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Mediterranean diet and life expectancy; beyond olive oil, fruits and vegetables

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Abstract

Purpose—to review the recent relevant evidence of the effects of the Mediterranean diet and lifestyle on health (2015 and first months of 2016).

Recent findings—Large observational prospective epidemiological studies with adequate control of confounding and two large randomized trials support the benefits of the Mediterranean dietary pattern to increase life expectancy, reduce the risk of major chronic disease, and improve quality of life and well-being. Recently, 19 new reports from large prospective studies showed – with nearly perfect consistency– strong benefits of the Mediterranean diet to reduce the risk of myocardial infarction, stroke, total mortality, heart failure and disability. Interestingly, two large and well-conducted cohorts reported significant cardiovascular benefits after using repeated measurements of diet during a long follow-up period. Besides, PREDIMED, the largest randomized trial with Mediterranean diet, recently reported benefits of this dietary pattern to prevent cognitive decline and breast cancer.

Summary—In the era of evidence-based medicine, the Mediterranean diet represents the gold standard in preventive medicine, probably due to the harmonic combination of many elements with antioxidant and antiinflammatory properties, which overwhelm any single nutrient or food item. The whole seems more important than the sum of its parts.

Keywords

Feeding trials; olive oil; nuts; cardiovascular disease; coronary heart disease

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Introduction

Nowadays, a suboptimal quality of the dietary pattern represents the leading global, modifiable cause of morbidity and mortality (1). In nutritional epidemiology, the methodological approach addressing food patterns is currently the state-of-the-art. The analysis of overall food patterns captures different combinations of food intake, and better reflects the complexity of diet and its relationships with the risk of disease. Food pattern analysis has mostly replaced the traditional single-nutrient analysis, which was challenged by several conceptual and methodological limitations, specially because of the reductionist and overly optimistic approach of attributing all the health effects to a single nutrient or food. In contrast, the food pattern approach may be the most useful option because it goes beyond nutrients or foods and examines the effects of the overall diet. Focusing on isolated nutrients or single foods makes it difficult to take into account any interaction between them. Food patterns adequately capture between-food synergies and the additive effect of small changes in many nutrients, which are more likely to show an effect. In addition, dietary patterns overcome problems of confounding by other aspects of the diet (2). In this context, a substantial accrual of current knowledge supports the benefits of the traditional Mediterranean-style diet on health (3*, 4*). The traditional Mediterranean diet (MedDiet) is an overall food pattern characterized by high consumption of plant-based foods (vegetables, fruits, nuts, legumes, and unprocessed cereals); low consumption of meat and meat products (with special avoidance of red and processed meats); moderate to high consumption of fish, and low consumption of dairy products (with the exception of yogurt and the long-preservable cheeses). Alcohol consumption is included in moderation, in the form of wine and, as a rule, during meals. Total intake of lipids can be high (around or over 40% of total energy intake), but the ratio of the beneficial monounsaturated to the non-beneficial saturated lipids is high, because of the high monounsaturated content of liberally consumed olive oil, which represents a hallmark of the MedDiet, and its main culinary fat (5). The purpose of this review is to update the available evidence of the benefits of the MedDiet and the Mediterranean lifestyle on health.

New prospective studies reporting reduced risk of cardiovascular disease and increased life expectancy associated with the Mediterranean diet

Better adherence to a dietary pattern score appraising the traditional MedDiet has been reported to be associated with decreased risk of fatal and non-fatal clinical events of cardiovascular disease (CVD) - including coronary heart disease (CHD), stroke and heart failure - reduced total mortality, or reduced disability in initially healthy subjects, in 15 out of 17 recently published large cohort studies (6–22). These large cohort studies have been conducted not only in the Mediterranean area, but also in other geographical regions, such as the United States or Non-Mediterranean European countries. In addition, two clinical studies of patients with stable CHD were conducted; one in a collaborative research involving 39 participating countries (23*), and another one in a small cohort in Hong Kong (24). Both studies reported substantial cardiovascular benefits in secondary cardiovascular prevention, associated with better adherence to the MedDiet. All these 19 observational studies are summarized in Table 1.

This new evidence is in agreement with previous systematic reviews (3*,4,25,26) and with the Series of Systematic Reviews on the relationship between dietary patterns and health outcomes conducted by the US Department of Agriculture (27).

In total, and after discounting duplicate cohorts, the 19 studies shown in Table 1 included 541,113 subjects followed-up for an average period of 12.4 years. The decreased risk of CVD ranged from 9% (8*) to 52% (24), and the decreased risk in total mortality ranged from 7% (19) to 47% (21) for increased adherence to a Mediterranean dietary pattern (in general, the studies estimated the association for the increase of 2 points - in a 0-9 score - or one standard deviation).

Cohort studies assessing cardiovascular outcomes: novel findings

Most studies relating the MedDiet to cardiovascular disease (CVD) have used coronary heart disease (CHD) or stroke as clinical outcomes. However, Tektonidis et al., in two large and well-defined Swedish cohorts, reported inverse associations of the MedDiet not only with CHD or stroke, but also with heart failure (10*,11*). Even more, among these 3 cardiovascular clinical end-points, the most frequent outcome was precisely the heart failure, that was inversely associated with the MedDiet, and showed significant relative risks of 0.69 (95% confidence interval (CI), 0.57–0.83) (11) and 0.79 (95% CI, 0.68–0.93) (10) respectively. This finding is of high interest because it provides a basis to include heart failure, and not only CHD and stroke, to assess the cardiovascular effects of the MedDiet. Another study conducted in Sweden with these same two cohorts concluded, after having adopted a relatively novel statistical approach (Laplace regression), that better adherence to the MedDiet was associated with increased life expectancy (23 months longer survival. 95% CI, 16-29 months) (12). The Multi-Ethnic cohort study is one of the largest studies in nutritional epidemiology (9*). This cohort included White, African-American, Native Hawaiian, Japanese-American, and Latino adults from the US (n=215,782) and followed-up them for mortality over 13–18 years. In this large cohort, the Alternate Mediterranean diet score (aMed) (28–30) measured at baseline with a 182-item quantitative food frequency questionnaire was found to be inversely associated with total mortality, cardiovascular mortality, and cancer mortality, both in men and women. This cohort also appraised other indexes of dietary quality. The aMED, together with the Alternate Healthy Eating Index-2010, exhibited the highest reductions in mortality risk among women. Both indexes, beyond fruits and vegetables, also included moderate consumption of alcohol, as well as low consumption of red/processed meats. The report from two large US studies by Sotos-Prieto et al. (8*) represents a strong methodological step forward in nutritional epidemiology, because the exposure to the MedDiet was not only measured at baseline (as in the previous studies), but also by repeated validated dietary assessments (using a full-length food frequency questionnaire every 4 years). In addition, biannual update of data regarding lifestyle was used to control for a wide array of potential confounding factors. This assessment is considerably more robust than previous observational approaches because it is less prone to measurement error, reduces the room for residual confounding, and allows to assess the effects of changes in diet during follow-up. Using the first 4-year changes in adherence to the MedDiet, Sotos-Prieto et al. (8*) found that increasing the aMED scores in that period was associated with a significant 9% lower risk of CVD risk in the long term

(Table 1). In addition, they found that maintaining a high adherence to that dietary pattern consistently was related to lower CVD risk compared to a consistently low adherence.

Cohort studies assessing disability and quality of life: novel findings

Two reports (13,14) in large cohort studies conducted in the Netherlands found reductions in disability, and improved quality of life associated with better adherence to the MedDiet. Whereas, one report (22) combining two smaller cohorts in Spain found an inverse association for physical dimensions, but not for mental dimensions, using the Short-Form 12 (a brief tool to assess quality of life). Methodological issues related to retention rates duration of follow-up, and inherent weaknesses of the tools used for appraising quality of life might explain this discrepancy.

The Mediterranean diet beyond olive oil?

The current food pattern framework that we mentioned in the introduction assumes that the effect of the MedDiet goes beyond olive oil. Besides, most of the previously mentioned studies (8–14,19,23*,24) did not specifically add the exclusive use of olive oil to the scoring systems used to classify participants regarding to their adherence to the MedDiet. This might be explained by the low prevalence of olive oil consumption in Sweden, the US, or the Netherlands. However, the use of olive oil is actually growing up in these countries. In any case, an appropriate definition of the traditional MedDiet should include it as the main culinary fat, together with an abundant daily use of extra-virgin olive oil (around 10-15% of total calories). Even though olive oil is not enough, these two items represent indisputable characteristics of the traditional MedDiet, supported by the screener used to deliver the intervention in the PREDIMED trial (31–33). Therefore, the adequate transferability of the MedDiet to non-Mediterranean countries requires to incorporate olive oil as the main source of fat. This is supported by the dramatic beneficial results specifically found for extra-virgin olive oil in the PREDIMED randomized trial against type 2 diabetes (34), peripheral artery disease (35), atrial fibrillation (36) and breast cancer (37*). These effects seem to be, at least partially, mediated by the anti-inflammatory effects of polyphenols from extra-virgin olive oil and other less-known and challenging mechanisms (4*,38,39).

Randomized trial evidence of the effect of the Mediterranean diet in the prevention of breast cancer and cognitive decline

Secondary analyses conducted within the PREDIMED randomized trial have shown exciting results for the MedDiet in 2015. Significant improvements in a battery of cognitive tests were reported in a small subgroup (n=334) of the trial after 4.1 years of follow-up (40*). Another study reported that the MedDiet with free provision of extra-virgin olive oil was associated with a significant reduction in the risk of developing breast cancer in 4280 women participating in this large trial, after 4.8 years of follow-up (37*). These two studies have attracted huge attention in both the scientific community and general media, because it is the first time that highest-level evidence, from a randomized trial, shows that an intervention based on changes in the food pattern is able to reduce the risk of breast cancer and to improve cognition. The improvement in cognitive function observed in this recent

sub-study (PREDIMED-BARCELONA) (40*) is consistent with two previous reports from another center (PREDIMED-NAVARRA) (41,42) with larger sample size and longer follow-up, but assessing only post-trial cognition, instead of changes in cognitive function. The main limitations of the secondary analysis on breast cancer were the small number of observed incident cases of invasive breast cancer, and also the absence of systematic and repeated mammographic evaluations of participants (37*).

Conclusions: a new trial has been launched

Taken together with previously available evidence, all these recent observational studies support impressive benefits for the MedDiet. In addition, they are also consistent with the results of the PREDIMED study, a rigorously conducted randomized primary prevention trial, specially when the consumption of extra-virgin olive oil was very high (4,31,32,34–37).

However, beyond diet, the evidence is largely missing for other aspects of the Mediterranean lifestyle, notably for a physically active lifestyle. The good news is that a new Spanish large primary prevention trial was launched in September 2013 in the same vanguard site that PREDIMED was launched 10 years before, specifically in the PREDIMED-NAVARRA center (www.predimed.es). This new trial labeled PREDIMED-PLUS (www.predimedplus.com) had recruited more than 4,500 participants up to May 2016. The target is to randomize 6,000 participants with metabolic syndrome and a body mass index between 27-40 kg/m² to two equally-sized groups: an intervention group randomized to an energy-restricted MedDiet, physical activity, and weight loss program; and a control group resembling the PREDIMED intervention with recommendations to follow the MedDiet but with total energy intake kept ad libitum, no special goals for weight loss and no special program of physical activity. This new trial, supported by the European Research Council, will allow, for the first time, the assessment of the long-term cardiovascular effects of a full package of Mediterranean lifestyles, which goes beyond the dietary pattern. The results are expected in 2021.

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Non-standard abbreviations

ATTICA	a health and nutrition survey carried out in the province of Attica
BP	Blood pressure
CHD	Coronary Heart Disease
CI	Confidence Interval
COSM	cohort of Swedish men
CVD	Cardiovascular Disease
DALYs	disability-adjusted life years
ENRICA	rationale and methods of the study on nutrition and cardiovascular risk in Spain (in Spanish)
EPIC-NL	Dutch collaboration to the European prospective investigation into cancer and nutrition
HAPIEE	health alcohol and psychosocial factors in Eastern Europe
HF	heart failure
HPFUS	health professionals follow-up study
HR	Hazard Ratio
MedDiet	Mediterranean Diet
MI	myocardial infarction
NHS	nurses' health study
PREDIMED	“PREvención con DIeta MEDiterránea” randomized trial (www.predimed.es)
QALYs	quality-adjusted life years
RR	Relative Risk
SD	standard deviation
SMC	Swedish mammography cohort
STABILITY	stabilization of atherosclerotic plaque by initiation of darapladib therapy trial
SUN	seguimiento universidad de Navarra

UAM universidad autónoma de Madrid

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Key points

- * The MedDiet represents the gold standard in preventive medicine, probably due to the harmonic combination of many elements with antioxidant and antiinflammatory properties, which overwhelm any single nutrient or food item.
- * Recent studies provide a basis to include heart failure, and not only CHD and stroke, to assess the cardiovascular effects of the MedDiet.
- * The PREDIMED study is the first randomized trial showing that an intervention based on changes in the food pattern is able to reduce the risk of breast cancer and to improve cognition.
- * The adequate transferability of the MedDiet to non-Mediterranean countries requires to incorporate olive oil as the main source of fat.
- * The PREDIMED-PLUS randomized trial aims to solve the lack of evidence regarding the effect of other aspects of the Mediterranean lifestyle (beyond diet) on health.

Main observational prospective studies published in 2015 and during Jan–May 2016 on health effects of the Mediterranean diet.

Author, year (ref)	Study	Location	Outcome(s)	Exposure	n	follow-up	Results/observations
Panagiotakos, 2015 (6)	ATTICA	Greece	CVD	MedDiet and lifestyles	2583	10 y	MedDiet associated with lower risk of CVD (RR, 0.98, 0.95–1.01), for each additional unit in a 0–55 score, equivalent to a HR, 0.78, 0.53–1.13 for 2 units in a 0 to 9 score
Panagiotakos, 2015 (7)	ATTICA	Greece	CVD	MedDiet and mediators	2583	10 y	MedDiet associated with lower risk of CVD (RR, 0.96, 0.93–1.00), for each additional unit in a 0–55 score, equivalent to a HR, 0.60, 0.41–1.00 for 2 units in a 0 to 9 score
Sotos-Prieto, 2015 (8)	HPFUS NHS	US	CVD	Several food patterns	80538	17.3 y	Improving adherence to MedDiet during the first 4 y of follow-up associated with a lower risk of CVD, HR, 0.91 (0.86–0.97)
Harmon, 2015 (9)	Multi-ethnic cohort	US	Mortality	Several food patterns	215782	15.5 y	MedDiet inversely associated with mortality both in men HR, 0.76 (0.73, 0.80) and in women HR, 0.78 (0.74, 0.82) for the 5th vs. 1st quintile
Tektonidis, 2015 (10)	SMC	Sweden	MI, stroke, HF	MedDiet	32921	10 y	MedDiet associated with lower risk of MI (RR, 0.74, 0.61–0.90), HF (RR, 0.79, 0.68–0.93) and ischemic stroke (RR: 0.78, 0.65–0.93), but not hemorrhagic stroke (RR: 0.88, 0.61–1.29).
Tektonidis, 2016 (11)	COSM	Sweden	Heart failure	MedDiet	37308	10.9 y	Inverse association of the Med Diet with HF, 0.85 (0.78–0.91) for each two additional points in a 0–8 score
Bellavia, 2016 (12)	COSM+SMC	Sweden	Mortality	MedDiet	71333	15 y	MedDiet inversely associated with total mortality, HR, 0.81, 0.75–0.86 for high versus low adherence
Fransen, 2015 (13)	EPIC-NL	Netherlands	QALYs	Several food patterns	33066	12.4 y?	MedDiet associated with a 2-month increase in QALYs (0.6–3.6 months)
May, 2015 (14)	EPIC-NL	Netherlands	DALYs	MedDiet and lifestyles	33066	12.4 y	MedDiet associated with reduced DALYs -0.24 (-0.44 to -0.02)
Menotti, 2016 (15)	Italian rural areas of Seven Countries	Italy	Mortality	MedDiet and lifestyles	1712	50 y	Inverse association of the MedDiet with all-cause mortality HR, 0.67 (0.57–0.78), CV mortality HR, 0.68 (0.54–0.86) and cancer mortality 0.54 (0.40–0.73). Life expectancy was 4.4 y longer for MedDiet.

Author, year (ref)	Study	Location	Outcome(s)	Exposure	n	follow-up	Results/observations
Prinelli, 2015 (16)	Lombardy cohort	Italy	Mortality	MedDiet	974	17.4 y	Inverse association of the MedDiet with mortality HR, 0.62 (0.43–0.89) for high versus low adherence
Bonaccio, 2016 (17)	Moli-Sani	Italy	Mortality	MedDiet	1995	4 y	In diabetics, MedDiet was inversely associated with mortality HR, 0.63 (0.49–0.81) for each 2 additional points in a 0 to 9 score
Bo, 2016 (18)	Turin study	Italy	Mortality, CVD	MedDiet	1658	12 y	High adherence to MedDiet inversely associated with all-cause mortality (HR, 0.83, 0.72–0.96), and CVD (HR, 0.79, 0.65–0.97). No association with mortality among high risk subjects
Stefler, 2015 (19)	HAPIEE	Czech Rep., Poland, Russia	Mortality, CVD	MedDiet	19333	7 y	One standard deviation (SD) in MedDiet adherence inversely associated with all-cause death (HR, 95 % CI 0.93, 0.88–0.98) and CVD (0.90, 0.81–0.99)
Hernandez-Hernandez, 2015 (20)	SUN cohort	Spain	CVD	Mediterranean alcohol drinking pattern (MADP)	14651	9.7 y	No significant association between the departure from the MADP and CVD, HR, 1.55 (0.58–4.16)
Martinez-Gonzalez, 2015 (21)	PREDIMED	Spain	Mortality, CVD	Empirically-derived food patterns	7216	4.3 y	MedDiet (empirically identified) associated with lower risk of CV, HR 4th vs. 1st quartile, 0.52 (0.36–0.74) and all-cause mortality, HR, 0.53 (0.38–0.75)
Pérez-Tasigchana, 2015 (22)	UAM cohort + Seniors ENRICA cohort	Spain	Quality of life	MedDiet	4287	2.5 y?	MedDiet associated with better physical quality of life, +1.34 (+0.21 to +2.47) for the third vs. the first tertile but no association with mental quality of life according to SF-12
Stewart, 2016 (23)	STABILITY (patients with stable CHD)	39 countries	CVD	MedDiet	15482	3.7 y	MedDiet associated with lower CVD HR, 0.95, 0.91–0.98), for each additional unit in a 0–24 score, equivalent to a HR, 0.76, 0.61–0.90 for 2 units in a 0 to 9 score, but only if >12 points in the 0–24 score
Lau, 2015 (24)	Patients with stable CHD	Hong-Kong	BP variability stroke	MedDiet	274	77 mo	Lower variability in BP, lower systolic BP and lower incidence of stroke, HR, 0.48 (0.24–0.94) associated with better adherence to MedDiet

BP: Blood pressure

CHD: Coronary Heart Disease

CI: Confidence Interval

CVD: Cardiovascular Disease

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HR: Hazard Ratio

MedDiet: Mediterranean Diet

PREDIMED: "PREvenición con Dieta MEDiterránea", randomized trial (www.predimed.es)

RR: Relative Risk

SD: standard deviation