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Dietary Patterns:
Nutrition, health, and the environment

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Summary

Abstract

Growing evidence stresses the critical role of nutrition and dietary patterns in maintaining human health and preventing several chronic non-communicable diseases and certain types of cancer. In particular during the last decades the Mediterranean Diet acquired more and more importance. Defined a nutritional model shared by the population surrounding the Mediterranean basin around the fifties by Ancel Keys, is nowadays composed by olive oil, cereals, seasonal fruit and vegetables, legumes and nuts, moderate-to-high fish intake, seafood, fermented dairy products, poultry and eggs, together with a limited consumption of red and processed meats and sweets, and a moderate alcohol intake - when culturally allowed. Firstly, the adherence to the MD of a sample of pregnant women from Gran Canaria (Spain) and its possible implications in their newborn anthropometrics, is described. In second instance, 44 subgroup analyses within the scope of the PREDIMED study are presented. It consists of a large, parallel group, multicentre, randomized, controlled, single-blind, nutritional-intervention trial, conducted in Spain in 2003-2011 on 7447 participants, originally designed to assess the effects of the MD on the primary prevention of cardiovascular disease.

Of note, beyond the largely demonstrated beneficial effects of the MD on human health, it is important to observe how food consumption, production and distribution patterns represent one of the main causes of ecological pressure on the environment. If so, global population's dietary patterns link worldwide human health with the environmental sustainability and, considering population's growing projections, this becomes an issue of major importance. In this perspective, we propose a new graphical representation of the MD pyramid, revisited according to the environmental aspects of food chain and represented with a third dimension. The overall value of the MD on the environmental, social, cultural, economic and nutritional/health dimensions, makes it a model that is considered as intangible heritage of humanity, but with added environmental value. The virtues of the MD and particularly its value for environmental preservation and protection need to be efficiently communicated and applied in an integrated manner at multiple levels. In this way diet will have a potential to nourish human beings and preserve our environment.

1. Background

"*Let food be thy medicine and medicine be thy food*", is a phrase commonly attributed to Hippocrates of Cos (460-377 B.C. approximately) and quoted by scientists for the last decades. If we consider that the majority of people ingests food at least two times a day, each single day of his life, does it exist a medicine that we take so frequently and for so long? The answer to this question gives us the idea of the wisdom enclosed in the abovementioned statement. Recent evidence suggests that this is a misquotation and, even if the Hippocratic medicine considered food as an important contributor to people's health or disease status, it cannot be attributed with certainty to the father of Western medicine [1]. Nevertheless, apart from these philological diatribes, it is well ascertained that a balanced diet, particularly rich in fruit and vegetables, has an essential role in maintaining health and preventing the development of chronic Non-Communicable Diseases (NCDs) and some type of cancers. The investigation about the benefits of diet on human health regarded traditional diets of several continents and populations (e.g. Western diet, Mediterranean Diet), dietary patterns and single nutrients.

1.1. The Mediterranean Diet: historical hints

The term Mediterranean Diet (MD) define a nutritional model proposed some decades ago by Ancel Keys (1904 – 2004), based on the dietary traditions shared around 1950s by the populations living between the Hellenic peninsula, southern Italy, and the countries overlooking the Mediterranean Sea [2]. In this sense, the

MD is the dietary pattern that historically and culturally prevailed among the populations residing in the Mediterranean region before globalization influenced culture and lifestyle, including feeding habits and dietary patterns [3,4]. The Mediterranean dietary pattern historically included non-starchy vegetables, which were present - according to the season - in abundancy and assortment, minimally processed whole-grain cereals, legumes, nuts, and seeds [5]. Nowadays the MD is composed by plentiful use of olive oil (which represents the principal source of fat), high consumption of cereals, fruit, vegetables, legumes and nuts, moderate-to-high fish intake, seafood, fermented dairy products (in particular yogurt and cheese), poultry and eggs, together with a limited consumption of red and processed meats and sweets, and a moderate alcohol intake - when culturally allowed, and preferably red wine during the main meals [6-8]. Of note, it is important to observe that, even if sharing common eating styles or patterns, the dietary traditions of the Mediterranean regions differ importantly from each other. Nevertheless, they all could be considered as variants of the wider and most comprehensive MD [9].

The scientific investigation on the effects of the MD on human health did not begin until the 20th century. Among those researches, the Seven Countries study was the first one to show a protective effect of the MD, or some of its components. In particular, the findings of the study showed a strong inverse association between monounsaturated fatty acid intake (of which the main source is represented by olive oil, an essential component of the MD) and overall mortality, especially due to coronary heart disease and cancer [10]. Afterwards, the MD and its effects on health were mostly investigated by means of observational studies and personal reviews. In this sense, analyzing cohorts of elderly participants, some authors observed that the MD was inversely associated with all-causes mortality. Trichopolou et al.'s study (1995), carried out on a cohort of 182 subjects aged 70 years or more, living in a Greek rural setting, showed that a one-point increase in the diet score (devised a priori on the components of the traditional Greek MD), was associated with a significant 17% reduction in overall mortality (95% confidence interval (CI) 1%, 31%) [6]. A prospective cohort study, involving 330 subjects of both sexes aged 70 years or more, carried out in Melbourne, Australia, evaluated if the adherence to the MD affected survival of elderly people in developed non-Mediterranean countries. The findings showed that a one-unit increase in a diet score, devised a priori on the characteristics of the diet traditionally present in the Mediterranean region, was associated with a 17% reduction in overall mortality (two-tailed P value 0.07) [11]. The study by Lasheras et al. (2000) evaluated the interactive effects of MD and age on survival of a cohort of 161 Spanish elderly participants, after controlling for several confounding factors. The results showed that the traditional MD was associated with a significant reduction in overall mortality in elderly subjects aged <80 years (but not in subjects aged 80 years or more). Moreover, a one-unit increase in the diet score predicted a 31% reduction in mortality in participants aged <80 years (95% CI: 7%, 57%) [12]. Similarly, the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort study was carried out in Greece on approximately 22,043 subjects to investigate the relation between adherence to the MD and total mortality. After a median of 44 months follow-up, the findings of this study showed that a higher adherence to the MD was associated with a reduction in mortality from all-cause, and especially coronary-heart disease mortality and mortality due to cancer [13]. Similar findings have been reported by the HALE (Healthy aging: a Longitudinal study in Europe) study follow-up, conducted on 1507 apparently healthy men and 832 women, aged 70 to 90 years from 11 European countries. The results of this study showed that the adherence to a MD (hazard ratio (HR), 0.77; 95% CI, 0.68-0.88) was associated with a lower risk of all-cause mortality (HRs controlled for age, sex, years of education, body mass index, study, and other factors). Similar results were observed for mortality from coronary heart disease, cardiovascular diseases, and cancer [14]. The NIH-AARP (National Institute for Health - American Association of Retired Persons) Diet and Health study, carried out on a sample of 214,284 men and 166,012 women, showed that the MD was associated with reduced all-cause and cause-specific mortality [15]. Similarly, the Nurse's Health study conducted on 74,886 women aged 38 to 63 years, showed that the subjects with a higher MD score were at lower risk for both coronary heart disease and stroke compared with those with the lowest score (relative risk (RR), 0.71; 95% CI, 0.62 to 0.82; P for trend<0.0001 for coronary heart disease; RR, 0.87; 95% CI, 0.73 to 1.02; P for trend=0.03 for stroke). Also, cardiovascular disease mortality was significantly lower among women presenting the higher score (RR, 0.61; 95% CI, 0.49 to 0.76; P for trend<0.0001) [16]. In line with that, two case-control studies showed an inverse association between MD adherence non-fatal coronary events incidence. The first one was conducted on 342 participants (171 patients who suffered their first acute myocardial infarction and 171 matched controls) [17], while the second was carried out on 848 cases and 1,078 controls [18]. Also, the Lyon Heart Study in France revealed that modified MDs were associated with remarkable reductions in coronary heart disease event rates and cardiovascular disease related mortality [19], as well as other small-scale clinical trials [20].

In the last years, the number of randomized controlled trials and meta-analyses regarding the effects of the MD on various health outcomes increased significantly. In a meta-analysis of observational studies and randomized trials, Dinu et al. (2018) observed a robust evidence (supported by a P-value<0.001, a large simple size, and not a considerable heterogeneity between studies), regarding that a greater adherence to the MD is associated with a reduced the risk of overall mortality, cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases and diabetes [21]. Nowadays, the importance of the MD pattern is increasing considerably, due to its role in the prevention of cardiovascular diseases. In particular, the results showed by the Seven Countries study [10], contributed to the increasing importance of the MD in cardiovascular epidemiology, up to the qualification of the Mediterranean Food Pattern as potentially effective for the prevention of coronary heart disease by the American Heart Association [22].

Although the first studies showing the benefits of the MD on health focused on the protective effect against cardiovascular diseases, later its effects on other health aspects were also investigated. As for example, an inverse association between specific nutrients, food components and the Mediterranean dietary pattern, and several health conditions (e.g. specific types of cancer, diabetes mellitus, obesity, cognitive decline and mental health, respiratory diseases, osteoarthritis, and quality of life or healthy aging) was reported [21]. To date, several studies have been carried out in the scope of MD and its relationship with human health, and the evidence of its beneficial role is being constantly enhanced [23]. Taking a step further, in addition to the effects of nutrition on human health, it has to be noted that food consumption, production and distribution patterns represent one of the main causes of ecological pressure on the natural environment. If so, global population's dietary patterns link worldwide human health with the environmental sustainability and, considering population's growing projections, this becomes an issue of major importance. Therefore, food policy, dietary guidelines and food security strategies need to evolve from their historical approach focused primarily on nutrients and health, to a new one that takes into consideration the environmental, socioeconomic and cultural impact of diets. In this way a healthy diet for the human would imply a healthy (and so ecologically sustainable) management of our environment.

The present work represents the compendium of the researches and investigations conducted during these two years of PhD in Sciences for Public Health. The first part of my path took place at the Università degli Studi di Milano, Department of Clinical and Community Sciences (DISCCO) under the guidance of Prof. Carlo La Vecchia, while the second took me to the Canary Islands (Spain) at the University of Las Palmas de Gran Canaria, Instituto de Investigaciones Biomédicas y Sanitarias (IUIBS), to collaborate with Prof. Serra-Majem. This collaboration lead to the production of several manuscripts, some in the scope of the PREDIMED (PREvención con DIeta MEDiterránea) and PREDIMED-Plus studies while others dealing with public health issues. In the course of the discussion you will find an introduction, briefly describing the background of the work and some historical hints regarding the Mediterranean Diet. Then, the published papers into which I have worked during these years will be described in detail. I will start from the studies dealing with the benefits of the dietary patterns (especially the Mediterranean Diet) for human health, up to the benefits of the Mediterranean diet for the planet. I hope you will enjoy it.

1.2. References

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2. Mediterranean Diet and human health

2.1. Adherence to Mediterranean diet during pregnancy. Results from a sample of Canarian pregnant women

From the published paper*: Tomaino L, Reyes Suárez D, Reyes Domínguez A, García Cruz LM, Ramos Díaz M, Serra Majem L. Adherence to Mediterranean diet is not associated with birthweight - Results form a sample of Canarian pregnant women. Nutr Hosp. 2020 Feb 17;37(1):86-92. English. doi: 10.20960/nh.02780. PMID: 31876428*

The prevalence of overweight and obesity showed and increasing trend over the past few years. The burden of this epidemic represents a public health issue worldwide. Spain, and especially the Canary Islands, are not exempt. Pregnancy is a situation of physiologic weight gain, and the amount of such increase during gestation can affect the health status of both the mother and her baby. Thus, an optimal dietary style becomes of importance. Given the benefits of the Mediterranean diet (MD) on various health outcomes, in the paper: "Adherence to Mediterranean diet is not associated with birthweight – Results form a sample of Canarian pregnant women" [1], we aimed to study the adherence to this dietary pattern in a sample of Canarian pregnant women, and to investigate its association with their newborn's weight. Briefly, the adherence to MD as well as clinical history and anthropometrics were assessed in a sample of pregnant women followed at a Canarian hospital. Similarly, their newborn characteristics were studied. The findings of this study showed an overall low adherence to MD, with no association between this trend and birthweight. In conclusion, specific tools should be tailored to the target population to assess adherence to MD, and further efforts should be made to promote a healthy eating pattern and lifestyle among the pregnant population [1].

2.1.1. Introduction

The World Health Organization (WHO) defines overweight and obesity as an abnormal or excessive fat accumulation that represent a risk to health, as well ascertained risk factors for chronic noncommunicable diseases (NCD) such as diabetes, cardiovascular diseases and cancer. In 2016, approximately 39% of adults over 18 years old were overweight, and 13% obese [2]. In Spain and in the Canary Islands, the prevalence of obesity represents a Public Health issue, as outlined by epidemiological studies over the last decade [3]. In 2004, the DORICA study, showed a prevalence of obesity in the Spanish adult population aged 25–60 years of 15.5% (13.2% in men and 17.5% in women) [4,5], and the highest prevalence was recorded in the south and north-east of Spain and in the Canary Islands (14,21% in men and 22,22% in women) [6]. The ENRICA study, conducted between the years 2008 and 2010, observed that about the 36% (32% of men and 39% of women) of the Spanish population aged 18 years old or more had abdominal obesity, with a higher prevalence of obesity in the Canary Islands and in the south of Spain [7]. Data collected between May 2014 and May 2015 showed that, in the Spanish population aged 25 to 64 years old, the prevalence of overweight and obesity was 39,3% and 21,6%, respectively [8]. The burden of this epidemic affects not only adults but also the pregnant population, as the number of women who are overweight or obese at the moment of conception is increasing. According to a study conducted at the Maternal and Child University Hospital of the Canary Islands, Spain, on a sample on women who gave birth at the same center during 2008 (n = 6693), the prevalence of overweight and obesity prior to gestation was 25.0% and 17.1%, respectively [9]. Pregnancy is an inevitable situation of weight gain, and the amount of such increase during gestation can affect the immediate and future health of both the mother and her baby. The available scientific evidence supports the association between excessive weight gain during pregnancy and increased weight of the newborn, and between inadequate weight gain during pregnancy and reduced birth weight [10]. For this reason, in 1990, the Institute of Medicine (IOM) developed guidelines for recommended ranges of gestational weight gain, in order to optimize fetal growth as well as maternal and infant consequences. In 2009, the recommendations have been revised according to the Body Mass Index (BMI) cut-off points of the

WHO [11,12]. Elevated BMI during pregnancy implies an increased risk of developing gestational hypertension and diabetes, preeclampsia, spontaneous abortion, episiotomy or cesarean sections [13]. In the newborn, maternal obesity increases the probability of congenital anomalies, macrosomia, and the appearance of obesity in childhood [14-16]. An adequate nutritional intake not only allows to enhance the health of the woman and prevent gestational diseases, but also relates to the health of the baby. In this sense, published data [17] show that the habitual consumption of foods representative of the Mediterranean Diet (DM) can have beneficial effects on gene expression, normal intrauterine growth, respiratory function, allergies, neural tube defects and preterm birth.

The aim of the present study is to investigate, in a Canarian sample of pregnant women, the possible associations between their adherence to the MD and the birthweight of their babies.

2.1.2. Materials and Methods

A retrospective cross-sectional study on a sample of 218 women and their newborns was conducted at the Hospital Insular Materno Infantil de Gran Canaria (HIMIGC), Spain. Eligible participants were healthy women who gave birth in the HIMIGC, Spain, between November the 1st and December the 31st, 2018. Subjects had a singleton pregnancy and expressed voluntary participation in the study providing a written informed consent. Women with any clinical condition other than type 1 or 2 diabetes mellitus (DM) or hypertension, women who underwent high-risk pregnancies, or who carried a multiple pregnancy, as well as those who gave birth to children with any pathology, were considered not eligible for the study. Participants' anthropometrical characteristics (weight and height) were assessed at the beginning of the pregnancy and at the end of it. The other variables investigated in the present study were assessed trough a questionnaire the women were provided and filled in the presence of the investigator. Among the variables related to the mother were: age, nationality, educational level, employment situation, marital status, family history of DM, obesity and/or hypertension, personal history of DM, hypertension, gestational diabetes and hypertension, preeclampsia, smoking, alcohol and drug intake, and physical activity. The corresponding Metabolic Equivalents (METs) were calculated assigning to light exercise (i.e. walking) a value of 2.5 METs, and to moderate exercise (i.e. weightlifting, running) a value of 4 METs [18,19]. Newborn's characteristics investigated in the present study were: gestational age (and subsequent classification in pre-term, at term, and post-term), gender, birthweight (in grams), birth-height (centimeters), and cranial circumference (in centimeters). In order to estimate mother's dietary habits, and in particular the degree of adherence to the MD, a survey validated by the PREDIMED study (Prevención con Dieta MEDiterránea) [20-22] was used. It consists of 14 items, known as the Mediterranean Diet Adherence Screener (MEDAS) [23]. Each item scores one point in case of a positive answer or does not score otherwise. The total value has a range of 0-14. The items included in the questionnaire are reported in Figure 1.

Figure 1. The 14-point Mediterranean Diet Adherence Screener (MEDAS)

	Frequency*
1. Do you use olive oil as the principal source of fat for cooking?	Yes
2. How much olive oil do you consume per day (including that used in frying, salads, meals eaten away from home, etc.)?	≥4 Tbsp[1]
3. How many servings of vegetables do you consume per day? Count garnish and side servings as 1/2 point; a full serving is 200 g	≥2
4. How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	≥3

5. How many servings of red meat, hamburger, or sausages do you consume per day? A full serving is 100–150 g.	<1
6. How many servings (12 g) of butter, margarine, or cream do you consume per day?	<1
7. How many carbonated and/or sugar-sweetened beverages do you consume per day?	<1
8. Do you drink wine? How much do you consume per week?	≥7 cups[2]
9. How many servings (150 g) of pulses do you consume per week?	≥3
10. How many servings of fish/seafood do you consume per week? (100–150 g of fish, 4–5 pieces or 200 g of seafood)	≥3
11. How many times do you consume commercial (not homemade) pastry such as cookies or cake per week?	<2
12. How many times do you consume nuts per week? (1 serving = 30 g)	≥3
13. Do you prefer to eat chicken, turkey or rabbit instead of beef, pork, hamburgers, or sausages?	Yes
14. How many times per week do you consume boiled vegetables, pasta, rice, or other dishes with a sauce of tomato, garlic, onion, or leeks sautéed in olive oil?	≥2

* Criterion to score 1 point. Otherwise, 0 recorded.
[1] 1 tablespoon = 13.5 g.
[2] 1 cup = 100 mL.

The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the referent Ethics Committee of the Hospital Insular Materno Infantil de Gran Canaria, Spain. Participants expressed voluntary participation in the study providing a written informed consent. All subject data were coded to preserve confidentiality.

Statistical analysis was performed using R software (www.r-project.org) and SPSS, version 25 (IBM). Tests for assessing the normal distribution of the continuous variables were performed, as well as test for the outliers detection. The sample was divided into three groups according to the MEDAS punctuation. The first group (score from 0 to 4) corresponds to a low adherence to MD, the second (ranging from 5 to 8) to an average adherence, while the third group (from 9 to 13) represents the best adherence to the MD. A descriptive analysis was performed according to the women's adherence to MD, with the objective of describing the sample according to their nutritional habits. The p-value was calculated by Student's t-test and Chi-square analysis or Fisher's test for continuous and discrete variables, respectively, in order to verify the existence of between-group statistically significant differences (p-value ≤ 0.05). To analyze the possible associations between the independent variable of MD adherence of the mother and the newborn's weight, a linear model of multiple regression was fitted to our data. According to the available evidence, the adjustment covariates that have been included in the model, due to their relationship with the newborn's weight, were: mother's age, BMI before pregnancy and the gestational weight gain, smoking, physical exercise, diabetes and gestational hypertension, and the gestational age of the newborn.

2.1.3. Results

The MEDAS showed a mean of 6.61 out of 13 points, indicative of an overall low adherence to the MD. Table 1 reports the anthropometric characteristics of the 218 pregnant women according to the MD adherence groups. The mean age of the study sample was 32 years old, ranging from a minimum of 17 to a maximum of 51 years old. A statistically significant difference in age was observed across the three MD adherence groups. Before pregnancy, the women with lower adherence to MD were characterized by a condition of normal weight, while the other groups by a condition of overweight. However, these differences did not show to be statistically significant. The differences between weight gain during pregnancy have not been significant either, although the average weight gain of the whole sample (12.6 ± 7.44 kg) is in line with the recommendations of the IOM for the normal weight women (increase of 11.3 - 15.9 kg throughout the whole pregnancy).

Table 1. Mother's anthropometric characteristics to the Mediterranean Diet Adherence Score (MEDAS) group

	Low adherence (0-4) N = 44		**Average adherence (5-8) N = 122**		**High adherence (9-13) N = 52**		**p-value**
	N	**Mean (sd)**	**N**	**Mean (sd)**	**N**	**Mean (sd)**	
Age (years)	44	28,9 (5,9)	122	32,4 (6,3)	52	34,6 (5,5)	< 0,001*
Weight at the beginning (kg)	44	63,69 (17,70)	120	69,58 (18,20)	50	67,67 (12,69)	0,145*
Weight at the end (kg)	44	77,38 (16,59)	121	81,71 (17,15)	50	79,54 (11,59)	0,282*
Weight increase (kg)	44	13,69 (5,53)	121	12,70 (8,79)	52	11,41 (5,04)	0,321*
BMI (kg/m^2) before pregnancy	44	24,22 (6,71)	120	25,78 (6,45)	50	25,65 (4,94)	0,346*
BMI (kg/m^2) after pregnancy	44	29,40 (6,02)	121	30,29 (6,08)	50	30,15 (4,46)	0,673*

** p-value obtained by ANOVA.*

Table 2 reports the clinical and sociodemographic characteristics of the pregnant women, as well as their personal clinical history. The majority of them were European, being the least of them from Asia, South America or Africa. The educational level across the three groups of MD adherence was statistically significant (p <0.001), being the basic level studies/baccalaureate the most represented ones. Similarly, differences in the employment situation across the three groups, turned out to be significant. Tobacco smoking and alcohol consumption have been investigated and, although represented by a restricted number of women, showed significance through the three groups of MD adherence (p = 0.042 and p = 0.001, respectively). The practice of some type of physical activity, either of light or moderate intensity, assessed through the questionnaires, showed to be statistically significant (p = 0.037) across the three groups, being the light intensity exercise the more practiced. The mean METs per week was 1254.78 ± 919.60 and 2640 ± 2336.15 METs, for the light and moderate intensity exercise, respectively. Neither arterial hypertension, defined by values of systolic and diastolic blood pressure higher than 140/90 mmHg, nor gestational hypertension showed significant differences among the three groups of MD adherence. The same observation was made as far as diabetes was concerned.

Table 2. Sociodemographic and clinical characteristics of the mother according to the Mediterranean Diet Adherence Score (MEDAS) group

	Low adherence (0-4) N = 44	Average adherence (5-8) N = 122	High adherence (9-13) N = 52	p-value
	N (%)	**N (%)**	**N (%)**	
European nationality	37 (84,1)	106 (86,9)	43 (82,7)	0,759
Education				< 0,001°
- Primary	27 (61,4)	40 (32,8)	17 (32,7)	
- Bachelor	15 (34,1)	43 (35,2)	14 (26,9)	
- University	2 (4,5)	39 (32,0)	21 (40,4)	
Occupation				0,036°
- Unemployed				
- Employed	18 (40,9)	30 (24,6)	7 (13,5)	
- Housewife	18 (40,9)	71 (58,2)	35 (67,3)	
	8 (18,2)	21 (17,2)	10 (19,2)	
Civil status (married/couple)	39 (88,6)	116 (95,1)	50 (96,2)	0,238
Smoking				0,042°
- No smoker	26 (59,1)	87 (71,3)	44 (84,6)	
- Smoker	11 (25,0)	15 (12,3)	5 (9,6)	
- Ex smoker	7 (15,9)	20 (16,4)	3 (5,8)	
Alcohol (occasionally)	24 (54,5)	37 (30,3)	11 (21,2)	0,001
Physical activity				0,037
- Light	16 (36,4)	66 (54,5)	33 (63,5)	
- Moderate	3 (6,8)	3 (2,5)	3 (5,8)	
1st gestation	16 (36,4)	50 (41,0)	16 (30,8)	0,438
Arterial hypertension	1 (2,3)	4 (3,3)	1 (1,9)	1,000
Diabetes	0 (0)	1 (0,8)	0 (0)	1,000
Gestational hypertension	8 (18,2)	11 (9,0)	4 (7,7)	0,188
Gestational diabetes	2 (4,5)	24 (19,7)	36 (16,5)	0,054
Preeclampsia	0 (0)	6 (4,9)	4 (7,7)	0,201

° *p-value obtained by Fisher's exact test. The other p-values have been obtained according to the Chi-square test*

Table 3 shows the newborns characteristics according to the mother's MD adherence group. The sample was represented by the same number of males and females. The estimate of the mean birthweight was 3282,52 (± 554,26) grams, the mean length was 50,07 (± 2,40) centimeters and the mean cranial circumference was (34,09 ± 1,8) centimeters. The association between gestational age and MEDAS showed to be statistically significant (p = 0.047), as well as the association between length at birth and mother's MEDAS (p = 0.011).

Table 3. Characteristics of newborns according to the Mediterranean Diet Adherence Score (MEDAS) group of the mother

	Low adherence (0-4) N = 44	Average adherence (5-8) N = 122	High adherence (9-13) N = 52	p-value
	N (%)	N (%)	N (%)	
Male gender	28 (63,6)	55 (45,1)	26 (50)	0,109
At term/post-term	43 (97,7)	109 (89,3)	51 (98,1)	0,047
	Mean (sd)	**Mean (sd)**	**Mean (sd)**	
Birthweight (g)	3275,98 (501,74)	3251,94 (598,82)	3380,31 (498,41)	0,378*

Length at birth (cm)	50,36 (2,20)	49,67 (2,61)	50,81 (1,81)	0,011*
Cranial circumference at birth (cm)	34,51 (1,53)	33,95 (2,00)	34,14 (1,54)	0,217*

** p-value obtained by ANOVA. The other p-values have been obtained according to the Chi-square test.*

Table 4 describes the results obtained by the multiple linear regression model fitted to our data. Of the covariates analyzed in the model, mother's BMI before pregnancy showed to be statistically significant (p = 0.001), as well as the weight gain during pregnancy (p = 0.020). Finally, the gestational age was statistically associated with the weight of the newborn (p<0,001).

Table 4. Multiple linear regression model

	Coefficient	Signif.
Low MD adherence group vs Average	5,79	0,950
High MD adherence group vs Average	61,91	0,465
Mother's age (years old)	-2,07	0,718
BMI before pregnancy	22,10	0,001
Weight gain during pregnancy	14,43	0,020
Smoker vs no-smoker	-125	0,206
Ex-smoker vs no-smoker	-103,50	0,304
Gestational diabetes	174,78	0,068
Gestational hypertension	-136,21	0,234
At term/post-term vs pre-term	708,60	<0,001

Abbreviations: MD: Mediterranean Diet; BMI: Body Mass Index

2.1.4. Discussion

Overweight and obesity represent well established risk factors for NCD such as type 2 diabetes, cardiovascular diseases and cancer, and their burden is increasing over the last years [2]. Such conditions represent a risk factor also in the pregnant population and could possibly influence the intrauterine growth of the fetus and the newborn's health outcomes. Nutrition during pregnancy play an important role in the evolution of gestation and in the health of the newborn. An adequate nutritional intake not only allows to enhance the health of the woman and prevent gestational diseases, but also relates to the health of her baby. A systematic review conducted by Amati et al. [17] examining 22 published papers on the issue, showed that following a MD during pregnancy has a beneficial role on a wide range of outcomes, among others gestational diabetes in the mother and congenital defects in the offspring. Similar findings were observed in a recent case control-study by Olmedo-Requena et al., where the authors concluded that a high adherence to the MD prior to pregnancy was associated with a lower risk of developing gestational diabetes [24]. Moreover, various authors observed that the adherence to a Mediterranean dietary pattern, was associated, among others congenital defects and clinical outcomes, with a reduced risk of gastroschisis [25], and spina bifida in the newborn [26]. The beneficial effects of adherence to the MD during pregnancy on the mother's and offspring heath are well known and supported by growing evidence [27]. Nevertheless, in our study, an overall low adherence to the MD was observed, being such figure inferior to the expected. In other words, the population examined did not follow an optimal diet even in that period of life in which it would be more desirable: pregnancy.

Two hypotheses can be advanced in order to explain this observation. The first one is that dietary habits among the Canarian population had changed over the last years. This is possibly due to the adoption of an occidental-style diet in the nineties, parallel to the increasing of tourism in these areas [28]. The second hypothesis is that the MEDAS does not fit with our study's population, particularly because it is not addressed to pregnant women. In fact, as reported by Schroder et al., the Mediterranean Diet Adherence Score was validated for Spanish older men and women at high risk for chronic heart disease [23]. Although successfully utilized in many trials, such as the PREDIMED Study, we consider that the MEDAS is not able to provide exhaustive information on diet quality in the population of pregnant women. Moreover, the MEDAS assess diet quality but does not account for the daily caloric intake nor for the intake of other kind of foods that could affect negatively subjects' health.

Therefore, among the limitations of the present study, we have to outlie that the MEDAS questionnaire was not accompanied by any food frequency questionnaire, which could have allowed us to compare the MEDAS punctuation with a reference method, as done by other authors [29]. Another important limitation is that the MEDAS questionnaire have been administered to the women just once during the whole pregnancy, while a double (or multiple) administration, i.e. at the beginning and at the end of the gestation would have provided more detailed information about the adherence to the MD. All these reasons may be invoked to explain why, in our study, the mother's adherence to the MD during pregnancy is not significantly associated with the newborn's weight. Moreover, we have to consider a presumable selection bias as the subjects enrolled in this study were voluntary participants, even if, given the results obtained in our population sample, an overestimation of the MD adherence seems unlikely.

Growing evidence suggests that physical activity practice on a regular basis, is associated with improved physiological, metabolic and psychological outcomes. This observation is valid also for pregnant women, where exercise provide benefits not only to the mother (i.e. improvement of cardiovascular function, limited gestational weight improvement, lower limb edema), but also to the newborn (i.e. reduced fat mass or improved stress tolerance) [30,31]. Nevertheless, given the beneficial role of physical activity during pregnancy, an important number of women stop to exercise when they discover to be pregnant. In our sample, the proportion of participants who practiced physical activity of light or moderate intensity was higher in the groups of better adherences to the MD. These findings are possibly due to a more health-conscious lifestyle, as supported by a low prevalence of smoking and alcohol intake, and a high prevalence of higher education among these groups.

In the present study, in order to investigate the association between the mother's adherence to the MD and the newborn's weight, a multiple linear regression model was fitted to the data. We adjusted the model for the covariates known to be associated with the birthweight. The observed significative association between such covariates and the outcome variable is in agreement with the available evidence. According to our data, BMI before pregnancy is significantly associated with birthweight. This finding is in line with the available evidence according to which intra-utero exposure to obesity and diabetes mellitus could even represent a risk factor for the further development of childhood type 2 diabetes mellitus and hypertension [15,32]. Mother's weight gain during pregnancy is associated with some maternal and fetal outcomes [33,34]; for this reason, the optimal weight improvement for the pregnant women have been established by the Institute of Medicine, US, according to their BMI prior to gestation [11]. As weight improvement during pregnancy reflects fetus development, this explain the significant association between such covariate and the birthweight observed in the present study. The gestational age is extremely associated to birthweight as these two features represent the degree of development of the fetus and define its capability to survive in an extra-uterine environment. This explains the results we observed in the present study relative to the gestational age and birthweight.

In conclusion, after adjusting for the covariates known to play a role in the offspring’s birthweight, the mother’s adherence to the MD, assessed by mean of the MEDAS, does not seem associated to the birthweight. These findings confirm the need to combine questionnaire assessing both diet quality than quantity when investigating MD adherence over a sample of subjects, and pave the way for the implementation of questionnaires with better capabilities to characterize the eating habits of the pregnant population. Nevertheless, a healthy lifestyle especially among pregnant women in the Canary Islands should be further promoted in order to improve mothers’ and newborns’ health outcomes.

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2.2. Experimental Outcomes of the Mediterranean Diet: analysis of 44 reports form the PREDIMED dataset

From the published paper: *Kargin D, Tomaino L, Serra-Majem L. Experimental Outcomes of the Mediterranean Diet: Lessons Learned from the Predimed Randomized Controlled Trial. Nutrients. 2019 Dec 6;11(12):2991. doi: 10.3390/nu11122991. PMID: 31817731; PMCID: PMC6949939.*

2.2.1. Background

The PREvención con DIeta MEDiterránea (PREDIMED) study was carried out to test the hypothesis that the MD would be superior to a low-fat diet for cardiovascular disease protection in asymptomatic patients presenting high cardiovascular risk [1]. It is a large, parallel group, multicentre, randomized, controlled, single-blind, nutritional-intervention trial originally designed to assess the effects of the MD on the primary prevention of cardiovascular disease (the complete study protocol is available at: https://www.predimed.es) [2]. The study included two intervention groups (MD supplemented with either nuts or Extra Virgin Olive Oil, EVOO) and a control group (low-fat diet). The PREDIMED study was conducted in Spain from 2003 to 2011 and was funded exclusively by “Instituto de Salud Carlos III”, the public research organization of the Spanish Government, responsible for funding and executing national biomedical research, while food industries provided EVOO and nuts, free of charge.

The study protocol, design and methods of the trial are reported elsewhere [2], and their detailed description goes beyond the objectives of the present work. Briefly, community-dwelling men and women, aged 55–80 and 60–80 years old respectively, without predetermined diagnosis of any cardiovascular disease were included in the study. Subjects were considered eligible to participate if they presented the following inclusion criteria: type 2 diabetes mellitus (DM), or at least three of the following major cardiovascular risk factors: hypertension, high plasma low-density lipoprotein (LDL) cholesterol, low plasma high-density lipoprotein (HDL) cholesterol, overweight or obesity (BMI $\geq$ 25 kg/m^2), current history of smoking and family history of premature coronary heart disease (CHD). The enlistment period started on October 2003 up to June 2009, and enrolled a total of 7447 participants. Subjects were then randomly assigned to one of the three intervention groups (ratio 1:1:1): two groups followed a MD enriched with either EVOO (n = 2543) or nuts (walnuts, almonds and hazelnuts, n = 2454), and the third group (control) was prescribed a low-fat diet (n = 2450). Neither energy restrictions were applied to the groups, nor physical activity status modifications. Adherence to the MD was assessed through a 14-items questionnaire [3] and validated food frequency questionnaires covering 137 food items and vitamin and minerals supplements. Also, fasting blood and urine samples were obtained, and serum, plasma and DNA specimens were stored. Biomarkers of adherence to the supplemental foods (urinary hydroxytirosol as marker of EVOO consumption and plasma α-linolenic acid as marker of walnut consumption) were determined in random sub-samples [4].

The primary objective of the PREDIMED study was to assess the effects of the MD (supplemented with nuts or EVOO) on a composite endpoint of cardiovascular death, myocardial infarction and stroke (which was the primary outcome), compared to a low-fat diet. Several were the secondary endpoints; among them death of any cause, incidence of heart failure, DM, dementia or other neurodegenerative disorders, and major cancers (colorectal, breast, lung, stomach and prostate). Moreover, intermediate outcomes such as blood pressure (BP) variations, blood lipids levels, fasting glycaemia, weight gain, and markers of inflammation modifications were also evaluated [5].

2.2.2. Materials and Methods

With the aim analyse the results of the main and secondary outcomes as the PREDIMED study, we carried out a review and meta-analysis including the records published between February 2006 and August 2019, using the MeSH term “PREDIMED” was used as a key word for the bibliographic research [6]. Titles and abstracts were independently scanned to include all potential studies identified as a result of the researches.

The exclusion criteria were: studies not carried out within the scope of PREDIMED, protocols, letters, commentaries, reviews, studies related to PREDIMED-Plus and studies written in languages other than English. Information for the following variables: number of participants at baseline and at the end of the intervention, characteristics of the participants, duration of the intervention, main objective of the intervention, and conclusions were obtained, as they appeared in the article.

2.2.3. Results

The PubMed search resulted in 375 abstracts. After applying the exclusion criteria, 197 articles remained for analysis. Observational studies, cross-sectional, case control and cohort studies were excluded, as the aim of the review was to examine only experimental studies, so the final selection included 44 papers, as showed in Figure 1. Participants of the PREDIMED study were followed for a median of 4.8 years (interquartile range: 2.8–5.8) [1].

Figure 1. Flow-chart of the selection process

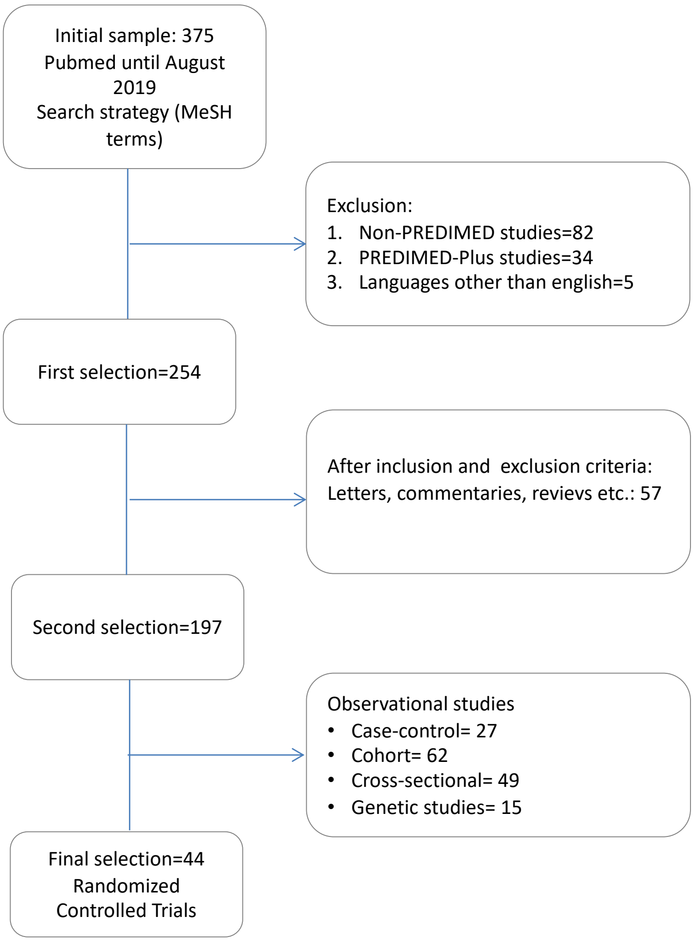

Table 1. Characteristics of the RCTs conducted within the frame of the PREDIMED study, investigating the role of Mediterranean Diet (MD) on cardiovascular disease (CVD) and cardiovascular risk factors.

Aim of the study	Number of subjects	Follow-up median (years)	Main results of the study			1st author, journal, year	Ref.
Cardiovascular Disease							
Incidence of primary endpoint (a composite of CV events: Non-fatal acute myocardial infarction, non-fatal stroke or death from CV causes)	7447	4.8		**MD + EVOO vs control**	**MD + Nuts vs control**	Estruch et al. *N. Engl. J. Med.* 2018	[1]
			HR (95% CI)				
			ITT adjusted analysis *	0.69 (0.53–0.91)	0.72 (0.54–0.95)		
			Primary endpoint excluding site D and second household members °	0.66(0.49–0.89)	0.64 (0.47–0.88)		
			* The intention-to-treat analysis (ITT) included 7447 participants. ° The analysis included 6405 participants. Second members of the same household (*n* = 425) and participants from site D (*n* = 617) were excluded.				
Incidence of heart failure	7403	4.8	**Initial**	**MD + EVOO**	**MD + Nuts**	Papadaki et al. *Eur. J. Heart. Fail.* 2017	[7]
			HR (95% CI) *	0.68 (0.41–1.13) $p = 0.139$	0.92 (0.56–1.49) $p = 0.725$		
			Rectified	**MD + EVOO**	**MD + Nuts**	Papadaki et al. *Eur. J. Heart. Fail.* 2019	[8]
			HR (95% CI **)	0.63 (0.38–1.04) $p = 0.068$	0.91 (0.55–1.50) $p = 0.706$		
			* Models stratified according to centre and history of diabetes and used robust variance estimators ** Models stratified according to centre and history of diabetes and used robust estimate of the variance adjusted for intra-cluster correlation, considering members of the same household and participants in the same clinics of centre D as clusters.				
Incidence of atrial fibrillation	6705	4.7		**MD + EVOO**	**MD + Nuts**	Martínez-González et al. *Circulation* 2014	[9]
			HR (95% CI)	0.62 (0.45–0.85) $p = 0.003$	0.89 (0.65–1.20) $p = 0.43$		

Cardiovascular Risk Factors						
Long-term consumption of a MD could decrease the atherogenicity of LDL particles	210	1.0	**LDL lag time (compared to baseline):**	MD-EVOO: + 6.77%, $p < 0.001$ MD-Nuts: + 6.45%, $p = 0.002$	Hernaez et al. *Mol. Nutr. Food Res.* 2017	[10]
			Cholesterol content in LDL (versus low-fat diet):	MD-EVOO: + 2.41%, $p = 0.013$		
			The cytotoxicity of LDL (compared to baseline):	MD-EVOO: −13.4%, $p = 0.019$		
Improvement of BP induced by a MD would be mediated by the modulation of NO bioavailability/ET-1 levels	90 Non-smoking women with moderate hypertension	1.0	Effect of 1-year follow-up on:		Storniolo et al. *Eur. J. Nutr.* 2017	[11]
			Diastolic BP	MD + Nuts: decreased 5%, $p < 0.0498$		
			Serum stable NO metabolites concentration	MD + EVOO: increased 63.9%, $p = 0.009$		
			Serum ET-1 concentrations	MD + Nuts: decreased 19%, $p < 0.0492$		
Effects of high polyphenol consumption on BP and its relation about production of plasma NO	200	1.0	Changes in BP associated with changes in plasma NO (unadjusted model):		Medina-Remón et al. *Nutr. Metab. Cardiovasc Dis.* 2015	[12]
				MD + EVOO vs control / **MD + Nuts vs control**		
			Systolic BP, coef.B (95% CI)	−6.14 (−12.04 to −2.33) $p = 0.042$ / −2.69 (−8.62 to −3.24) $p = 0.372$		
			Diastolic BP, coef.B (95% CI)	−5.23 (−8.20 to −2.25) $p = 0.001$ / −1.74 (−4.73 to 1.25) $p = 0.253$		
Effects of MD on inflammatory biomarkers related to atherosclerosis and plaque vulnerability	164	1.0	Mean differences (95% CI) in the expression of circulating markers of plaque instability from baseline to 1-months:		Casas et al. *PloS. One.* 2014	[13]
				MD + EVOO / **MD + Nuts** / **Low-fat diet**		
			VCAM (ng/ml)	−138 (−251 to −25.2) * / −208 (−327 to −89.6) * / −55.6 (−173 to 61.5)		

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<tr><td>ICAM (ng/mL)</td><td>−220 (−273 to −166) *</td><td>−30.3 (−76.1 to 15.5)</td><td>62.3 (15.5 to 109) *</td><td>0.04</td></tr>
<tr><td>sE-sel (ng/mL)</td><td>−1.7 (−4.5 to 1.2)</td><td>−4.7 (−7.7 to −1.7) *</td><td>−2.2 (−5.3 to 0.9)</td><td>0.55</td></tr>
<tr><td>IL-6 (pg/mL)</td><td>−0.3 (−0.9 to 0.3) *</td><td>−0.4 (−1.0 to 0.2) *</td><td>0.3 (−1.1 to 1.7) *</td><td></td></tr>
<tr><td>CRP (mg/mL)</td><td>−1.9 (-2.4 to −1.6) *</td><td>−1.4 (−2.1 to −0.7) *</td><td>−0.3 (−1.3 to 0.8)</td><td></td></tr>
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* significant difference ($p < 0.05$) between before and after the intervention
</td><td></td><td></td></tr>
<tr><td>MD effect on 24-hour ambulatory BP, blood glucose, and lipids</td><td>235</td><td>1.0</td><td>
Ambulatory BP, blood glucose and lipids changes at 1 year:
<table>
<tr><th></th><th>MD-EVOO</th><th>MD-Nuts</th><th>Control</th><th>p *</th></tr>
<tr><td>Systolic BP (24 h)</td><td>−2.3
(−4.0 to −0.5)</td><td>−2.6
(−4.3 to −0.9)</td><td>1.7
(–0.1 to 3.5)</td><td><0.001</td></tr>
<tr><td>Diastolic BP (24 h)</td><td>−1.2
(−2.2 to −0.2)</td><td>−1.2
(−2.2 to −0.02)</td><td>0.7 (−0.4 to 1.7)</td><td>0.017</td></tr>
<tr><td>Glucose (mg/dL)</td><td>–6.13 (−11.62 to−0.64) °</td><td>–4.61 (−9.82 to 0.60)</td><td>3.51 (−0.51 to 7.54)</td><td>0.016</td></tr>
<tr><td>Total cholesterol (mg/dL)</td><td>–11.3 (−16.8 to −5.7)</td><td>−13.6 (−18.3 to−9.0) °</td><td>−4.6 (−9.9 to 0.6)</td><td>0.043</td></tr>
<tr><td>Triglycerides (mg/dL)</td><td>−10.3 (−22.9 to 2.3)</td><td>−6.7 (−15.7 to 2.3)</td><td>−4.7 (−16.4 to 7.1)</td><td>0.774</td></tr>
<tr><td>LDL cholesterol (mg/dL)</td><td>−6.5 (−11.5 to −1.6)</td><td>−11.3 (−15.9 to −6.6)</td><td>−5.8 (−10.5 to −1.2)</td><td>0.211</td></tr>
<tr><td>HDL cholesterol (md/dL)</td><td>0.48 (−0.68 to 1.64)</td><td>0.36 (−0.53 to 1.25)</td><td>0.40 (−0.56 to 1.36)</td><td>0.986</td></tr>
</table>
</td><td>Doménech et al.
Hypertension
2014</td><td>[14]</td></tr>
</table>

			* between group differences ° significant differences compared to the control group (Bonferroni multiple comparisons)		
Effect of the MD on heart failure biomarkers	930	1.0	**Mean (95% CI), between-group difference** **MD + VOO vs low-fat diet** / **MD + Nuts vs low-fat diet** **NT-proBNP, pg/mL**: −70.3(−133 to −7.37) $p = 0.029$ / −84.7 (−145 to −24.5) $p = 0.006$ **Oxidized LDL, U/L**: −8.27 (−13.9 to −2.6) $p = 0.004$ / −4.20 (−9.82–1.42) $p = 0.143$ **Lipoprotein(a), mg/dL**: −4.17 (−8.12 to −0.23) $p = 0.038$ / −2.62 (−6.36–1.13) $p = 0.170$ **Urinary albumin, mg/l**: 4.55 (−4.73 to 13.7) $p = 0.336$ / 1.12 (−8.22 to 10.4) $p = 0.812$ **Urinary albumin/creatinine, mg/g**: 6.25 (−9.3 to 21.8) $p = 0.428$ / 3.54 (−12.1 to 19.1) $p = 0.618$	Fitó et al. Eur. J. Heart Fail. 2014	[15]
Incidence of Peripheral Artery Disease (PAD)	7435	4.8	HR (95% CI) for PAD by intervention group: **MD + EVOO** / **MD + Nuts** **HR (95% CI)**: 0.32 (0.19–0.56) / 0.51 (0.32–0.83)	Ruiz-Canela et al. JAMA 2014	[16]
Effects of MD on BP	7158	3.8	Mean differences in BP changes after 4 years follow-up (median follow-up 3.8 years), unadjusted analysis: **MD + EVOO vs control group** / **MD + Nuts vs control group** **Systolic BP**: 0.42 (−0.46 to 1.30) $p = 0.35$ / −0.90 (−1.77 to −0.03) $p = 0.04$	Toledo et al. BMC medicine 2013	[17]

			Diastolic BP	−1.41 (−1.92 to −0.91) *p* < 0.001	−0.61 (−1.12 to −0.09) *p* = 0.02				
Effects of MD on progression of subclinical carotid atherosclerosis	187	1.0		**MD + VOO** **mm (95% CI)**	**MD + Nuts** **mm (95% CI)**	**Control** **mm (95% CI)**	***p***	Murie-Fernández et al. Atherosclerosis 2011	[18]
			1-year change in IMT	−0.016 (−0.043; 0.011)	−0.033 (−0.058; −0.008)	−0.010 (−0.026; 0.005)	0.38		
			Baseline IMT ≥ 0.9 mm *	−0.093 (−0.146; −0.039)	−0.086 (−0.138; −0.034)	−0.014 (−0.067; 0.039)	0.04		
			* 1-year change for age, sex ah hyperlipidemia at baseline among those with baseline IMT ≥ 0.9mm.						
The short-term effects of MD versus those of a low-fat diet on intermediate markers of CV risk.	772	0.25		**MD + VOO vs low-fat diet** **Mean (95% CI between-group difference °)**	**MD + Nuts vs low-fat diet** **Mean (95% CI between-group difference °)**			Estruch et al. Ann. Int. Med. 2006	[19]
			BMI, kg/m^2	0.09 (−0.12 to 0.29) *p* = 0.40	0.15 (−0.06 to 0.35) *p* = 0.165				
			Systolic BP	−5.9 (–8.7 to −3.1) *p* < 0.001	−7.1 (–10.0 to −4.1) *p* < 0.001				
			Diastolic BP	−1.60 (–3.00 to −0.01) *p* = 0.048	−2.6 (−4.2 to 1.0) *p* = 0.001				
			HOMA index ‡	−0.91 (–1.40 to −0.46) *p* < 0.001	−1.1 (−1.6 to −0.55) *p* < 0.001				
			Total cholesterol, mmol/L	−0.09 (−0.25 to 0.07) *p* = 0.26	−0.16 (−0.31 to −0.01) *p* = 0.040				
			LDL, mmol/L	−0.10 (−0.25 to 0.04) *p* = 0.177	−0.09 (−0.23 to 0.05) *p* = 0.119				
			HDL, mmol/L	0.08 (0.04 to 0.10) *p* < 0.001	0.04 (0.01 to 0.07) *p* = 0.006				
			Triglycerides, mmol/L	−0.08 (−0.20 to 0.04) *p* = 0.21	−0.15 (−0.26 to −0.02) *p* = 0.022				
			Cholesterol-HDL cholesterol ratio	−0.38 (−0.55 to −0.22) *p* < 0.001	−0.26 (−0.42 to −0.10) *p* = 0.002				

			‡ Determined only for 305 participants without diabetes ° adjusted for centre, age, sex and baseline body weight		

BMI: Body Mass Index; BP: Blood Pressure (mmhg); CV: Cardiovascular; MD: Mediterranean Diet; ET-1: Endothelin 1; EVOO: Extra Virgin Olive Oil; HDL: High-Density Lipoprotein; HOMA: Homeostatic Model Assessment; ICAM: Soluble İntercellular Adhesion Molecule; IL-6: İnterleukin 6; IMT: Intima-Media Thickness; LDL: Low-Density Lipoprotein; MCP-1: Monocyte Chemotactic Protein 1; NO: Nitric Oxide (Um); NT-proBNP: N-terminal pro-brain natriuretic peptide; Se-Sel: Soluble E Selectin; TNF- A: Tumor Necrosis Factor Alpha; VCAM: Vascular Cell Adhesion Molecule; VOO: Virgin Olive Oil.

Table 2. Characteristics of the RCTs conducted within the frame of the PREDIMED study, investigating the role of Mediterranean Diet (MD) on: diabetes mellitus (DM), metabolic syndrome (MetS) and obesity.

Aim of the study	Number of subjects	Follow-up median (years)	Main results of the study				1st author, journal, year	Ref.
Diabetes Mellitus								
Effects of MD versus a low-fat diet on the need for glucose-lowering medications	3230 T2DM	3.2		**MD + EVOO**	**MD + Nuts**	**Both MDs vs control *** **	Basterra-Gortari et al. *Diab. Care.* 2019	[20]
			HR (95% CI) of starting a 1st glucose-lowering medication *:	0.78 (0.62–0.98)	0.89 (0.71–1.12)	0.85 (0.69–1.05)		
			Probability of requiring insulin therapy, HR (95% CI):	0.87 (0.68–1.11)	0.89 (0.69–1.14)	0.92 (0.73–1.16)		
			* multivariable analysis adjusting for baseline characteristics and propensity scores. ** adjusted HRs after a mean follow-up of 5.1 years. *** sensitivity analysis after excluding second members of the same household and all participants form site D					
Long-term effect of a MD on microvascular diabetes complications	3614 T2DM	6.0		**MD + EVOO**	**MD + Nuts**	**Both MDs vs control**	Díaz-López et al. *Diab. Care.* 2015	[21]
			Diabetic retinopathy, HR (95% CI):	0.56 (0.32–0.97)	0.63 (0.35–1.11)	0.60 (0.37–0.96)		
			Diabetic nephropathy, HR (95% CI):	1.15 (0.79–1.67)	1.06 (0.72–1.58)	1.11 (0.79–1.55)		
			(Adjusted model)					
			Erratum:				Díaz-López et al. *Diab. Care.* 2018	[22]
				MD + EVOO	**MD + Nuts**	**Both MDs vs control**		
			Diabetic retinopathy,	0.57 (0.33–0.98)	0.62 (0.34–1.11)	0.59 (0.37–0.95)		

			HR (95% CI):					
			Diabetic nephropathy,	1.22 (0.83–1.81)	1.15 (0.76–1.73)	1.19 (0.84–1.69)		
			HR (95% CI):					
			(Adjusted model)					

Incidence of diabetes	3541	4.1	Multivariate adjusted HR (95% CI) of diabetes by intervention group:				Salas-Salvadó et al. *Ann Int Med.* 2014	[23]
				MD + EVOO vs control	**MD + Nuts vs control**	**Both MDs vs control**		
			Unadjusted	0.69 (0.51–0.92)	0.81 (0.61–1.08)	0.75 (0.58–0.96)		
			Multivariate -adjusted	0.60 (0.43–0.85)	0.82 (0.61–1.10)	0.70 (0.54–0.92)		
Metabolic Syndrome								
Plasmatic antioxidant capabilities in Metabolic Syndrome (MetS) patients	75	5.0	Plasma and red blood cells antioxidant and pro-oxidant enzyme activities (mean ± SEM) at the end of the intervention:				Sureda et al. *Mol. Nutr. Food Res.* 2016	[24]
				Enzyme	**MD + EVOO**	**MD + Nuts**	**Low-fat diet**	***p*** **°**
			Plasma	Superoxide dismutase activity (pkat/L)	11.6 ± 1.3 *	14.2 ± 1.4 *	6.69 ± 1.43	<0.003
			Plasma	Catalase activity (k/L)	39.7 ± 3.7 *	33.6 ± 3.4 *	22.3 ± 2.8	<0.004
			Plasma	Xanthine oxidase activity (U/L)	202 ± 10 *	204 ± 10 *	246 ± 10	0.008
			Blood cells	Superoxide dismutase activity (pkat/mL)	2.25 ± 0.17	2.12 ± 0.13	2.53 ± 0.18	0.233
			Blood cells	Catalase Activity (k/mL)	71.3 ± 3.7	61.4 ± 3.6	64.8 ± 3.4	0.225
			* Significant differences vs. the control group (p < 0.05)					
			° *p*-value obtained by ANCOVA					
Long-term effects of MD on MetS	5801	4.8	Risk of MetS, HR (95% CI):				Babio et al.	[25]

				MD + EVOO vs control	MD + Nuts vs control		*Cmaj*	
			Incidence	1.10 (0.94–1.30)	1.08 (0.92–1.27)		2014	
			Reversion	1.35 (1.15–1.58)	1.28 (1.08–1.51)			
			(Multivariable adjusted model)					
MD effects on MetS status	1224	1.0		**MD + EVOO**	**MD + Nuts**		Salas-Salvadó et al. Arch. Int. Med. 2008	[26]
			Crude OR (95% CI) for MetS reversion:	1.4 (0.9–2.1)	1.7 (1.1–2.7)			
			Crude OR (95% CI) for incident MetS among individuals without it at baseline:	1.0 (0.6–1.7)	0.7 (0.4–1.3)			
Obesity								
Effect of a MD on bodyweight and waist circumference	3985	4.8	Weight and waist circumference changes during the follow-up in the intervention groups compared with the control group. Coefficient B (95% CI), multivariable adjusted.				Estruch et al. *The Lancet. Diab. Endocr.*2019	[27]
				MD + EVOO	**MD + Nuts**	**Control**		
			Weight changes (kg)	−0.410 (−0.830 to 0.010) *p* = 0.056	−0.016 (−0.453 to 0.421) *p* = 0.942	0		
			Waist circumference changes (cm)	−0.466 (−1.109 to 0.176) *p* = 0.154	−0.923 (−1.604 to −0.241) *p* = 0.008	0		
Effect of MD on anthropometric variables and body composition parameters	305	1.0	% change in the anthropometric and body composition variables:				Álvarez-Pérez et al. *J. Am. Coll. Nutr.* 2016	[28]
				MD + EVOO	**MD + Nuts**	**Control**		
			Weight, kg	–1.1 (–2.0 to –0.2)	−0.7 (−1.7 to 0.3)	−1.2 (−2.2 to −0.3)		
			BMI, kg/m^2	−1.1 (−2.0 to −0.2)	−0.8 (−2.3 to 0.8)	−1.1 (−2.2 to 0.2)		
			WC, cm	−0.9 (−2.0 to 0.2)	−2.2 (−3.3 to −1.0)	−2.9 (−4.1 to −1.6)		
			%TBF	−0.1 (−2.4 to 2.2)	1.3 (−1.4 to 3.8)	3.3 (1.0 to 5.7)		
			FFM	−1.0 (−2.4 to 0.3)	−0.8 (−2.4 to 0.8)	−2.8 (−4.0 to −1.6)		
			TrFM, kg	−0.6 (−4.1 to 2.9)	2.3 (−3.8 to 8.4)	9.0 (0.2 to 18.1)		
Effect of MedD on plasma total	187	3.0	Multiple regression model to predict plasma TAC according to nutritional intervention:				Razquin et al.	[29]

antioxidant capacity (TAC)	MD + EVOO	MD + Nuts	Control	*Eur. J. Clin. Nutr.*
	B coef. (95% CI)	**B coef. (95% CI)**	**B coef. (95% CI)**	2009
	1.497 (1.095–1.900) $p < 0.001$	1.011 (0.605–1.416) $p < 0.001$	1	

BMI: Body Mass Index; CI: Confidence Interval; EVOO: Extra Virgin Olive Oil; FFM: Free Fat Mass; HR: Hazard Ratio; MetS: Metabolic Syndrome; MD: Mediterranean Diet; OR: Odds Ratio; Q: Quartile; TAC: Total Antioxidant Capacity; T2DM: Type 2 Diabetes Mellitus ; TFM: Total Fat Mass; TrFM: Truncal Fat Mass; WC: Waist Circumference; %TBF: percentage of Total Body Fat.

Table 3. Characteristics of the RCTs conducted within the frame of the PREDIMED study, investigating the role of Mediterranean Diet (MD) on neurologic disorders and other various conditions.

Aim of the study	Number of subjects	Follow-up median (years)	Main results of the study	1st author, journal, year	Ref.
Neurologic Disorders					
Effect of MD on cognition	522	6.5	Adjusted differences versus control (95% CI): MD + EVOO / MD + Nuts / Control Mini-Mental State Examination: +0.62 (+0.18 to +1.05) $p = 0.005$ / +0.57 (+0.11 to +1.03) $p = 0.015$ / 0 (ref.) Clock Drawing Test: +0.51 (+0.20 to +0.82) $p = 0.001$ / +0.33 (+0.003 to +0.67) $p = 0.048$ / 0 (ref.)	Martínez-Lapiscina et al. *J. Neurol. Neurosurg Psychiatry* 2013	[30]
Effect of MD on Mild Cognitive Impairment (MCI)	268	6.5	MD + EVOO / MD + Nuts / Control OR (95% CI) for MCI: 0.34 (0.12–0.97) $p = 0.044$ / 0.56 (0.22–1.43) $p = 0.226$ / (ref.)	Martínez-Lapiscina et al. *J. Nutr. Health Aging* 2013	[31]
Effects of MD on depression risk	3923	5.4	Risk of incident depression: MD + EVOO / MD + Nuts HR (95% CI) adjusted for age, sex, and recruiting center: 0.85 (0.62 to 1.15) / 0.73 (0.52–1.03)	Sánchez-Villegas et al. *BMC medicine* 2013	[32]

Effect of MD on plasma Brain-Derived Neurotrophic Factor (BDNF) levels	243	3	Risk of very low plasma BDNF concentrations (< 13 µg/mL, 10th percentile) after 3 years: **MD + EVOO** / **MD + Nuts** / **Control** Multivariate-adjusted OR (95% CI): 1.02 (0.38–2.76) *p* = 0.97 / 0.22 (0.05–0.90) *p* = 0.04 / 1 (ref.)	Sánchez-Villegas et al. *Nutr. Neurosci.* 2011	[33]
Other Conditions					
MD effect on liver steatosis	100	3.0	**MD + EVOO** / **MD + Nuts** / **Control** / ***p*** Prevalence of hepatic steatosis, *n*(%): 3 (8.8) / 12 (33.3) / 10 (33.3) / 0.027 Mean values of liver fat content: 1.2% / 2.7% / 4.1% / 0.07 Values are expressed as *n* (%) or median (interquartile range).	Pintó et al. *J. Nutr.* 2019	[34]
MD effects on the Fatty Liver Index (FLI)	276	6.0	Mixed linear model **MD + EVOO** / **MD + Nuts** Changes from baseline in the FLI: −3.898 ± 1.873 *p* = 0.038 / 1.679 ± 2.253 *p* = ns. Time: −0.239 ± 0.532 *p* = ns / −1.633 ± 0.624 *p* = 0.009 ns.: not significant	Cueto-Galán et al. *Med. Clin.* 2017	[35]
Incidence of cataract surgery	5802	5.9	**MD + EVOO vs control** / **MD + Nuts vs control** Incidence of cataract surgery, HR (95% CI): 1.03 (0.84–1.26) *p* = 0.79 / 1.06 (0.86–1.31) *p* = 0.58	García-Layana et al. Nutrients 2017	[36]
Effect of MD on HDL properties	296	1.0	Differences between post- and pre-intervention values in HDL functional properties:	Hernáez et al.	[37]

				MD + EVOO		MD + Nuts		Control			
				Difference	***p***	**Difference**	***p***	**Difference**	***p***	Circulation 2017	
			HDL cholesterol/ApoA-I (unitless ratio)	−0.005 (0.020)	0.031	−0.010 (0.025)	<0.001	−0.005 (0.026)	0.129		
			Cholesterol efflux capacity (unitless ratio)	0.019 (0.074)	0.018	0.025 (0.095)	0.013	0.018 (0.10)	ns.		
			HDL cholesterol esterification index (unitless ratio)	0.57 (1.59)	0.007	0.028 (1.32)	ns.	0.16 (1.80)	ns.		
			Cholesterol ester transfer protein activity (unitless ratio)	−0.039 (0.11)	0.008	0.007	ns.	−0.009 (0.19)	ns.		
			HDL antioxidant capacity (on LDL lag time) (unitless ratio)	0.41 (0.68)	<0.001	0.054 (0.43)	ns.	0.018 (0.51)	ns.		
			HDL oxidation index (unitless ratio)	−0.067 (0.29)	0.028	−0.037 (0.21)	ns.	−0.072 (0.26)	0.011		
			HDL lag time (unitless ratio)	0.13 (0.32)	0.012	−0.025 (0.23)	ns.	0.016 (0.25)	ns.		
			Large HDLs (%)	4.34 (9.32)	<0.001	3.70 (9.03)	<0.001	4.85 (9.32)	0.001		
Effect of the MD on inflammatory markers related to atherogenesis	160	3.0 5.0	Changes in inflammatory serum biomarkers after 3 and 5 y of follow-up, mean differences (95% CI):	**MD + EVOO**		**MD + Nuts**		**Control**		Casas et al. J. Nutr. 2016	[38]

			MCP-1, pg/mL					
			Δ 3 years	−1.4 (−1.9, −0.9) *	−0.7 (−1.3, −0.1) [b,*]	−0.3 (−1.0, 0.4)		
			Δ 5 years	−1.2 (−1.9, −0.6) *	−1.4 (−2.1, −0.7) [*,†]	−0.1 (−0.9, 0.7)		
			IL-6, pg/mL					
			Δ 3 years	−0.5 (−0.9, −0.2) *	−0.4 (−0.8, −0.1) *	0.1 (−0.3, 0.5)		
			Δ 5 years	−0.6 (−0.9, −0.3) *	−0.6 (−0.9, −0.2) *	0.02 (−0.3, 0.4)		
			TNF-a, pg/mL					
			Δ 3 years	−1.6 (−2.5, −0.7) *	−0.1 (−1.9, −0.04) *	0.3 (−0.8, 1.5)		
			Δ 5 years	−1.9 (−2.7, −1.1) *	−1.2 (−2.0, −0.3) *	−0.4 (−1.4, 0.6)		
			hs-CRP, g/L					
			Δ 3 years	−1.8 (−2.4, −1.4) [a,*]	−1.3 (−1.8, −0.1) [a,*]	1.4 (0.9, 1.7)		
			Δ 5 years	−2.0 (−2.7, −1.4) [a,*]	−1.5 (−2.0, −1.1) [a,*]	1.1 (0.7, 1.7)		
			a different from control, p< 0.05; b different from MedDiet + EVOO, p < 0.05. * different from baseline, p < 0.05; † different from 3 year of intervention, p < 0.05.					
Effect of MD on telomere lenght	520	5.0	OR (95% CI) for telomere shortening (Δ age adjusted z-score TL ≤ 20th percentile) after 5 years follow-up, adjusted for sex and initial z-score TL:				García-Calzón et al. Clin. Nutr. 2016	[39]
				MD + EVOO	**MD + Nuts**	**Control**		
			Telomere shortening OR (95% CI)	1.23 (0.65–2.32)	02.95 (1.65–5.29)	1 (ref.)		
Breast cancer incidence	4282	4.8		**MD + EVOO vs control**	**MD + Nuts vs control**		Toledo et al. JAMA int. Med., 2015	[40]
			Incidence of invasive breast cancer, HR (95% CI)	0.32 (0.13–0.79)	0.59 (0.26–1.35)			

<table>
<tr>
<td>MD effect on lipoprotein subfractions</td>
<td>169</td>
<td>1.0</td>
<td>1-year changes in lipoprotein particle by intervention group

Means (95% CI):
<table>
<tr><th></th><th>MD + EVOO</th><th>MD + Nuts</th><th>Control</th><th>p</th></tr>
<tr><td>Total VLDL + CM, nmol/L</td><td>−2.7 (−9.4; 3.9)</td><td>−5.9 (-12.7; 0.8)</td><td>0.9 (−6.2; 7.9)</td><td>0.391</td></tr>
<tr><td>Total LDL, nmol/L</td><td>−13.8 (-99.4; 71.9)</td><td>−97.6 (−184.2; −11.1)</td><td>43.7 (−47.5; 135.0)</td><td>0.085</td></tr>
<tr><td>IDL, nmol/L</td><td>7.5 (−6.7; 21.6) [a]</td><td>24.7 (−39.0; −10.3) [b]</td><td>3.7 (−11.4; 18.8) [a]</td><td>0.004</td></tr>
<tr><td>Total HDL, mmol/L [b]</td><td>0.5 (−0.5; 1.6)</td><td>1.1 (0.0; 2.1)</td><td>0.4 (−0.7; 1.5)</td><td>0.646</td></tr>
<tr><td>Mean VLDL size, nm</td><td>−0.4 (−2.1; 1.3)</td><td>−1.6 (−3.3; 0.0)</td><td>−0.5 (−2.3; 1.2)</td><td>0.547</td></tr>
<tr><td>Mean LDL size, nm</td><td>−0.1 (−0.2; 0.1) [a]</td><td>0.2 (0.1; 0.4) [b]</td><td>0.0 (−0.2; 0.1) [a]</td><td>0.004</td></tr>
<tr><td>Mean HDL size, nmb</td><td>0.0 (−0.1; 0.1)</td><td>0.0 (−0.1; 0.1)</td><td>0.0 (−0.1; 0.1)</td><td>0.957</td></tr>
</table>
[a] Values in a row with different superscript letters are significantly different

[b] Measured in 166 participants</td>
<td>Damasceno et al.

Atherosclerosis

2013</td>
<td>[41]</td>
</tr>
<tr>
<td>Effect of MD on plasma Non-Enzymatic Antioxidant Capacity (NEAC)</td>
<td>564</td>
<td>1.0</td>
<td>Multiple linear regressions evaluating the association between changes in plasma NEAC levels, B-coef. (95% CI) adjusted for sex and age:
<table>
<tr><th></th><th>MD + EVOO vs control</th><th>MD + Nuts vs control</th></tr>
<tr><td>TRAP, total radical-trapping antioxidant parameter</td><td>47.75 (2.89, 92.61)</td><td>50.10 (5.52, 94.68)</td></tr>
<tr><td>FRAP, ferric reducing antioxidant potential</td><td>38.86 (2.63, 75.09)</td><td>56.58 (20.58, 92.58)</td></tr>
</table></td>
<td>Zamora-Ros et al.

Nutr. Metab. Cardiovasc Dis.

2013</td>
<td>[42]</td>
</tr>
<tr>
<td>Effect of the MD on systemic oxidative biomarkers in MetS individuals</td>
<td>110 female participants with the</td>
<td>1.0</td>
<td>Changes in oxidation markers, mean ± SE:
<table>
<tr><th></th><th>MD + EVOO</th><th>MD + Nuts</th><th>Control</th><th>p</th></tr>
</table></td>
<td>Mitjavila et al.

Clin. Nutr.</td>
<td>[43]</td>
</tr>
</table>

	diagnosis of MetS		8-oxo-dG in mmol/mmol creatinine	−9.80 (0.58) *	−11.03 (0.60) *	−1.33 (0.58)	< 0.001	2013	
			F2-Isoprostanes in ng/mmol creatine	−13.71 (1.94)	−14.82 (1.81)	−9.32 (1.73)	0.059		
			* $p < 0.001$ (vs. control diet)						
Effects of MD on apolipoproteins B, A-I, and their ratio	551	0.25	Changes from baseline at three-monts; differences relative to control diet:					Solá et al. Atherosclerosis 2011	[44]
				MD + EVOO vs control		**MD + Nuts vs control**			
			Total cholesterol (mg/dL)	−3.7 (−9.3 to 1.8), $p = 0.187$		−6.8 (−12.4 to −1.3), $p = 0.016$			
			LDL cholesterol, mg/dL	−3.2 (−8.4 to 2.0), $p = 0.230$		−4.8 (−10.0 to 0.43), $p = 0.072$			
			HDL cholesterol, mg/dL	2.1 (0.9 to 3.2), $p = 0.001$		1.21 (0.03 to 2.4), $p = 0.045$			
			Non-HDL cholesterol, mg/dL	−5.6 (−11.1 to −0.06), $p= 0.048$		−7.8 (-13.4 to −2.3), $p = 0.006$			
			Total/HDL cholesterol, mg/dL	−0.27 (−0.43 to −0.11), $p = 0.001$		−0.24 (−0.39 to −0.08), $p = 0.003$			
			LDL/HDL cholesterol ratio	−0.20 (−0.32 to −0.07), $p = 0.002$		−0.15 (−0.28 to −0.03), $p = 0.017$			
			Triglycerides (mg/dL)	−10.2 (−21.0 to 0.48), $p = 0.061$		−14.1 (−24.7 to −3.4), $p = 0.010$			
			ApoB (mg/dL)	−2.9 (−5.6 to −0.08), $p = 0.044$		−1.83 (−4.6 to 0.91), $p = 0.189$			
			ApoA-I (mg/dL)	3.3 (0.84 to 5.8), $p = 0.009$		1.32 (−1.1 to 3.7), $p = 0.339$			
			ApoB/ApoA-I ratio	−0.03 (−0.05 to −0.01), $p = 0.013$		−0.12 (−0.03 to 0.01), $p = 0.316$			
Effects of MD on VLDL concentration	50	0.25	Changes in the lipid and apolipoprotein composition of VLDL according to baseline levels:					Perona et al. J. Nutr. Biochem.	[45]
					MD + EVOO				
			VLDL cholesterol		Decrease ($p < 0.05$)				

			Triacylglicerol — Decrease ($p < 0.05$) Triacylglicerol/ApoB ratio — Decrease ($p < 0.05$) Numbers not available. No changes were observed in the other two groups.	2010	
Phytosterol intake from natural foods association with a cholesterol- lowering effect of MD	106	1.0	Changes in serum lipids and non-cholesterol sterols, mean changes from baseline (95% CI): **MD + EVOO vs control** / **MD + Nuts vs control** **Lipids (mmol/l)** Total cholesterol: −0.19 (−0.47 to 0.08), $p = 0.26$ / −0.15 (−0.42 to 0.12), $p = 0.51$ LDL cholesterol: −0.20 (−0.46 to 0.06), $p = 0.20$ / −0.27 (−0.53 to −0.01), $p = 0.036$ HDL cholesterol: 0.02 (−0.07 to 0.11), $p = 1.00$ / 0.06 (−0.02 to 0.15), $p = 0.24$ **Non-cholesterol sterols/cholesterol (l M/mM)** Lathosterol: −0.02 (−0.37 to 0.34), $p = 1.00$ / 0.10 (−0.45 to 0.25), $p = 1.00$ Campesterol: 0.10 (−0.52 to 0.71), $p = 1.00$ / 0.01 (−0.60 to 0.62), $p = 1.00$ Sitosterol: 0.16 (−0.27 to 0.59), $p = 1.00$ / 0.15 (−0.27 to 0.58), $p = 1.00$	Escurriol et al. Europ. J. Nutr. 2009	[46]
Effects of MD on in vivo lipoprotein oxidation	372	0.25	Unadjusted 3-months changes. Mean (95% CI): **MD + EVOO** / **MD + Nuts** / **Control** / ***p*** OxLDL, U/L: −10.1 (−15 to −5.1) / −7.5 (−12 to −2.6) / −2.6 (−8.0 to 2.9) / 0.04 ‡ GSH-Px, U/L: −16.4 (−44.6 to 11.8) / −10.4 (−35.9 to 15.1) / −20.1 (−50.6 to 10.4) / 0.35 ‡ Significant differences between MD + EVOO and control diet	Fitó et al. Arch. Int. Med. 2007	[47]

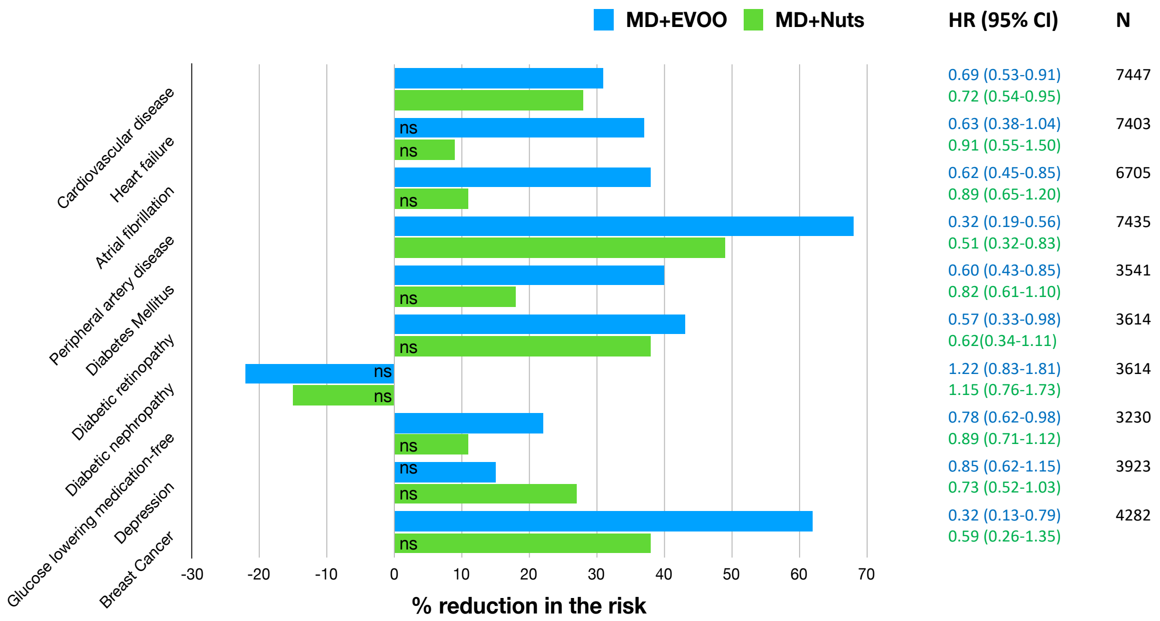
ApoA: Apolipoprotein A; ApoB: Apolipoprotein B; EVOO: Extra Virgin Olive Oil; FLI: Frally Liver Index; GSH-Px: Glutathione peroxidase; HDL: High-Density Lipoprotein; HR: Hazard Ratio; hs-CRP: high sensitivity C-Reactive Protein IDL: Intermediate-Density Lipoprotein; IL-6: Interleukin 6; LDL: Low-Density Lipoprotein; MCP-1: Monocyte Chemotactic Protein 1; MD: Mediterranean Diet; NEAC: Non-Enzymatic Antioxidant Capacity; OR: Odds Ratio; ns: not significant; OxLDL: Oxidized Low-Density Lipoprotein; TNF- A: Tumor Necrosis Factor Alpha; VLDL: Very-Low-Density Lipoprotein.

The majority of the RCTs included in our review dealt with cardiovascular diseases and the related risk factors, which is in accordance to the fact that the main objective of the PREDIMED study was to analyze the effects of MD on the primary prevention of cardiovascular disease. According to the intention to treat analysis by Estruch et al.'s study, which included all the 7447 participants, there was a 31% relative risk reduction for the MD + EVOO (HR 0.69, 95%CI 0.53, 0.91), and 28% MD + Nuts group (HR 0.72, 95%CI 0.54, 0.95) in the primary outcome assessed (a composite of acute myocardial infarction, stroke, or death for cardiovascular events), compared to control group [1]. Moreover, according to another study, the Hazard Ratio, HR (95% Confidence Interval, CI) for atrial fibrillation in the MD + EVOO group was 0.62 (0.45, 0.85), $p < 0.05$ [9]. Analyzing the effect of MD on diabetes it was found that the HR (95% CI) of diabetes incidence was 0.60 (0.43, 0.85) for the group MD + EVOO compared to controls, and 0.82 (0.61, 1.10) for the MD + Nuts group compared to control diet [23]. After the application of the Fine and Gray model for competing risk analysis, the results remained essentially unchanged [48]. Similarly, a subgroup analysis on the PREDIMED population (n = 418), showed a protective effect of the MD either supplemented with EVOO or nuts against the incidence of DM (HR, 95%CI for both MDs versus control 0.47 (0.26–0.87) [49-50]. Another study showed a significant effect of MD on the incidence of diabetic retinopathy: HR (95% CI) 0.59 (0.37, 0.95) for the MD groups [22]. Further trials evaluated the long-term effect of MD on incidence and reversion of MetS. Although there were no significant differences in incidence or reversion HRs by intervention, reversion occurred in 958 (28.2%) participants when considering only those subjects who had MetS at baseline [25]. Salas-Salvadó et al., examined the one-year effect of the MD on metabolic syndrome (MetS) status, as shown in Table 2. They found that, after 1-year follow-up, the MetS prevalence was reduced by a 6.7%, 13.7% and 2% in the MD + EVOO, MD + Nuts and control groups, respectively (MD + Nuts versus control group, $p < 0.05$). These differences may be due to the variations in incidence rates among subjects without MetS at baseline and in reversion rates among those who had the syndrome at the beginning of the trial [26]. Álvarez-Pérez et al., [28] found that MD had positive effects on body composition and anthropometric measurements in a subsample of the cohort. Nevertheless, no between-group statistically significant differences were found in anthropometric or body composition variables.

After analysing the influence of a Mediterranean dietary pattern on plasma total antioxidant capacity (TAC), the MD + EVOO group showed higher levels of plasma TAC and a reduction in body weight gain [29]. The effects of the MD on cognitive functions were also examined, as shown in Table 3. In a sub-study conducted on 522 participants in Navarra, it was found that the MD improved cognitive function, assessed with the Mini-Mental State Examination and the clock drawing test 30]. Likewise, another study observed that a long-term intervention with an EVOO-rich MD resulted in a better cognitive function in comparison with controls [31]. Toledo et al.'s study, aimed at investigating the incidence of breast cancer on the PREDIMED population, showed a HR (95% CI) of 0.38 (0.16, 0.87) for the MD + EVOO compared to the control group [53]. Other studies examining the effects of the MD on different conditions, other than CVDs, diabetes obesity and cognitive function, are reported in Table 3. In order to outline the results obtained by the trials analyzed in the present review, we calculated the percentage reduction of the risk of various clinical conditions, as shown in Figure 2.

Figure 2. Percentage reduction in the risk of different medical conditions in the PREDIMED Study, according to the group of treatment (MD + EVOO or MD + Nuts) versus the low-fat control diet. The % of risk reduction were computed as: 100 × (1–HR)% and it represents the reduction in the instantaneous risk of

the above mentioned events at any given point of time, or the reduction in the rate of such events. ns: not significant. MD: Mediterranean Diet; EVOO: Extra Virgin Olive Oil.



The % reduction in the risk of cardiovascular disease (a composite of death for cardiovascular cause, non-fatal acute myocardial infarction, and non-fatal stroke) was 31% (95% CI 47–9%) and 28% (95% CI 46–5%) for MD + EVOO and MD + Nuts groups, respectively [1]. Nevertheless, it is appropriate to observe that, although the % risk of CVD reduction vary according to the dietary intervention, it is not possible to infer that one is better than the other, as shown by the overlapping of the correspondent 95% confidence intervals. For the heart failure (HF), the % reduction observed was not significant in the MD + EVOO nor in the MD + Nuts [8], that is to say, none of the two dietary interventions turned out to be better than the control diet in the risk reduction of the outcome. For the atrial fibrillation the % risk reduction was 38% (95% CI 55–15%) for the MD + EVOO group, while not significant for the MD + Nuts group [9]. The risk reduction of peripheral artery disease was 68% (95% CI 81–44%) and 49% (95% CI 68–17%) for the MD + EVOO and MD + Nuts groups, respectively [16], but the difference between the two dietary interventions was not statistically significant due to the partial overlapping of the 95% CIs. For the probability of remaining free of the glucose-lowering medications, a reduction of 22% (95% CI 38–2%) was observed for the MD + EVOO; no significance was observed for the MD + Nuts group [20]. The reduction in the risk of diabetic retinopathy was significant only for the MD + EVOO group (43%, 95% CI: 67–2%) but not for the MD + Nuts group [22]. Interestingly, the long-term effect of MD on diabetic nephropathy was not beneficial, probably due to the higher salt intake than a hyposodic diet (Table 2) [22]. For the incidence of diabetes mellitus, the risk reduction was 40% (95% CI 57%, 15%) and 18% (39%, −10%) for the MD + EVOO and MD + Nuts intervention groups respectively [23], and the difference between the two dietary approaches did not turn out to be statistically significant. For the depression risk, the MD supplemented with either EVOO or Nuts did not lead to a significant reduction, compared to the control diet. However, a risk reduction was observed in the Nuts + MD group among the diabetic subjects only [32]. Finally, the % reduction in the risk of breast cancer incidence was 68% (87–21%) for the MD + EVOO group versus the low-fat control diet, while the MD + Nuts did not show to be statistically significant compared to the control group [40]. Overall, the MD + EVOO dietary intervention seemed to have more beneficial effects in terms of % reduction of the risk of different clinical condition. However, in those conditions where both MD + EVOO and MD + Nuts had significative effects compared to the control diet, it is not possible to conclude that the former is better than the latter. Table 4 shows the percentage reduction from baseline of different continuous variables assessed by the different randomized controlled trials conducted in the scope of the PREDIMED study.

Table 4. Percentage reduction from the baseline of different continuous variables assessed by the randomized clinical trials in the scope of the PREDIMED study

		MD + EVOO					MD + Nuts					
Continuous variable	**Time (yr)**	**N**	**Mean value at baseline**	**Mean change**	**% change from baseline**	***p*-value ***	**N**	**Mean value at baseline**	**Mean change**	**% change from baseline**	***p*-value ***	**Ref.**
Sistolic BP (24 h)	1.0	78	127.3	−3.14	−2.5%	-	82	125.3	−2.35	−1.9%	-	[14]
Diastolic BP (24 h)	1.0	78	71.8	−1.68	−2.3%	-	82	71.2	−1.00	−1.4%	-	[14]
BMI, kg/m^2	0.25	257	29.7	−0.12	−0.4%	-	257	29.4	−0.09	−0.3%	-	[19]
Weight, kg	1.0	112	77.9	−1.0	−1.3%	0.008	102	80.3	−0.5	−0.6%	0.197	[28]
BMI, kg/m^2	1.0	112	30.7	−0.5	−1.6%	0.012	102	31.2	−0.5	−1.6%	0.314	[28]
WC, cm	1.0	112	100.5	−1.1	−1.0%	0.046	102	102.6	−2.3	−2.2%	<0.001	[28]
Urinary albumin, mg/L	1.0	310	5.0	0.55	11.0%	-	310	5.1	−2.85	−55.9%	-	[15]
Urinary albumin/creatinine, mg/g	1.0	310	7.09	1.13	15.9%	-	310	7.21	−1.62	−22.5%	-	[15]
Intima-media thickness, mm	1.0	66	0.825	−0.016	−1.9%	-	59	0.854	−0.033	−3.8%	-	[18]
Total cholesterol, mg/dL	0.25	181	219.7	−3.7	−1.7%	ns.	193	216.7	−6.8	−3.1%	<0.05	[44]
Oxidized LDL, U/L	1.0	310	74.3	−9.75	−13.1%	-	310	71.1	−5.68	−8.0%	-	[15]
Ox-LDL, U/L	0.25	123	77.9	−10.1	−13.0%	-	128	74.4	−7.5	−10.1%	-	[47]
LDL cholesterol, mg/dL	0.25	181	146.2	−4.3	−2.9%	<0.05	193	141.6	−5.9	−4.2	<0.05	[44]
HDL cholesterol, mg/dL	0.25	181	51.9	1.8	+3.5%	<0.05	193	53.9	0.95	1.8%	<0.05	[44]
Non-HDL cholesterol, mg/dL	0.25	181	174.2	−5.4	−3.1%	<0.05	193	169.6	−7.6	−4.5%	<0.05	[44]
Total/HDL cholesterol, mg/dL	0.25	181	5.0	−0.24	−4.8%	<0.05	193	4.8	−0.20	−4.2%	<0.05	[44]
LDL/HDL cholesterol ratio	0.25	181	3.4	−0.20	−5.9%	<0.05	193	3.1	−0.15	−4.8%	<0.05	[44]

Triglycerides, mg/dL	0.25	181	139.9	−4.8	−3.4%	ns.	193	138.2	−8.62	−6.2%	<0.05	[44]
ApoB, mg/dL	0.25	181	102	−2.8	−4.4%	<0.05	193	101	−1.7	−1.4%	ns.	[44]
ApoA-I, mg/dL	0.25	181	135	2.5	+3.2%	<0.05	193	134	0.16	1.4%	ns.	[44]
ApoB/ApoA-I ratio	0.25	181	0.78	−0.03	−6.2%	<0.05	193	0.78	−0.009	−1.2%	ns.	[44]
Lipoprotein(a), mg/dL	1.0	310	24.8	0.68	2.7%	-	310	24.4	2.23	9.1%	-	[15]
NT-proBNP, pg/mL	1.0	310	572	−27.7	−4.8%	-	310	562	−42.0	−7.4%	-	[15]
GSH-Px, U/L	0.25	123	626	−16.4	−2.6%	-	128	613	−10.4	-1.7%	-	[47]
sVCAM-1, ng/mL	1.0	55	872	−138	−15.8%	0.02	55	935	−208	−22.2%	0.001	[13]

2.2.4. Discussion

Even if the results of the PREDIMED study reported in 2013 [51] have been partially retracted due to protocol deviations mainly regarding the randomization process, after new analyses with the appropriate corrections (excluding 1588 participants whose randomization process was altered), similar results were obtained [1]. When both the MD groups (MD + EVOO and MD + Nuts) were examined, the MD nutrition model used in the PREDIMED study turned out to potentially reduce the number of hard clinical events in a relatively short time [4]. The epidemiological evidence of the CVD protection provided by the adherence to the MD is strong. A meta-analysis by Liyanage et al., found that the MD was associated with a 37% relative reduction ($p < 0.001$) in the risk of major CV events [52]. These findings are in agreement with the results of the trials included in the present review, which showed positive effects of the MD on atrial fibrillation [9], and peripheral artery disease [16]. The underlying mechanisms of protection against CVD provided by the MD can be attributed to the abundance of antioxidant and anti-inflammatory molecules in its individual components such as fruits and vegetables, olive oil, nuts, whole grains, fish and red wine, although the specific protective mechanisms of MD on CVDs are not completely understood. One of the hypotheses suggests a possible role of the cell redox state in the modulation of the enzymatic systems related to the antioxidant capacity. Additionally, nutrients have the ability to regulate gene expression and protein synthesis. As reported by nutrigenomic studies, MD can play a role against the expression of several proatherogenic genes involved in vascular inflammation, foam cell formation and thrombosis [4].

As secondary endpoints of the PREDIMED study, diabetes incidence and MetS status were also assessed. The largest trial on the incidence of type 2 diabetes mellitus (T2DM) in the primary prevention PREDIMED study, reported a significant reduction of the incidence in both the intervention groups [23]. Moreover, the results of prospective cohort studies contributing to estimate T2DM risk according to different levels of MD adherence provided additional and consistent evidence [53]. Their results support the protective role of the MD against T2DM, with overall risk reductions ranging from 12% to 83% for subjects closely adhering to the MD compared to those reporting the lowest adherence, after adjusting for several confounders [53]. The authors also observed that higher adherence to the MD had a beneficial role in the prevention and treatment of MetS and its components [53]. In the PREDIMED study, although no differences in the onset of MetS were observed among the three groups, participants in the MD + EVOO and MD + Nuts were more likely to present disease reversion, if compared to the control group [25]. Esposito et al., (2015) specified that two meta-analyses assessed the relationship between adherence to a MD and future incidence of diabetes. According to their report, the analyses are consistent with a significant reduction, ranging from 19% to 23%, of new diabetes diagnosis associated with greater adherence to the MD [54]. In the Framingham Heart Study Offspring Cohort,1918 participants free of the condition at baseline were followed for seven years, and participants in the highest quintile category of the Mediterranean-style dietary pattern score had a lower incidence of metabolic syndrome than those in the lowest quintile category ($p = 0.01$) [55]. It is thought that highly important bioactive components of the MD such as unsaturated fatty acids, complex carbohydrates and fibre, vegetable protein, non-sodium minerals, phytosterols and polyphenols interact synergistically to advantageously affect various metabolic pathways at risk of MetS, T2DM and CVD [53]. The role of MD in the protection against cognitive decline, is being supported by growing evidence. Although the majority of the available studies in the issue present a longitudinal or a cross-sectional design, they point out the protective role of MD on cognitive impairment, cognitive function and decline [56]. Among the secondary outcomes of the PREDIMED study, the incidence of breast cancer was assessed. To date, the evidence on the role of Mediterranean diet in the onset of this neoplasm is still limited; nevertheless, the findings of Toledo et al.'s study (2015) are in agreement with the available literature [57,58], and are statistically strengthened by its prospective, randomized and controlled design. As a result, with the exception of the PREDIMED study, most of the studies on MD appear to be observational studies or short-term trials. Among many issues, the findings of the PREDIMED study include a large number of randomized controlled trials that provide a higher level of scientific evidence than cohort studies and represent the gold standard to clarify the actual effects of this intervention. The PREDIMED trial is a milestone of nutrition intervention that indicated with powerful evidence the benefits of the traditional MD in the primary prevention of CVD in individuals at high risk. As secondary endpoints of the PREDIMED study, it was observed that MD interventions could protect against diabetes in participants without diabetes and figure out a role in preventing or managing MetS. and certain metabolic abnormalities that predicts diabetes and cardiometabolic risk.

2.2.5. Conclusions

In conclusion, the contribution of the PREDIMED study as a commendable dietary intervention study is certain. This trial present as primary endpoint a composite of CV events and, in the frame of the study, sub-group analyses have been performed to assess various secondary outcomes. The scope of this review was to sum up the experimental outcomes of those studies. Randomized controlled trials within the scope of the PREDIMED study demonstrated the risk-reducing effects on major health problems and risk factors as well as the current and known effects of the Mediterranean diet. When the diet is considered as the main determinant of many health outcomes, we testify the Mediterranean diet as a comprehensive diet model that overcomes a single food or single nutrient approach.

2.2.6. References

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2.3. The PREDIMED-Plus study

PREDIMED-Plus (PREvención con DIeta MEDiterránea – Plus) is a multicenter, randomized, primary prevention trial carried out in community-dwelling men (aged 55 to 75 years) and women (aged 60 to 75 years), with a BMI ≥ 27 to <40 kg/m^2 and metabolic syndrome, whose primary outcome is cardiovascular disease and its manifestations. Participants were randomized in two groups. The control group consists of an intervention similar to that carried out in the described above PREDIMED study (MD supplemented with EVOO or nuts, without calorie restriction nor physical activity program nor weight-loss goals). The intervention group was prescribed a hypocaloric MD (with a 30% calorie restriction) supplemented with EVOO and nuts, together with physical activity prescription (i.e. walking 45 minutes/day or equivalent) and weight-loss goals, including behavioral support. A total of 6,874 participants were recruited in 23 Spanish centers and randomized into the study between 2013 and 2016. A detailed description of the study protocol goes beyond the objective of the present work, and additional information can be found elsewhere and is available at http://www.predimedplus.com/). In the scope of the PREDIMED-Plus study two were the works I took part in, which are described in the following paragraphs.

2.3.1. Isotemporal substitution of inactive time with physical activity and time in bed: cross-sectional associations with cardiometabolic health in the PREDIMED-Plus study [1]

> Form the published paper: *Galmes-Panades AM, Varela-Mato V, Konieczna J, et al. Isotemporal substitution of inactive time with physical activity and time in bed: cross-sectional associations with cardiometabolic health in the PREDIMED-Plus study. Int J Behav Nutr Phys Act. 2019 Dec 23;16(1):137. doi: 10.1186/s12966-019-0892-4. PMID: 31870449; PMCID: PMC6929461.*

This study explored the association between inactive time and measures of adiposity, clinical parameters, obesity, type 2 diabetes (T2D) and metabolic syndrome (MetS) components. It further examined the impact of reallocating inactive time to time in bed, light physical activity (LPA) or moderate-to-vigorous physical activity (MVPA) on cardio-metabolic risk factors, including measures of adiposity and body composition, biochemical parameters and blood pressure in older adults. The study design is a cross-sectional analysis of baseline data from 2,189 Caucasian men and women (age 55-75 years, BMI 27-40 Kg/m^2) from the PREDIMED-Plus. All participants presented ≥3 components of the metabolic syndrome. The study aimed to provide new evidence about the associations of inactive time with cardio-metabolic risk factors in an aging population. The outcomes were markers of cardiometabolic health: measures of MetS syndrome components. The objectives of the present study were a) to explore cross- sectional associations between inactive time and cardio-metabolic risk factors; and b) to assess the impact of replacing 30 min per day of inactive time by 30 min of LPA, MVPA and time in bed on markers of cardio-metabolic health. Inactive time, physical activity and time in bed were objectively determined using triaxial accelerometers for 7 days. Multiple adjusted linear and logistic regression models were used. Isotemporal substitution regression modelling was performed to assess the relationship of replacing the amount of time spent in one activity for another, on each outcome, including measures of adiposity and body composition, biochemical parameters and blood pressure in older adults. Briefly, inactive time was associated with indicators of obesity and the metabolic syndrome. Reallocating 30 min per day of inactive time to 30 min per day of time in bed was associated with lower BMI, waist circumference and glycated hemoglobin (HbA1c) (all p-values < 0.05). Reallocating 30 min per day of inactive time with 30 min per day of LPA or MVPA was associated with lower BMI, waist circumference, total fat, visceral adipose tissue, HbA1c, glucose, triglycerides, and higher body muscle mass and HDL cholesterol (all p-values < 0.05). Inactive time was associated with a poor cardio-metabolic profile. Isotemporal substitution of inactive time with MVPA and LPA or time in bed could have beneficial impact on cardio-metabolic health. The complete paper describing in detail the study can be find elsewhere [1].

2.3.2. Dietary folate intake and metabolic syndrome in participants of PREDIMED-Plus study: a cross-sectional study [2]

From the published paper: *Navarrete-Muñoz EM, Vioque J, Toledo E, et al. Dietary folate intake and metabolic syndrome in participants of PREDIMED-Plus study: a cross-sectional study. Eur J Nutr. 2020 Aug 24. doi: 10.1007/s00394-020-02364-4. Epub ahead of print. PMID: 32833162.*

A detailed description of this study goes beyond the objectives of the present work, but can be find elsewhere [2]. Briefly, this paper examined the association between dietary folate intake and a score of metabolic syndrome (MetS) and its components among older adults at higher cardiometabolic risk participating in the PREDIMED-Plus trial. A cross-sectional analysis with 6,633 with overweight/obesity participants with MetS was conducted. Folate intake (per 100 mcg/day and in quintiles) was estimated using a validated food frequency questionnaire. A MetS score was calculated using the standardized values as in the formula: [(body mass index + waist-to-height ratio)/2] + [(systolic blood pressure + diastolic blood pressure)/2] + plasma fasting glucose–HDL cholesterol + plasma triglycerides. The MetS score as continuous variable and its seven components were selected as the outcome variables. Multiple robust linear regression using MM-type estimator was performed to evaluate the association adjusting for potential confounders. The findings of this study showed that an increase in energy-adjusted folate intake was associated with a reduction of MetS score (β for 100 mcg/day = − 0.12; 95% CI: − 0.19 to − 0.05), and plasma fasting glucose (β = − 0.03; 95% CI: − 0.05 to − 0.02) independently of the adherence to Mediterranean Diet (MD) and other potential confounders. It was also found a positive association with HDL-cholesterol (β = 0.07; 95% CI: 0.04–0.10). These associations were also observed when quintiles of energy-adjusted folate intake were used. In conclusion, this study suggests that a higher folate intake was associated with a lower MetS score, a lower plasma fasting glucose and a higher plasma HDL cholesterol among older adults with MetS patients. Though further observational longitudinal or experimental studies are needed, investigating the effect of a higher intake of vegetables, fruits, legumes and cereals as main sources of folate may be a possible approach to reducing the risk of cardio-vascular disease and diabetes.

2.3.3. References

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2. Navarrete-Muñoz EM, Vioque J, Toledo E, Oncina-Canovas A, Martínez-González MÁ, Salas-Salvadó J, Corella D, Fitó M, Romaguera D, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, López-Miranda J, Bueno-Cavanillas A, Matía-Martín P, Daimiel L, Sánchez VM, Vidal J, de Cos Blanco AI, Ros E, Diez-Espino J, Babio N, Fernandez-Carrion R, Castañer O, Colom A, Compañ-Gabucio L, Lete IS, Crespo-Oliva E, Abete I, Tomaino L, Casas R, Fernandez-Garcia JC, Santos-Lozano JM, Sarasa I, Garcia-Rios JMA, Martín-Pelaez S, Ruiz-Canela M, Díaz-López A, Martinez-Lacruz R, Zomeño MD, Rayó E, Sellés CG, Canudas S, Goday A, García-de-la-Hera M. Dietary folate intake and metabolic syndrome in participants of PREDIMED-Plus study: a cross-sectional study. Eur J Nutr. 2020 Aug 24. doi: 10.1007/s00394-020-02364-4. Epub ahead of print. PMID: 32833162.

3. Mediterranean Diet and environmental sustainability

3.1. The new Mediterranean Diet Pyramid

From the published paper: *Serra-Majem L, Tomaino L, Dernini S, Berry EM, Lairon D, Ngo de la Cruz J, Bach-Faig A, Donini LM, Medina FX, Belahsen R, Piscopo S, Capone R, Aranceta-Bartrina J, La Vecchia C, Trichopoulou A. Updating the Mediterranean Diet Pyramid towards Sustainability: Focus on Environmental Concerns. Int J Environ Res Public Health. 2020 Nov 25;17(23):E8758. doi: 10.3390/ijerph17238758. PMID: 33255721.*

3.1.1. Background

As mentioned in the Background section of this work, over the past decades the concept of the MD underwent a progressive change. From the initial notion of the MD as a healthy dietary pattern traditionally spread around the Mediterranean basin [1], it evolved to include socio-cultural, economic and environmental aspects [2,3]. In fact, not only food consumption, but also the production and supply chain, represent some of the main causes of ecological pressure on the environment [4,5]. Nowadays food production represents the largest cause of global environmental change. According to recent estimates agriculture occupies about 40% of global land [6], and food production is responsible for up to 30% of global greenhouse gas (GHG) emissions [7] and 70% of freshwater use [8]. Moreover, as the global population is constantly increasing and could grow up to 8.5 billion in 2030 and up to 9.7 billion in 2050, according to estimates [9], the environmental pressure to feed these figures could increase further. As adequate nutrition is highly related to the environment and its balance, it is possible to state that diet represents a link between human health and environmental sustainability [10].

Compared to the current dietary habits spread among most of the industrialized countries (i.e., the Western dietary pattern), the MD showed to have a better ecological footprint [11-13]. This is due to the higher consumption of local and in-season plant-derived foods and lower consumption of animal products. In fact, it has been observed that dietary patterns rich in plant-based foods and low in animal derivates have a lower environmental impact [14-17]. Nevertheless, the current dietary pattern in many Mediterranean countries has shifted from the traditional MD pattern to a nearer Western one. A return to the latter would be beneficial for human health and the natural environment of these areas, attenuating the environmental pressure of food supply [18,19], with a lot of benefits for humans and the planet [20]. Nevertheless, such a transition requires substantial changes in consumers' values, education and choices. If so, food policies, dietary guidelines and food security measures need to move on from the traditional approach focused primarily on nutrients and health, to a new one embracing also the environmental, socioeconomic and cultural implications of the dietary patterns [21]. Consequently, it will be necessary to take into account those mechanisms influencing dietary choices and address their implications in order to provide optimal interventions regarding policies, education, agriculture and the food industry [22,23]. Also, improvements in the training of primary care and nutrition professionals [24], as well as modifications in agricultural and fishing industry practices, public catering supply, trading policies and areas of investigation would be required.

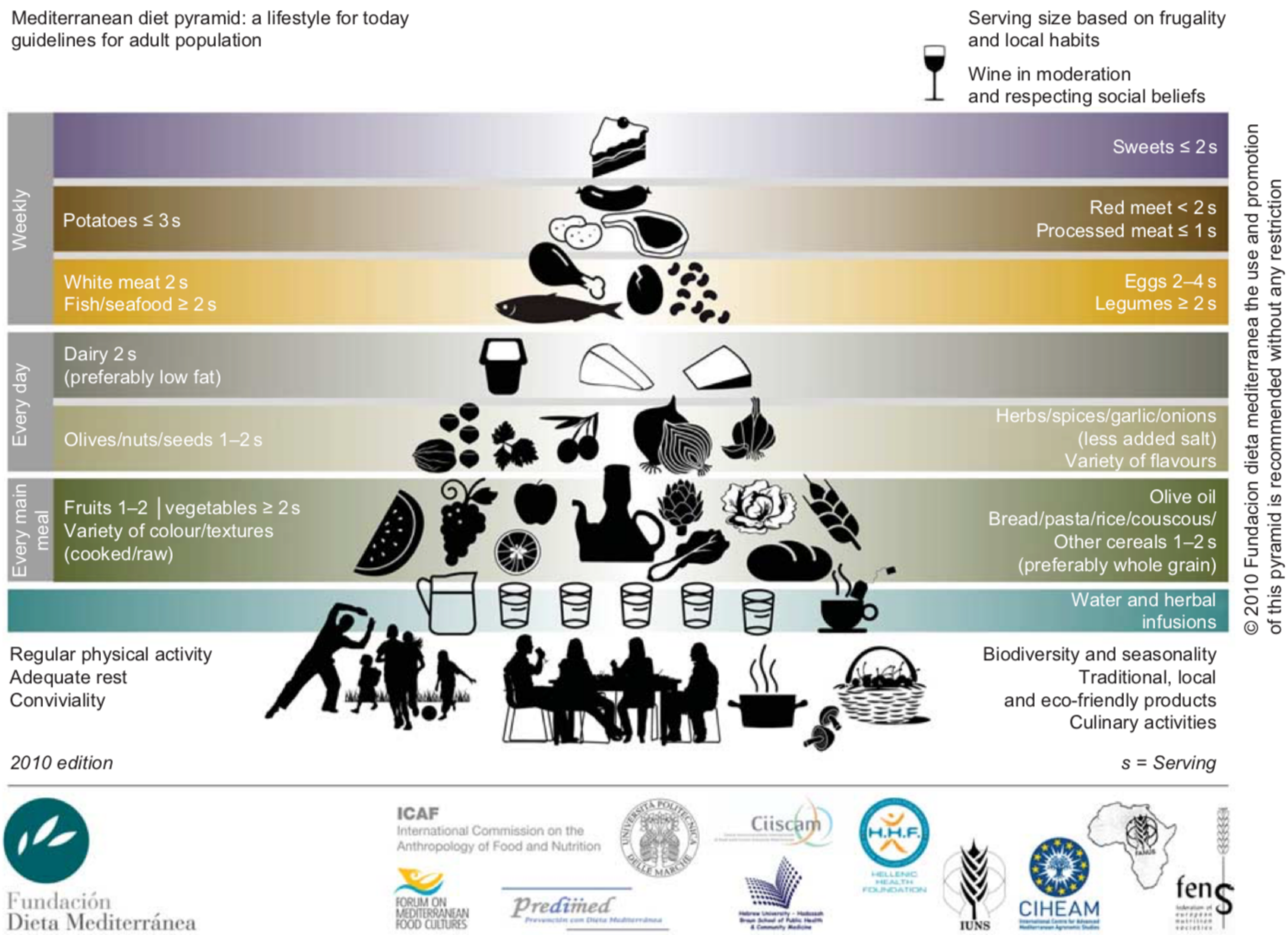
The following discussion is a dissertation based on the paper by Serra-Majem L, Tomaino L, Dernini S, et al. entitled: "Updating the Mediterranean Diet Pyramid towards Sustainability: Focus on Environmental Concerns" [25].

3.1.2. Materials and Methods

The first graphical representation of the Mediterranean Diet Pyramid was developed in 1993 in collaboration with Oldways, Harvard University and the World Health Organization (WHO) [1]. The pyramid was then updated in 2009 and 2010 by a network of institutions and experts coordinated by the Mediterranean Diet

Foundation in collaboration with the Forum on Mediterranean Food Cultures, Centre International de Hautes Etudes Agronomiques Méditerranéennes (CIHEAM), Centro Interuniversitario Internazionale di Studi sulle Culture Alimentari Mediterranee (CIISCAM), Sapienza University of Rome, Hebrew University of Jerusalem, the Federation of European Nutrition Societies (FENS) and the International Commission on the Anthropology of Food and Nutrition (ICAF) [3]. Then, in November 2010 the MD was recognized as Intangible Cultural Heritage of Humanity by the United Nations Educational, Scientific and Cultural Organization (UNESCO) [13]. The traditional MD pyramid used at the time was intended not only to provide nutritional advice, but also to describe a healthy lifestyle using a simple, practical framework adaptable to the different cultural and socio-economic contexts of the Mediterranean area [4].

Figure 3. The previous Mediterranean Diet pyramid [3].

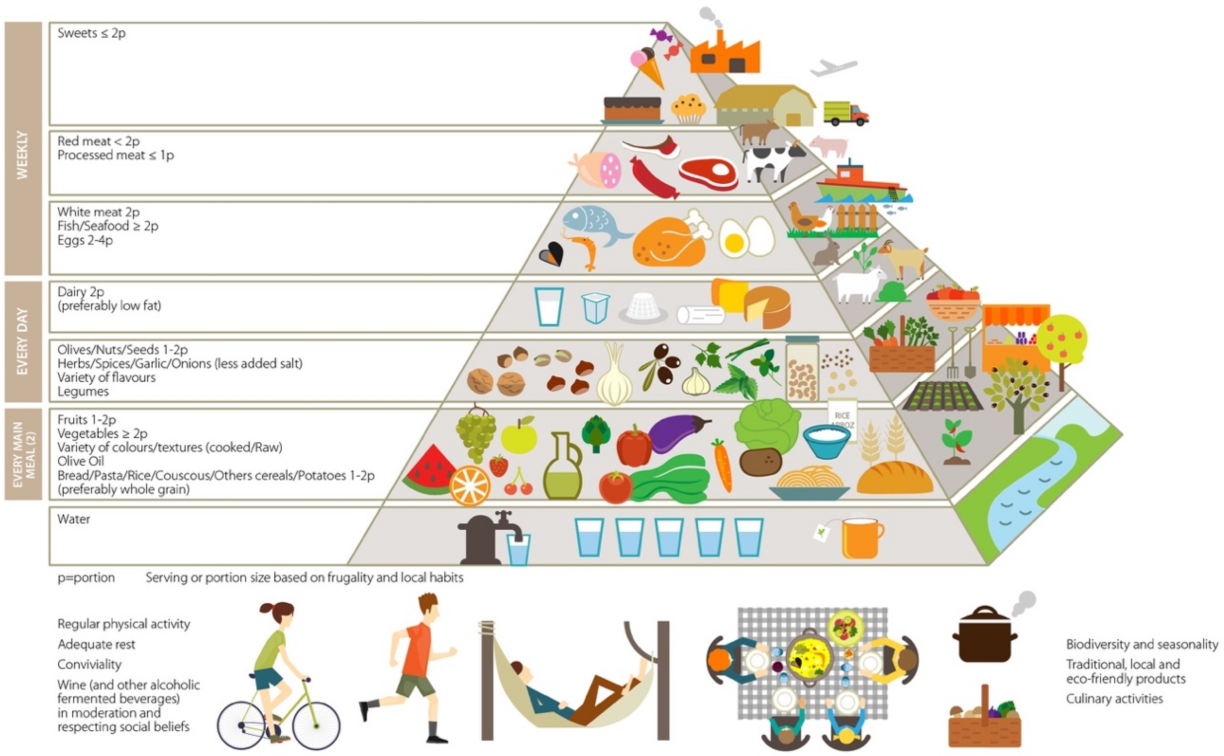


In November 2014, the International Mediterranean Diet Foundation (IFMeD) was created as an international center of multi-disciplinary knowledge and expertise, with the objective to revalorize the MD. Collaborating with the organizations and experts who were involved in the previous revision of the MD pyramid, the IFMeD continued its consultation process with the goal of establishing an updated consensus position on a newly revised representation of the MD pyramid to incorporate recent scientific evidence addressing the benefits of sustainability. This proposed new graphical representation responds to the need for a common framework among Mediterranean countries in the form of food-based dietary guidelines [26] which are in line with the 2010 definition of sustainable diets elaborated by the Food and Agriculture Organization of the United Nations (FAO) [27]. Growing evidence shows the importance of a diet to be environmentally sustainable [28]. The main goal of this updated representation of the MD, is to integrate the beneficial role of the MD for the human, with its beneficial effect for his habitat and environment. To achieve such a goal, a fruitful dialogue between professionals from various disciplines (e.g., public health nutrition, medicine, food sciences, social anthropology, sociology, home economics, agriculture, environment and cultural heritage), has been developed. Despite there are several methods to reach consensus between experts in a given fields, such as the Delphi process [29], this new revision of the MD pyramid was drafted by a scientific consensus among the respective experts and is supported by the available and most recent research in the fields of nutrition, health and environment.

3.1.3. Results

This new graphical representation [30] is not prescriptive. Rather, it was conceived as a simplified framework, to be adapted by different countries of the Mediterranean region to their geographical, socio-economic and cultural contexts, dietary needs and meal patterns. The recommendations target the healthy adult population (18-65 years old) and should be adapted to the needs of children, pregnant women, elderly, and individuals with health problems such as cardiovascular diseases. In this updated pyramid, food items at the base of the pyramid contribute the highest intake levels in terms of grams/day. Animal protein sources are positioned to suggest a lower frequency of consumption and contribution to total intake. The items at the top of the pyramid should only be consumed occasionally (e.g., red and processed meat, pastries and sweets). The novelty of the updated MD pyramid lies in its third dimension. This represents the environmental impact of the food items included, as well as aspects of food production sustainability, as shown in Figure 1. Preference for local, seasonal, fresh and minimally processed food is emphasized, supporting biodiversity, eco-friendly and traditional foods [30].

Figure 4. New Pyramid for a Sustainable Mediterranean Diet [30]



Main meals consumed daily should be a combination of cereals, vegetables and fruits, possibly with a small quantity of legumes (though not in every meal). Bread, pasta, rice, couscous or bulgur (cracked wheat) should be consumed as 1-2 servings per meal, preferably with whole or partly refined grains. Vegetable should be consumed in 2 or more servings per day, in raw form at least for lunch or dinner. Fruit should be considered as the primary form of dessert, with 1-2 servings per meal [30]. Consuming a variety of colors of both vegetables and fruit is strongly recommended to help ensure intake of a broad range of micronutrients and phytochemicals. The less these foods are cooked, the higher the retention of vitamins and the less use of fuel, thus minimizing environmental impact. Along with the highlighted triad of elements for the main meals, other plant foods (i.e. unsalted nuts or seeds) also constitute the core of the MD since they are important sources of vitamins, minerals, fiber, as well as other compounds with antioxidant potential. Those elements have a beneficial role in the prevention of several chronic non-communicable diseases and for healthy weight management, as well as for reduced use of natural resources and GHG emissions [31]. Also, agroecological production methods (free from chemical pesticides) contribute to minimize human and nature's exposure to these chemicals [32]. The preference should always be for fresh, seasonal and minimally processed vegetables and fruits. Moreover, choosing local products when possible and available supports the local economy and reduce the ecologic impact of the production chain.

Olive oil should be the principal source of dietary lipids. Due to its composition and resistance to high temperatures, Extra Virgin Olive Oil (EVOO) is recommended both for cooking and dressing. Traditionally, vegetables, other plant foods and pasta, potatoes or rice are cooked with olive oil, thus amplifying their nutritional value. Scientific evidence suggests that EVOO have a key role in the primary prevention of cardiovascular diseases [33] and has a protective effect against certain cancers [34-36]. Olive production (both for oil and table use) represents a significant utilization of land in the southern regions of the European Union, particularly Spain, Italy, Greece and Portugal [37]. Olive production may have a negative environmental effect, especially if form intensive agriculture [38,39]. Supporting traditional low-input plantations could help to reduce the environmental impact while maintaining the natural and social values connected to these cultivations. Also, olive trees represent a barrier to desertification and erosion and olive orchards are a CO_2 sink, removing CO_2 from the atmosphere and fixing it in the soil [40].

Table olives, nuts and seeds should be consumed daily in a moderate amount, as they are source of unsaturated healthy fats, proteins, minerals, vitamins and fiber [41]. Also, nuts showed to have a protective role in the primary prevention of cardiovascular and other non-communicable diseases [33].

Herbs, spices, garlic and onions give dishes flavor, increasing palatability, while allowing for a reduction in salt use and representing a source of micronutrients and antioxidants. Also, the contribute to the regional cultural identities and culinary specialties (e.g., “sofrito” in Italy and “ladera” in Greece).

In this updated MD pyramid [30], preference is given to vegetal protein sources such as legumes, and a daily amount of these should be prioritized (at least 1 small serving per day). Animal proteins low in saturated fats such as fish, poultry, rabbit and certain lean meats, as well as eggs are allowed in reasonable amounts. In particular, poultry provides high quality protein with low levels of saturated fat. Whole eggs, including those for cooking or baking, should not exceed 4 per week. Organically produced variety should be preferred, as animal welfare is safeguarded while helping to enrich the soil where hens roam and deposit waste.

Legumes may substitute animal protein foods in the diet, decreasing the environmental impact of the current MD. Legumes also help to fix atmospheric nitrogen in the soil, improving soil fertility and reducing dependence on energy-intensive or artificial fertilizers.

Milk and dairy products (especially yogurt and cheese) should be consumed on a daily basis in a moderate amount (maximum of 2 servings per day) [30]. They have a beneficial role for bone and muscle health, represent a source of proteins, calcium and micronutrients. Moreover, due to their probiotic content, they boost digestive tract health and positively affect the microbiome [42,43]. However, dairy production (together with meat) represents a major concern because of their environmental impact. Dairy farming in the EU is becoming more intensive and more specialized, with imported grains and soybeans being used as feed, except where national authorities actively intervene to help maintain small producers or promote organic production [44]. Thus, when possible, milk and dairy products from small producers and local farmers should be preferred, as well as organic products. This will help to reduce the environmental impact (i.e., packaging, transport), sustain the local economy, and also yield better quality products as grazing leads to better lipid profiles in milk.

Fish and seafood consumption (oily fish, lean fish and shellfish) is recommended on a weekly basis [30]. They represent a source of proteins and omega-3 fatty acids which reduce the risk of coronary heart disease and have anti-inflammatory properties [45]. An adequate management is required to maintain and preserve wild fish stocks [46]. Therefore, apart from seeking sustainably sourced and captured wild fish, aquaculture can be considered as an alternative [47,48].

Red meats should be eaten less frequently (≤2 servings/week), and preferably as lean cuts. Similarly, processed meat consumption should also be limited (≤1 serving/week) [30]. Intake of red and processed meats has been associated with increased risk of type 2 diabetes, cardiovascular disease, cancer, and all-cause mortality [49,50]. Moreover, livestock production affects land use and GHG emission in different ways: deforestation for grazing land and cropland for soy-feed production, soil carbon loss in pastures, energy required for growing feed-grains and processing and transporting grains and meat, NO releases from the use of nitrogenous fertilizers, and gases from animal manure and enteric fermentation [51,52].

Sweets and ultra-processed high sugar, high fat, foods and drinks (which are represented at the top of the pyramid) should be consumed occasionally and in small amounts. Sweetness in the diet should preferably be added with fresh and, to a lesser extent, dried fruits, honey or carob syrup [25].

Drinks and Fluid Balance

According to the European Food Safety Authority (EFSA), the reference values for adequate water intake are 2.0 and 2.5 liters per day for adult females and males, respectively [53], corresponding to an average amount of 6-8 servings per day. Water requirements may vary according to age, personal clinical/health status, physical activity intensity, weather and other environmental conditions. Water should be consumed freely, and local tap water is preferred [54] in order to reduce its environmental footprint (packaging and transport). Coffee, tea and herbal infusions are also included in the new MD pyramid. Each of these beverages, in varying degrees, represents a source of flavonoids and can potentially decrease consumption of highly sweetened beverages by substituting it. Certified fair trade and sustainably produced coffee and tea should be opted for as much as possible, and recipes for local, traditional herbal brews should be recorded for posterity [25].

Portion size

Portion sizes should be based on frugality and moderation and aligned with the energy needs of population's lifestyles. In general, the portion sizes of those foods at the base of the pyramid should be larger, as well as their frequency of consumption, while those items at the upper levels should be consumed in smaller amounts and less frequently [25].

The base of the pyramid

Situated outside, but at the base of the pyramid, the new concepts of sustainability and affordability are highlighted, adding on to aspects already present in the previous version [4]. Physical activity, adequate rest and socialization during meals are also represented, as practices integral to the definition of the Mediterranean lifestyle. The regular practice of moderate-intensity physical activity (150 minutes throughout the week, or at least 30 minutes a day for 5 days per week) [55], is considered a basic complement to the MD (i.e., for balancing energy intake, and maintaining a healthy body weight). A restorative nightly sleep, as well as daytime naps are part of a balanced lifestyle. Also, a slower lifestyle with reduced stress levels should be sought. Being active or relaxing in a natural setting is in keeping with the MD whilst not being detrimental to the natural environment. Culturally, the meal has a social and cultural value which goes beyond its nutritional and nourishing functions [56]. Moreover, cooking and dining together allow for transmission of culinary knowledge and recipes in an enjoyable atmosphere. These are key elements for the revitalization of the MD, at least in the Mediterranean region [25].

Biodiversity and seasonal and local foods

As reported in the previous representation of the MD pyramid [4], the importance of eating local and seasonal foods is emphasized, as it helps in maintaining local biodiversity. As far as possible fresh, seasonal and minimally processed foods should be preferred. This will maximize their nutritional properties and markedly reduce the environmental footprints of food production and processing, as well as long-distance transport of imported foods. Moreover, local production chains will be sustained, with beneficial effects on the local economy and employment. Also, the preference of traditional and local foods will sustain the local culinary heritage and promote the use of endemic ingredients [25].

Eco-friendly products

Finally, consuming eco-friendly products will help the preservation of Mediterranean landscapes and sea [45]. Thus, health for consumers as well as nature (land, rivers, sea, etc.) will be promoted. Indeed, recent large epidemiological studies have shown that consumers whose diet comprises a high share of organic foods adopt a healthier plant-based dietary pattern with lower pesticide exposure, lower impact on natural resources and lower GHG emissions [57-59]. Combining the MD with regular organic food consumption appears to be the optimal option [60].

Affordability

Adherence to a MD does not necessarily increase the expense of one's diet significantly [61,62]. Basing meals on legumes, cereals and local and seasonal vegetables, fruit and fish can help to offset the cost of other potentially more expensive foods such as meat or less healthy processed foods. Following the guidance of the new MD-P can assist those who are financially insecure to consume a healthier diet [25].

3.1.4. Discussion

Assessing the sustainability and especially the environmental impact, of the MD has been perceived as a complex task but one which is urgently required. With this objective, in 2016-2017 an informal international working group from different institutions worked to identify nutritional indicators to assess the sustainability of a healthy diet [63,64]. The group identified thirteen indicators belonging to five areas (biochemical characteristics, food quality, and environmental, lifestyle and clinical aspects). Such indicators were proposed as a useful methodological framework to address health, education and agricultural policies. The significance of the diet for environmental protection or degradation was integral to the choice of indicators, and the role of agriculture and fisheries in facilitating a sustainable diet was considered from different points of view [63].

Agriculture has historically shaped the rich biodiversity heritage of EU countries, including those of the South, but over the last decades this synergistic relationship has been undermined [65]. This is why the sustainable management of natural resources is now part of the objectives of the EU's Common Agricultural Policy agenda, focused on protecting biodiversity and the environment within agriculture [66-68]. Moreover, food consumption and production have implications for land use and GHG [37]: in 2017 the total GHG emissions in the EU's 28 member states (EU-28) were 4,483 million tons of CO_2 equivalents, of which agricultural practices represented around 10% [69]. The quantity and type of food consumed directly influences land use. However, the nature of this land-food/diet relationship depends on other factors such as population growth, agricultural productivity, land ownership and investment patterns, as well as land use efficiency [51]. Despite several limitations in addressing these issues (i.e., it is difficult to get the real estimates for each country), scientific evidence now supports that a plant-based diet, compared to the current widely consumed animal food-based diet (especially rich in ruminant foodstuffs), markedly minimizes land, water and resources use for production, along with reducing GHG emissions. Such a diet appears to be a significant direction with the potential to ensure food security for all, reduce impacts on climate change and facilitate the realization of the 2030 United Nations Sustainable Development Goals, as discussed below [70].

With the identification of the food production chain as one of the main contributors towards a negative environmental impact in the last decades, the study of such effects has often involved using the Life Cycle Assessment (LCA) method. In the specific case of food production, the LCA investigates the environmental impact of each phase, from agricultural production to the final consumer through industrial processing, packaging, distribution and retail, cooking and finally waste management [71,72].

As for example, the results of a study analyzing the average Spanish diet with this method, showed that the net Global Warming Potential (GWP) related to feeding a Spanish citizen for one year amounted to 2.1 tons of CO_2 equivalents. In the whole food production chain, the production stage was the most impacting [73].

The sustainability of the recommended MD versus present-day Spanish and Western dietary patterns in the Spanish setting was analyzed in 2012-2013 comparing the reference pattern of the MD pyramid [4] with an estimation of the current Spanish and Western dietary patterns derived from Food and Agriculture Organization data [74]. The MD showed to have the lowest environmental impact compared to current Spanish and Western dietary patterns, with an agricultural land use of 8,365*103 Ha/year (Spanish and Western dietary patterns 12,342*103 Ha/year and 33,162*103 Ha/year, respectively), energy consumption of 239,042 TJ/year (Spanish and Western dietary patterns 285,968 TJ/year and 611,314 TJ/year, respectively), water consumption of 13.2 Km^3/year (Spanish and Western dietary patterns 13.4 Km^3/year and 22.0 Km^3/year respectively) and GHG emissions amounting to 35,510 Gg CO_2 eq/year (Spanish and Western dietary patterns 72,758 Gg CO_2 eq/year and 217,128 Gg CO_2 eq/year, respectively). The food groups mainly responsible for environmental pressure were meat and dairy products [74].

The environmental burden of the MD in the Italian context was also analyzed with a modified LCA method [75]. The results showed that the national average diet lead to 402.91 kg CO_2 eq/month of GHG emissions, while the MD presented a 6.81% lower CO_2 eq/month [75].

Two recent studies (2013 and 2018) dealt with sustainability of the Mediterranean dietary pattern in Spain. In the first study, based on the SUN cohort (20,363 adults), it was observed that better adherence to the MD was significantly associated with lower land use, water and energy consumption and GHG emissions making it an eco-friendly option [12]. In the second study evaluating a cohort of 18,929 adults, the MD was compared to a partly vegetarian diet or Western diet, after 10 years of follow-up. Overall the MD was healthier, whereas the partly vegetarian diet was slightly better than the MD for environmental impacts, whilst the Western diet was better only because of its lower monetary cost. Thus, according to the findings of this study, the MD seemed to be the more sustainable option, closely followed by the partly vegetarian diet [13].

Besides the GHG emissions, the environmental impact of food production involves also water use, and the concept of a water footprint is gaining importance when analyzing the link between water resources and the food production chain. In the last decades, methodologies such as the Water Footprint Assessment (WFA) and the LCA have been implemented to study such relationship. The concept of a water footprint (WF) represents an indicator of freshwater use including both direct water use of a consumer or producer and the indirect water use. In other words, the WF of a product is the volume of freshwater used to produce a food, measured over the whole supply chain. WFA refers to the quantification and location of the WF of a food production chain, and to the assessment of the environmental, social and economic sustainability of this WF. This is carried out with the objective of informing policies and formulating response strategies [76,77].

A recent study [78] found that the current Spanish dietary habits presented higher WF than the recommended MD: the former consumed 2,554 liters/capita per day and the latter 1,835 liters/capita per day. This difference was mainly due to the higher consumption of red and processed meat, sugars, pastries, beverages and dairy products [79]. It was observed that, in addition to its beneficial effects on health, the adoption of the MD by the Spanish population (approx. 46.6 million) would save 474 million m^3 of blue water, a precious resource that could be allocated to other uses. Thus, the MD emerged as a healthy, more sustainable and more water-efficient model than the average Spanish diet. This finding is of major relevance, considering that some of the areas in the Mediterranean region are semi-arid zones.

Widespread international scientific consensus and a large body of evidence support the assertion that plant-based diets are healthier and more protective of natural resources and the general environment, including GHG emissions [11,15,60,80]. It is also worth noting that more and more countries are integrating sustainability into their Food-Based Dietary Guidelines (FBDG). For instance, in France the FBDG were extensively updated in 2019 by the Ministry of Health [81]. They now include the concept of environmental preservation and the reduction of pesticide exposure. In brief, they recommend adopting a plant-based diet with increased consumption of all plant foods (vegetables, fruits, whole grains, legumes and nuts) and preferably of organic origin, a reduction in dairy products and limitation of red and processed meats. In an article based on the NutriNet-Santé cohort (28,240 participants), the authors showed that a better adherence to the 2019 FBDG was related to higher plant-based food consumption, lower energy intake, lower exposure to chemical pesticides, lower expected population mortality and lower overall environmental impacts (land use, energy demand, GHGs), albeit at a somewhat higher cost [82]. These results suggest that overall, the French 2019 FBDG are overall in line with the multiple dimensions of diet sustainability, including health, although adherence is associated with a slight increase in cost. If adopted by a large part of the population, these dietary guidelines may help to prevent chronic diseases while reducing environmental impacts related to food consumption. The small increase in monetary cost would be balanced by lower externalized costs for the society. This implies that governments should take appropriate measures to help citizens and farmers to adopt sustainable attitudes and practices [25].

Despite the several benefits of the MD, the evidence supporting the environmental sustainability of the MD has some limitations that should be considered. First of all, there is limited information about each step of the food production chain, and assumptions are sometimes made in environmental impact analyses. Secondly, the food production system is a very complex one which requires that many aspects should be controlled and kept in mind. Unfortunately, this remains a challenge as the food production system, transport, distribution and retail are extremely globalized and also diverse. The evaluation of the sustainability of a certain dietary pattern should be context-specific and involve different professionals from the health, medical and educational fields, as well as from system engineering, and from agronomic, veterinary and environmental sciences. Moreover, extreme caution must be exerted when discussing the sustainability of food system issues in order to avoid the risk of trivializing problems characterized by extreme complexity, as well as their consequences and/or possible solutions [25].

3.1.5. Conclusions

Past versions of the MD pyramid have aimed to describe and summarize the MD patterns of different countries in the Mediterranean area whilst highlighting health benefits or recommendations. The various MD patterns have all evolved as a result of modern technology and globalization (e.g., many developments and innovations have changed the range of foods currently available throughout the year). The MD pattern is a shared cultural heritage that is widely recognized for its contribution to health and well-being and which should be preserved among the Mediterranean populations [25].

Figure 5. The United Nations Sustainable Development Goals (SDGs)

Moreover, according to the United Nations Sustainable Development Goals (SDGs), the MD complies with at least 11 out of 17 goals: SDG2 (Zero Hunger: End hunger, achieve food security and improved nutrition and promote sustainable agriculture); SDG3 (Good Health and Well-Being: Ensure healthy lives and promote well-being for all at all ages); SDG4 (Quality Education: Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all); SDG5 (Gender Equality: Achieve gender equality and empower all women and girls); SDG6 (Clean Water and Sanitation: Ensure availability and sustainable management of water and sanitation for all); SDG7 (Affordable and Clean Energy: Ensure access to affordable, reliable, sustainable and modern energy for all); SDG8 (Decent Work and Economic Growth: Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all); SDG11 (Sustainable Cities and Communities: Make cities and human settlements inclusive, safe, resilient and sustainable); SDG12 (Responsible Consumption and Production: Ensure sustainable consumption and production patterns); SDG13 (Climate Action: Take urgent action to combat climate change and its impacts); SDG14 (Life Below Water: Conserve and sustainably use the oceans, seas and marine resources for sustainable development); SDG15 (Life on Land: Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss) [70].

The updated edition of the MD pyramid presented here stresses the need to increase the sustainability of the MDP, decreasing the contribution of meat, high fat dairy products and highly processed foods, and increasing the consumption of legumes and as many locally grown vegetables, fruits and their products as feasible [25].

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5. Conclusions

The findings described in the present work are based on the following publications. Achieved during these two years of PhD:

- Tomaino L, Reyes Suárez D, Reyes Domínguez A, García Cruz LM, Ramos Díaz M, Serra Majem L. Adherence to Mediterranean diet is not associated with birthweight - Results form a sample of Canarian pregnant women. Nutr Hosp. 2020 Feb 17;37(1):86-92. English. doi: 10.20960/nh.02780. PMID: 31876428;
- Kargin D, Tomaino L, Serra-Majem L. Experimental Outcomes of the Mediterranean Diet: Lessons Learned from the Predimed Randomized Controlled Trial. Nutrients. 2019 Dec 6;11(12):2991. doi: 10.3390/nu11122991. PMID: 31817731; PMCID: PMC6949939;
- Galmes-Panades AM, Varela-Mato V, Konieczna J, Wärnberg J, Martínez-González MÁ, Salas-Salvadó J, Corella D, Schröder H, Vioque J, Alonso-Gómez ÁM, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, Garcia-Rios A, Riquelme-Gallego B, Gaforio JJ, Matía-Martín P, Daimiel L, Micó Pérez RM, Vidal J, Vázquez C, Ros E, Garcia-Arellano A, Díaz-López A, Asensio EM, Castañer O, Fiol F, Mira-Castejón LA, Moreno Rodríguez A, Benavente-Marín JC, Abete I, Tomaino L, Casas R, Barón López FJ, Fernández-García JC, Santos-Lozano JM, Galera A, Mascaró CM, Razquin C, Papandreou C, Portoles O, Pérez-Vega KA, Fiol M, Compañ-Gabucio L, Vaquero-Luna J, Ruiz-Canela M, Becerra-Tomás N, Fitó M, Romaguera D. Isotemporal substitution of inactive time with physical activity and time in bed: cross-sectional associations with cardiometabolic health in the PREDIMED-Plus study. Int J Behav Nutr Phys Act. 2019 Dec 23;16(1):137. doi: 10.1186/s12966-019-0892-4. PMID: 31870449; PMCID: PMC6929461;
- Navarrete-Muñoz EM, Vioque J, Toledo E, Oncina-Canovas A, Martínez-González MÁ, Salas-Salvadó J, Corella D, Fitó M, Romaguera D, Alonso-Gómez ÁM, Wärnberg J, Martínez JA, Serra-Majem L, Estruch R, Tinahones FJ, Lapetra J, Pintó X, Tur JA, López-Miranda J, Bueno-Cavanillas A, Matía-Martín P, Daimiel L, Sánchez VM, Vidal J, de Cos Blanco AI, Ros E, Diez-Espino J, Babio N, Fernandez-Carrion R, Castañer O, Colom A, Compañ-Gabucio L, Lete IS, Crespo-Oliva E, Abete I, Tomaino L, Casas R, Fernandez-Garcia JC, Santos-Lozano JM, Sarasa I, Garcia-Rios JMA, Martín-Pelaez S, Ruiz-Canela M, Díaz-López A, Martinez-Lacruz R, Zomeño MD, Rayó E, Sellés CG, Canudas S, Goday A, García-de-la-Hera M. Dietary folate intake and metabolic syndrome in participants of PREDIMED-Plus study: a cross-sectional study. Eur J Nutr. 2020 Aug 24. doi: 10.1007/s00394-020-02364-4. Epub ahead of print. PMID: 32833162;
- Serra-Majem L, Tomaino L, Dernini S, Berry EM, Lairon D, Ngo de la Cruz J, Bach-Faig A, Donini LM, Medina FX, Belahsen R, Piscopo S, Capone R, Aranceta-Bartrina J, La Vecchia C, Trichopoulou A. Updating the Mediterranean Diet Pyramid towards Sustainability: Focus on Environmental Concerns. Int J Environ Res Public Health. 2020 Nov 25;17(23):E8758. doi: 10.3390/ijerph17238758. PMID: 33255721.

The findings of these studies show how the dietary patterns, with particular regard to the Mediterranean Diet, are closely linked to human health - and to the prevention of several non-communicable disease - and to the safeguard and management of our environment. In other words, the MD represents the link of a chain that connects human and planet health, at least in the Mediterranean region. For this reason, we might define nutrition as an issue of Public Health importance which need a comprehensive approach. Therefore, the MD should be promoted not only as a healthy diet, but also as a culturally coherent way of life to be enjoyed in a sustainable manner. Even if other dietary patterns may have a better performance on given points (e.g., selected environmental impacts of plant-based diets) the overall value of the MD on four dimensions (e.g., environmental, social, cultural, economic and nutritional/health levels), makes it a model that is considered as intangible heritage of humanity, but with added environmental value. The virtues of the MD and particularly its value for environmental preservation and protection need to be efficiently communicated and applied in an integrated manner at multiple levels. This implies starting from the level of policymakers, and expanding to mass media and social media influencers, to community development Non-Governmental Organizations (NGOs), to educators, to food innovators in production and processing, to restaurateurs and finally to the individuals and families in households. In this picture, individuals' education plays a crucial role in self nutrition, health and food choices. We think that achieving an adequate civil awareness on the issue is a great challenge, but it would be of noteworthy value in order to empower a Public Health system based on self-responsibility and prevention, and to help people living a more-enjoyable life.

6. Collateral works

During these two years of PhD, in addition to the investigation related to the main project of my PhD (dietary patterns - with special regard to Mediterranean Diet - and health), I took part in other little projects related to nutrition and, more recently to the SARS-CoV-2 pandemics. Hereby you will find a brief description of them.

6.1. Impact of sandstorm and carnival celebrations on SARS-CoV-2 spreading in Tenerife and Gran Canaria (Canary Islands, Spain) [1]

In this curious work about an issue of Public Health relevance, we address the hypothesis that the extraordinary sandstorm occurred on 22-24 February 2020 might have a role in the different cumulated incidence of COVID-19 cases between the islands of Tenerife and Gran Canaria (Spain), since it obliged to reduce significantly air traffic and forced to suspend all major carnival street events in all most locations. A retrospective analysis of COVID-19 cases as to 1 April 2020 according to symptoms onset, weather-related data and Carnival events in Tenerife and Gran Canaria was carried out. The sandstorm occurred on February 22-24, 2020, forced air traffic to close, reducing the influx of tourists to the Canary Islands and suspending carnival events in most places, except in Santa Cruz de Tenerife. According to our results, cumulated incidence of SARS-CoV-2 cases as to 1 April 2020 was 132.81/100,000 in Tenerife, and 56.04/100,000 in Gran Canaria. The suspension of Carnival events due to the sandstorm in the Canary Islands contributed to reduce differently the SARS-CoV-2 spread in Tenerife and Gran Canaria [1] .

6.2. Epidemiological modeling and SARS-CoV-2

The article entitled: “Epidemiological modeling of the spread of SARS-CoV-2” (English version of “Modelizaciones epidemiológicas de la propagación del SARS-CoV-2”) was written in Spanish for a blog on Economy and Health. It described the “state of the art” of the epidemiological models developed and adopted during the first SARS-CoV-2 wave in Spain [2]. Similarly, the article: “COVID-19: mathematical modeling pandemic” (English version of: “COVID-19: pandemia de modelos matemáticos”), published in the blog “The Conversation”, illustrated the great variety of the mathematical models sprouted last spring to describe the SARS-CoV-2 spread and to predict its evolution [3].

6.3. Fibromyalgia and Nutrition: An Updated Review [4]

Due to the lack of specific and standardized treatments for the management of fibromyalgia (FM), available evidence suggests a multidisciplinary approach, and nutrition represents an important therapeutic strategy. This work aims to update the relationship between FM and nutrition, through a review of more recent scientific evidence based on a systematic research on PubMed. Of 66 records initially identified, 26 studies were selected and included in the present work. Although there is not sufficient evidence for the efficacy of specific nutritional protocols, the examined papers indicate a potential role of selected nutrients, micronutrients and food components in managing FM symptoms. However, several concerns persist as nutritional status and/or nutritional integration can improve FM symptoms, without expecting to lead to a remission of the disease. The use of targeted nutritional supplements may be of some relevance for the management of FM, but the up to date evidence remains weak. It is advisable, thus, to perform further studies of higher quality [4].

6.4. References

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