

**What is good and what is bad for you:  
the advantage of ambiguity.  
the case of alcohol and wine.**

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Fulvio Ursini

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University of Padova



BMJ


RESEARCH

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Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study

BMJ 2011;342:d1584

Conclusions In western Europe, an important proportion of cases of cancer can be attributable to alcohol consumption, especially consumption higher than the recommended upper limits. These data support current political efforts to **reduce or to abstain from alcohol consumption to reduce the incidence of cancer.**



The latest news from across the WCRF network.

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eNews



## Three alcoholic drinks a day can cause liver cancer

Today, World Cancer Research Fund International publishes global research which finds strong evidence that consuming approximately [three or more alcoholic drinks a day causes liver cancer](#). The finding provides the clearest indication to date of how many drinks actually cause liver cancer.

Alcohol has virtually no discernible health benefits and claims that a glass of wine is good for the heart have been exaggerated, a study has concluded.

Researchers at [University College London](#) argue that studies suggesting that moderate drinkers are healthier rely on flawed comparisons with people who have given up alcohol, often because they are already sick.

## IARC Monographs evaluate consumption of red meat and processed meat

**Lyon, France, 26 October 2015** – The International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization, has evaluated the carcinogenicity of the consumption of red meat and processed meat.

### Red meat

After thoroughly reviewing the accumulated scientific literature, a Working Group of 22 experts from 10 countries convened by the IARC Monographs Programme classified the consumption of red meat as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* that the consumption of red meat causes cancer in humans and *strong* mechanistic evidence supporting a carcinogenic effect.

This association was observed mainly for colorectal cancer, but associations were also seen for pancreatic cancer and prostate cancer.

### Processed meat

Processed meat was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that the consumption of processed meat causes colorectal cancer.

# Red Meat Consumption and Mortality

## Results From 2 Prospective Cohort Studies

An Pan, PhD; Qi Sun, MD, ScD; Adam M. Bernstein, MD, ScD; Matthias B. Schulze, DrPH; JoAnn E. Manson, MD, DrPH; Meir J. Stampfer, MD, DrPH; Walter C. Willett, MD, DrPH; Frank B. Hu, MD, PhD

**Background:** Red meat consumption has been associated with an increased risk of chronic diseases. However, its relationship with mortality remains uncertain.

**Methods:** We prospectively observed 37 698 men from the Health Professionals Follow-up Study (1986-2008) and 83 644 women from the Nurses' Health Study (1980-2008) who were free of cardiovascular disease (CVD) and cancer at baseline. Diet was assessed by validated food frequency questionnaires and updated every 4 years.

**Results:** We documented 23 926 deaths (including 5910 CVD and 9464 cancer deaths) during 2.96 million person-years of follow-up. After multivariate adjustment for major lifestyle and dietary risk factors, the pooled hazard ratio (HR) (95% CI) of total mortality for a 1-serving-per-day increase was 1.13 (1.07-1.20) for unprocessed red meat and 1.20 (1.15-1.24) for processed red meat. The corresponding HRs (95% CIs) were 1.18 (1.13-

1.23) and 1.21 (1.13-1.31) for CVD mortality and 1.10 (1.06-1.14) and 1.16 (1.09-1.23) for cancer mortality. We estimated that substitutions of 1 serving per day of other foods (including fish, poultry, nuts, legumes, low-fat dairy, and whole grains) for 1 serving per day of red meat were associated with a 7% to 19% lower mortality risk. We also estimated that 9.3% of deaths in men and 7.6% in women in these cohorts could be prevented at the end of follow-up if all the individuals consumed fewer than 0.5 servings per day (approximately 42 g/d) of red meat.

**Conclusions:** Red meat consumption is associated with an increased risk of total, CVD, and cancer mortality. Substitution of other healthy protein sources for red meat is associated with a lower mortality risk.

*Arch Intern Med.* 2012;172(7):555-563.  
Published online March 12, 2012.  
doi:10.1001/archinternmed.2011.2287

# Los Angeles Times

## All red meat is risky, a study finds

*Eating any amount or type increased the chances of early death among adults tracked more than 20 years.*

March 13, 2012 | Eryn Brown

   Comments 0  Recommend 4.1k  Tweet 135  Share 5857  +1 283

any amount and any type -- appears to significantly increase the risk of premature death, according to a long-range study that examined the eating habits and health of more than 110,000 adults for more than 20 years.

For instance, adding just one 3-ounce serving of unprocessed red meat -- picture a piece of steak no bigger than a deck of cards -- to one's daily diet was associated with a 13% greater chance of dying during the course of the study.



Eating any amount and any type of red meat increases the risk of premature... (William Thomas Cain / Getty...)

HOW IS INFORMATION ABOUT THE IMPACT OF  
FOOD ON HEALTH PRODUCED ?

SATISTICAL AND EPIDEMIOLOGICAL INFORMATION  
MUST CONVERGE WITH EVIDENCE GENERATED  
BY BASIC SCIENCE RESEARCH.

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# NUTRITIONAL EPIDEMIOLOGY

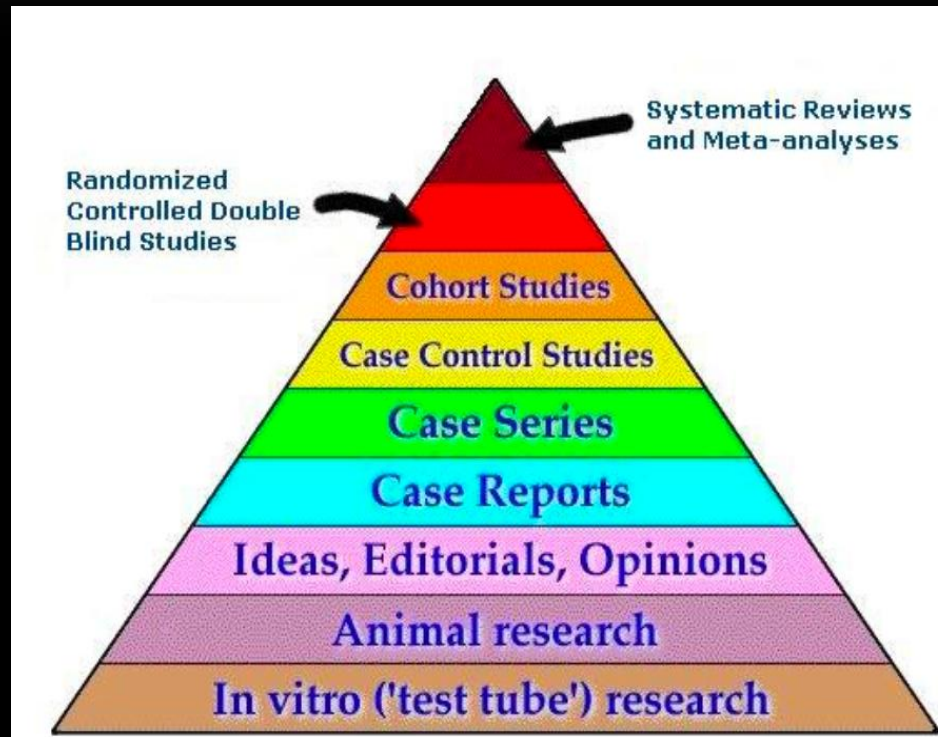
This branch of epidemiology studies the relationships between nutrition, health status and diseases.

The results are produced as “**soft data**” addressed to the identification of nutritional “**risk factors**” and “**protective factors**”.

Sometimes the approach generates paradoxes

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IN MEDICINE PARADOXES ARE GENERATED WHEN  
**SOFT** EPIDEMIOLOGICAL EVIDENCE  
IS NOT SUPPORTED BY **HARD** BIO-CHEMICAL EVIDENCE.



**We need more basic research**

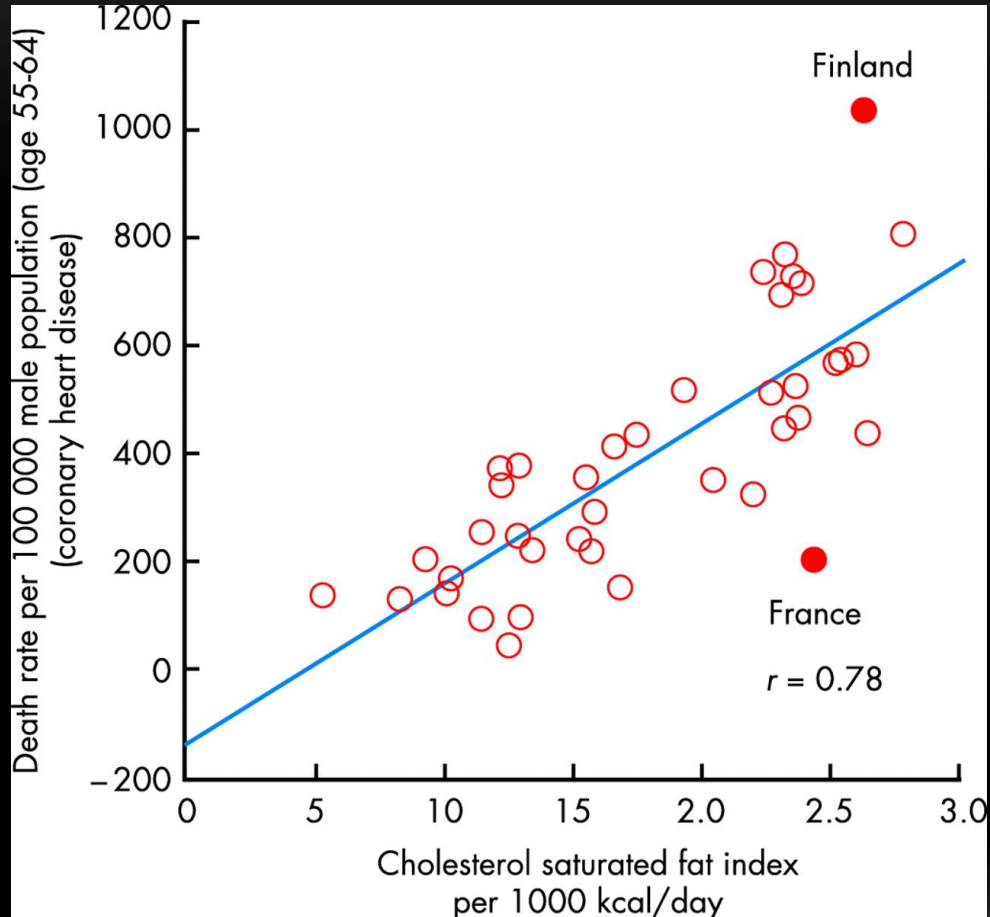
The divergence of a set of evidence from the “rule” descending from accepted bio-statistical analysis is often referred to as “**paradox**”.

The term describes an apparent contradiction when two events or concepts appear each-other incompatible although both being seemingly true.

**The truth is not-dual and there must be an epistemological bias**

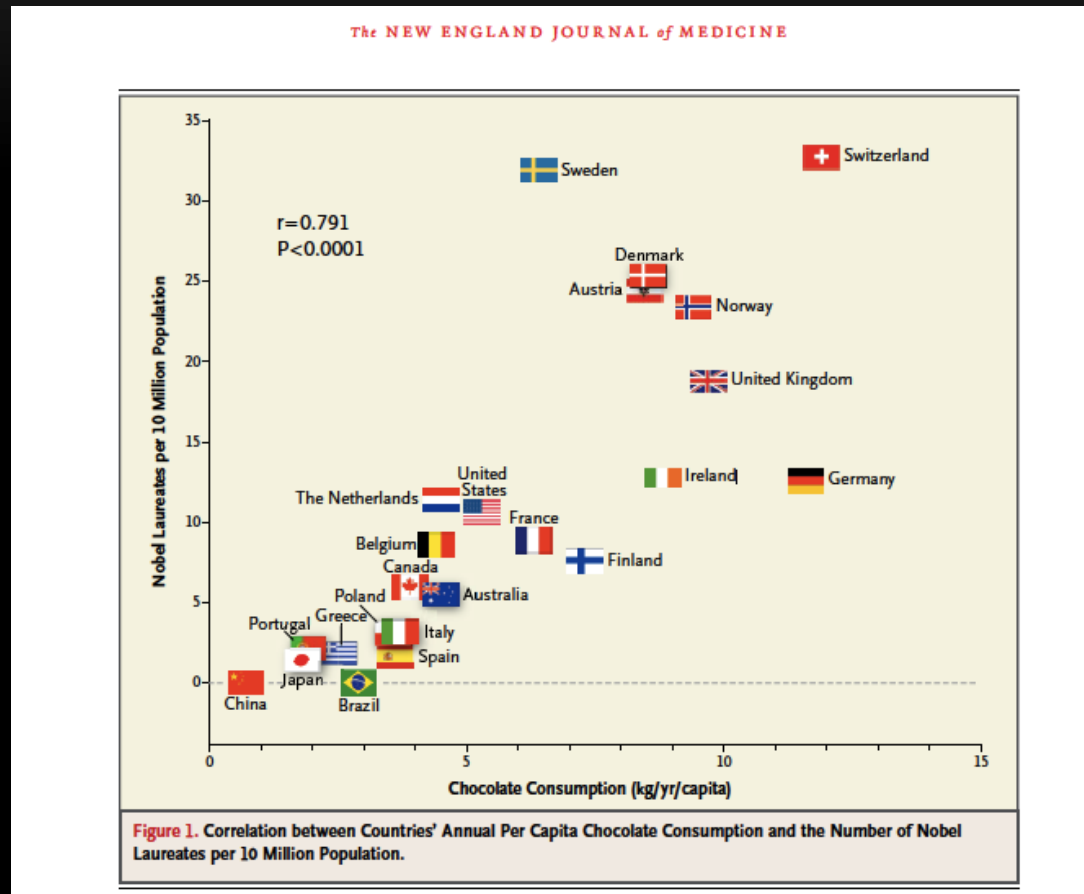
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# THE FRENCH PARADOX (RENAUD 1992)



French do not die enough in respect the cholesterol and saturated fat intake

# THE GERMAN PARADOX (NEJM, OCT 10, 2012)



Germans did not get enough Nobel Prizes in respect the chocolate consumption

# The case of beneficial effect of alcohol and wine

How come this “toxicant” that several people ask for being banned, may be “healthy” for others?

How can we discriminate between what is bad and what is good?

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Since ancient times, wine has been considered the “healthiest of beverages”

**“ ..During meals drink wine happily, little but often..” and “...to avoid harming the body never drink between meals...” .**

Arnoldo da Villanova (1253-1315) in the *Regimen Sanitatis Salernitani*

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Minireview

## Postprandial Oxidative Stress

**Fulvio Ursini<sup>1,\*</sup> and Alex Sevanian<sup>2</sup>**

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\* Corresponding author

**Consumption of a meal containing oxidized and oxidizable lipids gives rise to an increased plasma concentration of lipid hydroperoxides, detectable by a sensitive chemiluminescence procedure. This is associated with increased susceptibility of LDL to oxidation, apparently due a structural perturbation at the particle surface brought about by lipid oxidation products. The postprandial modification of LDL is at**



## **Grape Seed Proanthocyanidins Prevent Plasma Postprandial Oxidative Stress in Humans**

FAUSTA NATELLA,<sup>†</sup> FEDERICA BELELLI,<sup>†</sup> VINCENZO GENTILI,<sup>†</sup>  
FULVIO URSINI,<sup>‡</sup> AND CRISTINA SCACCINI<sup>\*,†</sup>

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ELSEVIER

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PII S0891-5849(01)00504-4



*Original Contribution*

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## RED WINE MITIGATES THE POSTPRANDIAL INCREASE OF LDL SUSCEPTIBILITY TO OXIDATION

FAUSTA NATELLA,\* ANDREA GHISELLI,\* ALESSIA GUIDI,\* FULVIO URSINI,<sup>†</sup> and CRISTINA SCACCINI\*

\* Free Radical Research Group, National Research Institute for Food and Nutrition, Roma, Italy; and <sup>†</sup>Department of Biological Chemistry, University of Padova, Padova, Italy

(Received 30 November 2000; Accepted 15 February 2001)

## **A novel function of red wine polyphenols in humans: prevention of absorption of cytotoxic lipid peroxidation products**

**Shlomit Gorelik,\* Moshe Ligumsky,<sup>†</sup> Ron Kohen,\* and Joseph Kanner<sup>‡,1</sup>**

\*Department of Pharmaceutics, David R. Bloom Center of Pharmacy, School of Pharmacy, the Hebrew University of Jerusalem, Jerusalem, Israel; <sup>†</sup>Gastrointestinal Unit, Division of Internal Medicine, Hadassah Medical Center, Jerusalem, Israel; and <sup>‡</sup>Department of Food Science, ARO, the Volcani Center, Bet Dagan, Israel

## Protection by Polyphenols of Postprandial Human Plasma and Low-Density Lipoprotein Modification: The Stomach as a Bioreactor

Joseph Kanner,<sup>\*,†</sup> Shlomit Gorelik,<sup>§</sup> Sirota Roman,<sup>§</sup> and Ron Kohen<sup>§</sup>

<sup>†</sup>Department of Food Science, ARO, Volcani Center, Bet Dagan, Israel

<sup>§</sup>Institute for Drug Research, School of Pharmacy, Hebrew University of Jerusalem, Jerusalem, Israel

**ABSTRACT:** Recent studies dramatically showed that the removal of circulating modified low-density lipoprotein (LDL) results in complete prevention of atherosclerosis. The gastrointestinal tract is constantly exposed to food, some of it containing oxidized compounds. Lipid oxidation in the stomach was demonstrated by ingesting heated red meat in rats. Red wine polyphenols added to the rats' meat diet prevented lipid peroxidation in the stomach and absorption of malondialdehyde (MDA) in rat plasma. In humans, postprandial plasma MDA levels rose by 3-fold after a meal of red meat cutlets. MDA derived from meat consumption caused postprandial plasma LDL modification in human. The levels of plasma MDA showed a 75% reduction by consumption of red wine polyphenols during the meat meal. Locating the main biological site of action of polyphenols in the stomach led to a revision in the understanding of how antioxidants work in vivo and may help to elucidate the mechanism involved in the protective effects of polyphenols in human health.

**KEYWORDS:** *stomach, lipid oxidation, malondialdehyde, plasma, modified LDL, polyphenols, antioxidants*

# Atherosclerosis: another protein misfolding disease?

Fulvio Ursini, Kelvin J.A. Davies, Matilde Maiorino, Tiziana Parasassi and Alex Sevanian

The secondary structure and conformation of apo-B 100 in low-density lipoproteins (LDL) are imposed by lipid-protein interactions and dynamics, and affected by the introduction or removal of lipids during the course of lipoprotein metabolism. Following an alteration of the water-lipid interface as a result of, for example, oxidation of lipids, the supramolecular structure becomes destabilized and apoB can misfold. These events have been observed in LDL<sup>-</sup>, a fraction of oxidatively modified LDL isolated *in vivo*. This modified lipoprotein possesses several atherogenic properties and represents an *in vivo* counterpart of *in vitro* modified LDL that is implicated in atherosclerosis. The misfolding of apoB, its aggregation, resistance to proteolysis, and cytotoxicity are common motifs shared by LDL<sup>-</sup> and amyloidogenic proteins. Based on these analogies, we propose that atherogenesis could be considered as a disease produced by the accumulation of cytotoxic and pro-inflammatory misfolded lipoproteins.

more proteins convert from a native soluble form to aggregates originally described as 'amyloid'. These fibrillar aggregates, which can be either extracellular or intracellular, are cytotoxic and result in alteration of cellular function. Although the initiating event might be distinct in different diseases, a general pattern is seen where loss of native protein stability (usually an  $\alpha$ -helix domain) is followed by a misfolding that leads to a relative increase in  $\beta$ -sheet structure. The  $\beta$  structure is particularly stable and 'seeds' further polymerization into largely intertwining  $\beta$ -strand structures. The resulting, stable, proteolytically resistant and cytotoxic fibrils are hallmarks of several degenerative diseases [7]. Recent results *in vitro* indicate that fibrillar aggregates of proteins not connected with specific diseases can be inherently cytotoxic, suggesting a common mechanism for all protein misfolding diseases [8].

Proper initial folding takes place when hydrophobic interactions among amino-acid side-chains participate in the initial formation of a 'molten globule' [1,7]. In this process, facilitation of folding provides a first defense against the formation of insoluble aggregates that contain inappropriate proportions of  $\beta$ -structure. When optimal interactions between lipophilic and amphipathic components are altered, for example by mild denaturation, whereby hydrogen bonds are preserved, an  $\alpha$ -helix to  $\beta$ -sheet transition can take

The “toxic” electrophiles produced during digestion of a food containing myoglobin interact in the GI tract with nucleophiles present in the same meal.

The association of nucleophiles to a food prone to produce electrophiles is typical of our culture and folk tradition. Green vegetables, pepper, paprika, tomatoes, onion, garlic can have this function.

**But the best nutritional nucleophile is wine !**

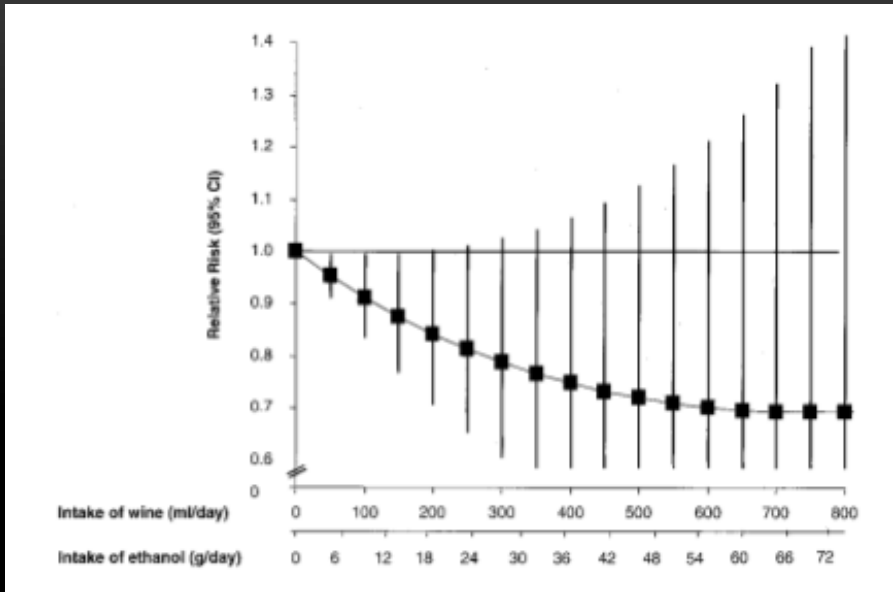
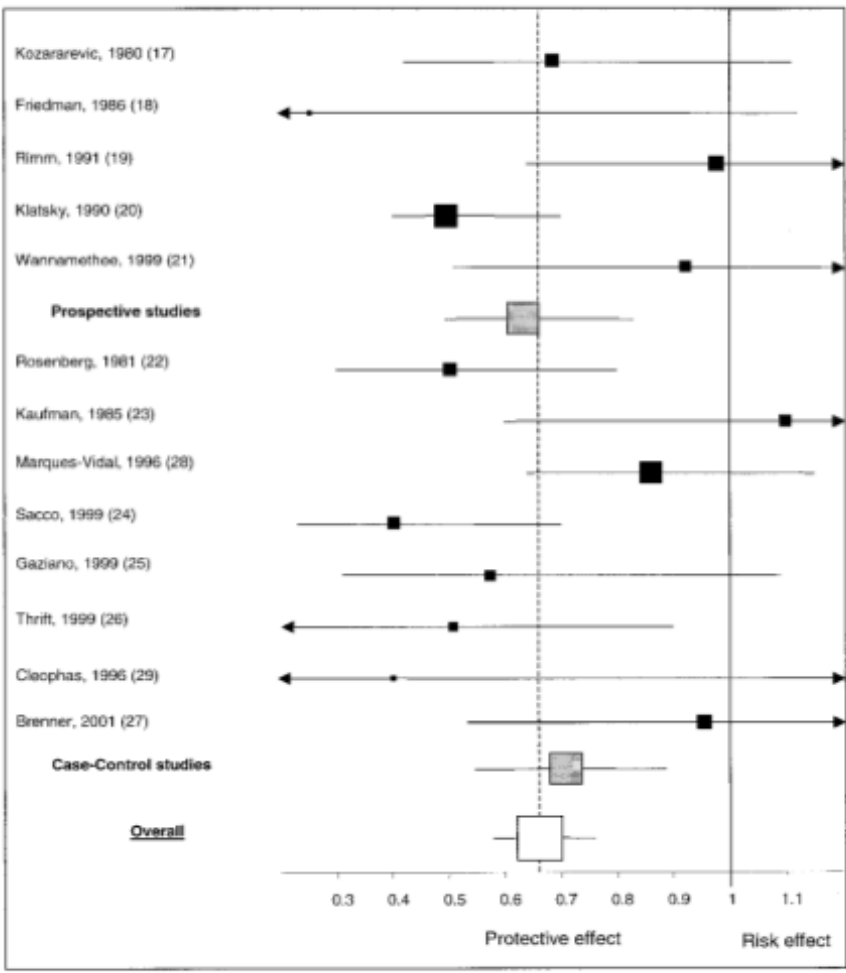
The 20<sup>th</sup> century brought a focus on alcohol *abuse*, and this led in the USA in the 1920s, to the **legal philosophy** of “Prohibitionism”

Fortunately, in the 1970s, the first rigorous epidemiologic studies began noting lower CHD rates among subjects who consumed some alcohol.

**CHD MORTALITY IN THE FRAMINGHAM HEART STUDY, BY ALCOHOL INTAKE (1974)  
(PERCENT DEATHS OVER 24 YEARS IN MEN)**

|               | Alcohol consumption, drinks/day |       |         |         |         |      |
|---------------|---------------------------------|-------|---------|---------|---------|------|
|               | None                            | < 0.5 | 0.5-1.0 | 1.1-2.0 | 2.1-5.9 | 6.0+ |
| Non-Smokers   | 16.3                            | 14.8  | 14.6    | 7.8     | 5.7     | 7.4  |
| Heavy Smokers | 28.3                            | 16.0  | 14.4    | 14.0    | 13.1    | 12.5 |

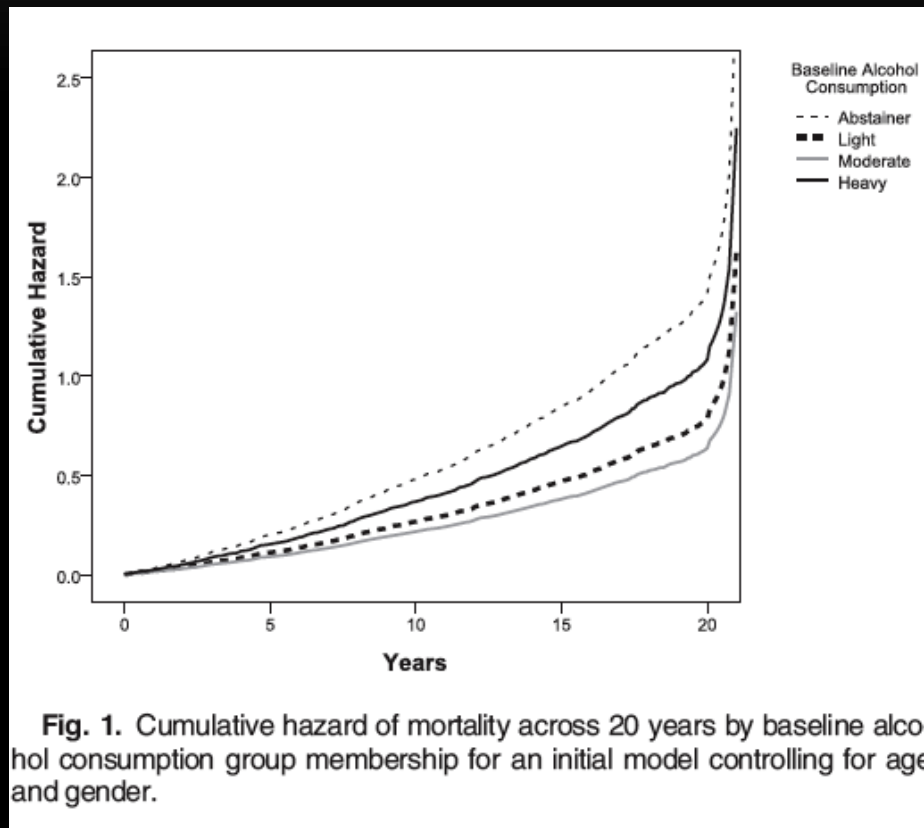




## Meta-Analysis of Wine and Beer Consumption in Relation to Vascular Risk

Augusto Di Castelnuovo, MS; Serenella Rotondo, MS; Licia Iacoviello, MD, PhD;  
 Maria Benedetta Donati, MD, PhD; Giovanni de Gaetano, MD, PhD

..AND EVENTUALLY THE CUMULATIVE HAZARD OF DEATH IS HIGHER FOR ABSTAINERS THAN FOR LIGHT, MODERATE AND ALSO HEAVY DRINKERS (MATHEMATICS SAYS)



C.J. Holahan et Al.  
Alcoholism; clinical and experimental research.  
Vol 34 Nov. 2010

The most recent evidence (Oct 2015)

## Effects of Initiating Moderate Alcohol Intake on Cardiometabolic Risk in Adults With Type 2 Diabetes

### A 2-Year Randomized, Controlled Trial

Yftach Gepner, MPH\*; Rachel Golan, RD, PhD\*; Ilana Harman-Boehm, MD; Yaakov Henkin, MD; Dan Schwarzfuchs, MD; Ilan Shelef, MD; Ronen Durst, MD; Julia Kovsan, MSc; Arkady Bolotin, PhD; Eran Leitersdorf, MD; Shoshana Shpitzen, MA; Shai Balag, MD; Elad Shemesh, MD; Shula Witkow, RD, MPH; Osnat Tangi-Rosental, BA†; Yoash Chassidim, PhD; Idit F. Liberty, MD; Benjamin Sarusi, MSc; Sivan Ben-Avraham, RD, MPH; Anders Helander, PhD; Uta Ceglarek, PhD; Michael Stumvoll, MD; Matthias Blüher, MD; Joachim Thiery, MD; Assaf Rudich, MD, PhD; Meir J. Stampfer, MD, DrPH; and Iris Shai, RD, PhD

**Conclusion:** This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.

# Alcohol consumption is associated with a lower incidence of acute myocardial infarction: results from a large prospective population-based study in Norway

■ K. Gémes<sup>1</sup>, I. Janszky<sup>1,2</sup>, L. E. Laugsand<sup>2</sup>, K. D. László<sup>3</sup>, S. Ahnve<sup>1</sup>, L. J. Vatten<sup>2</sup> & K. J. Mukamal<sup>4</sup>

From the <sup>1</sup>Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden; <sup>2</sup>Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; <sup>3</sup>Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; and <sup>4</sup>Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

**Conclusions.** Light-to-moderate alcohol consumption was linearly associated with a decreased risk of AMI in a population in which abstaining from alcohol is not socially stigmatized. Our results suggest that frequent alcohol consumption is most cardioprotective and that this association is not driven by misclassification of former drinkers.

# IS THERE A TRUE BENEFICIAL EFFECTS OF ALCOHOL OR JUST A “BLACK SWAN” ?

EVIDENCE ON :

ALL CAUSE MORTALITY  
CORONARY ARTERY DISEASE  
STROKE  
OSTEOPOROSIS  
RHEUMATOID ARTHRITIS  
OBESITY  
DIABETES



# Biomedical mechanistic aspects

# THE ROLE OF PHYSIOLOGICAL RESPONSE TO METABOLIC CHALLENGE AND REDOX HOMEOSTASIS

Insights from ancient wisdom and molecular  
medicine

---



The notion of disease as perceived by the Ayurvedic, Greek and Roman philosophy, and eventually acknowledged in its fundamentals by Hippocrates and Avicenna states that **the balance among the four humors of the body** (reminiscent of the four elements of the universe: air, fire, earth and water) **determines the temperament of a person and his susceptibility to diseases.** What was missing for centuries was the real cause of the impairment of the equilibrium among “humors”.

In the modern view, the perturbation of the *milieu intérieur* (Claude Bernard) – we overlap today to the notion of **offset of homeostasis**- drives the susceptibility, initiation and progression of a disease



In analyzing the intimate nature of different diseases, we generally accept that imbalance between counteracting mechanisms must have taken place and that the pathological phenotype reflects the **altered homeostasis**.

**Maintenance or re-establishment of homeostasis is the goal of preventive or therapeutic medicine**

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# Inflammation and redox homeostasis

January 23, 2004

BUSH'S  
MILITARY RECORDS  
IS DISNEY MOUSETRAPPED?

# TIME

## THE SECRET KILLER

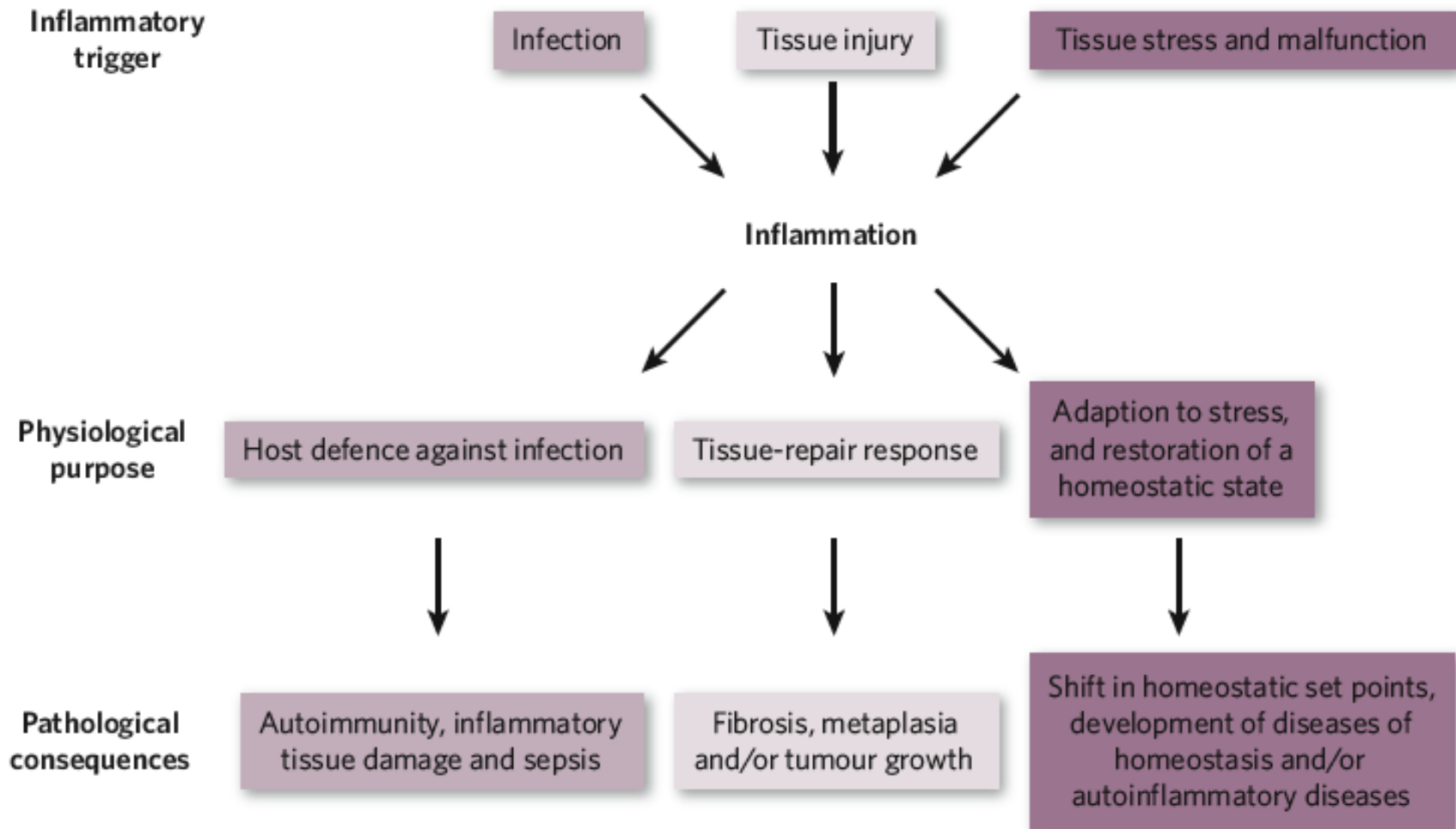
- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

[www.time.com/time/cover/012304.html](http://www.time.com/time/cover/012304.html)

Inflammation is the elementary system of defense, indispensable for surviving since living matter is continuously challenged by agents perturbing its physiological functions.

When hit by a challenge an integrated biological system reacts to eliminate the challenge and repair the damage.

Both these events affect the homeostasis and the resolution of the pathological status passes through the re-establishing of the *quo ante* homeostasis. Failure of this results in a chronic degenerative disease (or cancer).



**CAUSES, AND PHYSIOLOGICAL AND PATHOLOGICAL CONSEQUENCES OF INFLAMMATION**

MEDZHITOF 2008 NATURE, 454:428

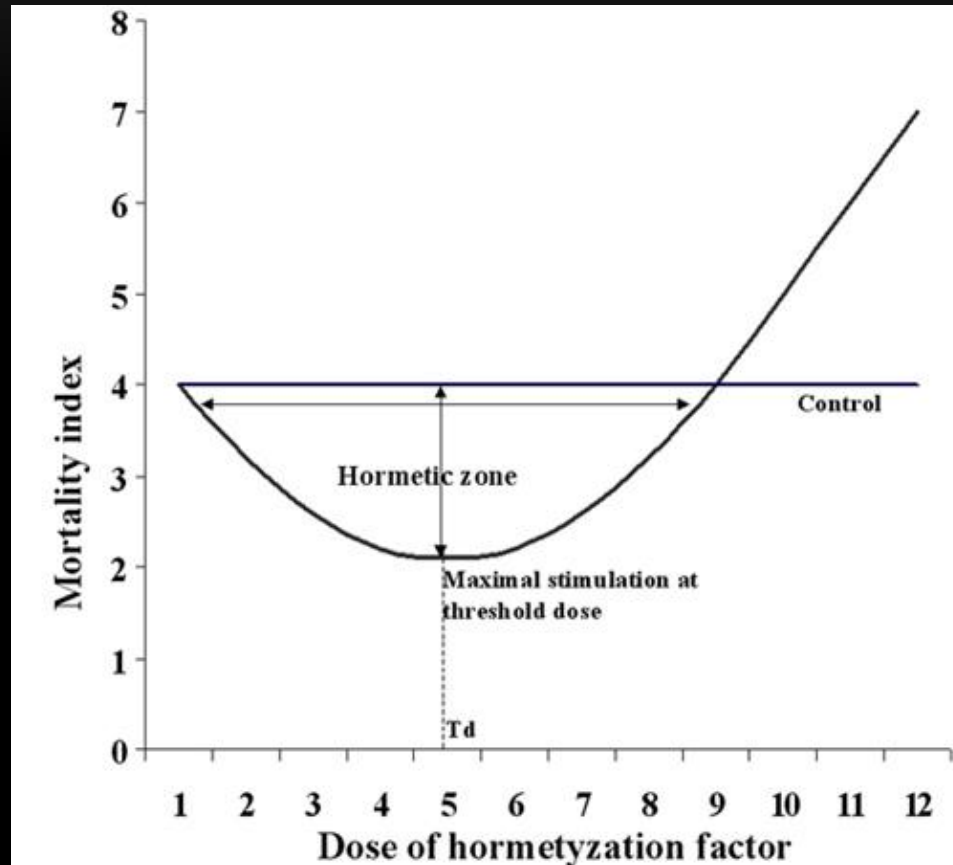
The triggers of inflammation (different challenges) use **electrophiles** (mainly hydroperoxides and species derived from them) in signaling pathways.

Redox homeostasis is re-established by a feedback activation of pathways increasing the **nucleophilic tone** (mainly thiols and related enzymes)



# Nutrition & hormesis

# HORMESIS IS THE POSITIVE OUTCOME OF ADAPTIVE MECHANISMS

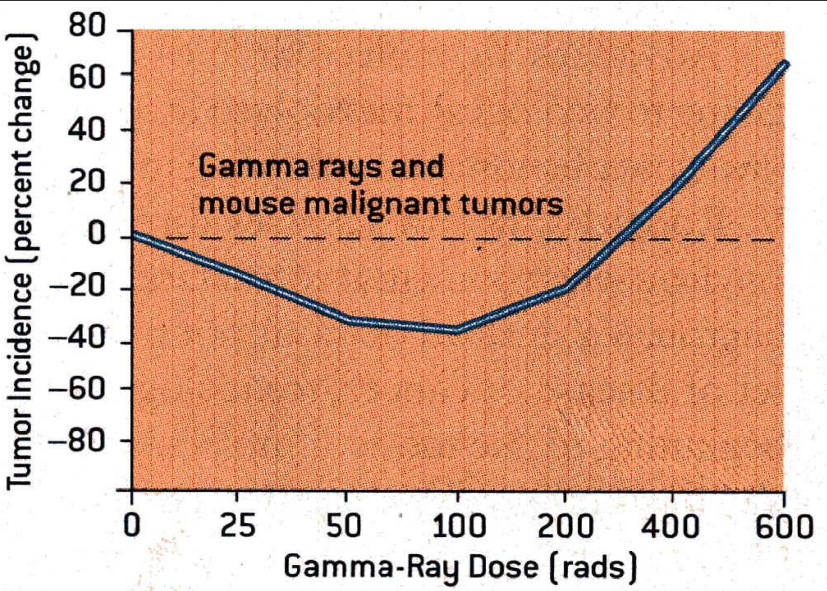


small (moderate) doses of a toxic compound -such as alcohol- can be health protecting when assumed in correct amount

## Nietzsche's Toxicology

Whatever doesn't kill you might make you stronger

By Rebecca Renner | August 18, 2003 | 0



Friederich Nietzsche  
1844-1900

The fact that the intake of a food component is good or bad for you is just matter of dose (Paracelusus)

Mild stimuli activate defense systems and metabolic flexibility.

Among hormetic stimuli there are: fasting, exercise, temperature, ethanol, xenobiotics and drugs such as metformin and statins, and finally also frank poisons as dioxin

# PARA-HORMESIS

We name **para-hormesis** the mechanism by which non toxic nutritional compounds activate the cellular antioxidant defense system mimicking toxic electrophiles.

This is the case of nutritional “antioxidants”

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# How do nutritional antioxidants impact of health?



**Fruit, vegetables and wine are the major sources of nutritional nucleophilic antioxidants**

# A PARA-HORMETIC MECHANISM ACCOUNTS FOR HEALTH PROMOTION EFFECT OF FOODS CONTAINING “ANTIOXIDANTS” (FRUITS, VEGETABLES AND WINE!)

They activate when oxidized, the endogenous antioxidant system that operates a feedback regulation of the inflammatory pathways.

This is a major contribution to the maintenance or redox homeostasis and prevents the excess of reaction to different stimuli.

# ACTIVATORS OF PARA-HORMESIS





# Why wine is better than spirits



+



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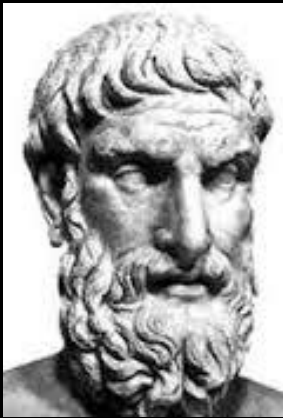


Hormetic effect

Para-hormetic effect

The health is protected when challenges are efficiently neutralized escaping from excess in either side. By living in peace with our internal and external environment, adopting *aurea mediocritas* (moderation) we will achieve **ἀταραξία** (tranquillity, and seemingly a better health).

Just an anticipation of the Claude Bernard physiology from the ethical phylosophy of Epicurus and Horace



342-270 BC



65-8 BC

Wine contributes to the maintenance of homeostasis by buffering the trend to an offset of the redox steady-state between pro and anti-inflammatory pathways

The wine, in this perspective, is not just a food protecting our health, but, remarkably, it does it in an ethical way.

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