# Olive Oil and health

*We are what we eat*

*Stephen Brabeck MD FACC, DUFUS*
*April 5, 2014*
*California Olive Oil Council Annual Members Meeting*

*OR:*

Plants Have no legs

(And we do!)

*“Leave your drugs in the chemist’s pot if you can cure the patient with food.”*

**Hippocrates, 420 BC**

**The Father of Medicine**

# FDA Decision 2004

- **Monounsaturated Fatty Acids From Olive Oil and Coronary Heart Disease**
- Docket No. 2003Q-0559
  11/01/2004 enforcement discretion letter[20]
- **Claim Statement**
- Limited and not conclusive scientific evidence suggests that eating about 2 tablespoons (23 grams) of olive oil daily may reduce the risk of coronary heart disease due to the monounsaturated fat in olive oil. To achieve this possible benefit, olive oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day. One serving of this product contains [x] grams of olive oil.
- Note: The last sentence of the claim "One serving of this product contains [x] grams of olive oil." is optional when the claim is used on the label or in the labeling of olive oil.

# Hypothesis:

- Plants have no legs, therefore they cannot run away from environmental threats, like animals.
- If not, they must have had, to survive, evolved an elegant system to thwart those threats.
- If we could harness that system, we also could have a leg-up against the same stresses that threaten our biology..

# Olive Oil and Health, Intro.

- Why we are “rusting”,
- Why plants aren’t.
- Why plants can help us not “rust”.
- How this all relates to plants not having legs

# Olive Oil and Health, Intro., cont'd

## We will:

- Discuss how plants protect themselves from environmental stress
- Understand the how and why of chronic diseases that can affect us
- Discuss how protection from environmental stress can be transferred from plants to us to help protect from those disease states
- Discuss some of the evidence
- Discuss what we can  and can't say about this.

# Olive Oil and Health, Into,. cont'd

We will also:

- Understand the basics of why chronic degenerative disease happens, focusing on vascular disease.
- Discuss concepts of oxidation, inflammation, degenerative diseases, especially vascular disease, and how the heck diet, and specifically extra virgin olive oil interacts with all this stuff.

# Olive Oil and Health

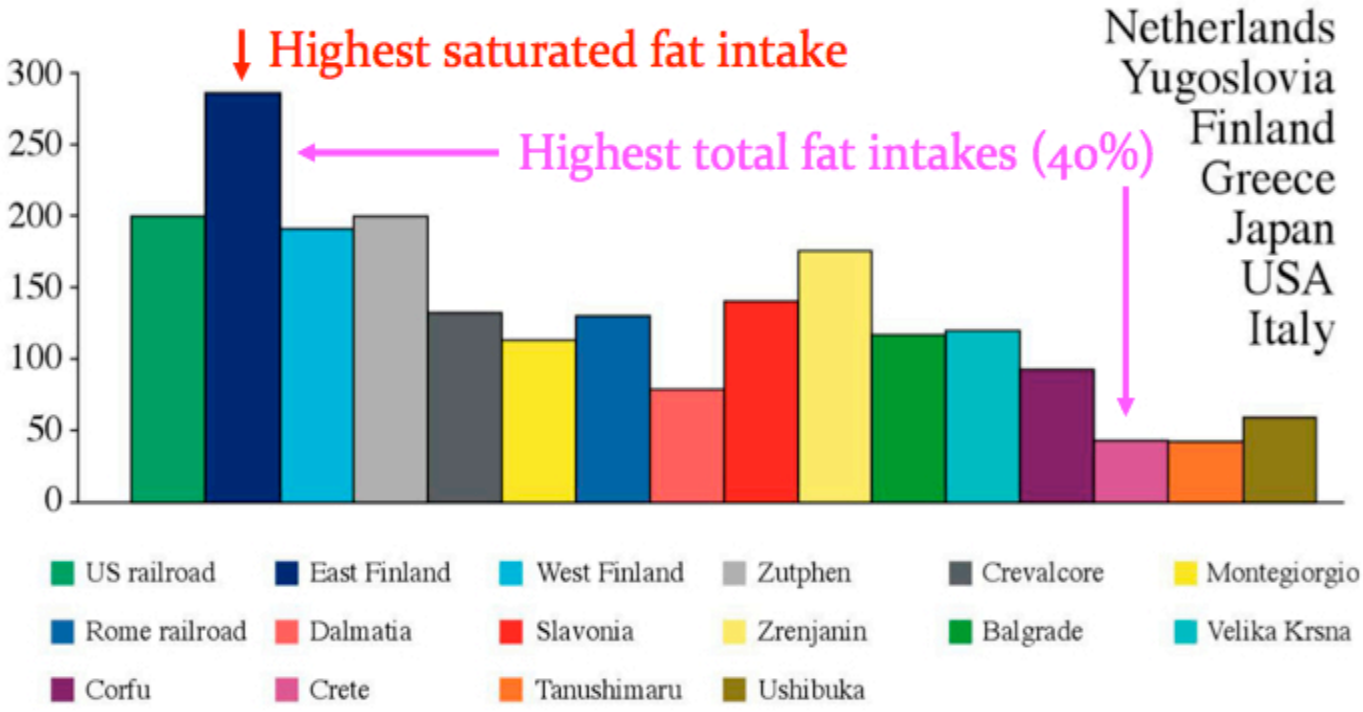
- I promise to make this as wonkish, boring and complicated as possible, because then you will all fall asleep and therefore will not be asking any questions at the end, ensuring that I will be out in time for the wine and cocktail reception.

# What's in the water? (or diet)


# 1958: Seven Countries Study

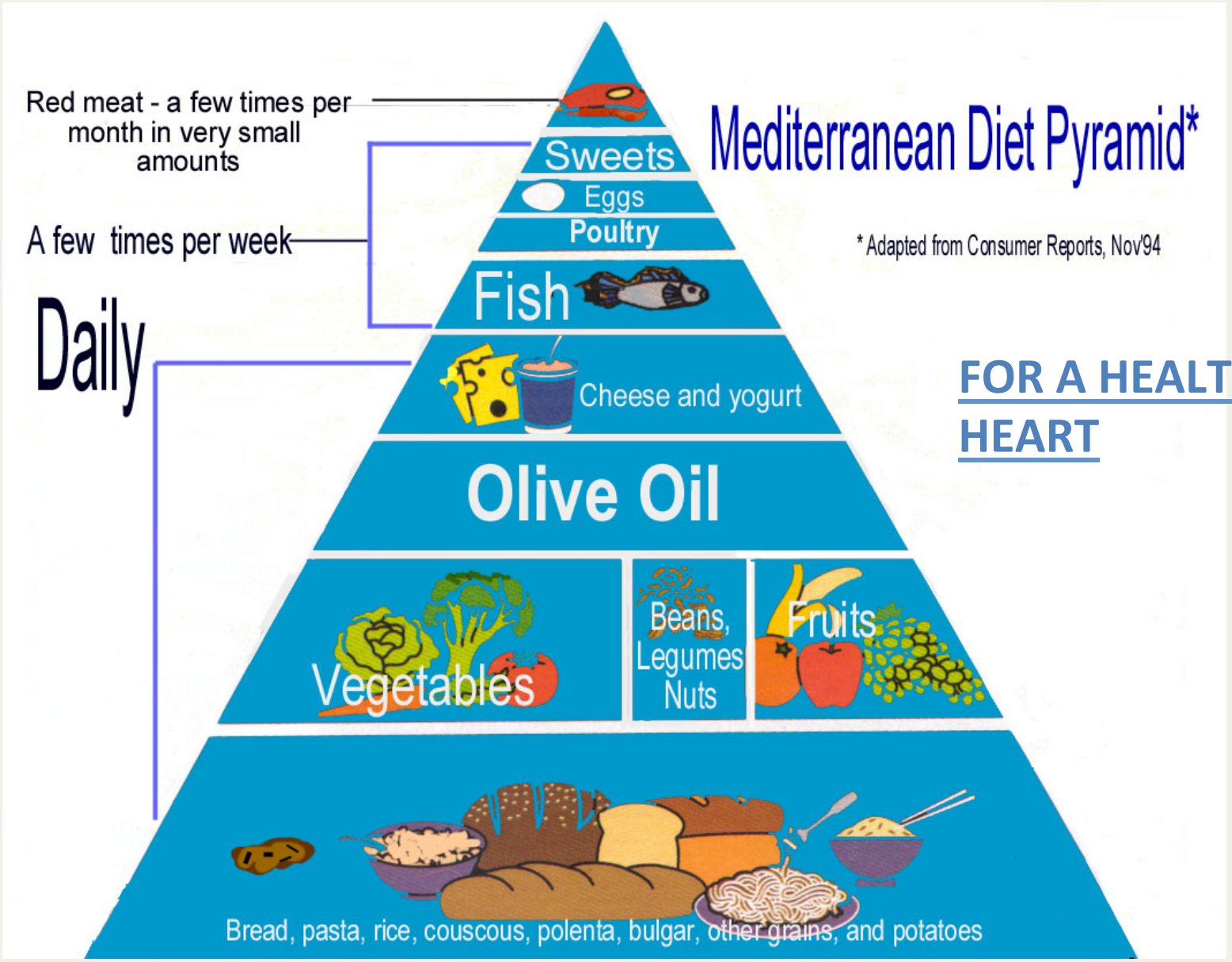
# The Seven Countries Study

## Age-adjusted 25-year CHD death rates per 1,000 in 16 cohorts



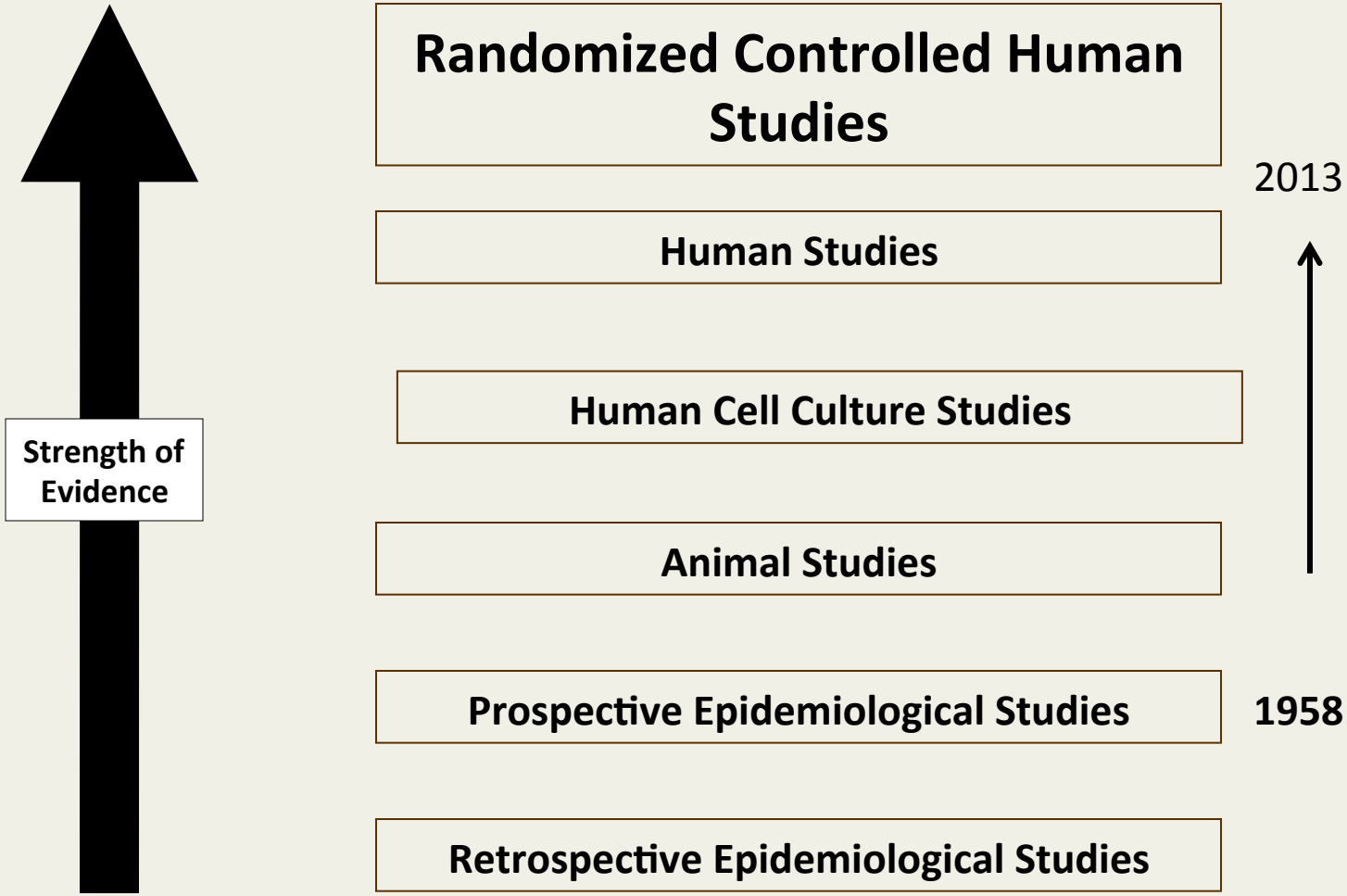
# Mediterranean Diet

The traditional Mediterranean diet is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals




**FOR A HEALTHY HEART**

# Types of Research Studies



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

# PREDIMED: Dietary Recommendations

| Mediterranean Diet (n=4,997*) | Low-fat Diet (control) (n=2,450) |
|---|---|
| **Recommended (Goal)** | **Recommended (Goal)** |
| •Olive oil (≥4 tbsp/d) | •Low-fat dairy products (≥3 servings/d) |
| •Tree nuts and peanuts (≥3 servings/wk) | •Bread, potatoes, pasta, rice (≥3 servings/d) |
| •Fresh fruits (≥3 servings/d) | •Fresh fruits (≥3 servings/d) |
| •Vegetables (≥2 servings/d) | •Vegetables (≥2 servings/wk) |
| •Fish (esp fatty fish), seafood (≥3 servings/wk) | •Lean fish and seafood (≥3 servings/wk) |
| •Legumes (≥3 servings/wk) | |
| •Sofrito† (≥2 servings/wk) | **Discouraged (Goal)** |
| •White meat (instead of red meat) | •Vegetable oils (including olive oil) (≤2 tbsp/d) |
| •Wine with meals‡ (≥7 glasses/wk) | •Commercial bakery goods, sweets, pastries (≤1 serving/wk) |
| **Discouraged (Goal)** | •Nuts and fried snacks (≤1 serving/wk) |
| •Soda (<1 drink/d) | •Red and processed fatty meats (≤1 serving/wk) |
| •Commercial bakery goods, sweets, pastries (<3 servings/wk) | •Visible fat in meats and soups (always remove) |
| •Spread fats (<1 serving/d) | •Fatty fish, seafood canned in oil (≤1 serving/wk) |
| •Red and processed meats (<1 serving/d) | •Spread fats (≤1 serving/wk) |
| | •Sofrito† (≤2 servings/wk) |

*Two treatment groups: Mediterranean diet + extra-virgin olive oil and Mediterranean diet + nuts;
†Sauce made with olive oil, tomato, garlic, onion, herbs; ‡Optional—only for habitual drinkers

PREDIMED=Prevención con Dieta Mediterránea

Estruch R, et al; for the PREDIMED study investigators. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1200303.

# PREDIMED Trial

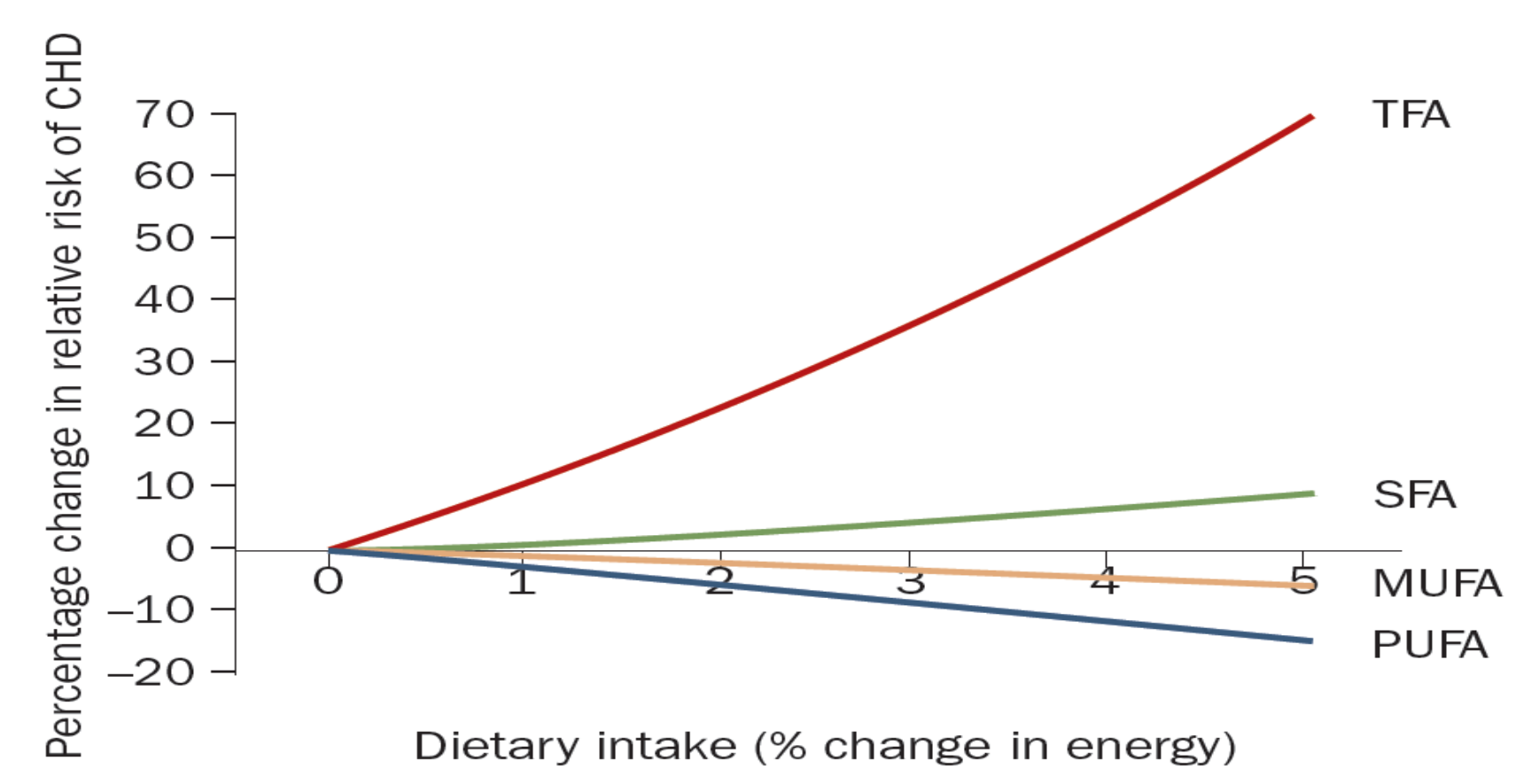
- The primary endpoint = composite of myocardial infarction (MI), stroke, or CV mortality.
- Secondary endpoints included stroke, MI, CV mortality, and all-cause mortality.
- The trial was stopped prematurely due to ethical concerns after a median of 4.8 years based on an interim analysis showing benefits seen with Mediterranean diets.
- “A Mediterranean diet supplemented with either extra virgin olive oil or mixed nuts may cut the risk of cardiovascular events by as much as 30% in subjects at high risk of developing heart disease, as compared with people advised to eat a reduced-fat diet .”

# Olive Oil and Health

- So if the Mediterranean diet seems to be healthful, and olive oil is a major part of that diet, what are the attributes of olive oil that contribute to this?

# Fats 101

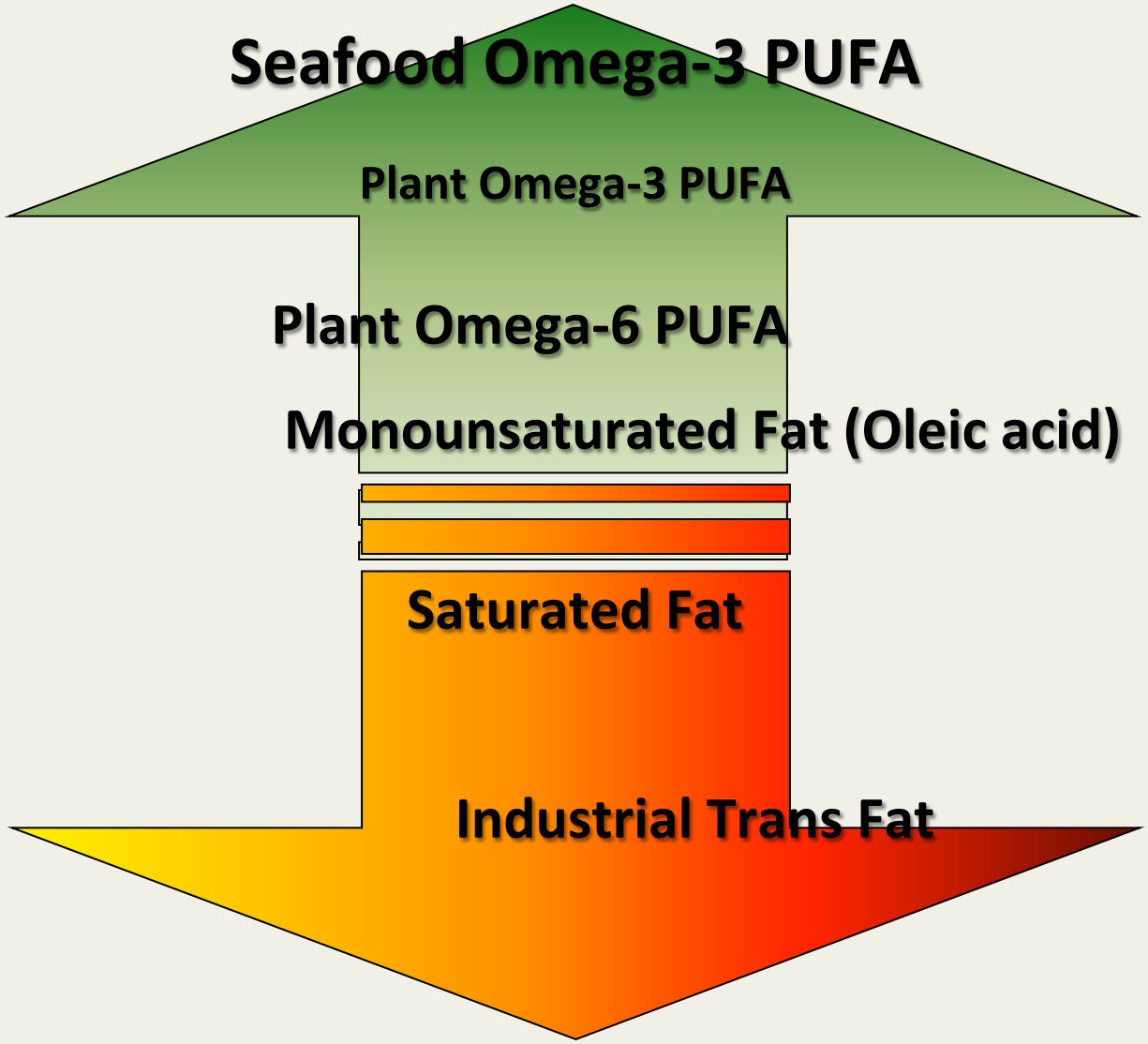
# Relationship of Dietary Fats with Coronary Heart Disease Events




*Compared to carbohydrate as the reference*

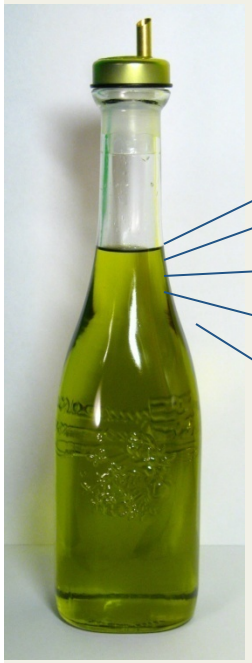
Source: Micha & Mozaffarian, Nature Endocrine Reviews 2009

# BENEFICIAL TO HUMAN HEALTH




# HARMFUL TO HUMAN HEALTH

# BENEFICIAL TO HUMAN HEALTH



Seafood Omega-3 PUFA

Plant Omega-3 PUFA

1%

11%

Plant Omega-6 PUFA

73%

Monounsaturated Fat (Oleic acid)

15%

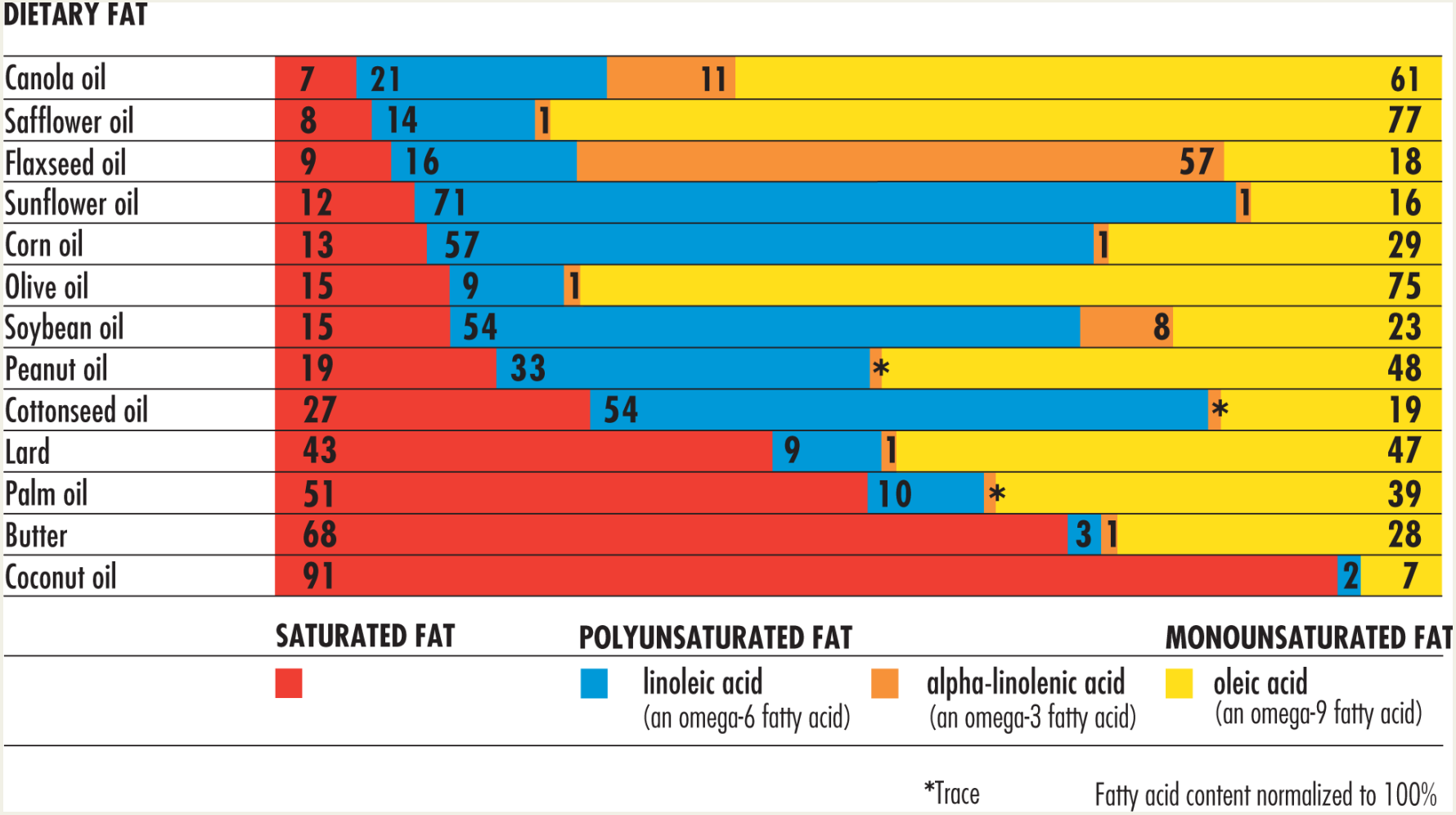
Saturated Fat

0%

Industrial Trans Fat

# HARMFUL TO HUMAN HEALTH

# How does olive oil compare to other oils?




Source: www.CanolaInfo.org

# Fats 101

- So what is the effect of oleic acid in EVOO?

❖There is a modest decrease in LDL and increase in HDL, resulting in an improvement in the LDL/HDL ratio

# Oxidation 101

# Oxidation

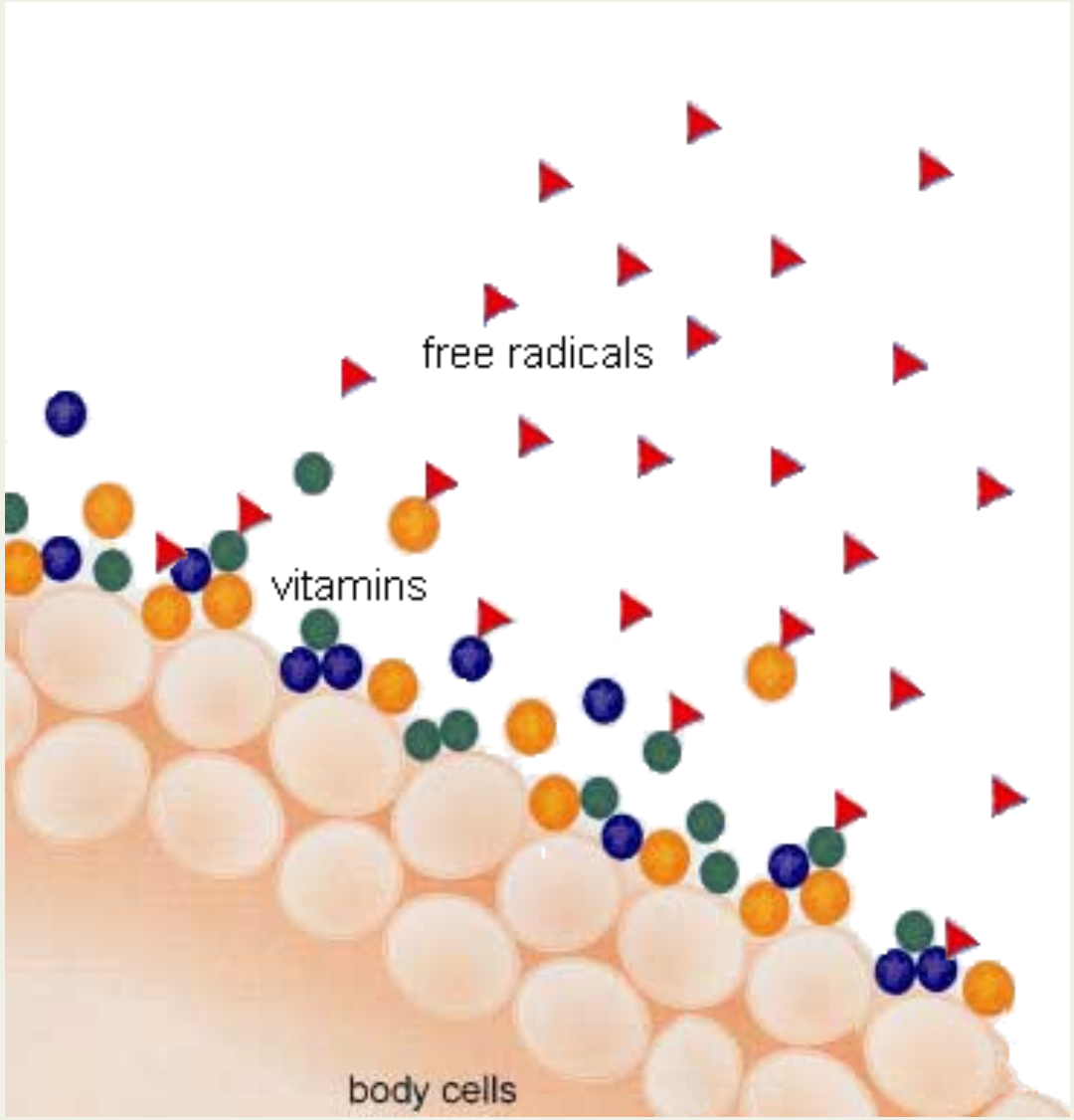
- Iron to Rust
- Apples and bananas turn brown
- Our tissues get oxidized

# We are in a continuous state of rust

# So how does this all happen?

# Free radicals 101

# Free Radicals




Not so free -
Very Costly!

# Free Radicals

# Oxidation and Free Radicals – What are they?

- Oxidation results from the interaction of molecules called Free Radicals
- Free Radicals are unstable molecules
- They lack an electron and are constantly scavenging healthy cells for a replacement electron
- Estimated ten thousand free radical attacks each hour of every day in our systems

# Free Radicals – What results?

- **They steal electrons from healthy cells,leaving those cells:**

❖Damaged and unstable

❖Creating a chain reaction of dangerous cell mutation

❖DNA – Cell replication incorrectly, or not at all

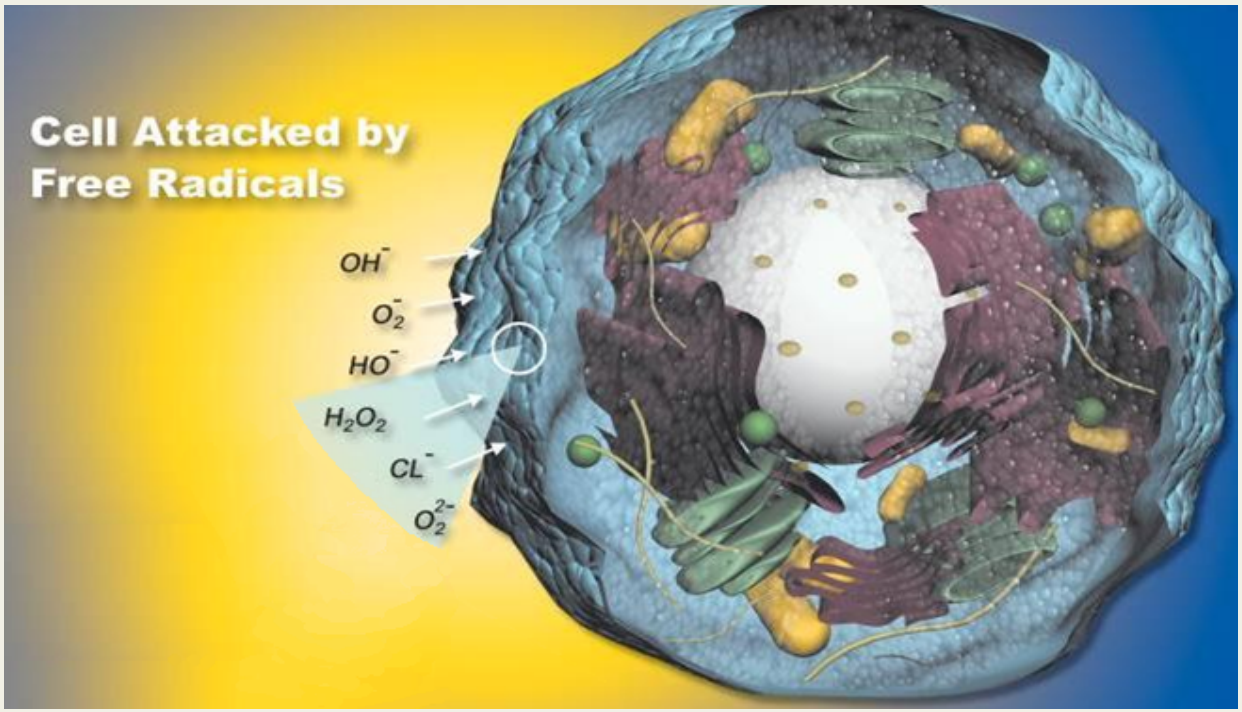
❖Improper cell function and premature cell death

❖Premature aging; cancers; chronic illness

# Oxidation – How does it happen?


***" Oxidative stress"***

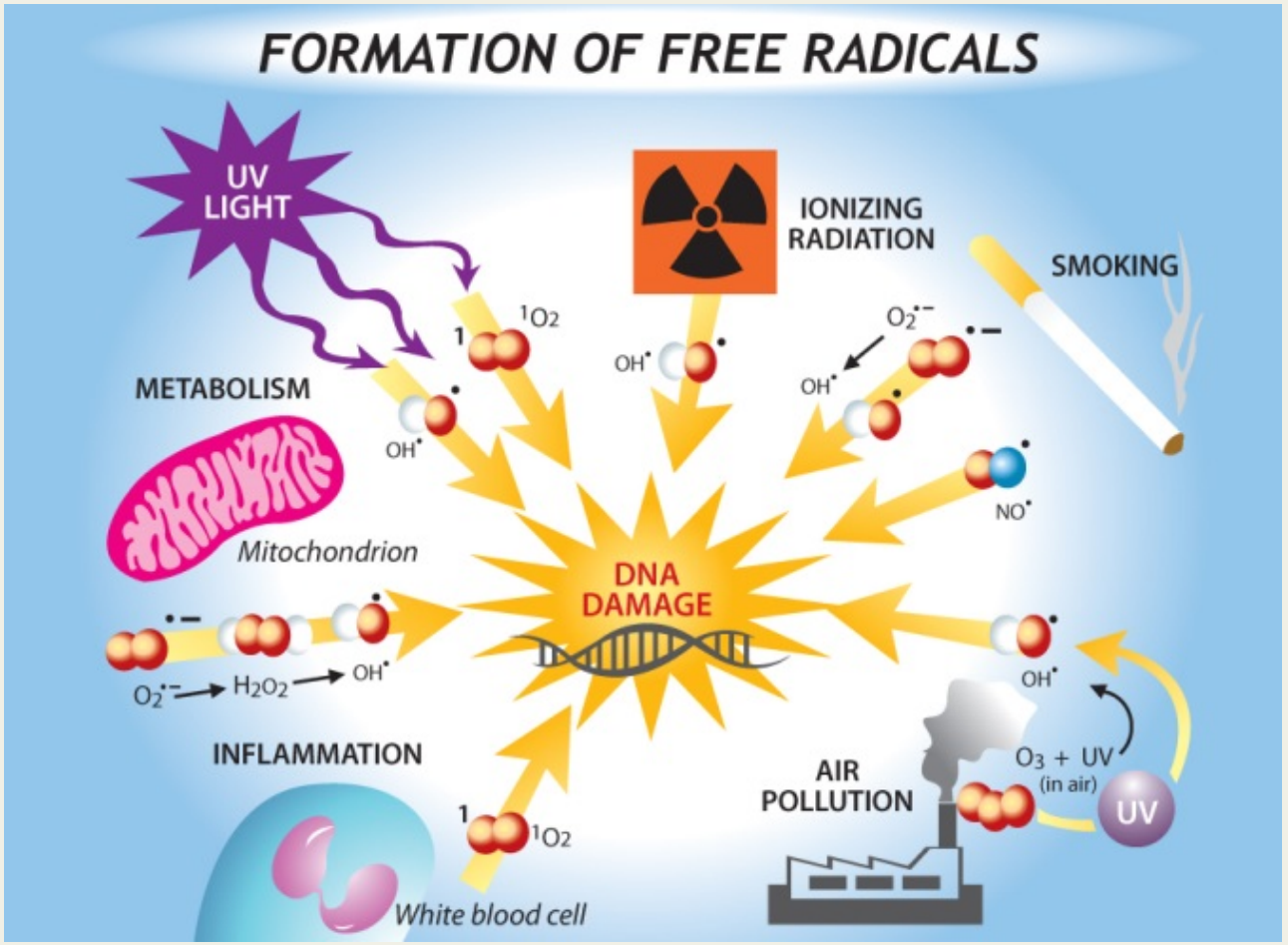
**Oxidation = Inflammation**



# Oxidation – What are the risk factors?

- Breathing
- Cigarettes
- Environmental chemicals and pesticides
- Contaminates in air and water
- Radiation
- High saturated fat diets

# Free Radicals



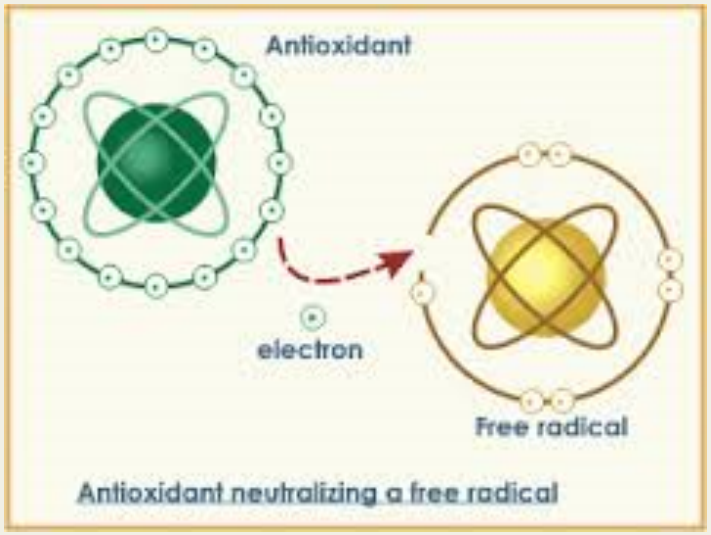
# Oxidative stress

- The oxidative interaction results when oxygen, short of an electron, voraciously attacks other compounds to obtain the electron they need, becoming free radicals.
- Oxidative interaction results in damage to a cell, tissue, or organ caused by free radicals. In essence, the tissue “rusts”.
- *Oxidative stress* is the totality of the oxidative burden the tissue is subjected to in it’s environment.

# Oxidative Stress and Cardiovascular Complications

- Oxidative stress is a regular characteristic of vascular complications when the action of antioxidant systems is overwhelmed by additional production of reactive oxygen species.
- Oxidative stress in aging can result from an imbalance of free radicals and antioxidants with excessive, destructive free radical chemistry.

# Antioxidants 101

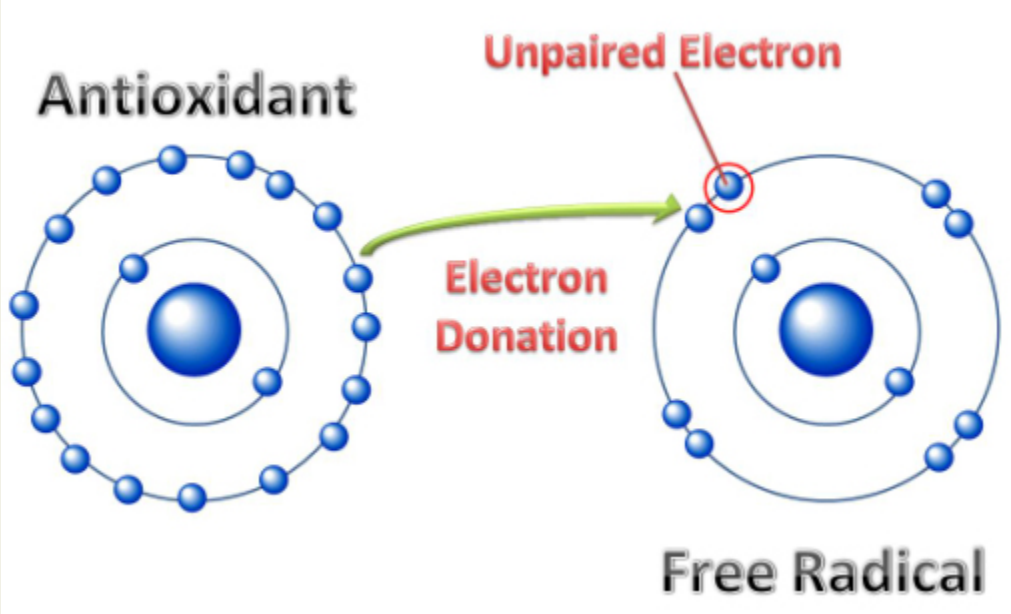


# Oxidation - how is the cell protected from free radicals and oxidative stress?

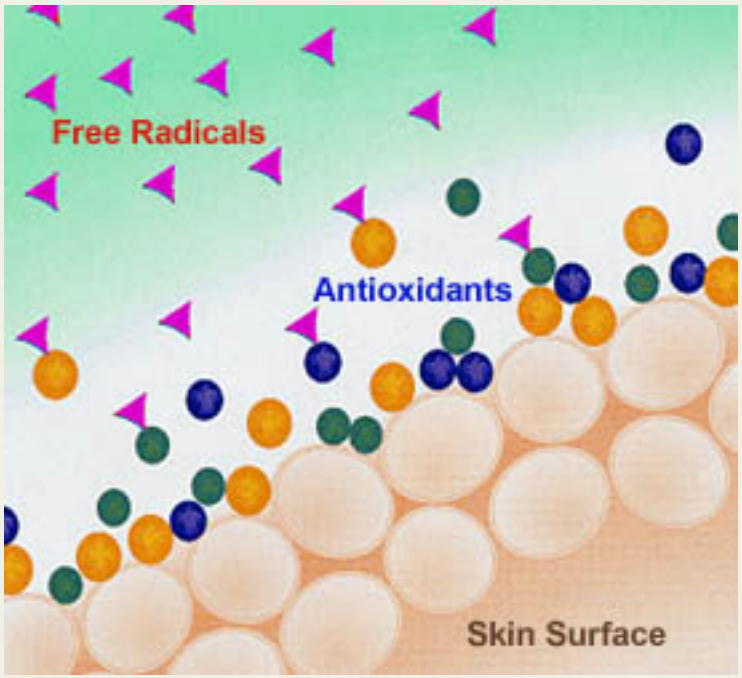
## Antioxidants

- Compounds found in natural plant sources
- Working at the cellular level to deactivate free radicals and add an electron to the unstable free radical molecule
- Chain-breaking reaction

# Antioxidants

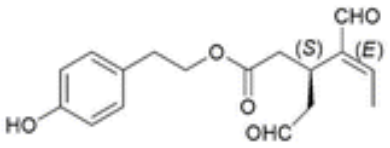


# Antioxidants

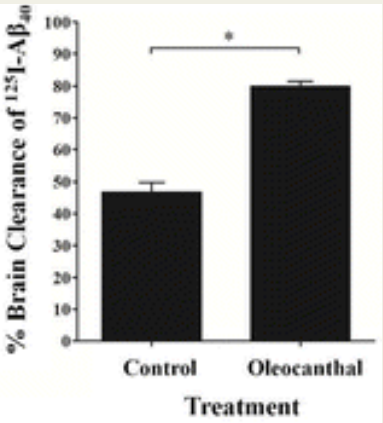


# OK, here we get to the "Plants have no legs" part (eventually): Phenolics 101

Olive Oil




Oleocanthal



# Phytonutrients

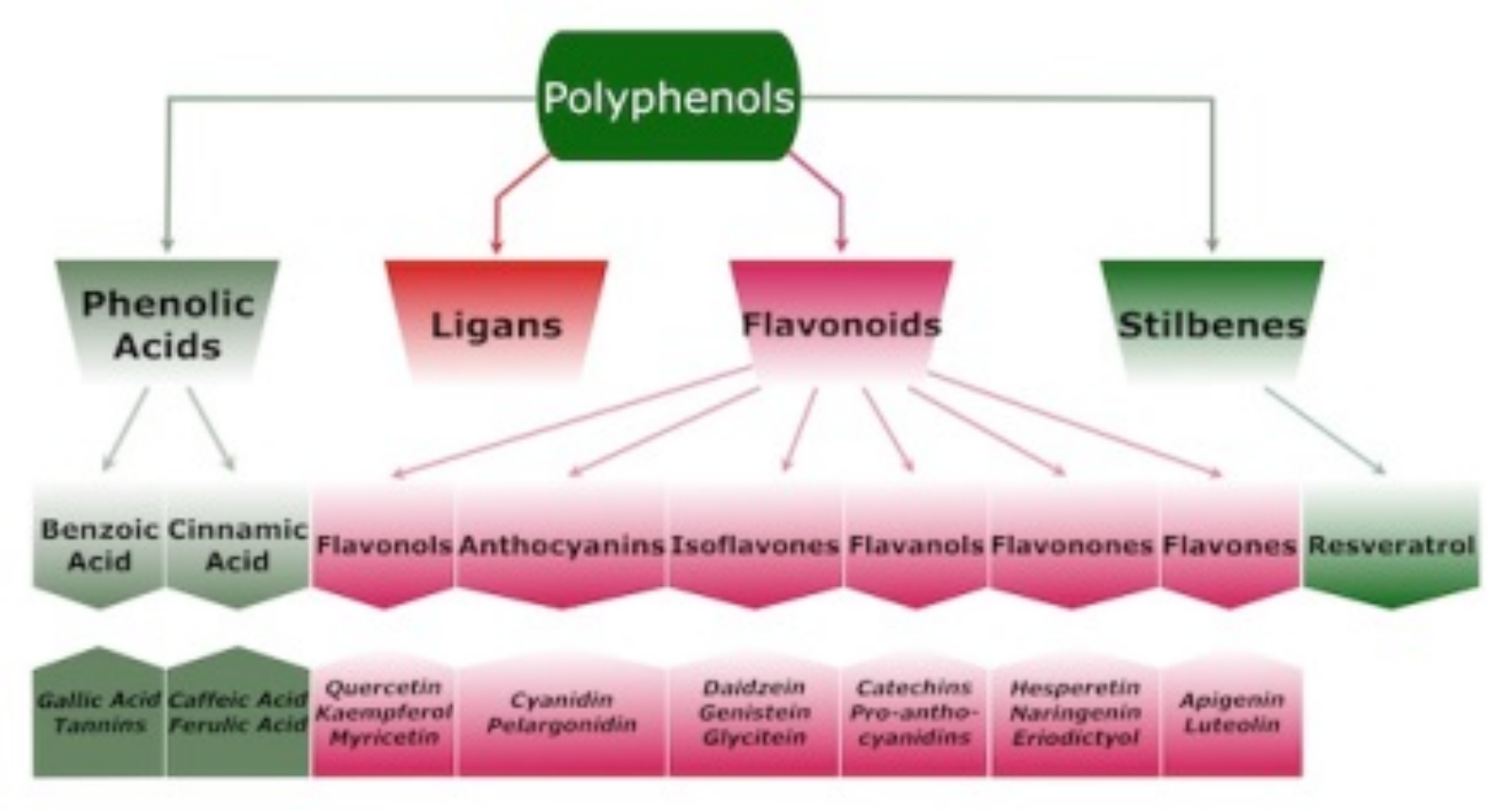
- Plant-derived substances containing Vitamins, Minerals, Carbohydrates and Fiber

# Flavonoids

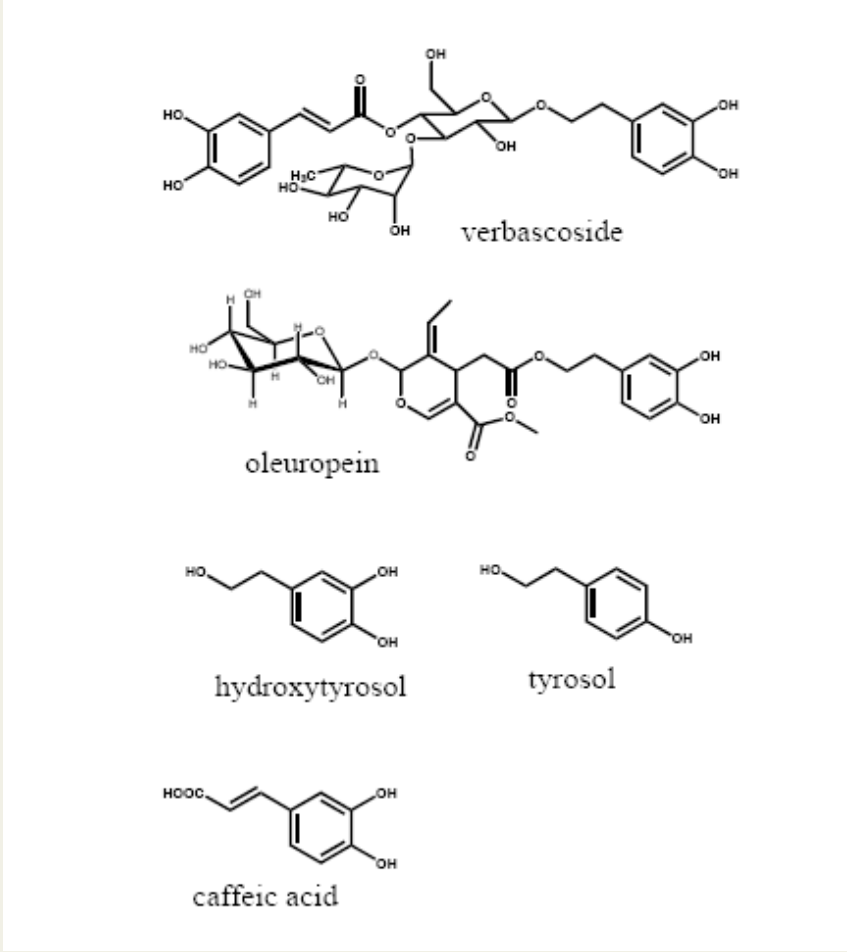
- Complex molecules found in plants – About 5,000 have been isolated and identified
- These plant-based molecules contain multiple medicinal properties, and are intensely antioxidant and antiinflammatory.

| | | |
|---|---|---|
| Anti-inflammatory | Antioxidant | Antibacterial |
| Antifungal | Antidepressant | Anti-cancer |
| Analgesic | Antihistaminic | Neuro-protective |
| Dilate blood vessels | Modify blood platelet clotting | |

# Polyphenols



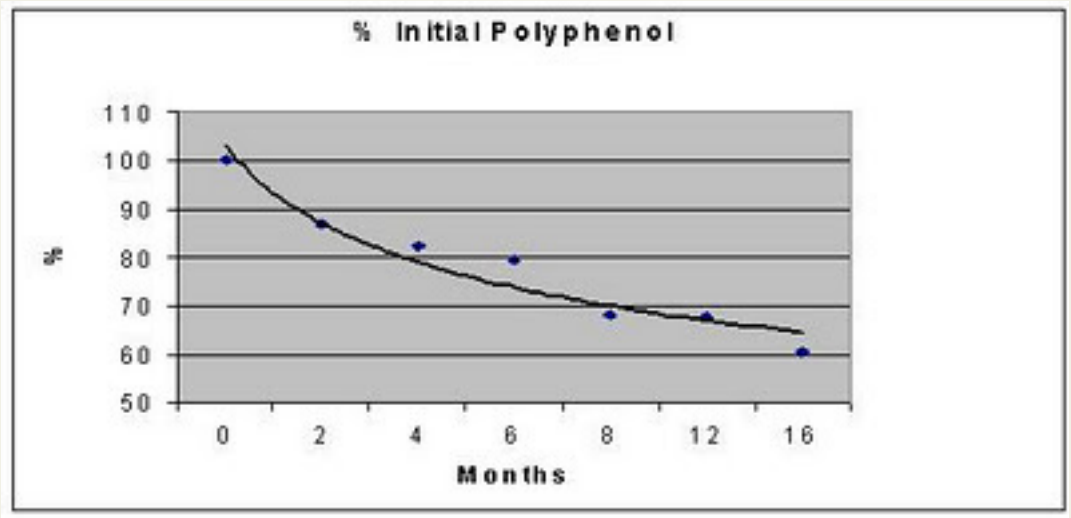
# Polyphenols



# Phenolics in Extra Virgin Olive Oil

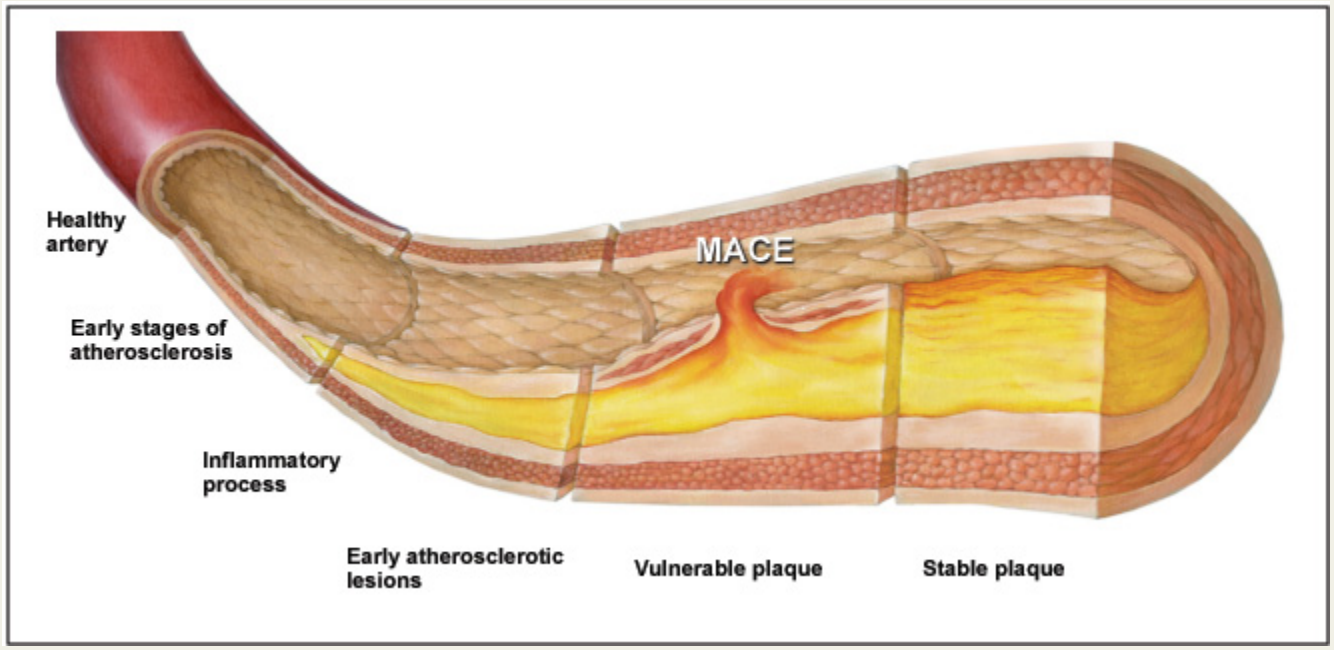
- Phenols are phytochemicals, substances produced by olive trees to protect the tree and the fruit from environmental stress.
- Phenols like **hydroxytyrosol**, **oleuropein**, **tyrosol** and **oleocanthal** found in extra virgin olive oil also affect flavor, pungency, and health benefit.
- Extra virgin olive oil is ~0.5% phenols.
- The polyphenols are intensely anti-inflammatory and antioxidant

# Polyphenols: What Happens Over Time?

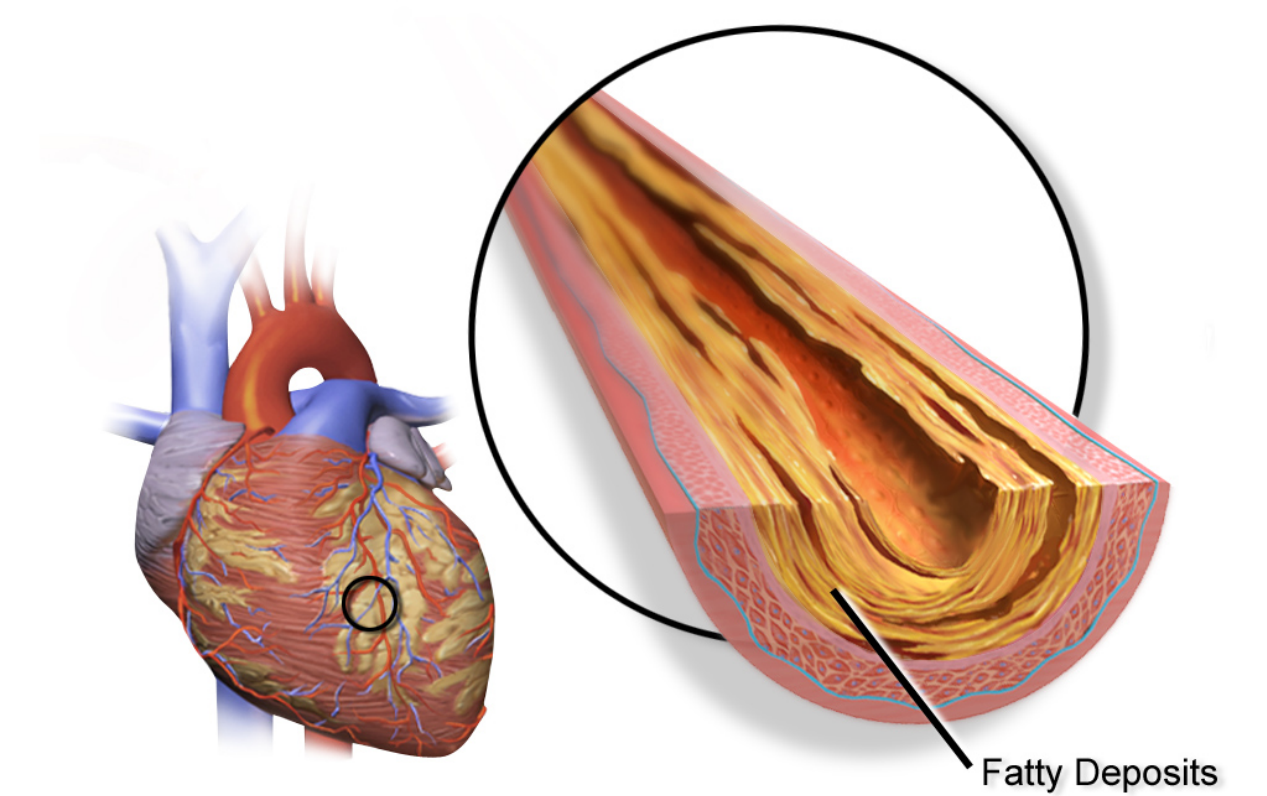


# Polyphenols

# Vascular Disease

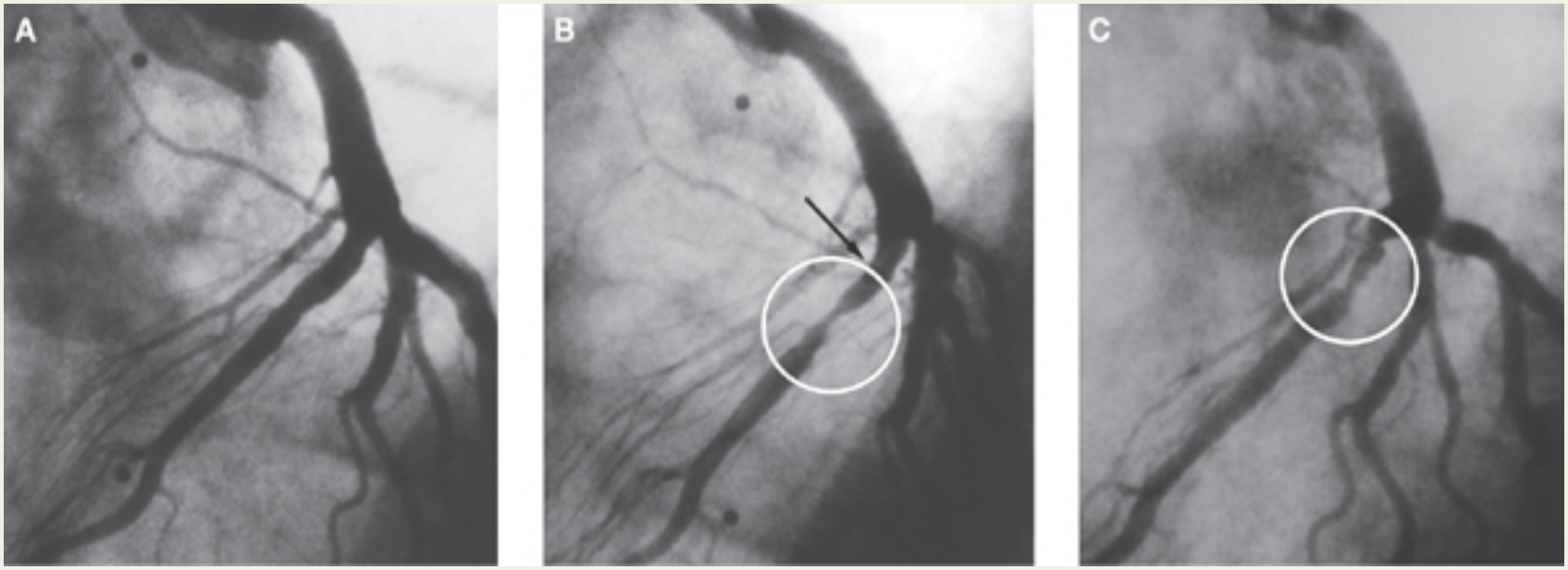


# Coronary Artery Disease




Partially Blocked Coronary Artery

# Coronary Artery Disease



# Polyphenols and CV Risk Factors

**Annals of Internal Medicine** | ARTICLE

## The Effect of Polyphenols in Olive Oil on Heart Disease Risk Factors

### A Randomized Trial

María-Isabel Covas, MSc, PhD; Kristiina Nyyssönen, MSc, PhD; Henrik E. Poulsen, MD, PhD; Jari Kaikkonen, MSc, PhD; Hans-Joachim F. Zunft, MD, PhD; Holger Kiesewetter, MD, PhD; Antonio Gaddi, MD, PhD; Rafael de la Torre, MSc, PhD; Jaakko Mursu, MSc; Hans Bäumler, MSc, PhD; Simona Nascetti, MD, PhD; Jukka T. Salonen, MD, PhD; Montserrat Fitó, MD, PhD; Jyrki Virtanen, MSc; and Jaume Marrugat, MD, PhD, for the EUROLIVE Study Group

**Background:** Virgin olive oils are richer in phenolic content than refined olive oil. Small, randomized, crossover, controlled trials on the antioxidant effect of phenolic compounds from real-life daily doses of olive oil in humans have yielded conflicting results. Little information is available on the effect of the phenolic compounds of olive oil on plasma lipid levels. No international study with a large sample size has been done.

**Objective:** To evaluate whether the phenolic content of olive oil further benefits plasma lipid levels and lipid oxidative damage compared with monounsaturated acid content.

**Design:** Randomized, crossover, controlled trial.

**Setting:** 6 research centers from 5 European countries.

**Participants:** 200 healthy male volunteers.

**Measurements:** Glucose levels, plasma lipid levels, oxidative damage to lipid levels, and endogenous and exogenous antioxidants at baseline and before and after each intervention.

**Intervention:** In a crossover study, participants were randomly assigned to 3 sequences of daily administration of 25 mL of 3 olive oils. Olive oils had low (2.7 mg/kg of olive oil), medium (164 mg/kg), or high (366 mg/kg) phenolic content but were otherwise similar. Intervention periods were 3 weeks preceded by 2-week washout periods.

**Results:** A linear increase in high-density lipoprotein (HDL) cholesterol levels was observed for low-, medium-, and high-polyphenol olive oil: mean change, 0.025 mmol/L (95% CI, 0.003 to 0.05 mmol/L), 0.032 mmol/L (CI, 0.005 to 0.05 mmol/L), and 0.045 mmol/L (CI, 0.02 to 0.06 mmol/L), respectively. Total cholesterol–HDL cholesterol ratio decreased linearly with the phenolic content of the olive oil. Triglyceride levels decreased by an average of 0.05 mmol/L for all olive oils. Oxidative stress markers decreased linearly with increasing phenolic content. Mean changes for oxidized low-density lipoprotein levels were 1.21 U/L (CI, −0.8 to 3.6 U/L), −1.48 U/L (−3.6 to 0.6 U/L), and −3.21 U/L (−5.1 to −0.8 U/L) for the low-, medium-, and high-polyphenol olive oil, respectively.

**Limitations:** The olive oil may have interacted with other dietary components, participants' dietary intake was self-reported, and the intervention periods were short.

**Conclusions:** Olive oil is more than a monounsaturated fat. Its phenolic content can also provide benefits for plasma lipid levels and oxidative damage.

*Ann Intern Med.* 2006;145:333-341. www.annals.org
For author affiliations, see end of text.
International Standard Randomised Controlled Trial number: ISRCTN09220811.

Polyphenol intake has been associated with low cancer and coronary heart disease (CHD) mortality rates (1). Antioxidant and anti-inflammatory properties and improvements in endothelial dysfunction and the lipid profile have been reported for dietary polyphenols (2). Studies have recently suggested that Mediterranean health benefits may be due to a synergistic combination of phytochemicals and fatty acids (3). Olive oil, rich in oleic acid (a monounsaturated fatty acid), is the main fat of the Mediterranean diet (4). To date, most of the protective effect of olive oil within the Mediterranean diet has been attributed to its high monounsaturated fatty acid content (5). However, if the effect of olive oil can be attributed solely to its monounsaturated fatty acid content, any type of olive oil, rapeseed or canola oil, or monounsaturated fatty acid–enriched fat would provide similar health benefits.

Whether the beneficial effects of olive oil on the cardiovascular system are exclusively due to oleic acid remains to be elucidated. The minor components, particularly the phenolic compounds, in olive oil may contribute to the health benefits derived from the Mediterranean diet. Among olive oils usually present on the market, virgin olive oils produced by direct-press or centrifugation methods have higher phenolic content (150 to 350 mg/kg of olive oil) (6). In experimental studies, phenolic compounds in olive oil showed strong antioxidant properties (7, 8). Oxidized low-density lipoprotein (LDL) is currently thought to be more damaging to the arterial wall than native LDL cholesterol (9). Results of randomized, crossover, controlled clinical trials on the antioxidant effect of polyphenols from real-life daily doses of olive oil in humans are, however, conflicting (10). Growing evidence suggests that dietary phenols (11–15) and plant-based diets (16) can modulate lipid and lipoprotein metabolism.

The Effect of Olive Oil on Oxidative Damage in Eu-

*See also:*

**Print**
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Summary for Patients . . . . . I-53

**Web-Only**
Appendix Tables
Conversion of figures and tables into slides

 

"Olive oil is more than a monosaturated fat. It's phenolic content can also provide benefits for plasma lipid levels and oxidative damage."

# Polyphenols and Colon Cancer

Genes Nutr (2011) 6:63–69
DOI 10.1007/s12263-010-0177-7

RESEARCH PAPER

## Effects of olive oil polyphenols on fatty acid synthase gene expression and activity in human colorectal cancer cells

**Maria Notarnicola · Simona Pisanti · Valeria Tutino · Domenica Bocale · Maria Teresa Rotelli · Antonio Gentile · Vincenzo Memeo · Maurizio Bifulco · Enzo Perri · Maria Gabriella Caruso**

Received: 9 March 2010 / Accepted: 4 May 2010 / Published online: 16 May 2010


**Abstract** Oleuropein (OL) and hydroxytyrosol (HT), the main olive oil polyphenols, possess anti-proliferative effects in vitro. Fatty acid synthase, a key anabolic enzyme of biosynthesis of fatty acids, plays an important role in colon carcinoma development. Our aim was to investigate whether gene expression of FAS, as well as its enzymatic activity, is regulated by HT and OL in two human colon cancer cell lines, as HT-29 and SW620. In addition, we investigated the effects of these polyphenols on growth and apoptosis in these cells. FAS gene expression and activity in treated HT-29 and SW620 cells were evaluated by real-time PCR and radiochemical assay, respectively. Cell growth and apoptosis, after polyphenols treatment, were measured by MTT test and flow cytometry, respectively. The inhibition of proliferation, detected after HT treatment, was mediated by an inhibition of FAS expression and its enzymatic activity in SW620 cells, while the anti-proliferative effect in HT-29 cells seems to be independent from FAS. OL exerted an anti-proliferative effect only on SW620 cells with a mechanism which excluded FAS. Olive oil polyphenols used were able to induce apoptosis in both cell lines studied. The increase of apoptosis in these cells was accompanied by the block of cell cycle in the S phase. This study demonstrates that HT and OL may induce anti-proliferative and pro-apoptotic effects only in certain human colorectal cancer cell types. These effects are FAS mediated only in SW620 cells after treatment with HT.

**Keywords** Hydroxytyrosol · Oleuropein · Fatty acid synthase · Colorectal cancer

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### Introduction

Olive oil is a key component of the Mediterranean diet and is believed to beneficially affect numerous biological processes [22, 29]. Epidemiological studies have shown a lower incidence of atherosclerosis, cardiovascular diseases and certain kinds of cancer, in particular colon cancer, in the Mediterranean countries compared to those in Northern Europe [7, 21, 25].

In this respect, olive oil consumption has been demonstrated to reduce the incidence of aberrant crypt foci in azoxymethane-treated rats [28]. Furthermore, olive oil is able to down-regulate the expression of COX-2 and BCL-2 proteins that play a crucial role in colorectal carcinogenesis [2].

In particular, olive oil healthy effects can be attributed not only to the higher relationship between unsaturated and saturated fatty acids, but also to the antioxidant property of its phenolic compounds [18]. Among phenolic compounds, oleuropein (OL) and hydroxytyrosol (HT) are those which give to the extra-virgin olive oil its bitter, pungent taste and possess powerful antioxidant properties in vitro [5]. As

# Polyphenols and Breast Cancer

Public Health Nutr. 2011 Dec;14(12A):2323-32. doi: 10.1017/S1368980011002588.
**Olive oil, an essential component of the Mediterranean diet, and breast cancer.**
Escrich E[1], Moral R, Solanas M.
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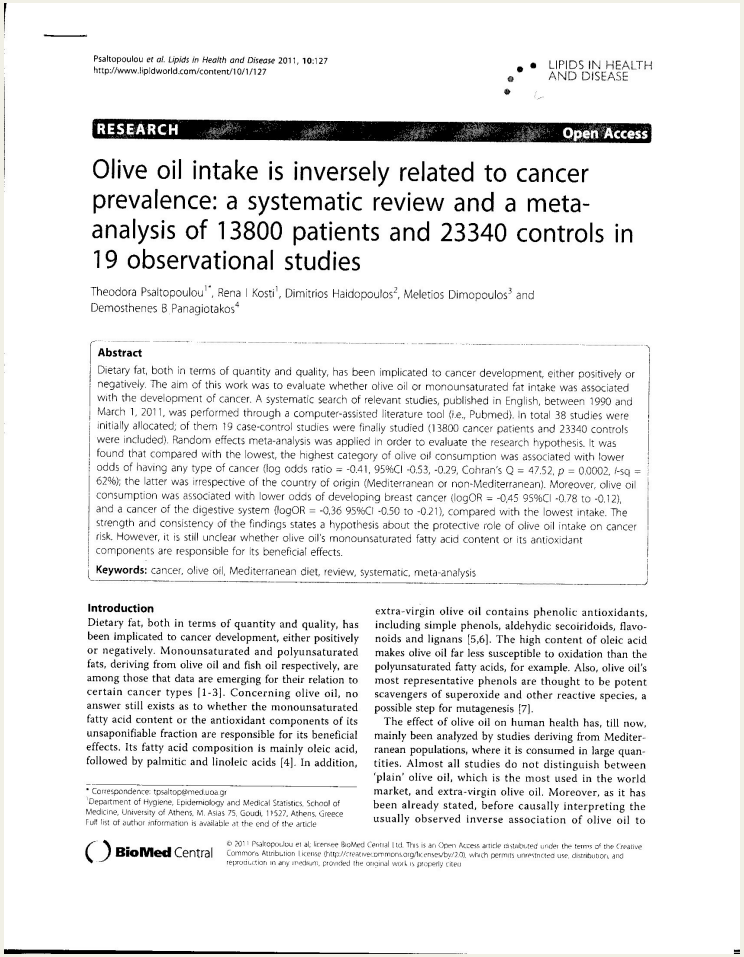
**DESIGN:**
Data from sixteen experimental series analysing the effects of dietary lipids on mammary carcinogenesis in an animal model, in the context of the international literature on the Mediterranean diet, olive oil and breast cancer risk.

**CONCLUSIONS:**
‘Consumption of EVOO in moderate quantities and throughout the lifetime appears to be a healthy choice and may favorably influence breast cancer risk.’

# EVOO and Cancer



Psaltopoulou et al. Lipids in Health and Disease 2011, 10:127
http://www.lipidworld.com/content/10/1/127

LIPIDS IN HEALTH AND DISEASE

RESEARCH Open Access

Olive oil intake is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies

Theodora Psaltopoulou[1*], Rena I Kosti[1], Dimitrios Haidopoulos[2], Meletios Dimopoulos[3] and Demosthenes B Panagiotakos[4]

**Abstract**

Dietary fat, both in terms of quantity and quality, has been implicated to cancer development, either positively or negatively. The aim of this work was to evaluate whether olive oil or monounsaturated fat intake was associated with the development of cancer. A systematic search of relevant studies, published in English, between 1990 and March 1, 2011, was performed through a computer-assisted literature tool (i.e., Pubmed). In total 38 studies were initially allocated; of them 19 case-control studies were finally studied (13800 cancer patients and 23340 controls were included). Random effects meta-analysis was applied in order to evaluate the research hypothesis. It was found that compared with the lowest, the highest category of olive oil consumption was associated with lower odds of having any type of cancer (log odds ratio = -0.41, 95%CI -0.53, -0.29, Cohran's Q = 47.52, $p$ = 0.0002, $I$-sq = 62%); the latter was irrespective of the country of origin (Mediterranean or non-Mediterranean). Moreover, olive oil consumption was associated with lower odds of developing breast cancer (logOR = -0.45 95%CI -0.78 to -0.12), and a cancer of the digestive system (logOR = -0.36 95%CI -0.50 to -0.21), compared with the lowest intake. The strength and consistency of the findings states a hypothesis about the protective role of olive oil intake on cancer risk. However, it is still unclear whether olive oil's monounsaturated fatty acid content or its antioxidant components are responsible for its beneficial effects.

**Keywords:** cancer, olive oil, Mediterranean diet, review, systematic, meta-analysis

**Introduction**

Dietary fat, both in terms of quantity and quality, has been implicated to cancer development, either positively or negatively. Monounsaturated and polyunsaturated fats, deriving from olive oil and fish oil respectively, are among those that data are emerging for their relation to certain cancer types [1-3]. Concerning olive oil, no answer still exists as to whether the monounsaturated fatty acid content or the antioxidant components of its unsaponifiable fraction are responsible for its beneficial effects. Its fatty acid composition is mainly oleic acid, followed by palmitic and linoleic acids [4]. In addition, extra-virgin olive oil contains phenolic antioxidants, including simple phenols, aldehydic secoiridoids, flavonoids and lignans [5,6]. The high content of oleic acid makes olive oil far less susceptible to oxidation than the polyunsaturated fatty acids, for example. Also, olive oil's most representative phenols are thought to be potent scavengers of superoxide and other reactive species, a possible step for mutagenesis [7].

The effect of olive oil on human health has, till now, mainly been analyzed by studies deriving from Mediterranean populations, where it is consumed in large quantities. Almost all studies do not distinguish between 'plain' olive oil, which is the most used in the world market, and extra-virgin olive oil. Moreover, as it has been already stated, before causally interpreting the usually observed inverse association of olive oil to

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- …"The strength and consistancy of the findings states a hypothesis about the protective role of olive oil intake on cancer. However, it is still unclear whether olive oil's monostaturated fatty acid content or its antioxidant components are responsible for its beneficial effect."

# Polyphenols and cognitive function

J Alzheimers Dis. 2012;29(4):773-82. doi: 10.3233/JAD-2012-111799.
Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk.
Valls-Pedret C[1], Lamuela-Raventós RM, Medina-Remón A, Quintana M, Corella D, Pintó X, Martínez-González MÁ, Estruch R, Ros E.
**Author information**

**“The results reinforce the notion that Mediterranean diet components might counteract age-related cognitive decline.”**

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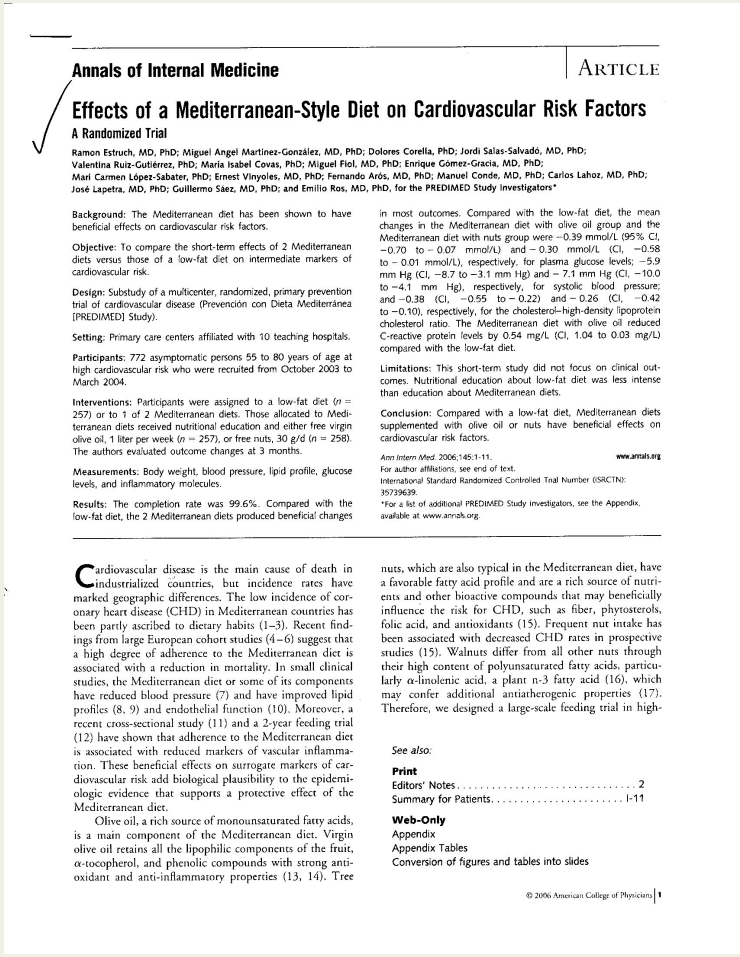
# EVOO and Diabetes



**Annals of Internal Medicine** | ARTICLE

## Effects of a Mediterranean-Style Diet on Cardiovascular Risk Factors

### A Randomized Trial

**Ramon Estruch, MD, PhD; Miguel Angel Martínez-González, MD, PhD; Dolores Corella, PhD; Jordi Salas-Salvadó, MD, PhD; Valentina Ruiz-Gutiérrez, PhD; María Isabel Covas, PhD; Miguel Fiol, MD, PhD; Enrique Gómez-Gracia, MD, PhD; Mari Carmen López-Sabater, PhD; Ernest Vinyoles, MD, PhD; Fernando Arós, MD, PhD; Manuel Conde, MD, PhD; Carlos Lahoz, MD, PhD; José Lapetra, MD, PhD; Guillermo Sáez, MD, PhD; and Emilio Ros, MD, PhD, for the PREDIMED Study Investigators***

**Background:** The Mediterranean diet has been shown to have beneficial effects on cardiovascular risk factors.

**Objective:** To compare the short-term effects of 2 Mediterranean diets versus those of a low-fat diet on intermediate markers of cardiovascular risk.

**Design:** Substudy of a multicenter, randomized, primary prevention trial of cardiovascular disease (Prevención con Dieta Mediterránea [PREDIMED] Study).

**Setting:** Primary care centers affiliated with 10 teaching hospitals.

**Participants:** 772 asymptomatic persons 55 to 80 years of age at high cardiovascular risk who were recruited from October 2003 to March 2004.

**Interventions:** Participants were assigned to a low-fat diet ($n$ = 257) or to 1 of 2 Mediterranean diets. Those allocated to Mediterranean diets received nutritional education and either free virgin olive oil, 1 liter per week ($n$ = 257), or free nuts, 30 g/d ($n$ = 258). The authors evaluated outcome changes at 3 months.

**Measurements:** Body weight, blood pressure, lipid profile, glucose levels, and inflammatory molecules.

**Results:** The completion rate was 99.6%. Compared with the low-fat diet, the 2 Mediterranean diets produced beneficial changes in most outcomes. Compared with the low-fat diet, the mean changes in the Mediterranean diet with olive oil group and the Mediterranean diet with nuts group were −0.39 mmol/L (95% CI, −0.70 to − 0.07 mmol/L) and − 0.30 mmol/L (CI, −0.58 to − 0.01 mmol/L), respectively, for plasma glucose levels; −5.9 mm Hg (CI, −8.7 to −3.1 mm Hg) and − 7.1 mm Hg (CI, −10.0 to −4.1 mm Hg), respectively, for systolic blood pressure; and −0.38 (CI, −0.55 to − 0.22) and − 0.26 (CI, −0.42 to −0.10), respectively, for the cholesterol–high-density lipoprotein cholesterol ratio. The Mediterranean diet with olive oil reduced C-reactive protein levels by 0.54 mg/L (CI, 1.04 to 0.03 mg/L) compared with the low-fat diet.

**Limitations:** This short-term study did not focus on clinical outcomes. Nutritional education about low-fat diet was less intense than education about Mediterranean diets.

**Conclusion:** Compared with a low-fat diet, Mediterranean diets supplemented with olive oil or nuts have beneficial effects on cardiovascular risk factors.

*Ann Intern Med.* 2006;145:1-11. www.annals.org

For author affiliations, see end of text.

International Standard Randomized Controlled Trial Number (ISRCTN): 35739639.

*For a list of additional PREDIMED Study investigators, see the Appendix, available at www.annals.org.

Cardiovascular disease is the main cause of death in industrialized countries, but incidence rates have marked geographic differences. The low incidence of coronary heart disease (CHD) in Mediterranean countries has been partly ascribed to dietary habits (1–3). Recent findings from large European cohort studies (4–6) suggest that a high degree of adherence to the Mediterranean diet is associated with a reduction in mortality. In small clinical studies, the Mediterranean diet or some of its components have reduced blood pressure (7) and have improved lipid profiles (8, 9) and endothelial function (10). Moreover, a recent cross-sectional study (11) and a 2-year feeding trial (12) have shown that adherence to the Mediterranean diet is associated with reduced markers of vascular inflammation. These beneficial effects on surrogate markers of cardiovascular risk add biological plausibility to the epidemiologic evidence that supports a protective effect of the Mediterranean diet.

Olive oil, a rich source of monounsaturated fatty acids, is a main component of the Mediterranean diet. Virgin olive oil retains all the lipophilic components of the fruit, α-tocopherol, and phenolic compounds with strong antioxidant and anti-inflammatory properties (13, 14). Tree nuts, which are also typical in the Mediterranean diet, have a favorable fatty acid profile and are a rich source of nutrients and other bioactive compounds that may beneficially influence the risk for CHD, such as fiber, phytosterols, folic acid, and antioxidants (15). Frequent nut intake has been associated with decreased CHD rates in prospective studies (15). Walnuts differ from all other nuts through their high content of polyunsaturated fatty acids, particularly α-linolenic acid, a plant n-3 fatty acid (16), which may confer additional antiatherogenic properties (17). Therefore, we designed a large-scale feeding trial in high-

*See also:*

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Summary for Patients . . . . . I-11

**Web-Only**
Appendix
Appendix Tables
Conversion of figures and tables into slides

- "A Mediteranean diet enriched with EVOO but without energy restrictions reduced diabetes risk smong persons with high cardiovascular risk"

# What other health benefits?

- Subset analysis of PREDIMED shows prevention of onset of diabetes
- Improved blood pressure control
- Work in progress showing prevention of certain cancers, ie breast, colon.
- Prevention of neuro-degenerative diseases (Alzheimers)
- Chronic inflammatory conditions, ie arthritis
- **Note: Non of the above are FDA approved claims**

- **FAT IN OLIVE OIL:**
  - 85% unsaturated fat (oleic acid)
- **PHENOLICS**
  - includes antioxidants and anti-inflammatory substances
- **FLAVOR**
  - incredibly appealing ingredient due to the flavor contributions to other healthful foods


# 1958: Seven Countries Study

The New York Times

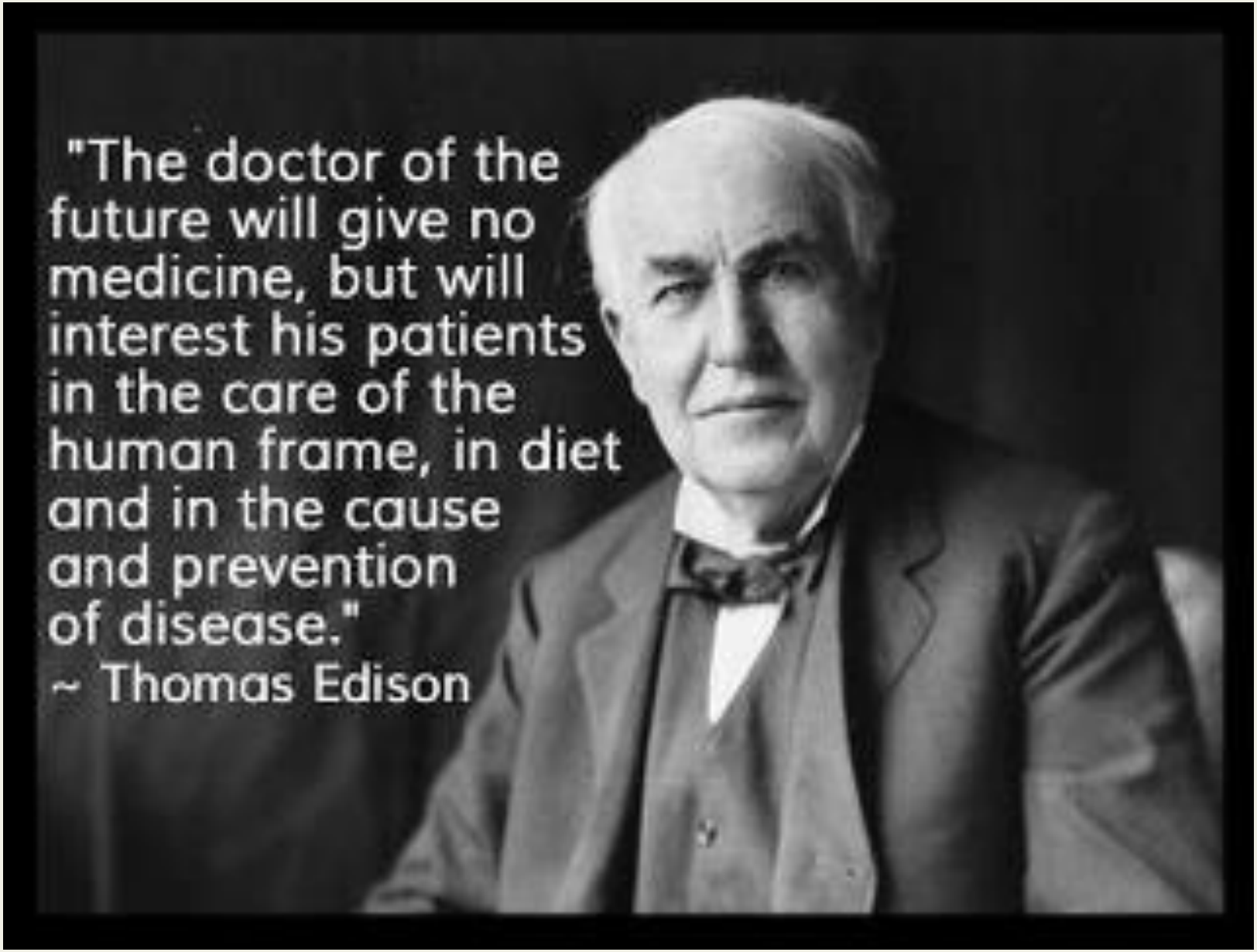
February 25, 2013

# Mediterranean Diet Shown to Ward Off Heart Attack and Stroke

By GINA KOLATA

About 30 percent of heart attacks, strokes and deaths from heart disease can be prevented in people at high risk if they switch to a Mediterranean diet rich in olive oil, nuts, beans, fish, fruits and vegetables, and even drink wine with meals, a large and rigorous new study has found.

The findings were based on the first major clinical trial to measure the diet's effect on heart risks. The magnitude of the diet's benefits startled experts. The study ended early, after almost five years, because the results were so clear it was considered unethical to continue.


"The doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet and in the cause and prevention of disease."
~ Thomas Edison