DYSLIPIDAEMIAS: PRESENT AND FUTURE APPROACHES TO PHARMACOLOGICAL INTERVENTION

November 9th-10th, Sorrento (NA) - Italy

NON PHARMACOLOGICAL THERAPEUTIC APPROACHES

Lifestyle interventions

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Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

EAS · ESC — European Society of Cardiology

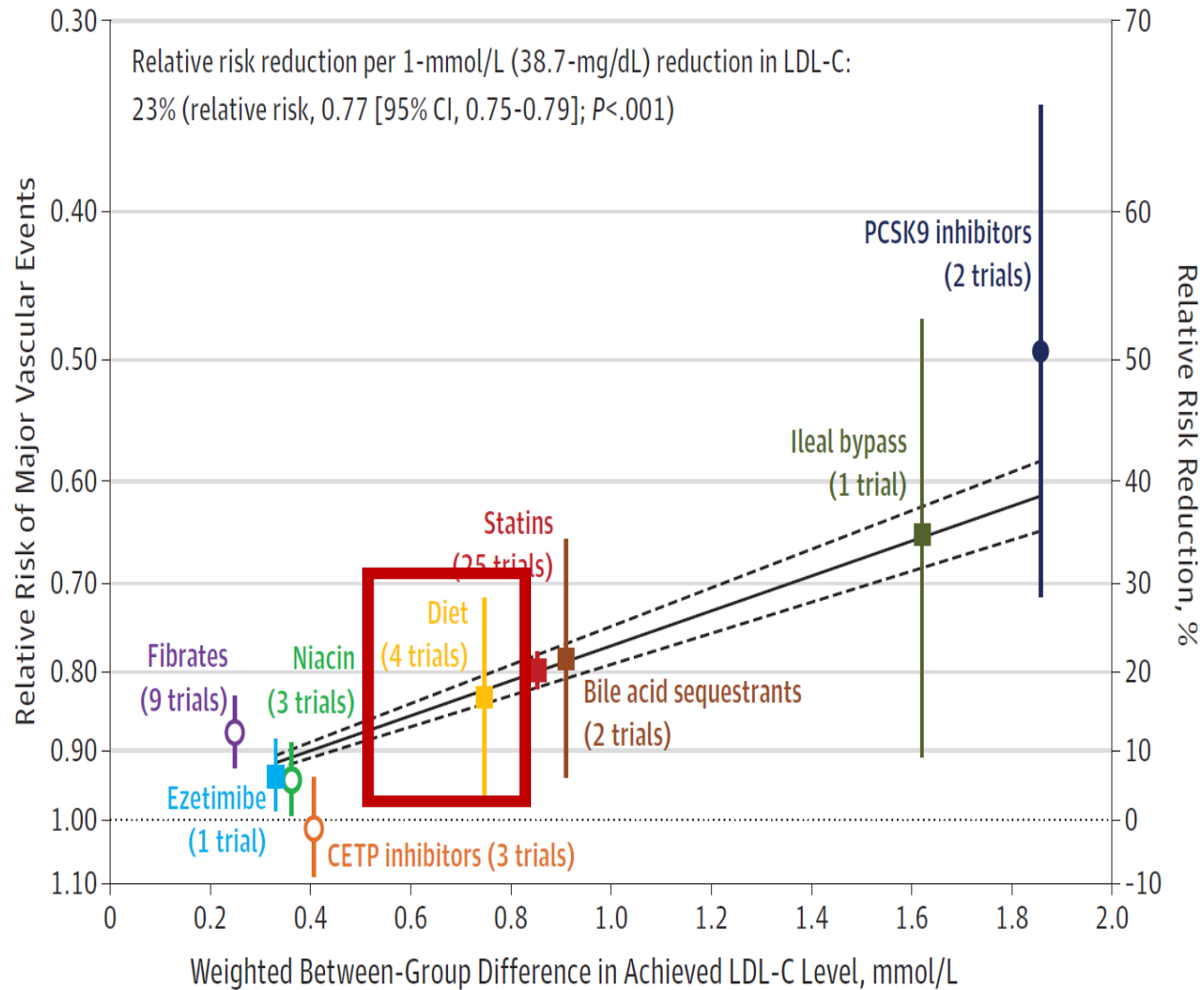| Total CV risk (SCORE) %		Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Primary Prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Classª/Levelᵇ	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Classª/Levelᵇ	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high- risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Classª/Levelᵇ	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Classª/Levelᵇ	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary Prevention	Very-high risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Classª/Levelᵇ	IIa/A	I/A	I/A	I/A	I/A	I/A

©ESC

7 Lifestyle modifications to improve the plasma lipid profile

Table 7 **Treatment targets and goals for cardiovascular disease prevention**

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5−7 h moderately vigorous physical activity per week or 30−60 min most days.
Body weight	BMI 20−25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).

Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions
A Systematic Review and Meta-analysis

Relative risk reduction per 1-mmol/L (38.7-mg/dL) reduction in LDL-C:
23% (relative risk, 0.77 [95% CI, 0.75-0.79]; $P<.001$)

Relative Risk of Major Vascular Events (left axis)
Relative Risk Reduction, % (right axis)

PCSK9 inhibitors (2 trials)

Ileal bypass (1 trial)

Statins (25 trials)

Diet (4 trials)

Fibrates (9 trials)

Niacin (3 trials)

Bile acid sequestrants (2 trials)

Ezetimibe (1 trial)

CETP inhibitors (3 trials)

Weighted Between-Group Difference in Achieved LDL-C Level, mmol/L

Silverman MG, et al. JAMA. 2016;316:1289-1297

- Nutrition has a pivotal role in the prevention of ASCVD.
- Dietary factors influence the development of CVD either directly or through their action on traditional risk factors, such as plasma lipids, BP, or glucose levels.
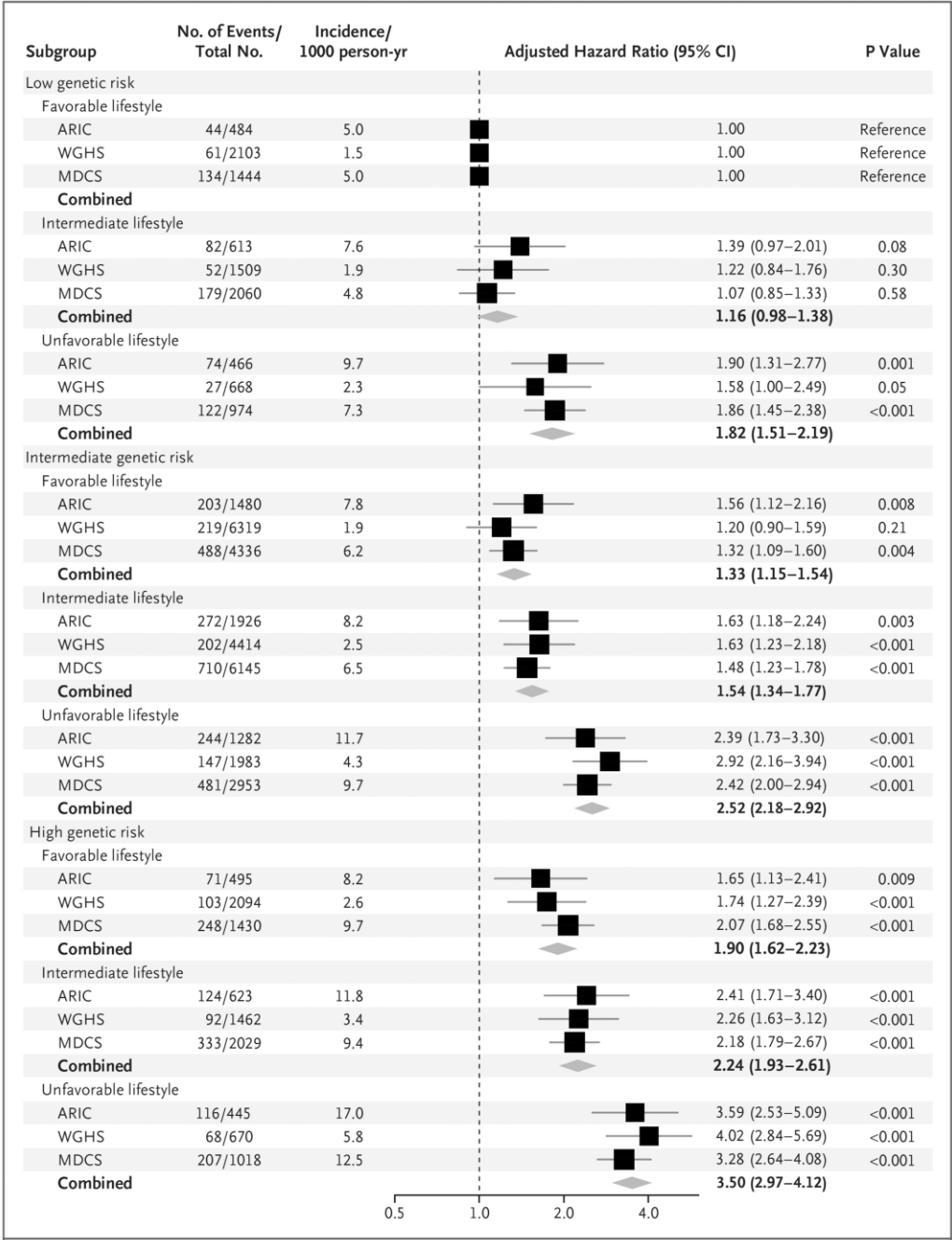
Eur Heart J. 2019. doi:10.1093/eurheartj/ehz455

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

- Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease.

- Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavorable lifestyle.

Khera AV, et al. N Engl J Med. 2016;375:2349–58.

Risk of Coronary Events, According to Genetic and Lifestyle Risk in the Prospective Cohorts

Subgroup	No. of Events/ Total No.	Incidence/ 1000 person-yr	Adjusted Hazard Ratio (95% CI)	P Value
Low genetic risk				
Favorable lifestyle				
ARIC	44/484	5.0	1.00	Reference
WGHS	61/2103	1.5	1.00	Reference
MDCS	134/1444	5.0	1.00	Reference
Combined				
Intermediate lifestyle				
ARIC	82/613	7.6	1.39 (0.97–2.01)	0.08
WGHS	52/1509	1.9	1.22 (0.84–1.76)	0.30
MDCS	179/2060	4.8	1.07 (0.85–1.33)	0.58
Combined			**1.16 (0.98–1.38)**	
Unfavorable lifestyle				
ARIC	74/466	9.7	1.90 (1.31–2.77)	0.001
WGHS	27/668	2.3	1.58 (1.00–2.49)	0.05
MDCS	122/974	7.3	1.86 (1.45–2.38)	<0.001
Combined			**1.82 (1.51–2.19)**	
Intermediate genetic risk				
Favorable lifestyle				
ARIC	203/1480	7.8	1.56 (1.12–2.16)	0.008
WGHS	219/6319	1.9	1.20 (0.90–1.59)	0.21
MDCS	488/4336	6.2	1.32 (1.09–1.60)	0.004
Combined			**1.33 (1.15–1.54)**	
Intermediate lifestyle				
ARIC	272/1926	8.2	1.63 (1.18–2.24)	0.003
WGHS	202/4414	2.5	1.63 (1.23–2.18)	<0.001
MDCS	710/6145	6.5	1.48 (1.23–1.78)	<0.001
Combined			**1.54 (1.34–1.77)**	
Unfavorable lifestyle				
ARIC	244/1282	11.7	2.39 (1.73–3.30)	<0.001
WGHS	147/1983	4.3	2.92 (2.16–3.94)	<0.001
MDCS	481/2953	9.7	2.42 (2.00–2.94)	<0.001
Combined			**2.52 (2.18–2.92)**	
High genetic risk				
Favorable lifestyle				
ARIC	71/495	8.2	1.65 (1.13–2.41)	0.009
WGHS	103/2094	2.6	1.74 (1.27–2.39)	<0.001
MDCS	248/1430	9.7	2.07 (1.68–2.55)	<0.001
Combined			**1.90 (1.62–2.23)**	
Intermediate lifestyle				
ARIC	124/623	11.8	2.41 (1.71–3.40)	<0.001
WGHS	92/1462	3.4	2.26 (1.63–3.12)	<0.001
MDCS	333/2029	9.4	2.18 (1.79–2.67)	<0.001
Combined			**2.24 (1.93–2.61)**	
Unfavorable lifestyle				
ARIC	116/445	17.0	3.59 (2.53–5.09)	<0.001
WGHS	68/670	5.8	4.02 (2.84–5.69)	<0.001
MDCS	207/1018	12.5	3.28 (2.64–4.08)	<0.001
Combined			**3.50 (2.97–4.12)**	

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

R. Estruch, E. Ros, J. Salas-Salvadó, M.-I. Covas, D. Corella, F. Arós,
E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, R.M. Lamuela-Raventos,
L. Serra-Majem, X. Pintó, J. Basora, M.A. Muñoz, J.V. Sorlí, J.A. Martínez, M. Fitó,
A. Gea, M.A. Hernán, and M.A. Martínez-González,
for the PREDIMED Study Investigators*

- Multicenter trial in Spain.
- 7,447 participants (55 to 80 years of age, 57% women), at high CV risk, but with no CV disease at enrollment.
- 3 diets:
  - Mediterranean diet supplemented with extra-virgin olive oil.
  - Mediterranean diet supplemented with mixed nuts.
  - Control diet (advice to reduce dietary fat).

* The amount of olive oil includes oil used for cooking and salads and oil consumed in meals eaten outside the home. In the group assigned to the Mediterranean diet with extra-virgin olive oil, the goal was to consume 50 g (approximately 4 tbsp) or more per day of the polyphenol-rich olive oil supplied, instead of the ordinary refined variety, which is poor in polyphenols. The participants received a free supply (15 liters every 3 months) to include the oil used for cooking and family needs.
† For participants assigned to the Mediterranean diet with nuts, the recommended consumption was one daily serving (30 g, composed of 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts). Participants received for free the needed allotments of tree nuts in packages of 2 kg of walnuts, 1 kg of almonds, and 1 kg of hazelnuts every 3 months, with the extra amounts to be shared with family members.
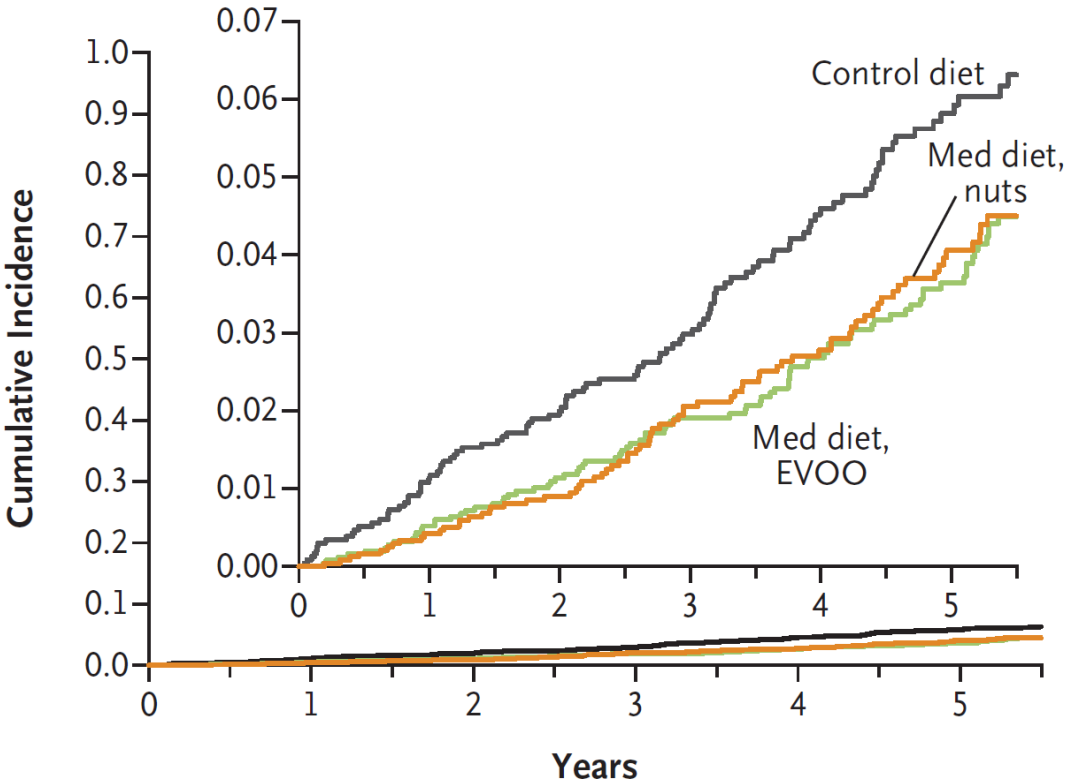‡ Sofrito is a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil.

Estruch R. et al. N Engl J Med 2018;378:e34.

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<2 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)¶	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Lean fish and seafood	≥3 sprvings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving/wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups‖	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts
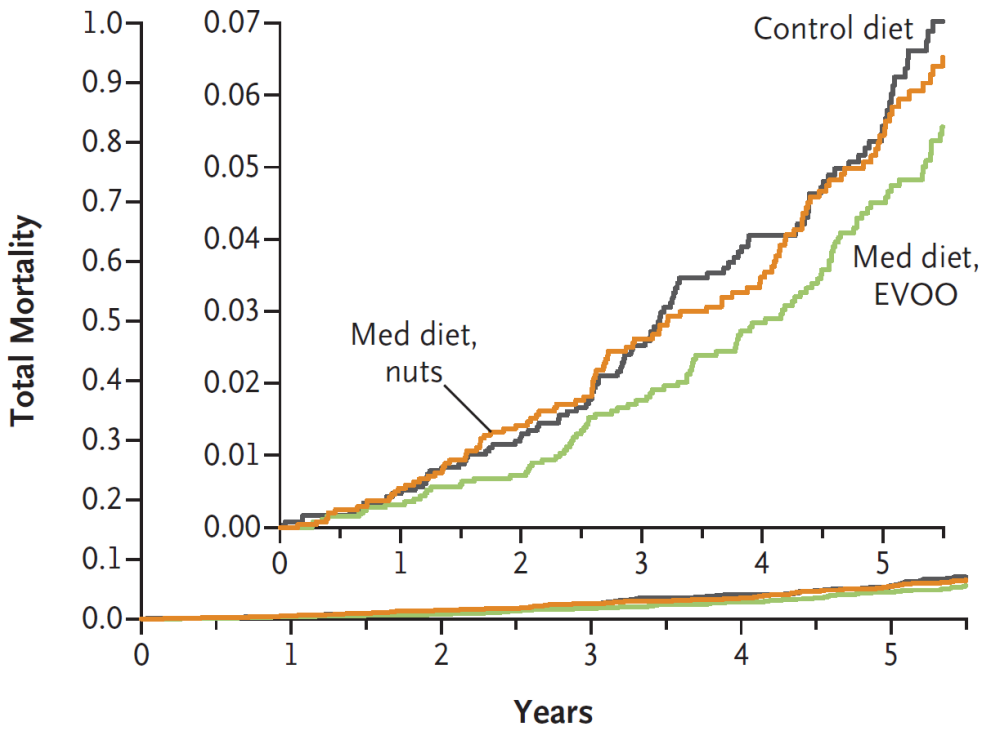

Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
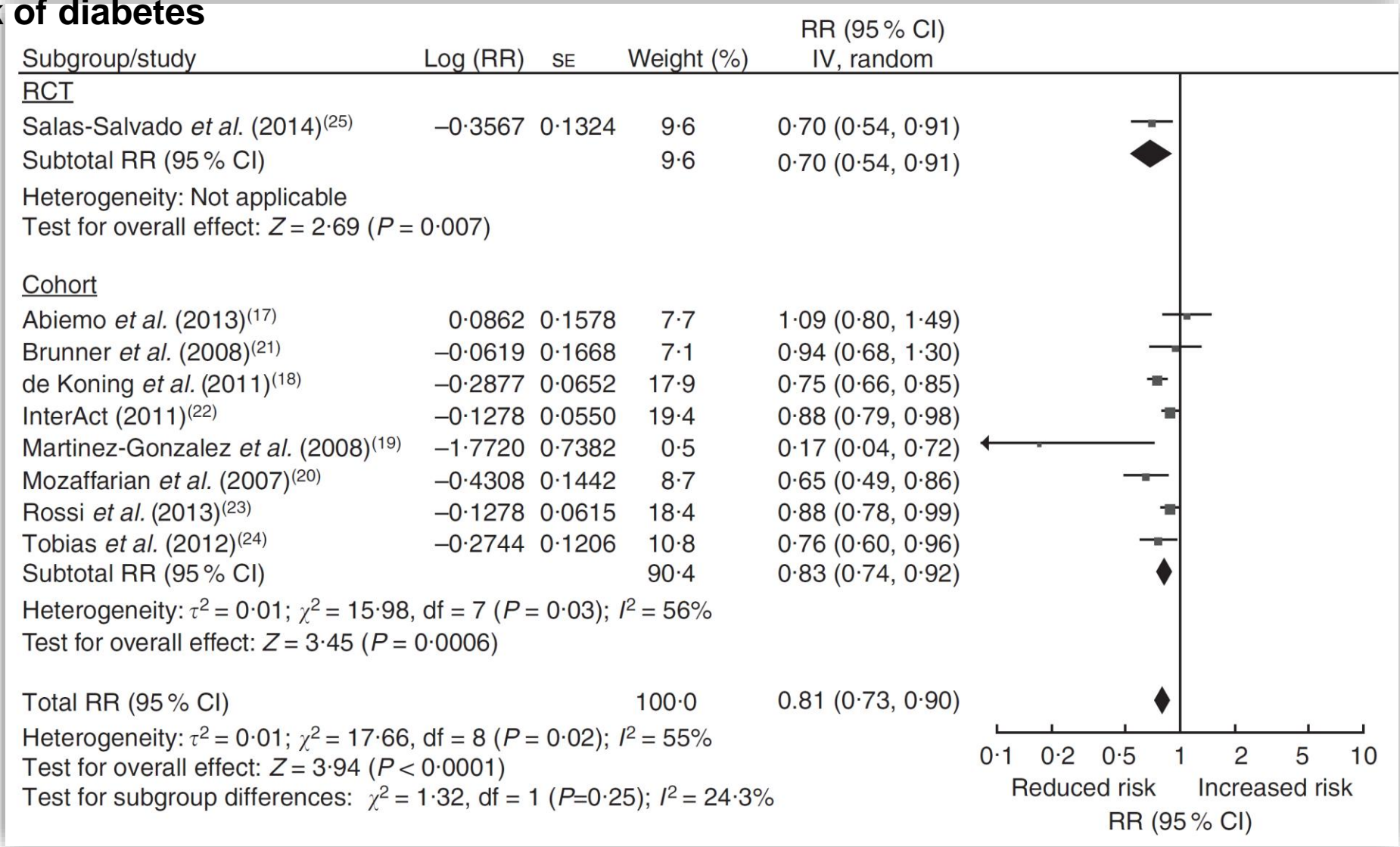Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)

Total Mortality

Med diet, EVOO: hazard ratio, 0.90 (95% CI, 0.69–1.18)
Med diet, nuts: hazard ratio, 1.12 (95% CI, 0.86–1.47)

Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis

Greater adherence to Mediterranean diet is associated with a significant reduction in the risk of diabetes

Subgroup/study	Log (RR)	SE	Weight (%)	RR (95 % CI) IV, random
RCT				
Salas-Salvado et al. (2014)[25]	−0·3567	0·1324	9·6	0·70 (0·54, 0·91)
Subtotal RR (95 % CI)			9·6	0·70 (0·54, 0·91)
Heterogeneity: Not applicable				
Test for overall effect: $Z = 2·69$ ($P = 0·007$)				
Cohort				
Abiemo et al. (2013)[17]	0·0862	0·1578	7·7	1·09 (0·80, 1·49)
Brunner et al. (2008)[21]	−0·0619	0·1668	7·1	0·94 (0·68, 1·30)
de Koning et al. (2011)[18]	−0·2877	0·0652	17·9	0·75 (0·66, 0·85)
InterAct (2011)[22]	−0·1278	0·0550	19·4	0·88 (0·79, 0·98)
Martinez-Gonzalez et al. (2008)[19]	−1·7720	0·7382	0·5	0·17 (0·04, 0·72)
Mozaffarian et al. (2007)[20]	−0·4308	0·1442	8·7	0·65 (0·49, 0·86)
Rossi et al. (2013)[23]	−0·1278	0·0615	18·4	0·88 (0·78, 0·99)
Tobias et al. (2012)[24]	−0·2744	0·1206	10·8	0·76 (0·60, 0·96)
Subtotal RR (95 % CI)			90·4	0·83 (0·74, 0·92)
Heterogeneity: $\tau^2 = 0·01$; $\chi^2 = 15·98$, df = 7 ($P = 0·03$); $I^2 = 56\%$				
Test for overall effect: $Z = 3·45$ ($P = 0·0006$)				
Total RR (95 % CI)			100·0	0·81 (0·73, 0·90)
Heterogeneity: $\tau^2 = 0·01$; $\chi^2 = 17·66$, df = 8 ($P = 0·02$); $I^2 = 55\%$				
Test for overall effect: $Z = 3·94$ ($P < 0·0001$)				
Test for subgroup differences: $\chi^2 = 1·32$, df = 1 ($P = 0·25$); $I^2 = 24·3\%$				

0·1 0·2 0·5 1 2 5 10
Reduced risk   Increased risk
RR (95 % CI)

Schwingshackl L, et al. Public Health Nutrition. 2014;18:1292–9

Metabolic and Vascular Effect of the Mediterranean Diet

Beneficial effect of the Mediterranean diet

BENEFICIAL EFFECT OF THE MEDITERRANEAN DIET	
DIABETES	**NEUROLOGICAL DISEASE**
Reduction of insulin resistance	Reducing incidence of ischemic stroke
Reduction of hyperinsulinemia	Reducing incidence of haemorrhagic stroke
Optimization of glycemic control	Protection of aging brains
Increase in the amount of incretins (GLP-1)	Less incidence of cognitive problems
CARDIOVASCULAR DISEASE	**DYSLIPIDEMIA**
Lowering blood pressure	Reduction in plasma LDL cholesterol concentrations
Reduction of foam cells formation and atherosclerosis	Reduction in the reabsorption of cholesterol and bile acids in the intestine
Reduction of arterial stiffness	Reduction of triglycerides
Less incidence of coronary artery disease	Increase in concentrations of adiponectin and HDL cholesterol
Less incidence of heart failure	Reduction in plasma ceramides

Tuttolomondo A, et al. Int J Mol Sci. 2019;20:4716

But, not all is Mediterranean diet

Only 5% of the vegetables grown are traded internationally.

http://agrination.org.in/vegetable-map-of-the-world/

- As foods are mixtures of different nutrients and other components, it is not appropriate to attribute the health effects of a food to only one of its components.

- To overcome, at least in part, these problems, in recent years nutrition research has focused on the relationship between ASCVD on the one hand, and foods and dietary patterns—rather than single nutrients—on the other.

- Consistent evidence from epidemiological studies indicates that higher consumption of fruit, non-starchy vegetables, nuts, legumes, fish, vegetable oils, yoghurt, and wholegrains, along with a lower intake of red and processed meats, foods higher in refined carbohydrates, and salt, is associated with a lower incidence of CV events.

- The replacement of animal fats with vegetable sources of fats and polyunsaturated fatty acids (PUFAs) may decrease the risk of CVD.

- Given the cultural diversity of the European populations, they should be translated into practical behaviours, considering local habits and socio-economic factors.

Effects on blood lipids of a blood pressure–lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial[1–3]

Eva Obarzanek, Frank M Sacks, William M Vollmer, George A Bray, Edgar R Miller III, Pao-Hwa Lin, Njeri M Karanja, Marlene M Most-Windhauser, Thomas J Moore, Janis F Swain, Connie W Bales, and Michael A Proschan, on behalf of the DASH Research Group

DASH (Dietary Approaches to Stop Hypertension) diet: diet increased in fruit, vegetables, and low-fat dairy products and reduced in saturated fat, total fat, and cholesterol. **FV**: diet increased in fruit and vegetables.

DASH diet: $P < 0.0001$ for TC, LDL cholesterol, and HDL cholesterol.
FV diet: $P = 0.055$ for TAG.

Effect of Plant Protein on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Siying S. Li, HBSc; Sonia Blanco Mejia, MD, MSc; Lyubov Lytvyn, MSc; Sarah E. Stewart, MSc, Effie Viguiliouk, MSc; Vanessa Ha, MSc; Russell J. de Souza, ScD, RD; Lawrence A. Leiter, MD; Cyril W. C. Kendall, PhD; David J. A. Jenkins, MD, PhD, DSc; John L. Sievenpiper, MD, PhD

What Are the Clinical Implications?

- Because the intake of plant protein from soy, nuts, and pulses remains low, there is an opportunity for people to realize the lipid-lowering benefits of sustainable plant-based dietary strategies that substitute plant protein for animal protein.
- Plant protein, especially in combination with other cholesterol-lowering foods (eg, viscous fiber and plant sterols) and/or as an adjunct to lipid-lowering pharma-cotherapy, may have a clinically meaningful benefit in helping people to achieve lipid targets and reduce cardiovascular risk.

Subgroup	Trials	Participants	Mean Difference (95% CI)	Overall Effect P-value	I²	Heterogenity P-value
LDL-C (mmol/L)	108	5582	-0.16 (-0.20 to -0.12)	P<0.00001	55%	P<0.00001
Non-HDL-C (mmol/L)	102	5401	-0.18 (-0.22 to -0.14)	P<0.00001	52%	P<0.00001
Apo B (g/L)	37	1506	-0.05 (-0.06 to -0.03)	P<0.00001	30%	P=0.05

Mean Difference (95% CI) for Primary Outcomes — Favors plant protein / Favors animal protein

Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile

CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet)

What Are the Clinical Implications?

- Our findings suggest that in the context of behavioral counseling that promotes a reduced caloric intake, VD and MD determine similar reduction in body weight and fat mass.
- The present results suggest that following a VD leads to a significant reduction in low-density lipoprotein cholesterol, whereas the MD could be more effective in reducing triglyceride levels.
- This work could improve the awareness of the general population that both VD and MD may help in reducing cardiovascular disease risk factors.

	Vegetarian Diet: Before (n=104)	Vegetarian Diet: After (n=104)	Mediterranean Diet: Before (n=103)	Mediterranean Diet: After (n=103)	P (Δ_{VD} Versus Δ_{MD})†
TC, mg/dL	207.89 (200.74–215.29)	202.55 (195.98–209.56)*	205.41 (197.95–212.94)	205.30 (198.34–212.72)	0.15
HDL-C, mg/dL	53.36 (51.26–55.48)	52.56 (50.30–54.93)	53.09 (50.65–55.70)	53.41 (51.21–55.70)	0.62
LDL-C, mg/dL	128.25 (114.89–134.83)	121.27 (114.89–127.87)*	123.72 (116.86–130.84)	125.84 (119.22–132.69)	0.01
Triglycerides, mg/dL	108.74 (99.29–119.10)	114.66 (104.27–126.09)	114.66 (104.38–125.96)	107.88 (98.59–118.16)*	0.01

Sofi F, et al. Circulation. 2018;137:1103–1113.

Diet, physical activity and telomere length in adults

- Telomere length is a predictive biomarker of premature aging.

- Telomere shortening has been linked to age-related diseases and noncommunicable diseases.

- The predominant mechanisms through which a healthy diet and moderate physical exercise could mitigate telomere attrition include decreasing oxidative stress and inflammation.

Potential influence of healthy diet and physical activity on the maintenance of telomere length

Intrinsic factors

Cell division
DNA damage
Oxidative stress
Inflamation

Environmental factors

Nutrition
Stress
Obesity
Smoking

Telomere shortening

Cellular senescence

Genomic instability

Epigenetic modifications
Methylation/acethylation of histones
DNA methylation

↑ Antioxidant enzymes
DNA repare enzymes

↓ Inflammatory biomarkers (IL-6, TNF-α. C-reactive protein)
Reactive oxygen species

Lifestyle factors

Healthy diet
Physical activity/exercise

Navarro-Ibarra MJ, et al. Nutr Hosp. 2019 Oct 28. doi: 10.20960/nh.02673. [Epub ahead of print]

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

	Lifestyle interventions		
	To reduce TC and LDL-c levels	To reduce TG-rich lipoprotein levels	To increase HDL-c levels

The magnitude of the effect: +++ >10%; ++: 5-10%; +: <5%.

Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile

	To be preferred	To be used in moderation	To be chosen occasionally in limited amounts
Cereals	Wholegrains	Refined bread, rice, and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, ice lollies/popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, sweets/candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork, and veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skimmed milk and yoghurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yoghurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

Summary of lifestyle measures and healthy food choices for the management of total cardiovascular risk

- Dietary recommendations should always take into account local food habits; however, interest in healthy food choices from other cultures should be promoted.

- A wide variety of foods should be eaten. Energy intake should be adjusted to prevent overweight and obesity.

- Consumption of fruits, vegetables, legumes, nuts, wholegrain cereal foods, and fish (especially oily) should be encouraged.

- Foods rich in trans fatty acids should be totally avoided; foods rich in saturated fatty acids (tropical oils, fatty or processed meat, sweets, cream, butter, and regular cheese) should be replaced with the above foods, and with monounsaturated fat (extra-virgin olive oil) and polyunsaturated fat (non-tropical vegetable oils), in order to keep saturated fatty acids intake <10 % (<7% in the presence of high plasma cholesterol values).

Summary of lifestyle measures and healthy food choices for the management of total cardiovascular risk

- Salt intake should be reduced to <5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt.

- For those who drink alcoholic beverages, moderation should be advised (<10 g/day for women and for men) and patients with hypertriglyceridaemia should abstain.

- The intake of beverages and foods with added sugars, particularly soft drinks, should be discouraged, especially for persons who are overweight, have hypertriglyceridaemia, MetS, or DM.

- Physical activity should be encouraged, aiming at regular physical exercise for ≥30 min/day every day.

- Use of and exposure to tobacco products should be avoided.

Body weight and physical activity

- In the case of excess weight, body weight reduction, even if modest (5-10% of basal body weight), improves lipid abnormalities and favourably affects the other CV risk factors often present in dyslipidaemic individuals.

- Weight reduction can be achieved by decreasing the consumption of energy-dense foods, inducing a caloric deficit of 300-500 kcal/day.

- The intervention should combine diet and exercise.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary

Social determinants are also important

Topic/Domain	Example Considerations
Cardiovascular risk	■ Adults should be routinely assessed for psychosocial stressors and provided with appropriate counseling (S2.1-26). ■ Health literacy should be assessed every 4 to 6 y to maximize recommendation effectiveness (S2.1-27).
Diet	■ In addition to the prescription of diet modifications, body size perception, as well as social and cultural influences, should be assessed (S2.1-28,S2.1-29). ■ Potential barriers to adhering to a heart-healthy diet should be assessed, including food access and economic factors; these factors may be particularly relevant to persons from vulnerable populations, such as individuals residing in either inner-city or rural environments, those at socioeconomic disadvantage, and those of advanced age* (S2.1-30).
Exercise and physical activity	■ In addition to the prescription of exercise, neighborhood environment and access to facilities for physical activity should be assessed (S2.1-31–S2.1-33).
Obesity and weight loss	■ Lifestyle counseling for weight loss should include assessment of and interventional recommendations for psychosocial stressors, sleep hygiene, and other individualized barriers (S2.1-34–S2.1-36). ■ Weight maintenance should be promoted in patients with overweight/obesity who are unable to achieve recommended weight loss.
Diabetes mellitus	■ In addition to the prescription of type 2 diabetes mellitus interventions, environmental and psychosocial factors, including depression, stress, self-efficacy, and social support, should be assessed to improve achievement of glycemic control and adherence to treatment (S2.1-37–S2.1-40).
High blood pressure	■ Short sleep duration (<6 h) and poor-quality sleep are associated with high blood pressure and should be considered (S2.1-41). Because other lifestyle habits can impact blood pressure, access to a healthy, low-sodium diet and viable exercise options should also be considered.
Tobacco treatment	■ Social support is another potential determinant of tobacco use. Therefore, in adults who use tobacco, assistance and arrangement for individualized and group social support counseling are recommended (S2.1-42,S2.1-43).

Adherence to a Mediterranean Diet and Survival in a Greek Population

Antonia Trichopoulou, M.D., Tina Costacou, Ph.D., Christina Bamia, Ph.D., and Dimitrios Trichopoulos, M.D.

Greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.

N Engl J Med 2003;348:2599-608.

Table 4. Hazard Ratios for Death Associated with a Two-Point Increment in the Mediterranean-Diet Score.*

Variable	No. of Deaths/ No. of Participants	Hazard Ratio for Death (95% CI)		
		Crude	Age- and Sex-Adjusted	Fully Adjusted
Death from any cause	275/22,043	0.74 (0.65–0.86)	0.79 (0.69–0.91)	0.75 (0.64–0.87)
Death from coronary heart disease	54/22,043	0.68 (0.50–0.94)	0.74 (0.54–1.02)	0.67 (0.47–0.94)
Death from cancer	97/22,043	0.81 (0.64–1.03)	0.85 (0.67–1.08)	0.76 (0.59–0.98)
Sex				
Male	179/8895	0.72 (0.61–0.86)	0.77 (0.65–0.92)	0.78 (0.65–0.94)
Female	96/13,148	0.67 (0.52–0.86)	0.71 (0.55–0.91)	0.69 (0.53–0.90)
Age				
<55 Yr	46/12,645	0.98 (0.69–1.38)	0.86 (0.61–1.21)	0.89 (0.62–1.27)
≥55 Yr	229/9398	0.72 (0.62–0.84)	0.75 (0.64–0.88)	0.73 (0.61–0.86)
Smoking status				
Never smoked	121/11,908	0.67 (0.54–0.83)	0.72 (0.58–0.89)	0.67 (0.53–0.84)
Ever smoked	154/10,135	0.79 (0.65–0.95)	0.77 (0.64–0.93)	0.82 (0.67–1.00)
Body-mass index				
<28.06	122/10,969	0.72 (0.59–0.90)	0.74 (0.59–0.92)	0.77 (0.61–0.97)
≥28.06	153/11,074	0.76 (0.63–0.92)	0.76 (0.63–0.92)	0.73 (0.60–0.89)
Waist-to-hip ratio				
≥0.87	204/10,967	0.75 (0.63–0.88)	0.79 (0.67–0.93)	0.79 (0.66–0.94)
<0.87	71/11,076	0.61 (0.45–0.81)	0.65 (0.49–0.87)	0.64 (0.48–0.88)
Education				
≥6 Yr	164/17,887	0.79 (0.66–0.95)	0.77 (0.64–0.92)	0.77 (0.63–0.93)
<6 Yr	111/4156	0.73 (0.58–0.91)	0.74 (0.59–0.93)	0.72 (0.56–0.91)
Level of physical activity				
≥35.01 MET-hr/day	79/11,009	0.93 (0.71–1.22)	0.88 (0.67–1.14)	0.83 (0.63–1.09)
<35.01 MET-hr/day	196/11,034	0.72 (0.61–0.85)	0.72 (0.61–0.85)	0.74 (0.61–0.88)

Adherence to the "Mediterranean Diet" in Spain and Its Relationship with Cardiovascular Risk (DIMERICA Study)

- A total of 1732 subjects were asked to complete a questionnaire designed to assess their nutrient intake, dietary habits, and exercise.
- A diet score assessed the adherence of participants to the Mediterranean diet (range 0–10)

	Total (n = 1732)	Area 1 (n = 210)	Area 2 (n = 147)	Area 3 (n = 617)	Area 4 (n = 262)	Area 5 (n = 456)	p Value
Physical activity level, %							
Daily, %	39.5	37.5	34.9	35.8	33.5	32.4	NS
4–5 times per week, %	12.9	10.3	9.9	12.9	8.9	11.7	NS
2–3 times per week, %	24.1	20.1	16.4	20.8	20.3	24.0	NS
Never (sedentary), %	23.1	18.8	26.3	16.6	24.2	21.7	NS
Watching Television, h/day, %							
<1, %	22.9	19.2	23.1	20.6	19.6	25.0	NS
1–2, %	42.6	42.9	45.4	37.5	38.4	40.7	NS
≥2, %	34.2	31.7	28.5	33.4	35.2	29.4	NS

Table 5. MD adherence according to score (out of 10) in the different areas of Spain.

	Area 1 (n = 221)	Area 2 (n = 149)	Area 3 (n = 621)	Area 4 (n = 277)	Area 5 (n = 464)	p Value
Score	5.3 (4.0, 6.0) *,†	5.3 (4.0, 6.0) *,†	4.6 (3.3, 6.0)	5.3 (4.0, 6.0) *,†	4.6 (3.3, 4.6)	<0.001

Abellán Alemán J, et al. Nutrients 2016, 8, 680; doi:10.3390/nu8110

Dietary advice for reducing cardiovascular risk

- **Dietary advice**: decrease consumption of one or more of fat, saturated fatty acids, cholesterol or salt; or increase consumption of one or more of fruit, vegetables, polyunsaturated fatty acids, monounsaturated fatty acids, fish, fiber or potassium; or both.
- **The control group** received no or minimal dietary advice.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Total cholesterol (mmol/L), change from baseline	22	3044	Mean Different (IV, Random, 95% CI)	−0.13 [−0.21, −0.05]
LDL cholesterol (mmol/L), change from baseline	17	1654	Mean Different (IV, Random, 95% CI)	−0.16 [−0.24, −0.08]
HDL cholesterol (mmol/L), change from baseline	16	1700	Mean Different (IV, Random, 95% CI)	−6.89 [−0.02, 0.02]
Triglycerides (mmol/L), change from baseline	8	648	Mean Different (IV, Random, 95% CI)	−0.02 [−0.13, 0.08]

RESULTS: Reduction of LDL-c of 0.16 mmol / L (6.2 mg / dL) after 3 to 24 months

Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome

Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial

- Preliminary exploratory interim analysis of an ongoing randomized trial.
- 6874 individuals aged 55 to 75 years with metabolic syndrome and no CVD.
- Intervention group that encouraged an energy-reduced Mediterranean diet, promoted physical activity, and provided behavioral support.
- Control group that encouraged an energy-unrestricted Mediterranean diet.
- The primary outcome was 12-month change in adherence based on the energy-reduced Mediterranean diet (er-MedDiet) score:
  - Range: 0-17.
  - Higher scores indicate greater adherence.

Figure 2. Changes in the Primary End Point of Diet Adherence in a Study of the Effect of an Energy-Reduced Mediterranean Diet (er-MedDiet) Among Adults With Metabolic Syndrome
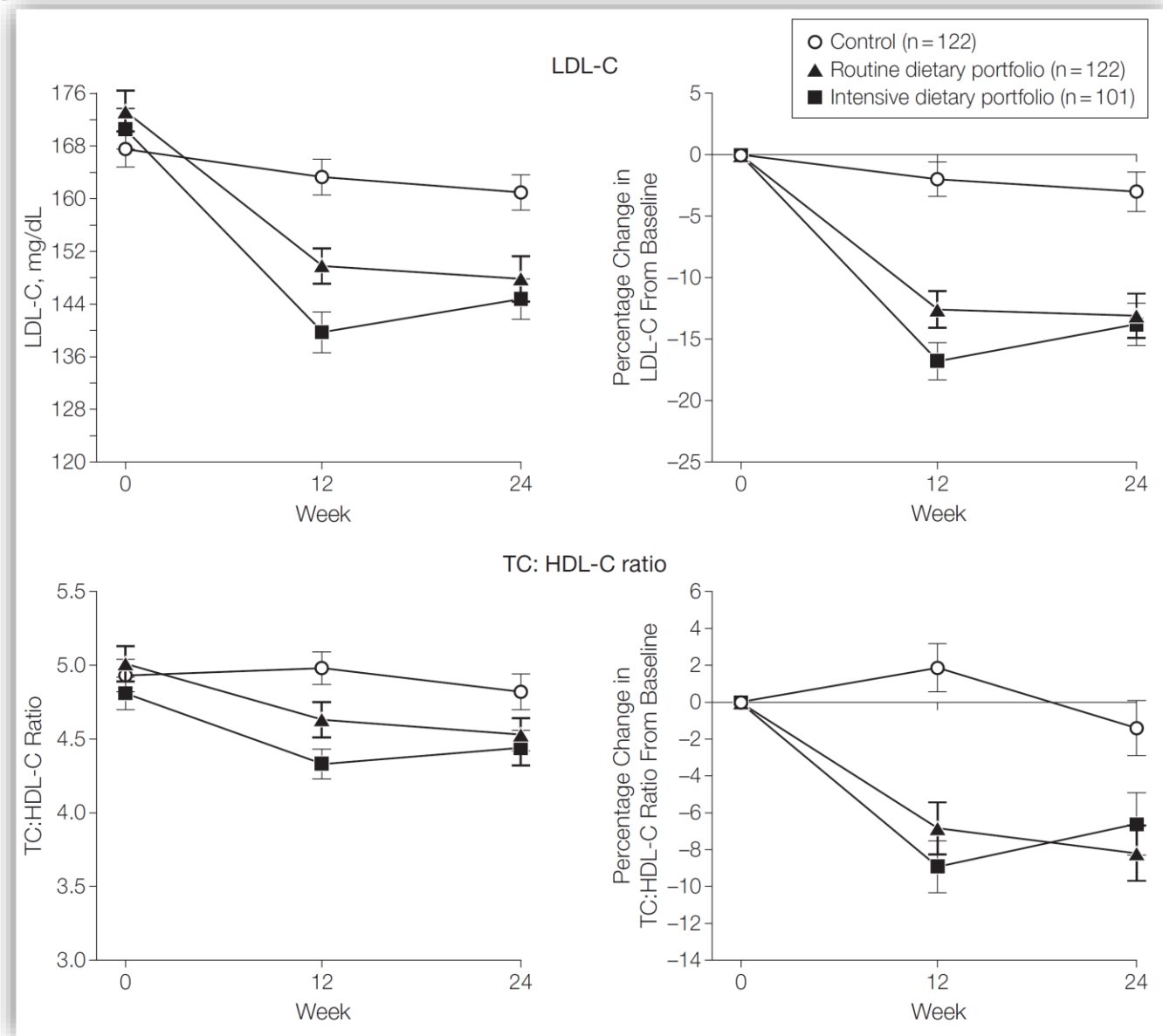
Sayón-Orea C, et al. JAMA. 2019;322:1486-1499.

Effect of a Dietary Portfolio of Cholesterol-Lowering Foods Given at 2 Levels of Intensity of Dietary Advice on Serum Lipids in Hyperlipidemia

A Randomized Controlled Trial

Participants received dietary advice for 6 months on either:

- A low−saturated fat therapeutic diet (control).
- A dietary portfolio, for which counseling was delivered at different frequencies, that emphasized dietary incorporation of plant sterols, soy protein, viscous fibers, and nuts.
  - Routine dietary portfolio involved 2 clinic visits over 6 months
  - Intensive dietary portfolio involved 7 clinic visits over 6 months

Economic modeling for improved prediction of saving estimates in healthcare costs from consumption of healthy foods: the Mediterranean-style diet case study

Jason P.H. Jones[1†], Mohammad M.H. Abdullah[2†], Dallas Wood[1] and Peter J.H. Jones[3*]

	20% increase in adherence scenario	80% increase in adherence scenario
Direct savings		
Hospitals	2.5 (2.3–2.7)	9.4 (8.6–10.1)
Drugs	2.0 (1.8–2.1)	7.6 (7.0–8.2)
Physicians	0.8 (0.7–0.8)	2.9 (2.7–3.1)
Formal caregiving	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Total direct	5.2 (4.8–5.6)	19.9 (18.3–21.4)
Indirect savings		
Mortality	0.1 (0.0–0.1)	0.8 (0.7–0.8)
Morbidity and long-term caring	0.2 (0.2–0.2)	1.0 (0.9–1.1)
Total indirect	0.3 (0.2–0.3)	1.8 (1.6–1.9)
Total savings	5.5 (5.1–5.9)	20.9 (19.3–22.5)

Popular scientific summary
- Dramatic rates of major public health concerns, such as heart disease and cancer place great pressure on national economies worldwide.
- The Mediterranean diet is a classic example of healthy dietary habits and has consistently shown favorable impacts on the heart health.
- This economic model suggests a significant reduction in healthcare costs associated with the management of heart disease by following the dietary principles of the Mediterranean diet.

Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

EAS · ESC European Society of Cardiology

Total CV risk (SCORE) %	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
<1 low-risk (Primary Prevention)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Classa/Levelb	I/C	I/C	I/C	I/C	IIa/A	IIa/A
≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Classa/Levelb	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Classa/Levelb	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Classa/Levelb	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Very-high risk (Secondary Prevention)	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Classa/Levelb	IIa/A	I/A	I/A	I/A	I/A	I/A

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