linolenic fatty acid, fact that distorted the interpretation of results, as margarine is not a component of traditional Mediterranean diet. Something similar happens with the Indo-Mediterranean Diet Heart Study (Singh et al., 2002).

The *Indo Mediterranean Diet Heart* study is a randomized, single-blind trial in 1000 patients with angina pectoris, myocardial infarction, or surrogate risk factors for CVD. 499 patients were allocated to a diet rich in whole grains, fruits, vegetables, walnuts, and almonds. 501 controls consumed a local diet similar to the step I National Cholesterol Education Program (NCEP) prudent diet. They showed that an Indo-Mediterranean diet, that is rich in alpha-linolenic acid, might be more effective in primary and secondary prevention of CVD than the conventional step I NCEP prudent diet. However, as in the Lyon Diet Heart Study, the intervention group with Mediterranean diet increased the consumption of alpha-linolenic fatty acid from soybean and mustard oil, which are not typical from Mediterranean countries.

3. Mediterranean diet in determining intermediate cardiovascular disease phenotypes

There is a great number of studies analysing the effect of the consumption or adherence to Mediterranean diet and intermediate CVD phenotypes. In the following sections we review the studies analysing Mediterranean diet and obesity, lipid metabolism, glucose concentrations, blood pressure and inflammation. Table 1 shows the effect of Mediterranean diet on the aforementioned phenotypes.

3.1 Mediterranean diet and obesity

Currently, it is not known which is the best diet is to lose weight (low-carb, high protein, low fat diet, etc.). Consumption of nuts, and high fat diets (rich in MUFA), characteristics of the Mediterranean diet, have been traditionally associated with an increased body weight by its high contain in fats. However, recent scientific evidence does not support these data. Adherence to Mediterranean diet was inversely associated with BMI and obesity in a cross-sectional survey carried out in the northeast of Spain (Schröder et al., 2004). Obesity risk decreased in both men and women with increasing adherence to the traditional Mediterranean diet.

Results from epidemiological studies on large populations indicate that subjects who usually consume nuts have lower BMI than those who do not consume (Bes-Rastrollo et al, 2009, Garcia-Lorda et al, 2003; Schroder et al, 2004). In addition, the SUN cohort (Seguimiento Universidad de Navarra) (follow-up University of Navarra) evaluated 11,895 participants and found an inverse association between consumption of nuts and weight gain

per year (Martinez-Gonzalez & Bes-Ballostro, 2011). Similarly, a recent study carried out in EPIC-PANACEA project showed that individuals with high adherence to Mediterranean diet, according to the score based on a questionnaire of adherence to Mediterranean diet (11-18 points), showed in a weight change of 20.16 kg (95% CI :20,2-20, 7 kg) 5 years and they were also 10% less likely to become overweight and obese compared with individuals with lower adherence (0-6 points) (Romaguera et al., 2010). Furthermore, a study that evaluated 497,308 individuals aged between 25-70 years in 10 European countries found that high adherence to the Mediterranean diet is associated with lower abdominal adiposity, using waist circumference as a measure (Romaguera et al., 2009).

With respect to intervention studies, it has been shown that subjects that consume daily tree nuts in their diet are less likely to gain weight (Li et al., 2010). A study evaluating the intake of almonds (42-72 g daily) in 81 patients over 6 months found that there was no significant weight gain (Fraser et al., 2002). Similarly, García-Londa et al, (2003) found that in the short term, the addition of tree nuts to diet, in amounts up to 50 g daily, does not increase weight. After one year of intervention in the PREDIMED study, beneficial effects on waist circumference were shown (Martinez-Gonzalez & Bes-Ballostro, 2011).

Finally, a meta-analysis regarding Mediterranean diet and weight loss analyzing randomized controlled trials has been recently published (Esposito et al., 2011), and it concludes that Mediterranean diet does not cause weight gain, which removes the objection to its relatively high fat content. Mediterranean diet could be a strategy to help people lose weight.

Some of the proposed mechanisms that might explain these facts are that the absorption of nuts may be incomplete, thus some of its fat content may not be absorbed by the body and would be excreted in the feces. Moreover, the consumption of nuts may have a satiating effect, producing a decrease in consumption of other foods and helping to control total energy intake. Although it still has not been proved, there may be an adaptation of the metabolism, so that energy consumption could be more efficient and get the body burn more energy, thus avoiding an accumulation of body fat (Brennan et al., 2010; Garcia-Lorda et al., 2003; Rajaram & Sabaté, 2006).

3.2 Mediterranean diet and lipid metabolism

Mediterranean diet has been largely studied in relation to lipid metabolism because of its beneficial effect on CVD. However, different results have been shown regarding a variety of studies, designs, and sample sizes. Cross-sectional studies with similar characteristics, with a sample size between 1762 and 2032 participants in Greece (ATTICA study), evaluated the adherence to Mediterranean diet and lipid profile. Thus, Tzima et al (2007) reported that subjects who are overweight (BMI 25-29.9) or obese (BMI \geq 30) in the highest tertile of the Mediterranean diet score had lower total cholesterol (TC) (-13 %, P = 0.001) after adjusting for age, sex and BMI compared to the first tertile. However, there were no significant differences in triglycerides (TG) and HDL-C. This increase in the adherence to Mediterranean diet was also associated with lower total cholesterol (p <0.001) in a study carried out by Panagiotakos et al (2006). In addition to that, individuals with abdominal obesity and less physically active had lower adherence to Mediterranean diet (p = 0.008) with lower HDL-C (p <0.05) (Pitsavos et al., 2007).

Moreover, seven studies of 29 clinical trials with 3,822 subjects (2,202 assigned to Mediterranean diet and 1,903 assigned to a control diet) reported beneficial effects of adherence to Mediterranean diet on HDL-C (Papadaki & Scott, 2008; Esposito et al., 2004; Estruch et al., 2006; Esposito et al., 2003; Esposito et al., 2009; Athyros et al., 2011). A recent meta-analysis (Kastorini et al., 2011) showed that, overall, adherence to Mediterranean diet was associated with higher HDL-C levels as compared with a control diet.

Benefits in TC have also been shown in some randomized controlled trials (Estruch et al., 2006; Vincent-Baudry et al., 2005; Ambring et al., 2004). In this sense, Estruch et al., (2006) carried out a study of 3 months with individuals who had diabetes mellitus or one or more cardiovascular risk factors, which were assigned to three intervention groups ($n = 257-8$ / group) (2 Mediterranean diet (one supplemented with VOO and another one with 15g of almonds+15g walnuts/day) and one control diet low in fats). Regarding the lipid profile, both Mediterranean diets showed significant increase in HDL-C levels ($p = <0.001$ and $p = 0.006$, respectively) and a significant reduction ($p <0.001$ and $p = 0.002$, respectively) in the atherogenic index (TC/HDL-C) in contrast to the control group. However, only Mediterranean diet supplemented with nuts showed a significantly reduction in TC ($p = 0.040$) and TG ($p = 0.022$), compared to control. Neither of the Mediterranean diets significantly reduced LDL-C compared to the control diet (low fat diet).

Concerning TG, three observational studies reported a beneficial effect of Mediterranean diet (Chrysohoou et al., 2004; Tzima et al., 2007; Barzi et al., 2003) as compared with low adherence to Mediterranean diet. Five interventional studies showed beneficial effects of Mediterranean diet on TG concentrations (Shai et al., 2008; Esposito et al., 2004; Estruch et al., 2006; Esposito et al., 2009; Elhayany et al., 2011), whereas other studies did not find significant differences (de Lorgeril et al., 1994; Castro et al., 2000; Michalsen et al., 2006).

Moreover, results from a crossover study during 4 weeks for each intervention (22 healthy people (12H/10M)) found an improvement in lipid profile to compare a Mediterranean diet (rich in omega 3) with a Swedish standard diet (Ambring et al., 2004). The results showed a significant decrease in TC, LDL-C, TG (17%, 22%, and 17%) in the group with Mediterranean diet. On the other hand, one non-randomize control trial carried out in Italy (47 obese women) during 4-month with an hypoenergetic Mediterranean diet together with a program of physical exercise showed a significant decrease in total cholesterol and TG concentrations. Levels of LDL-C decreased ($p <0.001$) after 4 months of intervention, whereas HDL-C increased (Andreoli et al., 2008). However, another study carried out in 71 healthy Canadian found a significant decrease in TC at 6 weeks of intervention ($p <0.05$), whereas no significant changes were observed after 12 weeks. Levels of HDL-C, LDL-C and TG were not affected after 6 or 12 weeks of intervention (Goulet et al., 2003). Different characteristics of the recruitment of individuals can influence the final results of the studies.

The relationship between nut consumption and reduced risk of CVD has been established in numerous epidemiological studies. Thus, Ros et al (2004), in a crossover study carried out in hypercholesterolemia subjects in Spain, determined whether a diet containing nuts (18% of energy) could improve markers related to endothelial function against another typical Mediterranean diet with similar energy intake, fat, protein, carbohydrates, but not MUFA intake, after 4 weeks. Estruch et al (2006) also found a significant decrease in TC ($p = 0.017$) and LDL-C ($p = 0.010$). However, no differences were found in TG concentrations and HDL-

C. Pooled analysis in 25 clinical trials to evaluate nut consumption in blood lipids showed that the most important finding is that the cholesterol-lowering effects of nut consumption are dose related and are more pronounced in subjects with higher baseline LDL-C or lower BMI. Nut consumption also lowered TG levels in subjects with hypertriglyceridemia (Sabate et al., 2010).

3.3 Mediterranean diet and glucose concentrations

The increasing incidence of type 2 diabetes throughout the world is also linked to westernized dietary patterns. Lifestyle changes are effective measures to prevent diabetes. The Mediterranean diet has also shown beneficial effects on diabetes risk and glucose concentrations.

Two observational studies reported a beneficial effect of close adherence to Mediterranean diet as compared with a control diet in lowering fasting glucose (FG) levels (Tzima et al., 2007; Panagiotakos et al., 2007).

Furthermore, Estruch et al., 2006 found that participants in the intervention group with Mediterranean diet supplemented with VOO or nuts, showed a significant reduction in FG compared with the control group (-0.39 mmol / L and -0.30 mmol / L, respectively).

In this sense, in another randomized controlled trial (Vincent-Baudry et al., 2005) with Mediterranean diet or low-fat diet, after 3 months of intervention, both diets significantly reduced blood glucose, insulinemia, insulin resistance and HOMA-IR index. Insulin levels remained significant after adjusting for BMI. However, there was no interaction between time and type of diet for any of the variables. Negative results were shown in a study that compared the intervention with Mediterranean diet rich in omega 3 versus the standard Swedish diet (Ambring et al., 2004). Recently, results from PREDIMED study also reported that, after a median follow-up of 4 years, diabetes incidence was lower in the groups with Mediterranean diet as compared with control group (10,1% in Mediterranean diet with VOO, 11% in Mediterranean diet with nuts, 17,9% in control group) (Salas-Salvado et al., 2011).

In conclusion, overall adherence to Mediterranean diet is associated with lower FG levels as compared with the control diet (Kastorini et al., 2011). Among the mechanisms associated with that decrease in glucose levels are the properties of the components of Mediterranean diet. Fiber delays gastric emptying, antioxidants increase oxidative capacity and moderate alcohol could have a role in adiponectin. As a consequence, it ends in the prevention of insulin resistance and, finally, in prevention of type 2 diabetes (Schröder, 2007).

3.4 Mediterranean diet and blood pressure

Nutritional factors and dietary patterns have been associated with hypertension. Hypertensive individuals can remarkably reduce their blood pressure through nutritional changes. Mediterranean diet has also shown beneficial effects in the prevention and control of blood pressure.

Cross-sectional studies associate the consumption of Mediterranean diet with lower systolic blood pressure (SBP). Higher adherence to Mediterranean diet was associated with lower SBP ($p < 0.001$) (Tzima et al., 2007; Panagiotakos et al., 2006) as well as with 70% of decrease of prevalence of hypertension (Alvarez-León et al., 2006). In contrast, lower adherence was

associated with increased blood pressure (BP) (Pitsavos et al., 2007). However, one study showed higher SBP in the group more closely following the Mediterranean diet in the SUN cohort in young individuals after a median follow-up of 4.2 years (Nunez-Cordoba et al., 2009). Most of the effects of the Mediterranean diet on blood pressure have been attributed to the consumption of olive oil, fruits, nuts and vegetables. Psaltopoulou et al (2004) in the Greek-EPIC cohort studied whether Mediterranean diet together or olive oil in particular reduced blood pressure in 20,343 people without a diagnosis of hypertension. In this study, the Mediterranean diet score was inversely and significantly associated with both, SBP and diastolic blood pressure (DBP), as well as the intake of olive oil, fruits and vegetables. However, Giuseppe et al (2008) found a significant and positive association of BP with the rate of adaptation to the Mediterranean diet. However, we have to consider that the study was carried out in older women (> 60 years). In the Italian EPIC Florence cohort, which include more than 10,000 non-hypertensive women aged 35-64 years, consumption of olive oil was inversely associated with DBP (Masala et al., 2008). However, with regard to DBP and Mediterranean diet as a whole, observational studies did not found significant associations (Kastorini et al., 2011).

Regarding randomized clinical trials (level I scientific evidence) in a meta-analysis, it was found that the overall adherence to Mediterranean diet was associated with lower SBP and DBP as compared with control diet (Kastorini et al., 2011). In the PREDIMED study, results showed a significant decrease in both SBP and DBP in the two groups with Mediterranean diet (one supplemented with VOO and another with nuts) as compared with control group (Estruch et al., 2006). Finally, in a non-randomized clinical trial whose aim was to evaluate the effect of a moderately hypoenergetic Mediterranean diet with an exercise program in women with overweight-obesity, DBP decreased significantly ($p < 0.001$) after two months of intervention, while the SBP was not changed significantly after four months of intervention (Andreoli et al., 2008).

In conclusion, as we mention before, the beneficial effects of the Mediterranean diet on blood pressure have been attributed to a synergy of its components, especially to fruits, vegetables, nuts and olive oil. These components are low in sodium and rich in minerals (magnesium, potassium and calcium), antioxidant, fiber, PUFA and MUFA, all of them with potentially protective properties against hypertension.

3.5 Mediterranean diet and inflammation

Obesity and other related diseases associated with CVD are caused or related to inflammation. Three of five cross-sectional studies, showed a significant decrease in inflammation markers with higher adherence to Mediterranean diet (Sotos-Prieto et al., 2010). Thus, Panagiotakos et al (2006) found significant negative association between adherence to Mediterranean diet and protein C reactive (CRP) ($p < 0.001$). Also, the highest score in the AHEI index (Alternate Healthy Eating Index) and AMED (alternate mediterranean diet index) was associated with lower inflammation biomarkers concentrations (IL-6 and CRP) (24% and 16% respectively). This study was carried out in 690 nurses, in the Nurses' Health Study (Fung et al., 2005). Moreover, subjects in the highest tertile of adherence to Mediterranean diet had 20 % lower CRP levels ($p = 0.015$) and 17% IL-6 ($p = 0.025$) (Chrysohoou et al., 2004), while the lower adherence to Mediterranean diet was associated with higher levels of CRP (> 3.0 mg / ml) (Pitsavos et al., 2007).

Salas-Salvado et al (2008), in a study that included subjects with high cardiovascular risk (339H/433M, 55-80 years), found an association between consumption of certain foods that characterized the Mediterranean pattern (fruits, cereals, VOO and nuts) with lower concentrations of inflammatory markers, especially those related to endothelial function (ICAM-1 and VCAM-1). However, participants with higher adherence to a Mediterranean diet showed no significant decrease in the inflammatory biomarkers' concentrations (CRP, IL-6, ICAM-1 and VCAM-1), although there was a statistical trend in the case of ICAM-1 and VCAM-1 ($p < 0.1$).

In two randomized controlled trials, CRP levels decreased only in the group with Mediterranean diet supplemented with VOO (-0.54 mg / L) compared with the control group (low-fat). The IL-6 decreased in both groups with Mediterranean diet (VOO and nuts), whereas it increased in the group with low-fat diet. Similarly, Esposito et al (Esposito et al., 2004), in a study conducted in Italy with 180 people with metabolic syndrome (99H, 81M), observed a significant decrease in CRP ($p = 0.01$) and IL-6 ($p = 0.04$) in the intervention group (instructed to follow a Mediterranean diet) compared with the control group (prudent diet with fat percentage $< 30\%$) after two years. By contrast, Michalsen et al (2006) found no changes in CRP levels, although there were some limitations in the study.

In a non-randomized clinical trial, plasma levels of CRP decreased significantly (6%, $P < 0.02$) after two hours of Mediterranean diet rich in MUFA intake (Blum et al., 2006).

In conclusion, Mediterranean diet is characterized by a high consumption of fruit and vegetables. This adds other mechanistic benefits provided by their polyphenolic content to its high antioxidant content that could be linked with the prevention of inflammation. Other components of the Mediterranean diet such as VOO and red wine gather antioxidants and anti-inflammatory actions that may contribute to the healthy effects of this diet on inflammation.

	Decrease	Increase	No significant
BMI (kg/m²)	Scröder et al., 2004 Romaguera et al., 201 Bes-Ballostro et al., 2009; Garcia-Londa et al., 2003 Martinez-Gonzalez & Bes-Ballostro, 2011		
Weight gain	Fraser et al., 2002 Martinez-Gonzalez & Bes-Ballostro, 2011		
Waist circumference	Romaguera et al., 2002 Martinez-Gonzalez & Bes-Ballostro, 2011		
TC	Estruch et al., 2006 Vicent-Baudry et al., 2005 Ambring et al., 2004		
LDL-C	Vicent-Baudry et al., 2005 Ambring et al., 2004 Ros et al., 2004 Andreoli et al., 2008		Michalsen et al., 2006 Goulet et al., 2003 Estruch et al., 2006

	Decrease	Increase	No significant
HDL-C	Pitsavos et al., 2007	Estruch et al, 2006 Andreoli et al.,2008 Papadaki & Scott, 2008 Esposito et al., 2004; Esposito et al., 2003; Esposito et al., 2009; Athyros et al., 2011 Ambring et al., 2004	Michalsen et al., 2006 Goulet et al., 2003
TG	Estruch et al.,2006 Vicent-Baudry et al., 2005 Ambring et al., 2004 Ros et al., 2004 Chrysohoou et al., 2004; Tzima et al., 2007; Barzi et al., 2003 Shai et al., 2008 Esposito et al., 2004 Esposito et al., 2009 Elhayany et al., 2011 Sabate et al., 2010		Michalsen et al., 2006 de Lorgeril et al., 1994 Castro et al., 2000 Goulet et al., 2003
Glucose	Estruch et al., 2006 Vicent-Baudry et al., 2005 Andreoli et al.,2008 Panagiotakos et al., 2007 Tzima et al., 2007 Salas-Salvado et al., 2011		Ambring et al., 2004
SBP	Estruch et al., 2006 Tzima et al., 2007 Psaltopoulou et al., 2004 Panagiotakos et al., 2006	Giussepe et al., 2008 Nunez-Cordoba et al., 2009	Andreoli et al., 2008
BP	Estruch et al., 2006 Andreoli et al., 2008 Alvarez-Leon et al., 2006 Psaltopoulou et al., 2004 Pitsavos et al., 2007 Masala et al., 2008		
CRP	Estruch et al., 2006 Esposito et al., 2004 Blum et al., 2006 Fung et al., 2005 Chrysohoou et al., 2004 Panagiotakos et al., 2006	Pitsavos et al., 2007	Michalsen et al., 2006 Salas-Salvado et al., 2008
IL-6	Estruch et al., 2006 Esposito et al., 2004		Salas-Salvado et al., 2008

BMI: Body mass index; TC: Total Cholesterol; LDL-C: Low density lipoprotein cholesterol
HDL: High density lipoprotein cholesterol; TG: Triglycerides; SBP: Systolic blood pressure; BP: Blood pressure; CRP: Protein C reactive; IL-6: Interleukin 6

Table 1. Studies that analyze Mediterranean diet and variation (decrease, increase, no significant) in intermediate cardiovascular disease phenotypes.

4. Nutritional genomics

Current changes in lifestyle, in part promoted by the nutritional transition, have contributed to the development of CVD, cancer and other non-communicable diseases.

Since the Human Genome Project finished in April 2003, we have the information about the complete genome. However, we still unknown the role of the majority of genes involved in the development of CVD. For that reason, currently, considering diet as one of the most important environmental factor, the molecular nutrition begins with the approach to better understand the mechanism involved in the gene-diet interaction and to personalize the diet with the aim to prevent common diseases, among them, CVD. Since Human Genome Project finished, the classic candidate gene approach and the new genome-wide association studies have identified genetic variants that predispose people to CVD.

In this sense, it was shown that human genome is sensitive to nutritional environment in two ways: nutrients may regulate genes and genes also influence the effect of diet (Loktionov, 2003). Nutritional health is dependent on the interaction between the environmental aspects of dietary components and the genetically controlled aspects (Figure 1). The concept of gene-diet interaction describes the modulation of the effect of a dietary component on a specific phenotype (plasma lipid concentrations, obesity, etc.) by a genetic polymorphism (Ordovas & Corella, 2004). A better understanding of these interactions has the potential to support disease prevention and will lead to different requirements between individuals via modification of dietary recommendations. This research has led to the development of concepts that study the effect of genetic variation on the interaction between diet and specific phenotypes known as *nutrigenetics*.

The goal of nutrigenetics is to generate personalized recommendations regarding the genetic susceptibility of each individual. It is also known as *personalized nutrition*.

On the other hand, the study of the characterization of gene products and the physiological function and interactions of these products is known as *nutrigenomics* (Figure 1). The unifying term "*nutritional genomics*" refers to nutrigenomics and nutrigenetics (Ordovas & Corella, 2004). The term Nutrigenetics was named for the first time by Brennan in 1975 in his book "*Nutrigenetics: New concepts for Relieving Hypoglycemia*", while nutrigenomics was used in 1999 by DellaPenna when he studied the plant genomics field. The new technology research together with the knowledge of the human genome sequence have led in the study of the new "omics" to better understand the molecular basis of the disease development. They are the disciplines known as:

- *Transcriptomic*: to quantify the level of gene expression by using techniques to analyse thousands of mRNA molecules at the same time by using a technique based on microarrays.
- *Proteomic*: large-scale study of proteins (particularly their structure and function) is possible to identify proteins that can diagnose disease or predict the evolution of it.
- *Metabolomics*: to study techniques dedicated to complete a system composed of a series of molecules that are metabolic intermediates, metabolites, hormones and other signal molecules, and secondary metabolites, which can be found in a biological system.
- *Systems Biology*: integration of proteomic data, genetic, metabolomics.
- *Bioinformatics*: to interpret the data to provide biological mechanisms to explain the experimental observations.

Following these new concepts, other related terms have emerged: *nutritranscriptomic* (the study of messenger RNA expression at the cellular level under some nutritional conditions), *nutriproteomic* (large-scale analysis of the structure and function of the protein, as well as protein-protein interactions in a cell to identify molecular targets of dietary components) or *nutrimetabolomic* (measuring all metabolites in response to stimuli nutritional body) (Panagiotou & Nielsen, 2009).

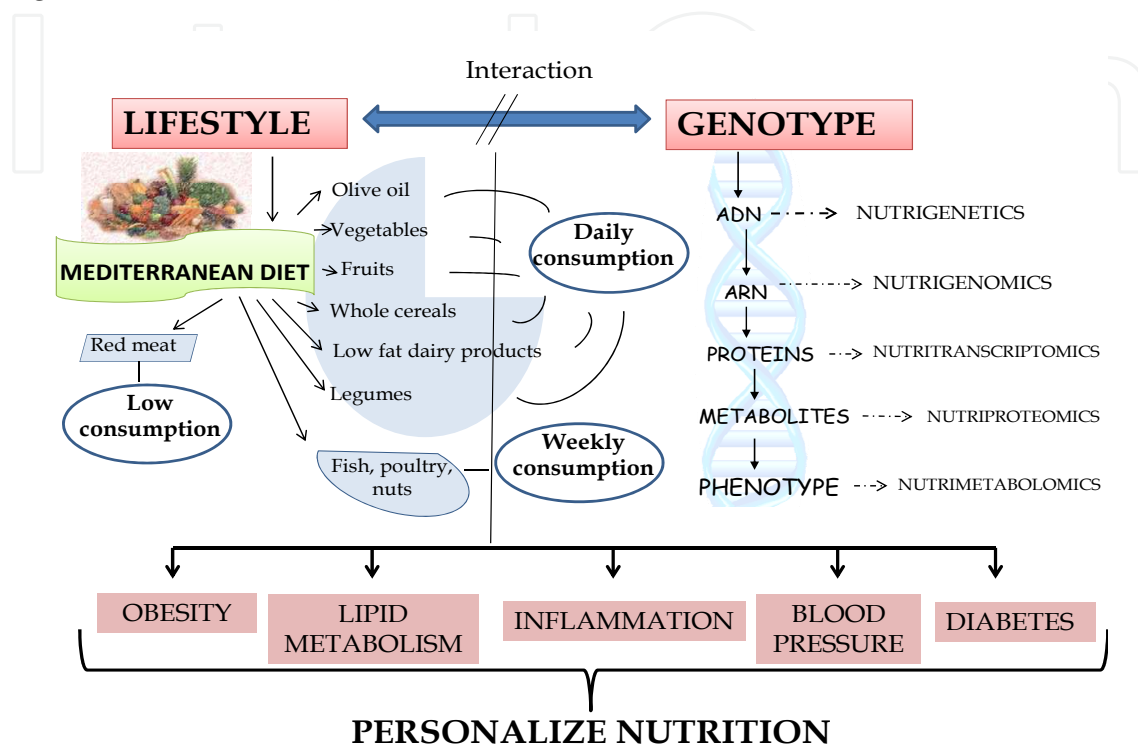


Fig. 1. Personalized Nutrition. As part of health determinants, lifestyle interacts with genetic susceptibility to modulate obesity risk, lipid metabolism, inflammation, blood pressure and diabetes. Among lifestyle factors, diet, and especially, Mediterranean diet, has an important role in gen-diet interactions. On the other hand, with the new technology research together with the knowledge of human genome sequence have led in the study of the nutrigenetics and nutrigenomics (nutritional genomics) to better understand the molecular basis of the disease development, they are the disciplines knows as: transcriptomic, proteomic, metabolomic that allow us to know phenotypes characteristics. These interactions between Mediterranean diet and genetic susceptibility will contribute to create personalized diets.

5. Gene-Mediterranean diet interaction in intermediate cardiovascular diseases phenotypes

In the following sections we are going to review some studies analyzing nutrigenetics and nutrigenomics effects on CVD.

5.1 Nutrigenetics in the prevention of cardiovascular diseases

In the last decades the eating pattern has changed considerably towards less healthy habits with excessive intake of calories and SFA. Considering this as a risk factor of CVD these

changes are contributing to the increase of CVD. As a result, researchers are wondering which could be the best diet to prevent CVD and related phenotypes. Different opinions have emerged about the virtues of low-carbohydrate diets, low fat diets, high-protein diets or Mediterranean dietary pattern in the control of body weight and factors related to CVD (Shai et al., 2008, Larsen et al., 2010, Sacks et al., 2009).

Given the great diversity that exists with regard to dietary recommendations and their effects, several authors insist on the fact that there is no perfect diet. Diet will be different depending on individual characteristics. The response to the same diet has not the same effectiveness on different two people. While some people appear to have no response to dietary intervention (hiporesponders), others have a high response (hiperresponders) (Katan MB et al., 1986). It has been suggested that this inter-individual variability to dietary modification is determined by genetic factors, especially for phenotypes related to lipid metabolism (Loktionov, 2003).

Most of the studies carried out to determine whether genetic factors could explain these differences are based on the study of single nucleotide polymorphisms (SNPs) as well as dietary factors, particularly those that characterize Mediterranean Diet. The table 2 shows some studies conducted to assess genetic modulations according to different types of diets or macronutrients. In the following paragraphs we describe the results from intervention studies and observational studies that analyze gene-diet interactions on CVD.

Results from intervention studies

Intervention studies in which subjects receive a controlled dietary intake provide the most valuable information for the study of gene-nutrient-phenotype association. However, intervention studies have some limitations, such as the low number of participants. The sample size is important in nutrigenetic studies because otherwise, there is a lack of statistical power to assess the main associations. Something similar happens with the study of some genetic variants. Prevalence of certain polymorphisms is small and requires a large sample size to study these associations. Another limitation is the short duration of these interventions. A review conducted by Masson et al, (2003) concluded that there is evidence to suggest that variations in the *APOA1*, *APOA4*, *APOB* and *APOE* genes contribute to the heterogeneity of the lipid response to dietary interventions, and that these genes are directly or indirectly regulated by PPAR or other nuclear receptors. New examples that confirm the importance of gene-diet interaction in the field of nutrigenetics are the study of the perilipin gene (*PLIN*) (Corella D et al., 2005, Smith CE et al., 2010) and *SR-BI* (Perez-Martinez P et al., 2005).

Recently, some studies investigating the genetic modulation of the Mediterranean diet in PREDIMED study have been published. Thus, a study examining a polymorphism in the *FTO* gene (associated with obesity) shows that the A allele of the polymorphism rs9939609 in the *FTO* gene was not associated with baseline body weight, but after 3 years of nutritional intervention with Mediterranean diet carriers of A allele had a lower body weight gain than subjects with the ancestral allele (Razquin C et al., 2010 A).

Another example carried out in the PREDIMED study showed that CC subjects for the polymorphism-174G / C in the *IL-6* gene had a lower weight gain after three years only in those subjects who followed a Mediterranean diet supplemented with nuts and olive oil (Razquin et al., 2010 B)

Results from observational studies

Observational studies have the advantage of incorporating a large number of participants and the ability to estimate dietary habits. They also have the advantage that the distribution of genetic variants in the population is independent of eating behaviors by the principle of Mendelian randomization. Although nowadays the number of studies examining gene-diet interactions is increasing, few studies have investigated the interaction between SNPs in candidate genes and cardiovascular risk factors analyzing the consumption of Mediterranean diet or intake of MUFA, PUFA or SFA.

One of the most studied genes has been the Pro12Ala polymorphism in the *PPARG* gene and its interaction with MUFA intake. Obese subjects with the Ala12 allele have higher HOMA index when they eat low amounts of MUFA. Another example analyzing MUFA intake and body weight depending on variation in *APOA5* gene is one carried out in the Framingham study. They found a significant interaction between the promoter polymorphism -1131T>C in the *APOA5* gene and fat intake, particularly MUFA, regulating body weight (Corella D et al., 2007). The study of C677T polymorphism in the gene for methylenetetrahydrofolate reductase (*MTHFR*) is another example of modulation of LDL oxidation by the Mediterranean diet (Pitsavos et al., 2006). Recently, we published a significant gene-diet interaction in a variant of the promoter of *APOA2* gene. This study included 3462 volunteers from three different populations and it studied the interaction between the polymorphism-265T>C in the *APOA2* gene, food intake, and BMI. Carriers of the variant allele which had higher intake of SFA had a higher prevalence of obesity while this was not showed if the source of fat was MUFA or PUFA. These results were replicated for the first time in three independent populations (Corella et al., 2009). Subsequently, the authors replicated this interaction in Mediterranean and Chinese populations (Corella et al., 2011) confirming the importance of genetic modulation by dietary factors, and also the need to replicate gene-diet interactions to increase the scientific evidence and finally to contribute to personalize diet based on genetic susceptibility.

Author	Phenotype	Gene	Gen-diet interaction	
Lopez-Miranda et al., 1994	Lipid metabolism	LDL-C	-75G>A <i>APOA1</i>	They studied the influence of the LDL-C postprandial response to MUFA intake. After high MUFA intake carriers of A allele had higher LDL-C but not the GG.
Jansen et al., 1997		LDL-C	Thr347Ser <i>APOA4</i>	347Ser carriers had lower LDL-C postprandial response when they switched from a diet rich in SFA to a diet based on NCEP.
Campos et al., 2001		VLDL, HDL-C	<i>APOE</i>	Higher VLDL and lower HDL-C in E2 with a high SFA intake.
Corella et al., 2001		LDL-C	<i>APOE</i>	E2 carriers had lower LDL-C in those with moderate alcohol consumption than in non-consumers. However, carriers of E4 allele that had a moderate alcohol consumption had higher LDL-C.
Brown et al., 2003		TC and LDL-C	T455C y T625 <i>APOC3</i>	In -45T and -625T homozygous subjects, SFA intake was associated with higher LDL-C.
Tai et al., 2005		TG and <i>APOCIII</i>	L162V <i>PPARA</i>	Carriers of 162V allele had higher TG concentrations and <i>APOC3</i> levels only in that subjects with a low PUFA consumption.

Author	Phenotype	Gene	Gen-diet interaction
Robitaill e et al., 2007	Lipids	Leu72Met Grelina	Interaction with fat intake modulating TG concentrations.
Ordovas, 2002	HDL-C	-514C>T <i>LIPC</i>	T allele was associated with higher HDL-C in subjects that had an intake of fat < 30% of total energy.
Luan et al., 2001	BMI	Pro12Ala <i>PPARG</i>	AlaPPARG carriers had higher BMI than ProPPRG, but when the ratio PUFA:SFA was high, opposite results were shown.
Memisoglu et al., 2003	BMI	Pro12Ala <i>PPARG</i>	Among ProPro subjects, those with higher fat intake of had higher BMI compared to those with lower intake . No association was shown for 12Ala.
Robitaill e et al., 2007	WC	Pro12Ala <i>PPARA</i>	Interaction Pro12Ala with the intake of fat modulating waist circumference.
Corella et al., 2009	BMI and Obesity	-265 T>C <i>APOA2</i>	C carriers that had high SFA intake had higher prevalence of obesity.
Corella et al., 2011	BMI and obesity	-265 T>C <i>APOA2</i>	Interaction of -265CC with SFA intake modulating risk of obesity.
Corella et al., 2010	BMI and obesity	rs9939609 <i>FTO</i>	Interaccion of rs9939609 with educational level. A carriers had higher risk of obesity and BMI only in those without university studies.
Razquin et al., 2010 (A)	Weight	rs9939609 <i>FTO</i>	A allele was associated with higher weight at the beginning of the study. After three years of intervention with Mediterranean diet, A carriers had a lower weight gain.
Razquin et al., 2010 (C)	Weight	+45T/G, +276G/T <i>Adiponectin</i>	Genotype GG (+45T/G) was associated with higher weight gained during three years of intervention. TT (+276G/T) was associated with higher weight gain in men. Mediterranean diet supplemented with VOO and nuts reverted this effects.
Razquin et al., 2010 (B)	Weight	-174G/C <i>IL-6</i>	CC subjects that followed Mediterranean diet supplemented with VOO had lower weight gain after three years of intervention.

LDL-C: Low density lipoprotein cholesterol; VLDL: Very low density lipoprotein cholesterol
HDL: High density lipoprotein cholesterol; TC: Total cholesterol; BMI: Body mass index
WC: Waist circumference

Table 2. Nutrigenetics studies analysing gene-diet interactions.

5.2 Nutrigenomics in the prevention of cardiovascular diseases

As we explained in the previous section, there is increasing evidence that Mediterranean diet, whose emblematic component is virgin olive oil (VOO), has a beneficial effect on diseases associated with CVD and other diseases (neurodegenerative diseases, cancer).

VOO is a functional food containing high levels of MUFA and a number of minor components (bioactive components). These components are known as phenolic compounds. These phenolic compounds have a key role in plasma lipid concentrations and oxidative damage (that is related to CVD). It is believed that the benefits from the consumption of VOO are due to the interaction of its nutrients and minor components with genes. Several studies have shown changes in gene expression mediated by the consumption of VOO. In table 3 some studies analyzing changes in gene expression of some genes related to CVD by Mediterranean diet or its components are shown.

Autor	N /duración	Intervención	Cambios de expresión	Ruta implicada
Konstantinidou et al., 2010	N=90 (20-50 years) 3 months	1. MD +VOO 2. MD+ VOO 3. Control	INF-y ARHGAP15 IL7R ADRB2 POLK	Inflammation Oxidative stress
Konstantinidou et al., 2009	N=6 Postprandial study (0-6h)	50 ml VOO (26082 genes)	USP48 OGT AKAP13 IL10 DCLRE1C POLK	Cellular process Inflammation DNA damage
Khymenets et al., 2009	N= 6 H(262-28 years; 4 M (20-44) 3 weeks	VOO (25 ml/ day)	ADAM17, ALDH1A, BIRC1, ERCC5, LIAS, OGT,PPARBP, TNFSF10, USP48, XRCC5	Mechanism involved in atherosclerosis
Camargo et al., 2010	N=20 with MS (56 years, 9 H, 11 M) Postprandial state	Breakfast with VOO (40 ml).	EGR1 IL1B, IL6 CCL3 CXCL1 CXCL2 CXCL3 CXCR4 TRIB1, NFKBIA	Inflammation
Llorente-Cortes et al., 2009	N=48 (55-80 years)	MD+VOO MD+nuts Control group	COX-2 LRP1 MCP-1 CD36 TFPI	Inflammation, foam cell formation, thrombosis
De Mello VD et al., 2008	34overweight MS 33 weeks	Weight reduction (n=24) Control group (n=10)	TLR4 TLR2 CCL5 TNFRSF1A IKBKB	Related to insulin sensitivity
Crujeiras et al., 2008	12 Obese (37,7 years) 8 weeks	Hypocaloric diet	SIRT1 SIRT2 NDUFS2	

MD: Mediterranean diet; VOO: Virgin olive oil; MS: Metabolic Syndrome

Table 3. Nutrigenomics studies

6. Conclusions and future directions

Current results of the studies analyzing the effect of Mediterranean diet on CVD suggest that adherence to the Mediterranean dietary pattern was associated with lower CVD phenotypes. Mediterranean diet has a beneficial effect on abdominal obesity, lipids levels, glucose metabolism, blood pressure and inflammation. The antioxidant and anti-inflammatory effects of the Mediterranean diet as a whole, and also the effects of the individual components, specifically VOO, fruits, vegetables, whole grains and fish could offer an explanation for the aforementioned beneficial effects of the Mediterranean diet.

These results are of considerable public health importance because this dietary pattern can be easily adopted by all population groups and various cultures, and they cost effectively serve for the primary and secondary prevention of CVD.

On the other hand, the current evidence from nutrigenetics studies is not enough to begin implementing specific personalized information. However, there is a large number of examples of common SNPs modulating the individual response to Mediterranean diet and other components as proof of concept of how gene-diet interactions can influence lipid metabolism, BMI, or other disorders, and it is expected that in the near future we will be able to harness the information contained in our genomes by using the behavioural tools to achieve successful personalized nutrition. In order to achieve that, it is recommended that future advises on nutrition will be based on studies using the highest level of epidemiological evidence and supported by mechanistic studies within the Nutritional Genomics and Systems biology. However, we have to take into account that in order to forget successful results in personalized nutrition through genetic variation, health professionals need to be prepared to learn and interpret genetic knowledge about their patients.

7. References

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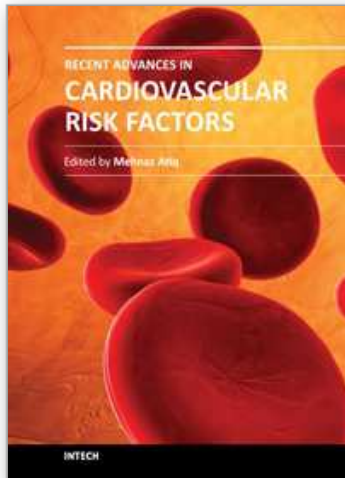
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Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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