

A working document from the proposed and under development of Yale Olive Sciences and Health Institute (YOSHI) to provide the rationale for a change in the way olive oil is categorized in the proposed NutriScore system

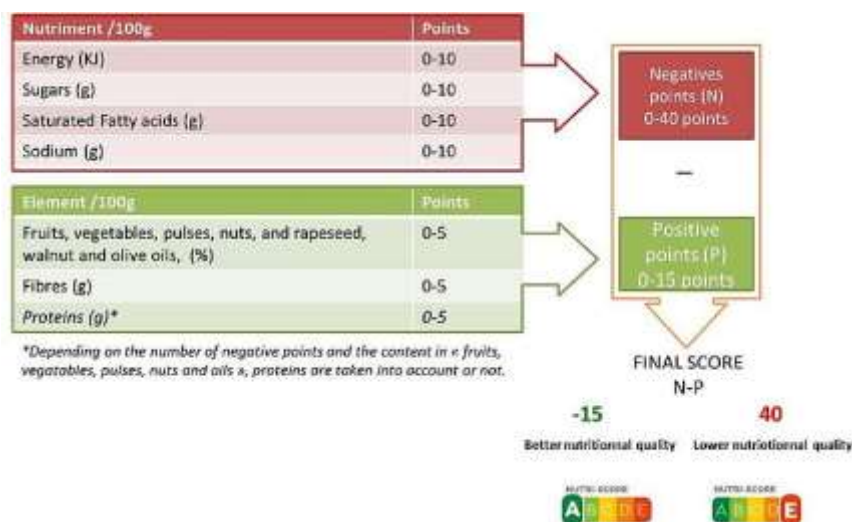
Olive Oil and NutriScore

Background

NutriScore, a front-of-pack labeling system (FOPL), has been proposed by the Nutritional Epidemiology Research Team (EREN), a French public nutrition research team and is based on the nutritional score created by the Food Standards Agency (FSA) in the UK.

The NutriScore was presented in the 2013 report "Proposals for a new impetus to the French public health nutrition policy in the framework of the National Health Strategy". The NutriScore advocates for the adoption of a system of grades from A to E on the front of food products to allow to easily compare the nutritional quality of products.

To calculate the NutriScore, favorable nutrients, which should be consumed in abundance, are set off against unfavorable nutrients, which should only be consumed in small quantities. Fiber, protein, fruit, and vegetables have a positive effect, while saturated fatty acids, sugar and salt have a negative effect. (source: <https://www.foodwatch.org/en/campaigns/sugar-fat-and-salt/how-the-nutri-score-works/>)



Prepared by:	Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health
Contributions and Review by:	
Version:	Version 1.1 last updated March 24, 2021

The result is translated into a five-level color scale, which is backed by the letters A-E. Rather balanced products get a dark green A or light green B, in the middle range there is a yellow C and rather unbalanced products like sweets or fatty snacks get an orange D or even a red E.

Olive oils are natural fruit juices that physicians, nutritionists, and dietitians recommend, based on ever increasing clinical research evidence, to their patients in place of less healthy (or even deleterious) eating and cooking fats, for the prevention and treatment of certain diseases, mostly of chronic nature. According to the NutriScore algorithm, olive oil falls on the C color; this will unavoidably lead to confusion among consumers with dire consequences on their health. Consequently, this can potentially discourage the public access to a superfood that has, time and again, proven to impact health benefits. Unarguably, this goes against the fundamentals of any sound Public Health policy in any country.

Olive oil should either (a) be assigned the Green-A grade or (b) not considered at all and thus not assigned any grade, in the NutriScore system. No other edible fat is as healthy and flavorful as olive oil, especially extra virgin olive oil.

Clearly, the proposed NutriScore labeling of olive oils will impede the realization of this superfood's multitude of associated health benefits. The European Food Safety Agency's (EFSA) approved health claims for olive oil are helping in the attempt to shift towards more healthful dietary eating patterns specifically including a Mediterranean-style nutrition—of which olive oil is the cornerstone. Recently, the Mediterranean diet was, for the fourth year in a row, named by an expert panel of nationally recognized experts in diet, nutrition, obesity, food psychology, diabetes and heart disease as the best diet overall (out of 35 diet plans) in the U.S News and World Report annual rankings.

Confusion that will arise from NutriScore labeling will certainly impact the public's ability to initiate and/or follow this healthy nutrition plan, with numerous downstream negative impacts on health and health-related costs. No matter how one tries to explain and justify the categorization of Coke Zero with a better NutriScore than extra virgin olive oil (B vs C), it is in clear contradiction to the accumulated science supporting and proving the health benefits of the natural juice from olives.

The European Union (EU) is by far the world's largest consumer of olive oil. According to IOC data, the E.U. was estimated to consume 1,545,000 metric tons in 2019.

Many of the health benefits of extra virgin olive oil are believed to be related to the presence of polyphenols, such as oleocanthal, which are unique to olive oils. In general, the more flavor an olive oil has, the higher its polyphenol content.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

The new NutriScore label that classifies olive oil and extra virgin olive oil as less than a healthy option not only will potentially discredit the accumulated evidence-based science that has, for the last 50 years or so, proven the health impact of olive oil in the context of the Mediterranean nutrition paradigm. Further, the labeling of olive oil with the NutriScore level C will undoubtedly create confusion among and dampen the trust of consumers to European guidance and regulations, as it is in clear contrast to the EFSA health claim (Commission Regulation (EU) 432/2012). This health claim unequivocally emphasizes the health benefits imparted from olive oil and states:

Olive oil polyphenols contribute to the protection of blood lipids from oxidative stress. The claim may be used only for olive oil, containing at least 5 mg of hydroxytyrosol and its derivatives (e.g. oleuropein complex and tyrosol) per 20 g of olive oil. In order to bear the claim information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 20 g of olive oil.

Replacing saturated fats in the diet with unsaturated fats contributes to the maintenance of normal blood cholesterol levels. The claim may be used only for food, which is high in unsaturated fatty acids, as referred to in the claim HIGH UNSATURATED FAT as listed in the Annex to Regulation (EC) No 1924/2006.

The NutriScore grade currently considered for olive oil needs to be reconsidered as this decision will not only affect a sector dedicated to health but also the consumer's overall trust in EU regulations, the olive oil sector and the countless studies on the product's positive affect on our bodies and overall health.

Prepared by:	Tassos C. Kyriakides. Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health
Contributions and Review by:	
Version:	Version 1.1 last updated March 24, 2021

Health Benefits of Olive Oil: The Evidence

Mediterranean nutrition, of which olive oil is the central food, has, over the decades, stood the test of time as the healthiest nutrition paradigm. Olive oil is a proven healthy superfood; a lot of scientific evidence has accumulated over the last fifty years, pointing to a plethora of direct and indirect health benefits of olive oil and other olive tree products like olives and olive leaves. Such health benefits are well-established and universally accepted by health experts, physicians, nutritionists, and dietitians. Multiple published reviews of the Mediterranean diet point to the numerous and varied health benefits on humans (1-8).

A summary of selected, important, and pertinent findings are provided as supporting evidence that, beyond doubt, the health benefits from olive oil and olives extend to many chronic diseases that greatly affect the human health.

1. **Cardiovascular/coronary heart disease.** This complex of disease conditions is a major public health burden. Heart disease is the leading cause of death in the United States among both men and women (9). Olive oil protects against heart disease due to its monounsaturated fatty acid profile, and, in the case of extra virgin grade, its polyphenol content, which operates in a number of different ways (10). The discovery of the anti-inflammatory (11-18) and antioxidant properties (19-21) of olive oils has shed light into such disease processes and downstream negative health impact.
 - a. **Inflammatory process:** Probably the key reason olive oil protects against heart disease is through its anti-inflammatory capacity (22). Oleic acid, an abundant monounsaturated fat in olive oil reduces inflammatory markers like C - reactive protein (CRP) (23). In addition, olive oil polyphenols—present in all olive oils, but especially in extra virgin—appear to be the main anti-inflammatory agents in olive oils (13). Some of the main polyphenols are the anti-inflammatory oleocanthal (14) as well as oleuropein. Oleocanthal has been shown to function as an anti-inflammatory like ibuprofen (18).
 - b. **Oxidative Process:** Phenols in olive oil have been shown to prevent oxidative DNA damage (20); further, phenolic compounds found in olive oil, especially extra virgin olive oil, along with other compounds like secoiridoids, lignans and squalene, have been shown to have antioxidant potential (21).
 - c. **HDL/LDL cholesterol:** Consumption of extra virgin olive oil has been shown to reduce age-related decrease in HDL in the context of anti-inflammatory activities (15); olive oil has also been shown to raise “good” HDL cholesterol and reduce “bad” LDL levels. In addition, unlike polyunsaturated oils which might also lower

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

LDL, olive oil has been shown to protect LDL particles from oxidation, which is what makes LDL cholesterol “bad” because it is a factor in heart disease.

- d. **Endothelial function:** Cardiovascular health is further promoted by the extent to which olive oil improves the function of the lining of the blood vessels (25, 26).
- e. **Blood clotting:** Olive oil can help prevent dangerous blood clotting that could lead to heart attack and/or stroke (27, 28).
- f. **Blood pressure:** Numerous studies on the impact of olive oil on blood pressure and subsequent impact on cardiovascular health further support the benefits of olive oil (26, 29, 30). One study of hypertensive patients found that olive oil reduced blood pressure significantly and reduced the need for medication as well (31). In addition, the rich flavor profile of olive oil enables patients with high blood pressure to reduce sodium intake without sacrificing taste.

In addition to the evidence provided above in specific areas of cardiovascular health, numerous clinical research studies conducted since 1970 have repeatedly shown the cardiovascular health benefits that the use of olive oil can impact on humans (26, 32-49).

- 2. **Other Chronic Conditions/Diseases.** In addition to cardiovascular health, olive oil has also been shown to be positively related to the prevention and/or treatment of **cancer, cognitive/neurological conditions, diabetes, and endocrine/metabolic syndrome.** Given that it has been established that chronic inflammation is a key factor in the natural history of these conditions/diseases, the prevailing hypothesis is that this benefit is due to olive oil’s anti-inflammatory properties.
 - a. **Cancer:** Research in cancer and olive oil is rapidly expanding. One should note that studies have shown that people residing in the Mediterranean countries have a fairly low risk of cancer which may be connected to olive oil (50). Oxidative cell damage due to the presence of free radicals is considered a potential cause of cancer, and extra virgin olive oil is high in antioxidants that reduce oxidative damage (51). The oleic acid, olive oils predominant monounsaturated fatty acid, is also highly resistant to oxidation and has been shown to have beneficial effects on genes linked to cancer (52, 53). To support these theories, many studies in test tubes have shown that compounds in olive oil can help fight cancer at the molecular level (54, 55). Several studies have shown the positive effect olive oil can have in the prevention and/or treatment of cancer (56-64).

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
- b. **Cognitive/Neurological Conditions:** A lot of research and evidence has been recently generated indicating the benefits of olive oil on cognitive and neurological health (65-84). Olive oil has been studied in the context of Alzheimer's disease, the world's most common neurodegenerative disease and a leading cause of dementia. One feature of Alzheimer's is a buildup of protein tangles called beta amyloid plaques, in certain neurons in the brain. A study in mice showed that oleocanthal can help to clear these plaques from the brain (85). Results from a recently completed randomized controlled clinical trial show that a Mediterranean diet that, by definition, includes olive oil had favorable effects on brain function and reduced the risk of cognitive impairment (86).
 - c. **Diabetes:** New clinical research projects as well as systematic reviews and meta-analysis are providing strong evidence that olive oil can help reduce the risk of Type-2 diabetes (T2D) and improve glycemic control in patients with T2D. Since these studies were carried out in the context of adherence to a Mediterranean diet, the hypothesis that olive oil, a main food in this dietary pattern, is the mediator of this positive health impact, has repeatedly been shown to hold (87-98)
 - d. **Endocrine/Metabolic Syndrome:** Early evidence, coming primarily from cross-sectional studies and meta-analyses, suggests that there is a positive association between a Mediterranean diet nutrition paradigm, of which olive oil is a main pillar, and metabolic health. Currently on-going and future research are expected to confirm findings and conclusions thus far reported (99-103).

It should be further noted that research in bone health and gut microbiome is extremely suggestive of the positive impact that olive oil can impart in this human health parameters (104, 105). Specifically, the gut microbiome is the subject of intense study in the recent years and has generated a lot of interest given its potential multi-faceted impact on human health (106).

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

Recommendations

Olive oil is a healthy superfood, and this is one of the primary reasons consumers purchase it. Use and application of the NutriScore algorithm on olive oil without consideration of its numerous health benefits, will substantially negatively impact its use. This, in turn, and unavoidably will have negative downstream effects on human health.

It is therefore recommended that, based on the constantly accumulating evidence about its health benefits, olive oil should either (a) be labeled as a NutriScore Green-A grade food or (b) be excluded all together from the NutriScore process and thus not assigned any NutriScore grade.

Next Steps

Local, national, and European level health and nutrition organizations, agencies, and other entities, should mobilize to oppose the use of NutriScore for olive oil.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

Resources and References

1. Dinu, M., et al. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr* (2018). 72(1): p. 30-43.
2. Nowson, C.A., et al. The Impact of Dietary Factors on Indices of Chronic Disease in Older People: A Systematic Review. *J Nutr Health Aging* (2018) 22(2): p. 282-296.
3. Sayon-Orea, C., S. Carlos, and M.A. Martinez-Gonzalez. Does cooking with vegetable oils increase the risk of chronic diseases? : a systematic review. *Br J Nutr* (2015). 113 Suppl. 2: p. S36-48.
4. Sofi, F., et al. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* (2010) 92(5): p.1189-96.
5. Roman, B., et al. Effectiveness of the Mediterranean diet in the elderly. *Clin Interv Aging* (2008) 3(1): p. 97-109.
6. Sofi, F., et al. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* (2008) 337: p. a1344.
7. Covas M-I, Ruiz-Gutierrez, Valentina, de la Torre, Rafael, Kafatos, Anthony, Lamuela-Raventos, Rosa, Osada, Jesus, Owen, Robert W .Visioli, Francesco. Minor components of olive oil: evidence to date of health benefits in humans. *Nutrition Reviews* (2006); 64: S20-S30.
8. Serra-Majem, L., B. Roman, and R. Estruch. Scientific evidence of interventions using the Mediterranean diet: a systematic review. *Nutr Rev* (2006). 64(2 Pt 2): p. S27-47
9. <https://www.cdc.gov/heartdisease/facts.htm>
10. María-Isabel Covas. Olive oil and the cardiovascular system. *Pharmacological Research* (2007); Volume 55, Issue 3, Pages 175-186

Prepared by:	<i>Tassos C. Kyriakides. Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
11. Hannah L Mayra, Catherine Itsiopoulos, Audrey C Tierney, Miguel Ruiz-Canelad, James R.Hebert, Nitin Shivappa, Colleen J Thomas. Improvement in dietary inflammatory index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: The AUSMED heart trial. *Nutrition Research* (2018). Volume 55, July 2018, Pages 108-121.
 12. Tanakal Wongwarawipat, Nikolaos Papageorgiou, Dimitrios Bertsiias, Gerasimos Siasos and Dimitris Tousoulis. Olive Oil-related Anti-inflammatory Effects on Atherosclerosis. *Endocrine, Metabolic & Immune Disorders - Drug Targets* (2018), 18, 51-62; doi: 10.2174/1871530317666171116103618
 13. Carmela Santangelo, Rosaria Vari, Beatrice Scazzocchio, Patrizia De Sanctis, Claudio Giovannini, Massimo D'Archivio and Roberta Masella. Anti-inflammatory Activity of Extra Virgin Olive Oil Polyphenols: Which Role in the Prevention and Treatment of Immune-Mediated Inflammatory Diseases? *Endocrine, Metabolic & Immune Disorders - Drug Targets* (2018), 18, 36-50.
 14. Lisa Parkinson and Russell Keast. Oleocanthal, a Phenolic Derived from Virgin Olive Oil: A Review of the Beneficial Effects on Inflammatory Disease. *Int. J. Mol. Sci.* (2014) 15, 12323-12334; doi:10.3390/ijms150712323.
 15. Soumaya Loued, Hicham Berrougui, Pamela Componova, Souad Ikhlef, Olfa Helal and Abdelouahed Khalil (2013). Extra-virgin olive oil consumption reduces the age-related decrease in HDL and paraoxonase 1 anti-inflammatory activities. *British Journal of Nutrition* (2013), 110, 1272–1284. doi:10.1017/S0007114513000482
 16. M Fito, M Cladellas, R de la Torre, J Martí´, D Munoz, H Schroder, M Alcantara, M Pujadas-Bastardes, J Marrugat, MC Lopez-Sabater, J Bruguera, MI Covas and the members of the SOLOS Investigators. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial. *European Journal of Clinical Nutrition* (2008), 62, 570–574
 17. Paola Bogani, Claudio Galli, Marco Villa, Francesco Visioli. Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis* 190 (2007), 181–186.
 18. Beauchamp GK, Keast RS, Morel D, et al. Ibuprofen-like activity in extra-virgin olive oil. *Brief communications. Nature* (2005), 437:45-6.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
19. Ramirez-Anaya J del P, Samaniego-Sanchez C, Castaneda-Saucedo MC, Villalon-Mir M, de la Serrana HL. Phenols and the antioxidant capacity of Mediterranean vegetables prepared with extra virgin olive oil using different domestic cooking techniques. *Food Chem* (2015), 188:430-8.
 20. Salvini S, Sera F, Caruso D, et al. Daily consumption of a high-phenol extra-virgin olive oil reduces oxidative DNA damage in postmenopausal women. *Br J Nutr* (2006); 95:742-51.
 21. Owen RW, Mier W, Giacosa A, Hull WE, Spiegelhalder B, Bartsch H. Phenolic compounds and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple phenols, secoiridoids, lignans and squalene. *Food Chem Toxicol* (2000); 38:647-59.
 22. Ross R. Atherosclerosis. An Inflammatory Disease *N Engl J Med* (1999); 340:115-126 DOI: 10.1056/NEJM199901143400207
 23. Yoneyama S, Miura K, Sasaki S, Yoshita K, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Nakagawa H. Dietary intake of fatty acids and serum C-reactive protein in Japanese. *J Epidemiol.* (2007) May; 17 (3):86-92.
 24. Aviram M, Eias K. Dietary olive oil reduces low-density lipoprotein uptake by macrophages and decreases the susceptibility of the lipoprotein to undergo lipid peroxidation. *Ann Nutr Metab.* (1993); 37(2):75-84.
 25. Ruano J, Lopez-Miranda J, Fuentes F, Moreno JA, Bellido C, Perez-Martinez P, Lozano A, Gómez P, Jiménez Y, Pérez Jiménez F. Phenolic content of virgin olive oil improves ischemic reactive hyperemia in hypercholesterolemic patients. *J Am Coll Cardiol.* (2005) Nov 15; 46(10):1864-8. Epub 2005 Oct 24
 26. Moreno-Luna R, Muñoz-Hernandez R, Miranda ML, Costa AF, Jimenez-Jimenez L, Vallejo-Vaz AJ, Muriana FJ, Villar J, Stiefel P. Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension. *Am J Hypertens.* (2012) Dec; 25(12):1299-304. doi: 10.1038/ajh.2012.128. Epub 2012 Aug 23.
 27. Smith RD, Kelly CN, Fielding BA, Hauton D, Silva KD, Nydahl MC, Miller GJ, Williams CM. Long-term monounsaturated fatty acid diets reduce platelet aggregation in healthy young subjects. *Br J Nutr.* (2003) Sep; 90(3):597-606.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
28. Brzosko S, De Curtis A, Murzilli S, de Gaetano G, Donati MB, Iacoviello L. Effect of extra virgin olive oil on experimental thrombosis and primary hemostasis in rats. *Nutr Metab Cardiovasc Dis.* (2002) Dec; 12(6):337-42.
 29. Galvão Cândido F, Xavier Valente F, da Silva LE, Gonçalves Leão Coelho O, Gouveia Peluzio MDC, Gonçalves Alfenas RC. Consumption of extra virgin olive oil improves body composition and blood pressure in women with excess body fat: a randomized, double-blinded, placebo-controlled clinical trial. *Eur J Nutr.* (2018) Oct; 57(7):2445-2455. doi:10.1007/s00394-017-1517-9.
 30. Perona JS, Canizares J, Montero E, Sanchez-Dominguez JM, Catala A, Ruiz-Gutierrez V. Virgin olive oil reduces blood pressure in hypertensive elderly subjects. *Clin Nutr* (2004); 23:1113-21.
 31. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello Russo A, Marotta T. Olive oil and reduced need for antihypertensive medications. *Arch* (2000); 160:837-42.
 32. Georgia - Maria Kouli, Demosthenes B. Panagiotakos, Ioannis Kyrou, Emanuela Magriplis, Ekavi N. Georgousopoulou, Christina Chrysohoou, Constantine Tsigos, Dimitrios Tousoulis, Christos Pitsavos. Olive oil consumption and 10-year (2002–2012) cardiovascular disease incidence: the ATTICA study. *Eur J Nutr* (2019) Feb; 58(1):131-138; doi 10.1007/s00394-017-1577-x
 33. 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. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* (2018); 378:e34. doi:10.1056/NEJMoa1800389
 34. Galvão Cândido F, Xavier Valente F, da Silva LE, Gonçalves Leão Coelho O, Gouveia Peluzio MDC, Gonçalves Alfenas RC. Consumption of extra virgin olive oil improves body composition and blood pressure in women with excess body fat: a randomized, double-blinded, placebo-controlled clinical trial. *Eur J Nutr.* (2018) Oct; 57(7):2445-2455. doi:10.1007/s00394-017-1517-9.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
35. Priscilla Azambuja Lopes de Souza, Aline Marcadenti and Vera Lúcia Portal. Effects of Olive Oil Phenolic Compounds on Inflammation in the Prevention and Treatment of Coronary Artery Disease. *Nutrients* (2017), 9(10), 1087; <https://doi.org/10.3390/nu9101087>
 36. Sleiman, D., M.R. Al-Badri, and S.T. Azar, Effect of Mediterranean diet in diabetes control and cardiovascular risk modification: a systematic review. *Front Public Health*, (2015). 3: p. 69
 37. Miguel A. Martínez-Gonzalez, Ligia J. Dominguez, and Miguel Delgado-Rodríguez. Olive oil consumption and risk of CHD and/or stroke: a meta-analysis of case–control, cohort and intervention studies. *British Journal of Nutrition* (2014), 112, 248–259 [doi:10.1017/S0007114514000713](https://doi.org/10.1017/S0007114514000713).
 38. Miguel Á. Martínez-González, MD, PhD; Estefanía Toledo, MD, PhD; Fernando Arós, MD, PhD; Miquel Fiol, MD, PhD; Dolores Corella, DPharm, PhD; Jordi Salas-Salvadó, MD, PhD; Emilio Ros, MD, PhD; Maria I. Covas, DPharm, PhD; Joaquín Fernández-Crehuet, MD, PhD; José Lapetra, MD, PhD; Miguel A. Muñoz, MD, PhD; Monserrat Fitó, MD, PhD; Luis Serra-Majem, MD, PhD; Xavier Pintó, MD, PhD; Rosa M. Lamuela-Raventós, DPharm, PhD; Jose V. Sorlí, MD, PhD; Nancy Babio, RD, PhD; Pilar Buil-Cosiales, MD, PhD; Valentina Ruiz-Gutierrez, PhD; Ramón Estruch, MD, PhD; Alvaro Alonso, MD, PhD for the PREDIMED INVESTIGATORS. Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation* (2014); 130:18–26; doi.org/10.1161
 39. RJ Widmer, MA Freund, AJ Flammer, J Sexton, R Lennon, A Romani, N Mulinacci, FF Vinceri, LO Lerman, and A Lerman. Beneficial effects of polyphenol-rich Olive Oil in patients with early atherosclerosis. *Eur J Nutr.* (2013) April; 52(3): 1223–1231. [doi:10.1007/s00394-012-0433-2](https://doi.org/10.1007/s00394-012-0433-2).
 40. Olga Castañer, Montserrat Fitó, M. Carmen López-Sabater, Henrik E. Poulsen, Kristiina Nyssönen, Helmut Schröder, Jukka T. Salonen, Karina De la Torre-Carbot, Hans-Franz Zunft, Rafael De la Torre, Hans Bäuml, Antonio V. Gaddi, Guillermo T. Saez, Marta Tomás, Maria- Isabel Covas for the EUROLIVE Study Group. The effect of olive oil polyphenols on antibodies against oxidized LDL. A randomized clinical trial. *Clinical Nutrition* (2011), Volume 30, Issue 4, August 2011, Pages 490-493.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
41. Covas MI, Nyyssonen K, Poulsen HE, et al. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med* (2006); 145:333-41.
 42. Maria-Isabel Covas, MSc, PhD; Kristiina Nyyssönen, MSc, PhD; Henrik E. Poulsen, MD, PhD; Jari Kaikkonen, MSc, PhD; Hans-Joachim F. Zunft, MD, PhD; Holger Kieseewetter, MD, PhD; Antonio Gaddi, MD, PhD; Rafael de la Torre, MSc, PhD; Jaakko Mursu, MSc; Hans Baumler, MSc, PhD; Simona Nascetti, MD, PhD; Jukka T. Salonen, MD, PhD; Montserrat Fito, MD, PhD; Jyrki Virtanen, MSc; and Jaume Marrugat, MD, PhD, for the EUROLIVE Study Group. The Effect of Polyphenols in Olive Oil on Heart Disease Risk Factors. A Randomized Trial. *Ann Intern Med.* (2006); 145:333-341.
 43. Fito M, Cladellas M, de la Torre R, et al. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. *Atherosclerosis* (2005); 181:149-58.
 44. Ruano J, Lopez-Miranda J, Fuentes F, Moreno JA, Bellido C, Perez-Martinez P, Lozano A, Gómez P, Jiménez Y, Pérez Jiménez F. Phenolic content of virgin olive oil improves ischemic reactive hyperemia in hypercholesterolemic patients. *J Am Coll Cardiol.* (2005) Nov 15; 46(10):1864-8. Epub 2005 Oct 24
 45. Perona JS, Canizares J, Montero E, Sanchez-Dominguez JM, Catala A, Ruiz-Gutierrez V. Virgin olive oil reduces blood pressure in hypertensive elderly subjects. *Clin Nutr* (2004); 23:1113-21.
 46. Smith RD1, Kelly CN, Fielding BA, Hauton D, Silva KD, Nydahl MC, Miller GJ, Williams CM. Long-term monounsaturated fatty acid diets reduce platelet aggregation in healthy young subjects. *Br J Nutr.* (2003) Sep; 90(3):597-606.
 47. Brzosko S, De Curtis A, Murzilli S, de Gaetano G, Donati MB, Iacoviello L. Effect of extra virgin olive oil on experimental thrombosis and primary hemostasis in rats. *Nutr Metab Cardiovasc Dis.* (2002) Dec; 12(6):337-42.
 48. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello Russo A, Marotta T. Olive oil and reduced need for antihypertensive medications. *Arch* (2000); 160:837-42.
 49. Keys A. Coronary heart disease in seven countries. *Circulation* (1970); 40:1-211.
 50. Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D. Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev.* (2000) Sep; 9(9):869-73.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
51. Owen RW, Haubner R, Würtele G, Hull E, Spiegelhalter B, Bartsch H. Olives and olive oil in cancer prevention. *Eur J Cancer Prev.* (2004) Aug; 13(4):319-26.
 52. Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalter B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *Eur J Cancer.* (2000) Jun; 36(10):1235-47.
 53. Menendez JA¹, Lupu R. Mediterranean dietary traditions for the molecular treatment of human cancer: anti-oncogenic actions of the main olive oil's monounsaturated fatty acid oleic acid (18:1n-9). *Curr Pharm Biotechnol.* (2006) Dec; 7(6):495-502.
 54. Menendez JA, Vellon L, Colomer R, Lupu R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification. *Ann Oncol.* (2005) Mar; 16(3):359-71. Epub 2005 Jan 10.
 55. Solanas M, Grau L, Moral R, Vela E, Escrich R, Escrich E. Dietary olive oil and corn oil differentially affect experimental breast cancer through distinct modulation of the p21Ras signaling and the proliferation-apoptosis balance. *Carcinogenesis.* (2010) May; 31(5):871-9. doi: 10.1093/carcin/bgp243. Epub 2009 Oct 13.
 56. Bruna Corominas-Faja, Elisabet Cuyàs, Jesús Lozano-Sánchez, Sílvia Cufí, Sara Verdura, Salvador Fernández-Arroyo, Isabel Borrás-Linares, Begoña Martín-Castillo, Ángel G. Martín, Ruth Lupu, Alfons Nonell-Canals, Melchor Sanchez-Martinez, Vicente Micol, Jorge Joven, Antonio Segura-Carretero and Javier A. Menendez. Extra-virgin olive oil contains a metabolo-epigenetic inhibitor of cancer stem cells. *Carcinogenesis* (2018), Vol. 39, No. 4, 601–613. doi:10.1093/carcin/bgy023
 57. Mary M. Flynn, Jennifer Cunningham, Joseph Renzulli, Anthony Mega. Including Extra Virgin Olive Oil May More Improve Glycemic Control despite Similar Weight Loss Compared to the Diet Recommended by the Prostate Cancer Foundation: A Randomized, Pilot Study. *Journal of Cancer Therapy* (2017), 8, 880-890
 58. Granados-Principal S, Liu Y, Guevara ML, Blanco E, Choi DS, Qian W, Patel T, Rodriguez AA, Cusimano J, Weiss HL, Zhao H, Landis MD, Dave B, Gross SS, Chang JC. Inhibition of iNOS as a novel effective targeted therapy against triple-negative breast cancer. *Breast Cancer Res.* (2015) Feb 22;17:25.doi:10.1186/s13058-015-0527-x

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
59. Estefanía Toledo, MD, MPH, PhD; Jordi Salas-Salvadó, MD, PhD; Carolina Donat-Vargas, PharmD; Pilar Buil-Cosiales, MD, PhD; Ramón Estruch, MD, PhD; Emilio Ros, MD, PhD; Dolores Corella, DPharm, PhD; Montserrat Fitó, PhD; Frank B. Hu, MD, PhD; Fernando Arós, MD, PhD; Enrique Gómez-Gracia, MD, PhD; Dora Romaguera, MSc, PhD; Manuel Ortega-Calvo, MD; Lluís Serra-Majem, MD, PhD; Xavier Pintó, MD, PhD; Helmut Schröder, PhD; Josep Basora, MD, PhD; José Vicente Sorlí, MD, PhD; Mònica Bulló, BSc, PhD; Merce Serra-Mir, RD; Miguel A. Martínez-González, MD. Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial. A Randomized Clinical Trial. *JAMA Intern Med.* (2015); 175(11):1752-1760. doi:10.1001/jamainternmed.2015.4838
 60. LeGendre O, Breslin PAS, Foster DA. (-)-Oleocanthal rapidly and selectively induces cancer cell death via lysosomal membrane permeabilization. *Mol Cell Onc* (2014); 2:e1006077. doi:10.1080/23723556.2015.1006077.
 61. Escrich E, Moral R, Grau L, Costa I, Solanas M. Molecular mechanisms of the effects of olive oil and other dietary lipids on cancer. *Mol Nutr Food Res* (2007); 51:1279-92.
 62. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol Res* (2007); 55:224-36.
 63. Hamdi HK, Castellon R. Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. *Biochem Biophys Res Commun* (2005); 334:769-78.
 64. Newmark HL. Squalene, olive oil, and cancer risk: a review and hypothesis. *Cancer Epidemiol Biomarkers Prev* (1997); 6: 1101-3.
 65. Radd-Vagenas, S., et al., Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *Am J Clin Nutr* (2018), 107(3): p. 389-404.
 66. Aridi, Y.S., J.L. Walker, and O.R.L. Wright. The Association between the Mediterranean Dietary Pattern and Cognitive Health: A Systematic Review. *Nutrients* (2017). 9(7).
 67. Knight, A., J. Bryan, and K. Murphy. The Mediterranean diet and age-related cognitive functioning: A systematic review of study findings and neuropsychological assessment methodology. *Nutr Neurosci* (2017). 20(8): p. 449-468.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
68. Lauretti E, Iuliano L, Praticò D. Extra-virgin olive oil ameliorates cognition and neuropathology of the 3xTg mice: role of autophagy. *Annals of Clinical and Translational Neurology* (2017); 4(8): 564–574
 69. Loughrey, D.G., et al. The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. *Adv Nutr* (2017). 8(4): p. 571-586
 70. Masana, M.F., et al., n-3 Fatty acids, Mediterranean diet and cognitive function in normal aging: A systematic review. *Exp Gerontol* (2017). 91: p. 39-50.
 71. Solfrizzi, V., et al., Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. *J Alzheimers Dis* (2017). 59(3): p. 815-849.
 72. Wu, L. and D. Sun, Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. *Sci Rep* (2017). 7: p. 41317.
 73. Yusufov, M., L.L. Weyandt, and I. Piryatinsky, Alzheimer's disease and diet: a systematic review. *Int J Neurosci* (2017). 127(2): p. 161-175.
 74. Cao, L., et al., Dietary Patterns and Risk of Dementia: A Systematic Review and Meta-Analysis of Cohort Studies. *Mol Neurobiol* (2016). 53(9): p. 6144-6154.
 75. Hardman, R.J., et al., Adherence to a Mediterranean-Style Diet and Effects on Cognition in Adults: A Qualitative Evaluation and Systematic Review of Longitudinal and Prospective Trials. *Front Nutr* (2016). 3: p. 22.
 76. Petersson, S. and E. Philippou, The effects of Mediterranean Diet on cognitive function and dementia: Systematic review of the evidence. *Clin Nutr ESPEN* (2016). 13: p. e67.
 77. Rahe, C., M. Unrath, and K. Berger, Dietary patterns and the risk of depression in adults: a systematic review of observational studies. *Eur J Nutr* (2014). 53(4): p. 997-1013
 78. Singh, B., et al., Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* (2014). 39(2): p. 271-82.
 79. Lourida, I., et al., Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology y* (2013). 24(4): p. 479-89.

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
80. Opie, R.S., R.A. Ralston, and K.Z. Walker, Adherence to a Mediterranean-style diet can slow the rate of cognitive decline and decrease the risk of dementia: a systematic review. *Nutrition & Dietetics* (2013). 70(3): p. 206-217.
 81. Psaltopoulou, T., et al., Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann Neurol* (2013). 74(4): p. 580-91.
 82. Shah, R., The role of nutrition and diet in Alzheimer disease: a systematic review. *J Am Med Dir Assoc* (2013). 14(6): p. 398-402.
 83. Quirk, S.E., et al., The association between diet quality, dietary patterns and depression in adults: a systematic review. *BMC Psychiatry* (2013). 13: p. 175
 84. Sanhueza, C., L. Ryan, and D.R. Foxcroft, Diet and the risk of unipolar depression in adults: systematic review of cohort studies. *J Hum Nutr Diet* (2013). 26(1): p. 56-70
 85. Alaa H. Abuznait, Hisham Qosa, Belnaser A. Busnena, Khalid A. El Sayed, Amal Kaddoumi. Olive-Oil-Derived Oleocanthal Enhances β -Amyloid Clearance as a Potential Neuroprotective Mechanism against Alzheimer's Disease: In Vitro and in Vivo Studies. *ACS Chem. Neurosci.* (2013), 4, 6, 973-982
 86. Martínez-Lapiscina EH1, Clavero P, Toledo E, San Julián B, Sanchez-Tainta A, Corella D, Lamuela-Raventós RM, Martínez JA, Martínez-Gonzalez MÁ. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J Nutr Health Aging.* (2013); 17(6):544-52. doi: 10.1007/s12603-013-0027-6.
 87. Dow, C., et al., Diet and risk of diabetic retinopathy: a systematic review. *Eur J Epidemiol*, (2018). 33(2): p. 141-156.
 88. Jannasch, F., J. Kroger, and M.B. Schulze, Dietary Patterns and Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Prospective Studies. *J Nutr* (2017). 147(6):p. 1174-1182.
 89. Assaf-Balut C, GarcõÂa de la Torre N, DuraÂn A, Fuentes M, BordiuÂ E, del Valle L, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM prevention study. *PLoS ONE* (2017) 12(10): e0185873. <https://doi.org/10.1371/journal.pone.0185873>

Prepared by:	<i>Tassos C. Kyriakides, Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
90. Khan TM, Iqbal S, Rashid MA. Comparison of Lipid Lowering Effect of Extra Virgin Olive Oil and Atorvastatins in Dyslipidaemia in Type 2 Diabetes Mellitus. *J Ayub Med Coll Abbottabad* (2017); 29(1):83–6
 91. Esposito, K., et al., A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. *BMJ Open*, 2015. 5(8): p. e008222.
 92. Huo, R., et al., Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. *Eur J Clin Nutr*, (2015). 69(11): p. 1200-8.
 93. Schwingshackl, L., et al., Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. *Public Health Nutr* (2015). 18(7): p. 1292-9.
 94. Emadian, A., et al., The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. *Br J Nutr* (2015). 114(10): p. 1656-66.
 95. Carter, P., et al., A Mediterranean diet improves HbA1c but not fasting blood glucose compared to alternative dietary strategies: a network meta-analysis. *J Hum Nutr Diet* (2014). 27(3): p. 280-97.
 96. Koloverou, E., et al., The effect of Mediterranean diet on the development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846 participants. *Metabolism* (2014). 63(7): p. 903-11.
 97. Ajala, O., P. English, and J. Pinkney, Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr* (2013), 97(3): p. 505-16.
 98. Maghsoudi, Z. and L. Azadbakht, How dietary patterns could have a role in prevention, progression, or management of diabetes mellitus? Review on the current evidence. *J Res Med Sci* (2012). 17(7): p. 694-709.
 99. Cristina Nocella, Vittoria Cammisotto, Luca Fianchini, Alessandra D'Amico, Marta Novo, Valentina Castellani, Lucia Stefanini, Francesco Violi and Roberto Carnevale. Extra Virgin Olive Oil and Cardiovascular Diseases: Benefits for Human Health. *Endocrine, Metabolic & Immune Disorders - Drug Targets* (2018), 18, 4-13.

Prepared by:	<i>Tassos C. Kyriakides. Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>

-
100. Garcia, M., et al., The Effect of the Traditional Mediterranean-Style Diet on Metabolic Risk Factors: A Meta-Analysis. *Nutrients* (2016). 8(3): p. 168.
 101. Ahluwalia, N., et al., Dietary patterns, inflammation and the metabolic syndrome. *Diabetes Metab* (2013). 39(2): p. 99-110.
 102. Esposito, K., et al., Mediterranean diet and metabolic syndrome: an updated systematic review. *Rev Endocr Metab Disord* (2013). 14(3): p. 255-63.
 103. Kastorini, C.M., et al., The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* (2011) 57(11): p. 1299-313.
 104. Mohsen Gavahian, Amin Mousavi Khaneghah, José M. Lorenzo, Paulo E.S. Munekata, Izaskun Garcia-Mantrana, María Carmen Collado, Antonio J. Meléndez-Martínez, Francisco J. Barba. Health benefits of olive oil and its components: Impacts on gut microbiota antioxidant activities, and prevention of noncommunicable diseases. *Trends in Food Science & Technology* (2019) Volume 88, June 2019, Pages 220-227
 105. J.F. García-Gavilan, M. Bullo, S. Canudas, M.A. Martínez-Gonzalez, R. Estruch, S. Giardina, M. Fito, D. Corella, E. Ros, J. Salas-Salvado. Extra virgin olive oil consumption reduces the risk of osteoporotic fractures in the PREDIMED trial. *Clinical Nutrition* (2018) Volume 37, Issue 1, February 2018, Pages 329-335.
 106. Cani PD. Human gut microbiome: hopes, threats and promises. *Gut* (2018); 67:1716–1725. doi: 10.1136/gutjnl-2018-316723

Prepared by:	<i>Tassos C. Kyriakides. Ph.D. and Vasilis Vasiliou, Ph.D.; Yale School of Public Health</i>
Contributions and Review by:	
Version:	<i>Version 1.1 last updated March 24, 2021</i>