Nutritional Solutions for Healthy Life

Vitamin E - emerging benefits

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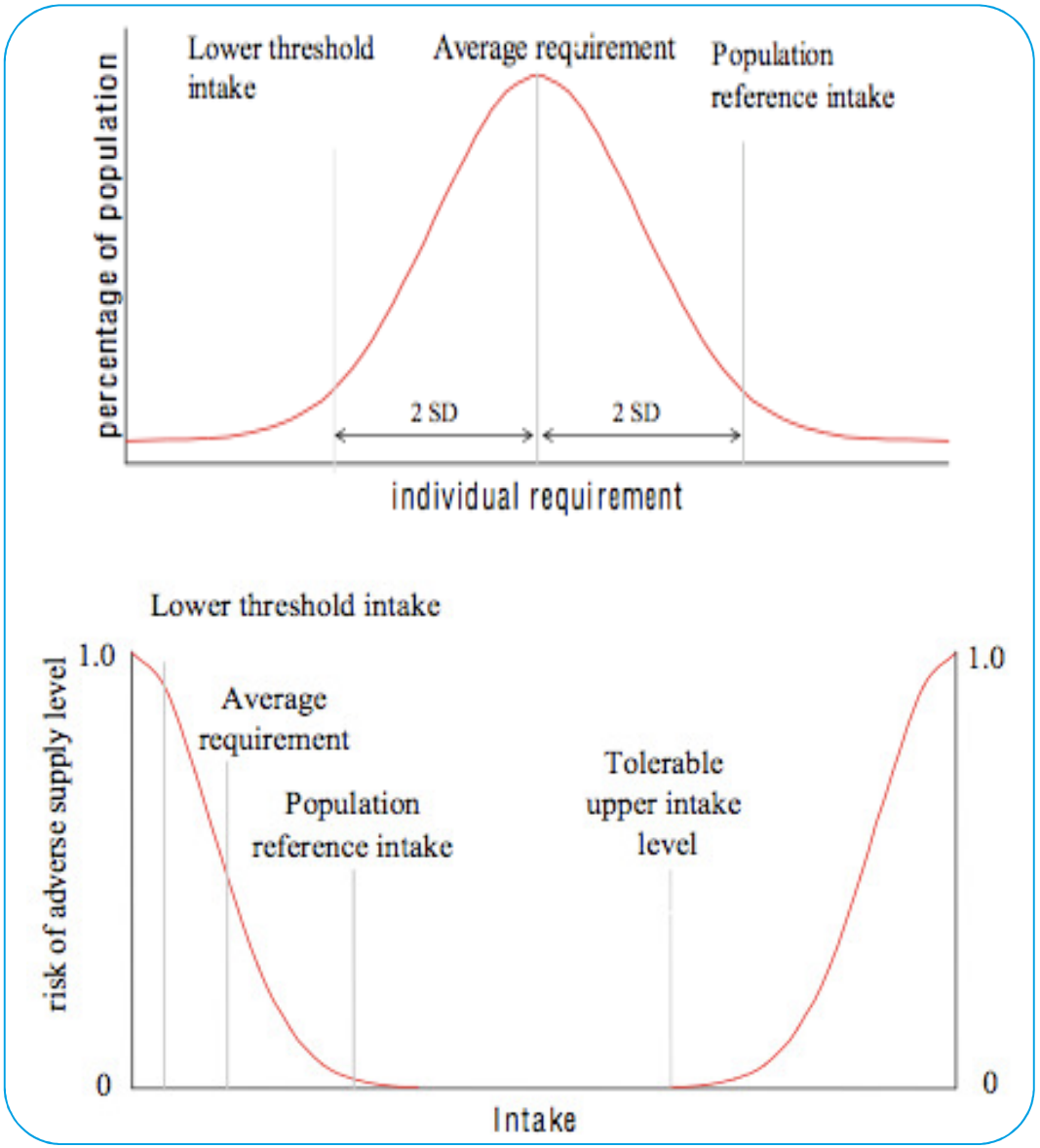
23rd September 2014, Valencia

HEALTH · NUTRITION · MATERIALS

Nutrient requirements/recommended intakes



Dietary reference values for nutrient intake are:

- Science-based
- Dependent on the existing data available
- Country or institution specific
- Potentially politically driven
- Reflect ‘eating cultures’

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Vitamin E

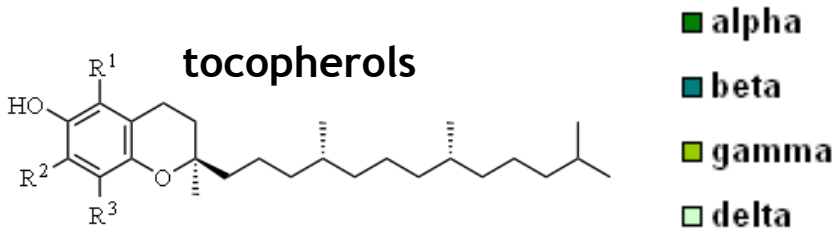
- Vitamin E is a generic term for eight related fat soluble molecules:

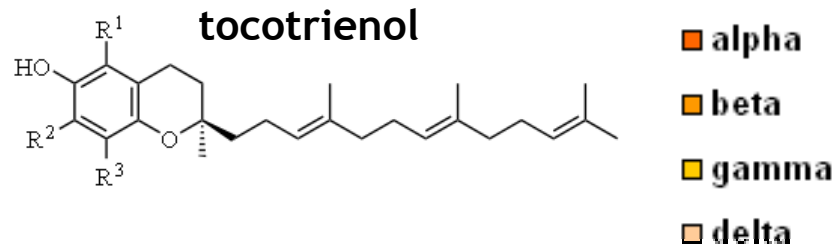
  α-,β-, γ-, and δ- tocopherol and
  α-,β-, γ-, and δ- tocotrienol.

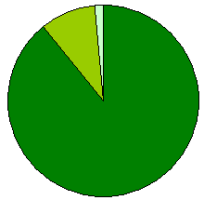
  The tocopherols and tocotrienols differ on the side chain, the
  α-,β-, γ-, and δ- forms on the ring groups (R^s)

- Vitamin E is naturally produced in plants only. The relative tocopherol and tocotrienol content varies (e.g. sunflower oil is rich in α-, soybean oil rich in γ-tocopherol.

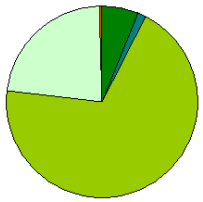
- α-tocopherol is specifically selected & retained in the human body, therefore recommendations on intake and plasma levels are based on α-tocopherol



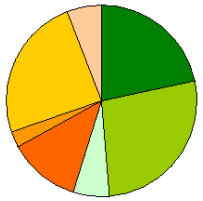




Sunflower Oil



Soybean Oil



Palm Oil

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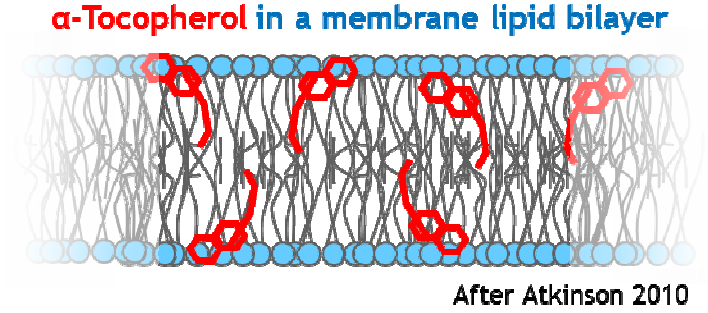
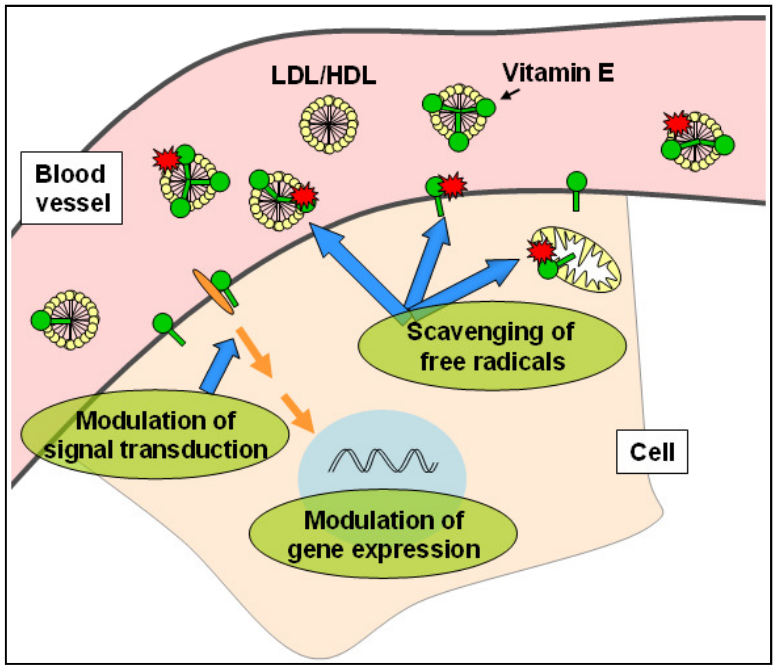
Function of vitamin E as antioxidant is established

- Vitamin E is a powerful antioxidant. Once oxidized, it can be regenerated by vitamin C.
- Due to its lipophilic nature, vitamin E localizes to lipid compartments, such as cell membranes (prevention of peroxidation of lipids and oxidation of proteins).
- Furthermore, vitamin E depletion and repletion affects gene expression in vitro in cells and in vivo in animal models, indicating broader effects than just protection from oxidation.
- Incorporation of vitamin E into cellular membranes can alter the activity of membrane-associated proteins and thereby changes signal transduction pathways.
- EFSA Health Claim in 2011: “Vitamin E contributes to the protection of cells from oxidative stress”





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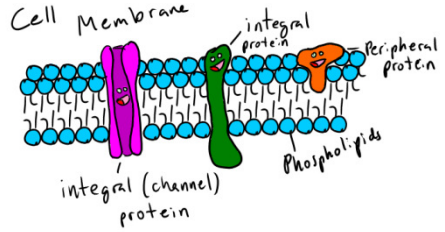
Current RDAs for vitamin E are based on markers of cell membrane integrity



→ *1. Lysis of red blood cells*

→ *2. PUFA intake*

- Lysis of erythrocytes are associated with decreases erythrocyte survival (which can be corrected by vitamin E supplementation)
- From research in a limited number of people, reported in the seventies a vitamin E serum level of 12 µmol/L was derived to prevent hemolysis
- To achieve a serum level of 12 µmol/L α-tocopherol an intake of 12 mg vitamin E is required
- 12 mg vitamin E is the intake to meet the requirements of 50% of the population (EAR) and 15 mg vitamin E will suffice to meet the needs of 97% of the population (RDA)
- Vitamin E requirements vary from 15 to 25 mg/day or more depending on PUFA intake
  → Additional vitamin E needs should become part of RDA

A higher intake of nutrients beyond nutritional requirements may provide additional benefits in defined groups

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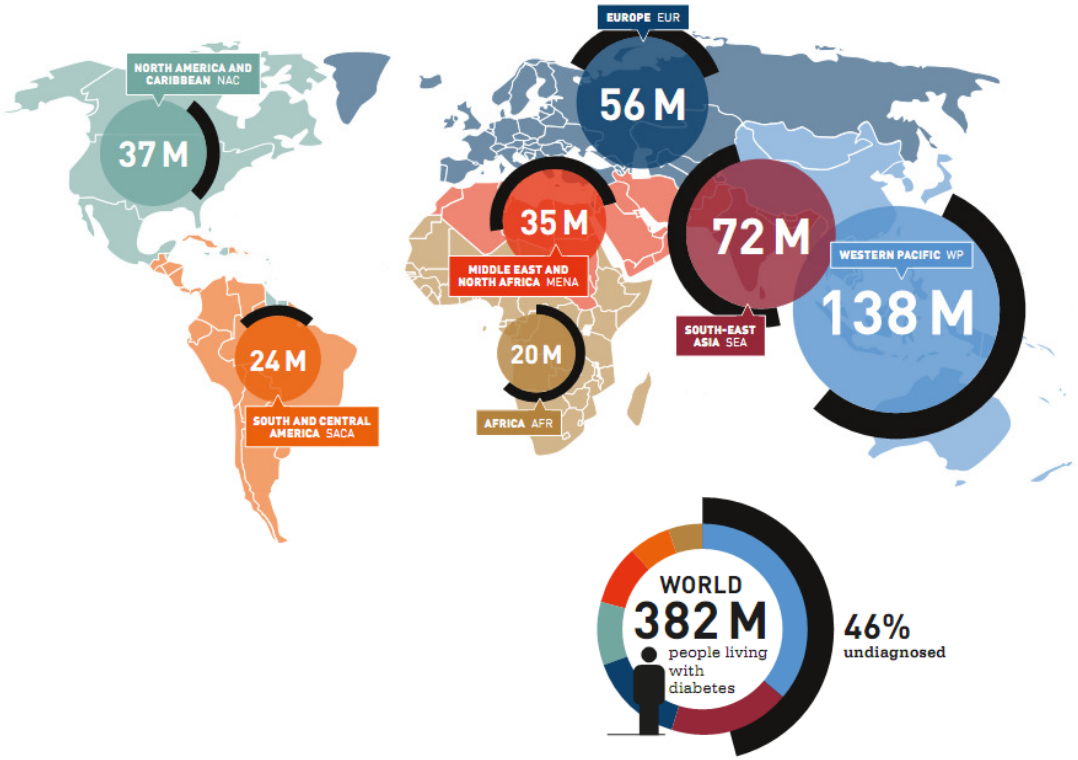
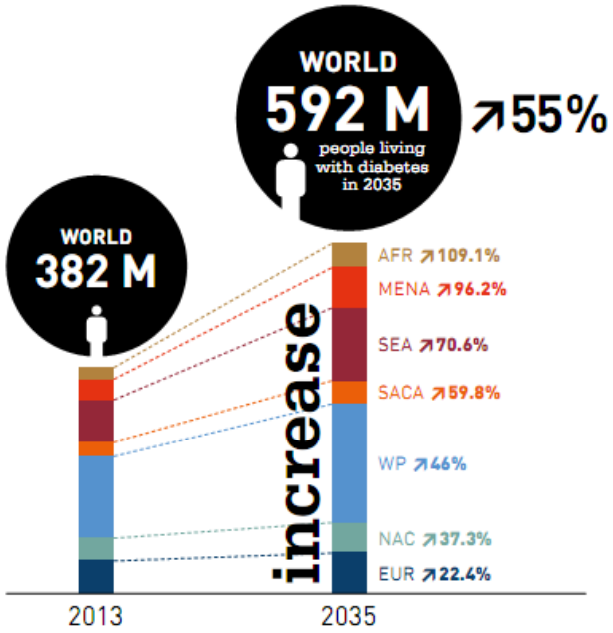
Diabetes is a huge and growing public health problem





1. At least 1 in 10 deaths among adults is attributable to diabetes
2. Diabetes deaths are projected to double between 2005 and 2030
3. >80% of diabetes deaths occur in low- and middle-income countries

IDF Diabetes Atlas, 6th ed. (2013)

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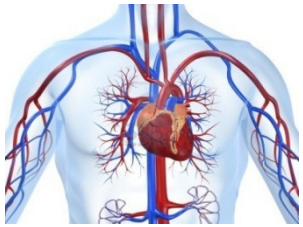
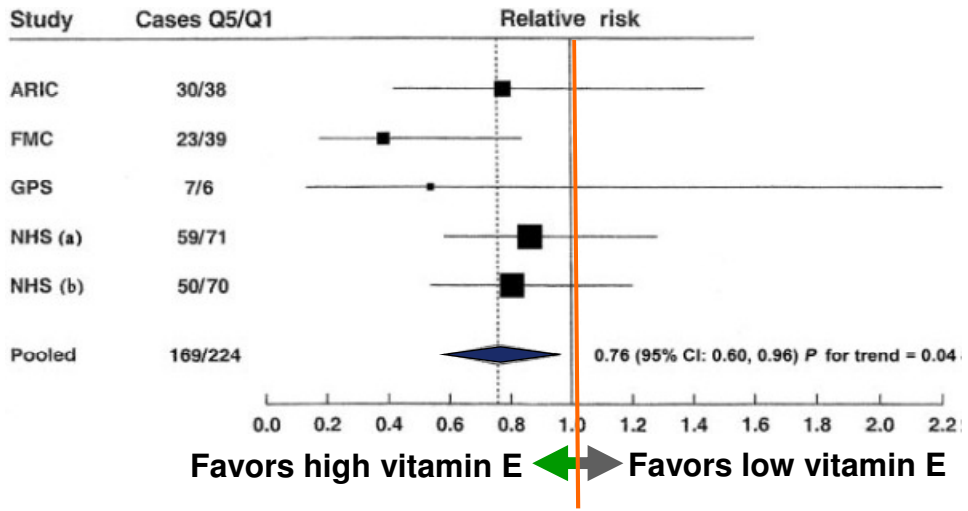
Epidemiological evidence for vitamin E benefits

- Lower plasma level of vitamin E has been reported in type 2 diabetic subjects compared to controls.
- Prospective epidemiological studies demonstrate that high serum vitamin E was associated with decreased risk of type 2 diabetes.
- Evidence from various observational human studies indicated that vitamin E has beneficial effects on the cardiovascular system.
- At least five studies reported that increased consumption of vitamin E is associated with decreased risk for heart attack or death from cardiovascular disease.
- It was therefore hypothesized that vitamin E supplementation could reduce the risk for cardiovascular events.



Major coronary heart disease risk in women
(after Knekt et al. 2004)



Salonen et al. (1995)
Maxwell et al. (1997)

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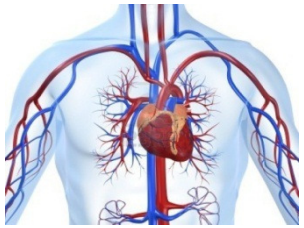
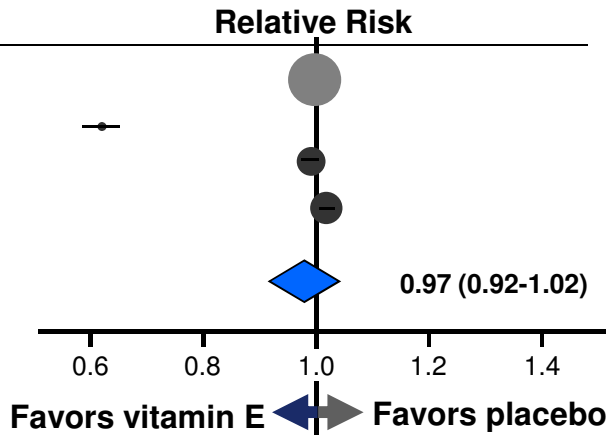
However, most RCTs find no vitamin E benefits for cardiovascular health

- Several randomized clinical trials have been performed to examine the efficacy of vitamin E in improving human health.
- Surprisingly, the results from the trials did not detect a consistent benefit of vitamin E supplementation on cardiovascular health.
- New scientific findings provide an explanation why a benefit was not detected and shows that genetics matters.



Meta-Analysis of the effect of Vitamin E on Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in large trials (modified from Yusuf et al. 2000)

Study	Dose	Duration	Cases
ATBC	50	5yr	3859
CHAOS	>400	1.3	105
GISSI	300	3.5	1155
HOPE	400	4.5	1511
Total			6630



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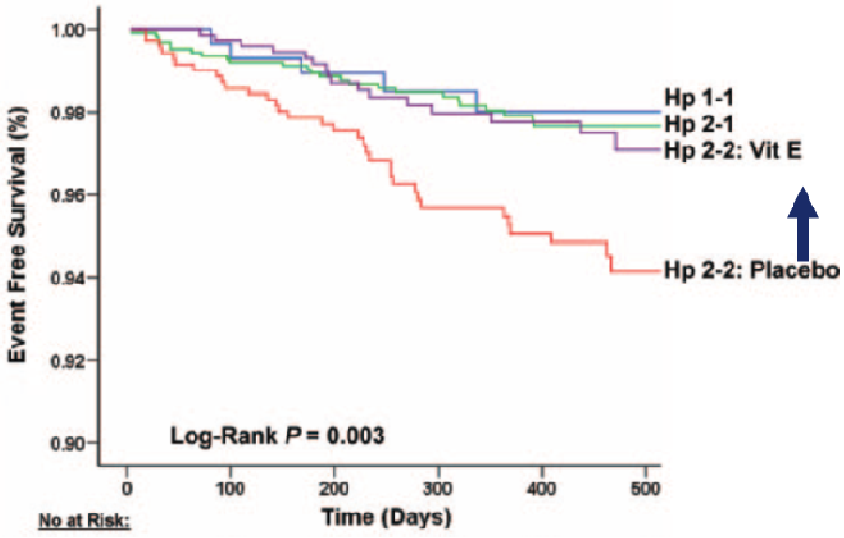
Vitamin E reduces cardiovascular events in diabetics and Hp 2-2 genotype

- Haptoglobin (Hp) is a protein that scavenges free hemoglobin in the blood.
- The Hp gene exists in two variants, the Hp1 and the Hp2 variant. In Western societies, 36% have haptoglobin genotype 2-2 (Hp 2-2)
- Diabetic individuals with Hp 2-2 have a marked increased oxidative stress
- Increased risk for cardiovascular events has been linked to Hp 2-2 genotype in diabetics.

Vitamin E supplementation at a dose of 400 mg reduces and normalizes the risk for cardiovascular events in diabetics with Hp 2-2

Results from the ICARE study (Milman 2008)

(RCT with 1434 diabetes patients with Hp2-2 genotype, receiving placebo or 400IU vit E/day)



Kaplan Meier-Plot of the composite end-point in Hp 1-1 & Hp 2-1 DM Individuals compared with Hp 2-2 individuals receiving placebo or vitamin E

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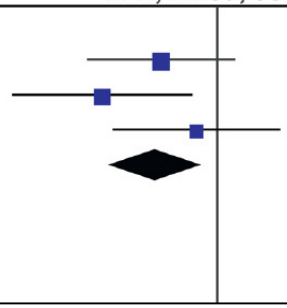
Findings from the ICARE Study were confirmed in the HOPE study

- N = 2545 women and 6996 men 55+ yrs, CVD or diabetes + one other risk factor, 400 IU/d vitamin E or ACE-inhibitor or placebo for 4.5 years, composite endpoint
- Vitamin E had no apparent effect on cardiovascular outcomes

Study or Subgroup	Vitamin E Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.4.1 Hp 2-2						
HOPE	37	222	40	177	38.8%	0.69 [0.42, 1.13]
ICARE	16	726	33	708	34.2%	0.46 [0.25, 0.85]
WHS	31	146	31	131	26.9%	0.87 [0.49, 1.53]
Subtotal (95% CI)		**1094**		**1016**	**100.0%**	**0.66 [0.48, 0.90]**
Total events	84		104			

Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 12%

Test for overall effect: Z = 2.60 (P = 0.009)



Findings from the ICARE Study were confirmed in a post-hoc retrospective subgroup analysis of the HOPE study:

Risk for cardiovascular events (CV death and nonfatal myocardial infarction) was significantly reduced only in the diabetics carrying the Hp 2-2 gene

Yusuf et al. (2000)
Levy et al. (2004)
Blum (2010)
Vardi et al. (2012)

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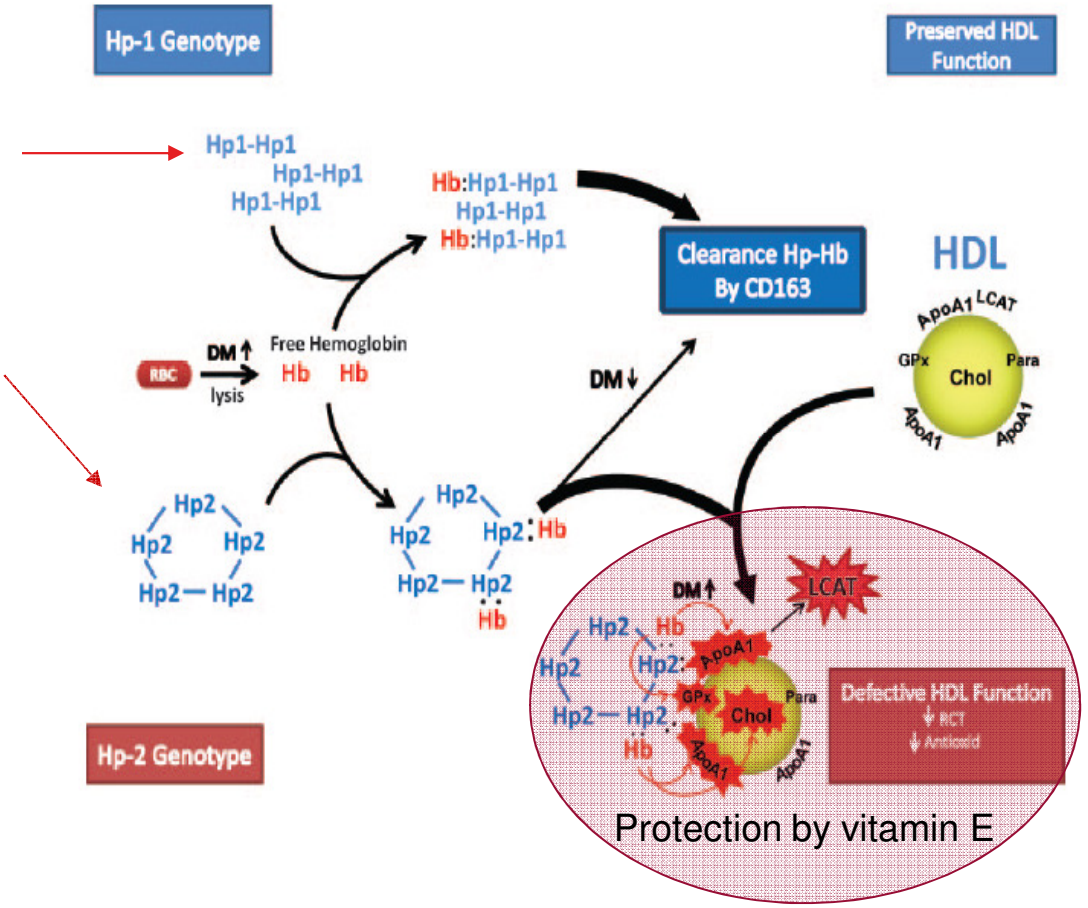
Proposed vitamin E function in diabetic Hp 2-2 individuals

- Haptoglobin binds and inhibits the oxidative activity of free hemoglobin (Hb), and targets it for clearance from the blood.
- The Haptoglobin 2 protein forms aggregates which affects its function. Hemoglobin is not cleared as efficiently.
- Furthermore, Hb-Hp2-2 complex binds to HDL, oxidizes proteins and lipids in HDL and renders HDL dysfunctional and prothrombic.
- Vitamin E protects lipids and proteins in HDL from oxidation



Asleh et al. (2008)

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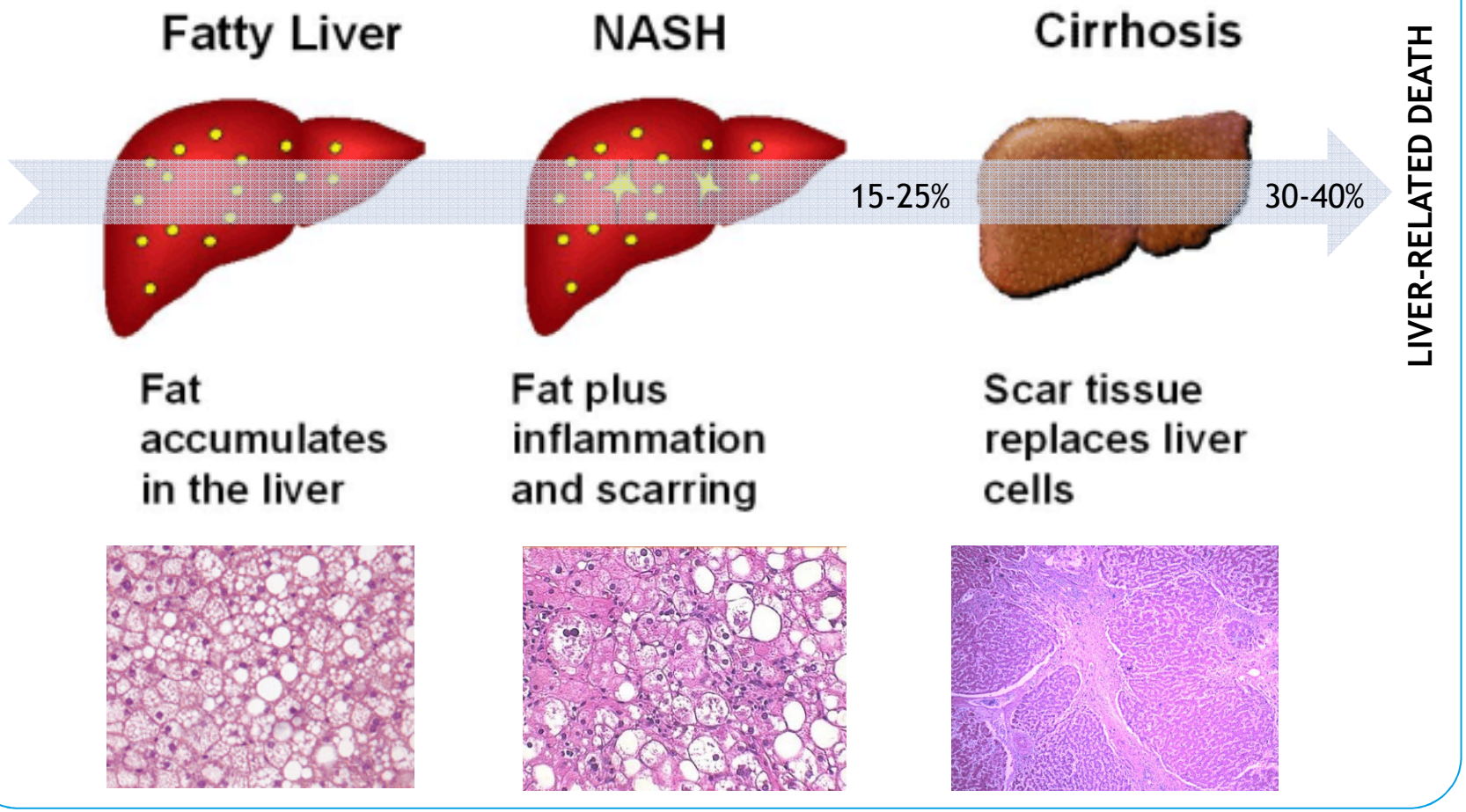
The spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD)

The **spectrum of fatty liver disease associated with metabolic determinants and not resulting from alcohol (NAFLD)** extends from hepatic steatosis through steatohepatitis to cirrhosis.



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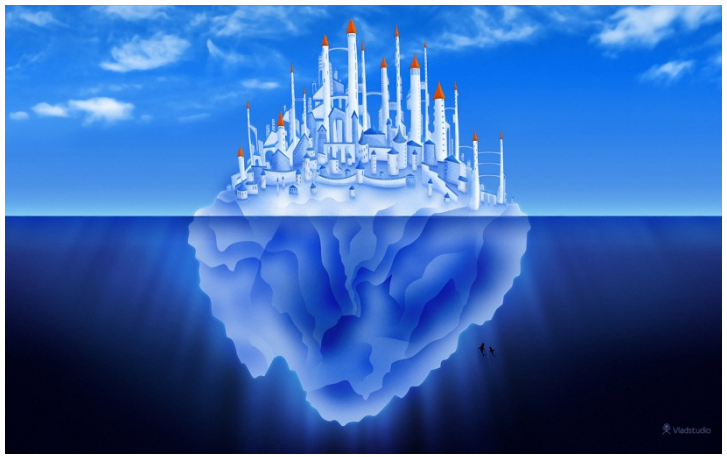
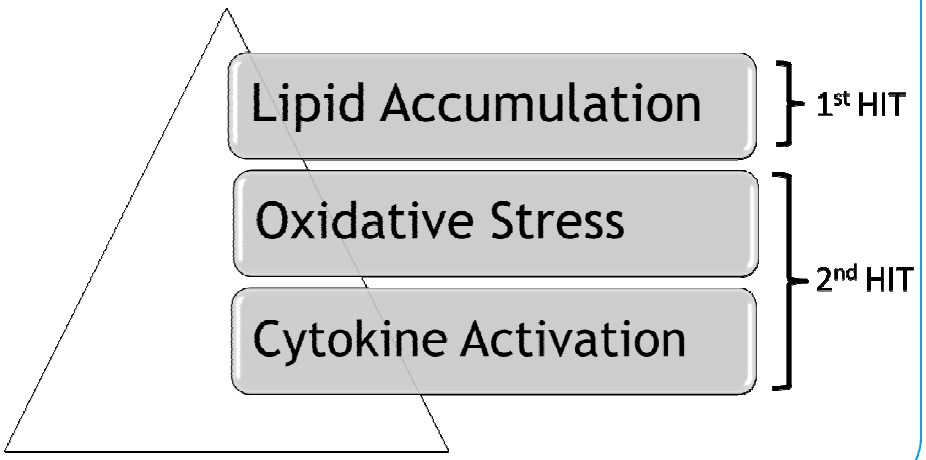
Impact and development of NAFLD/NASH

- High prevalence in urbanized communities with affluent economies (NAFLD: 17–33%, NASH: 6% - 17%)
- Most common cause of abnormal liver tests
- Standardized mortality of liver disease in type 2 DM greatly exceeds vascular disease
- NASH recurs after liver transplantation
- At present, there is no approved drug for the treatment of NASH





Fatty Liver Disease: NASH and Related Disorders, *Blackwell Publishing, 2005*
Day CP, James OF., *Gastroenterolgy 1998; 114: 842-5.*
Erhardt A. et al. *Eur J Med Res* 2011; 16:76-78.
Cankurtaran M. et al. *Acta gastro-enterologica Belgica* 2006; 69 (1) p.5-11.

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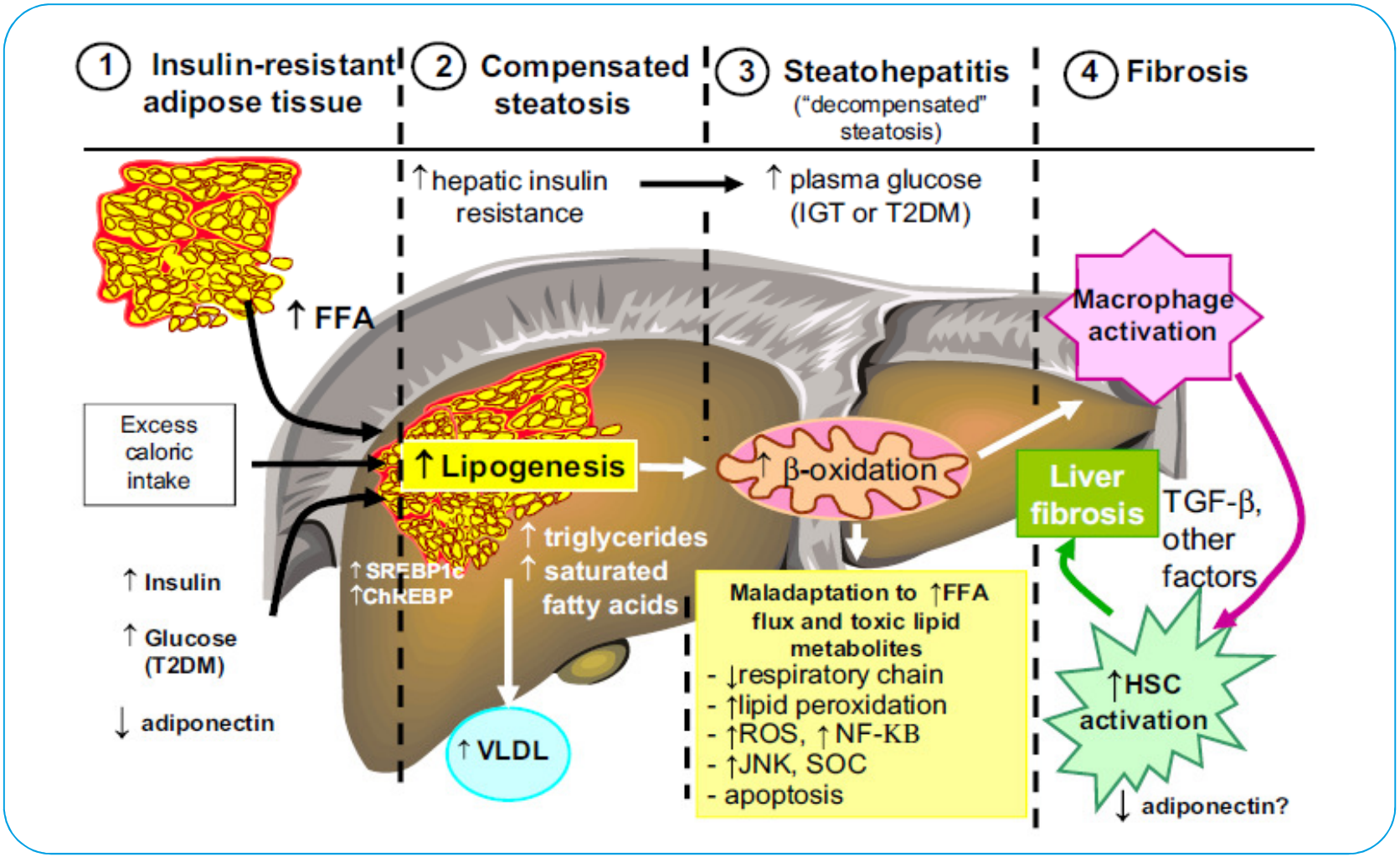
Possible role of adipose tissue insulin resistance and lipotoxicity



Cusi K., *Curr Opin Endocrinol Diabetes Obes* 2009; 16:141–9

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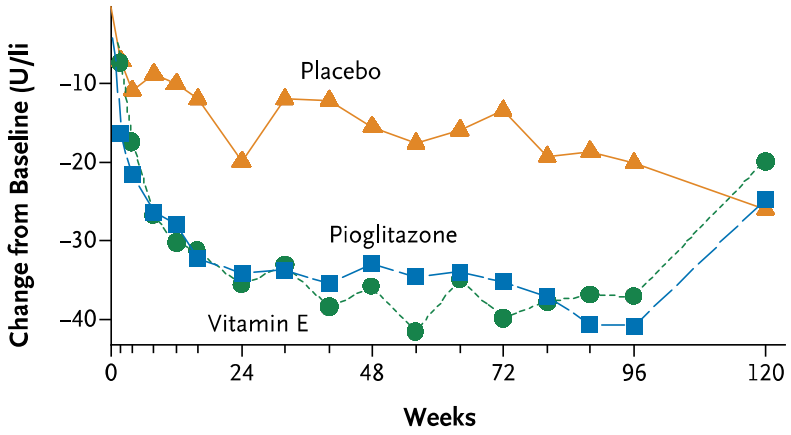
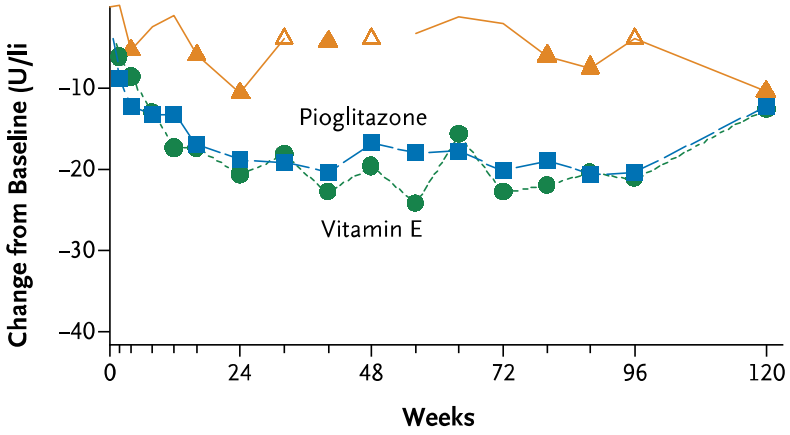
Vitamin E reduces risk for non-alcoholic fatty liver disease

- In 2010, more than 1,5 billion adults, 20 and older, were overweight worldwide
- As a consequence the risk for non alcoholic liver disease is increasing



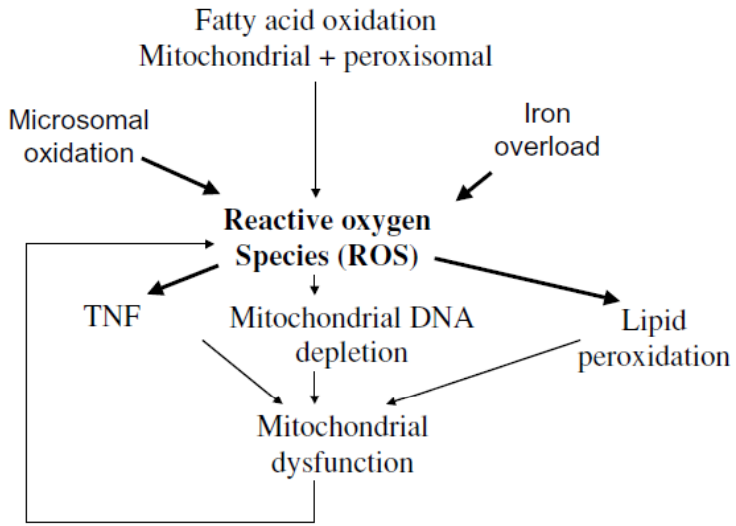


Supplementation with vitamin E (at a dose of 400 mg) was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes

www.who.int
Sanyal et al. N Engl J Med, 2010.
Pacana et al. Curr Opin Clin Nutr Metab Care, 2012.
Lomonaco et al. Drugs, 2013.

Possible mechanisms of action of vitamin E

1. **Chain-breaking antioxidant,** quenching free radicals
2. **Anti-inflammatory compound,** antagonizing the production of inflammatory mediators
3. There are measurable differences in the **metabolomics profile** of subjects who are likely (vs unlikely) to respond to vitamin E treatment for NASH
4. Vitamin E supplementation of the diet of mice led to PPAR-γ mediated increased adiponectin expression. This shows a potential **gene expression regulating role** for vitamin E.



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD PRACTICE GUIDELINE

Vitamin E (800 IU/day) improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.

Wu D, Meydani SN., *Leukoc Biol*, 2008. 84(4):900-914.
Cheng J. et al. *PLoS ONE* 2012. 7(9):e44106.
Landrier JF. et al. *Endocrinology*. 2009;150:5318-5325.
Chalasani et al. *Hepatology*, vol. 55, no. 6, 2012

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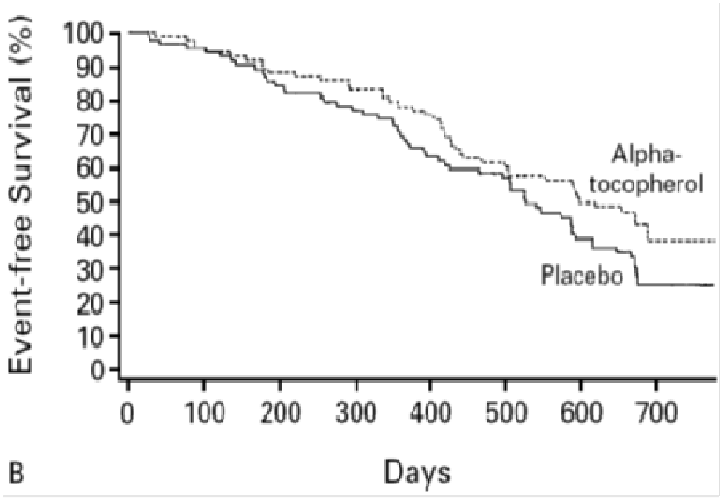
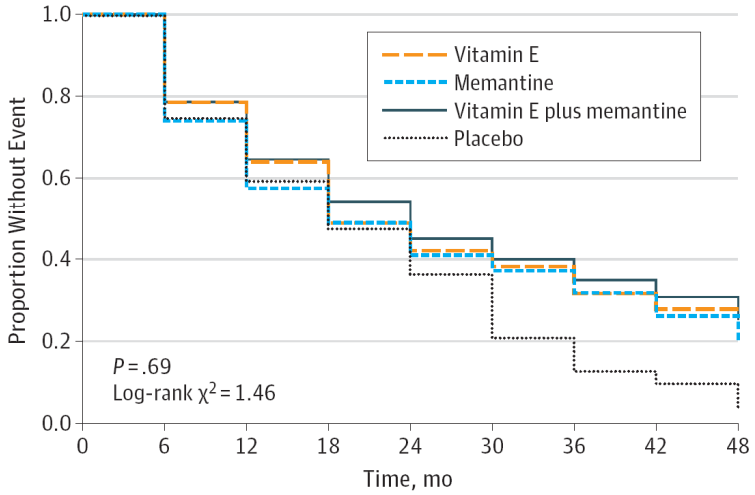
Vitamin E slows the progression of Alzheimer's disease

- AD is a age-dependent progressive neurological disease, is the leading cause of dementia and the fourth-leading cause of death in industrialized societies.
- Numbers of deaths due AD increased by 60% within 8 years.
- There is no pharmacological therapy available to causally prevent AD.



Survival time w/o pathological "event"



Level of dependency

➢ Supplementation with vitamin E (at a dose of 2000 IU) delays the pathologies.
➢ No severe adverse effect was associated with the vitamin E treatment

www.alz.org
Sano et al., N Engl J Med 1997;336:1216-22
Dysken et al., *JAMA*. 2014;311(1):33-44. doi:10.1001/jama.2013.282834,
Ortega et al., J. Nutr. 132: 2065-2068, 2002
Mohajeri et al., 2014

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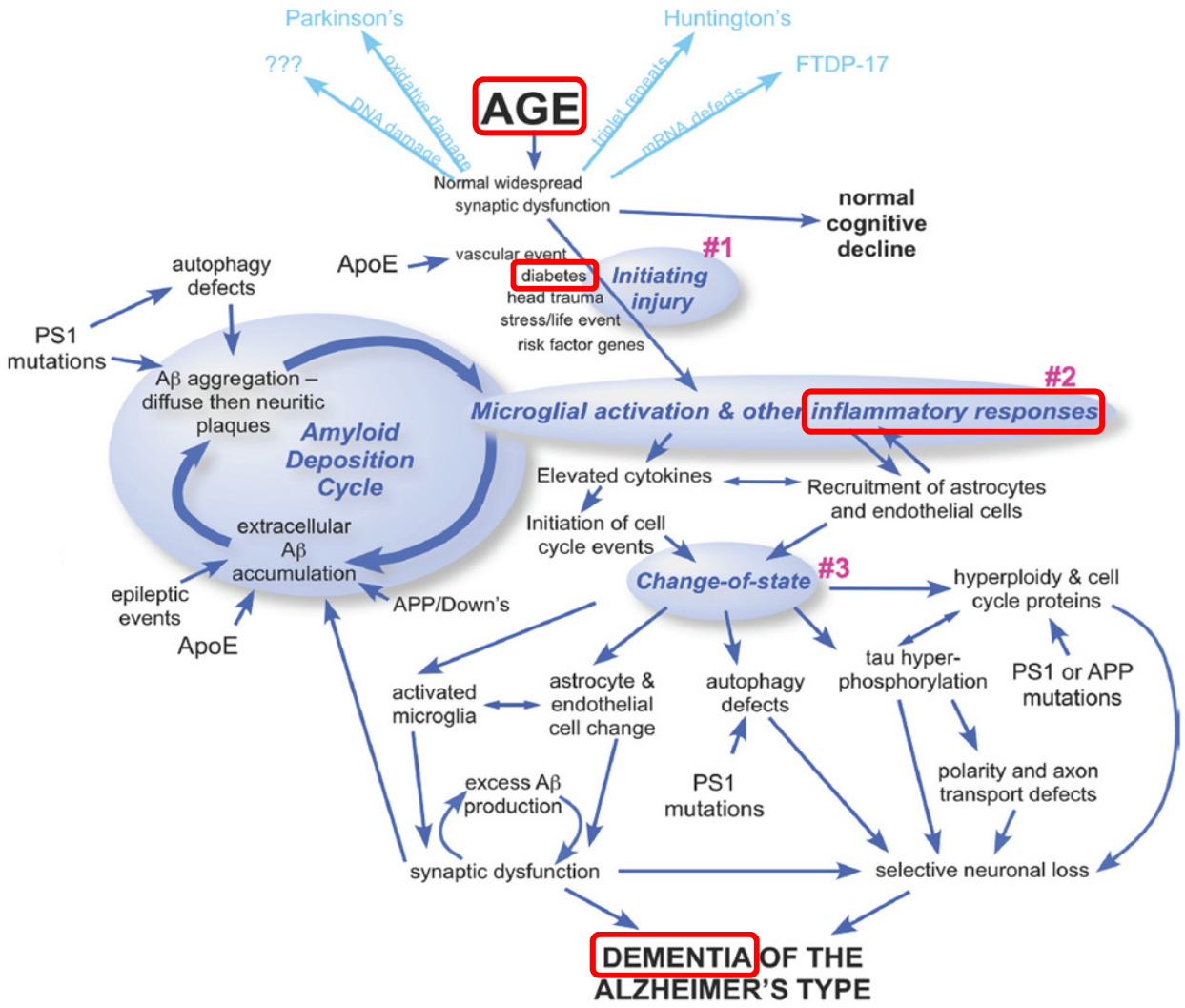
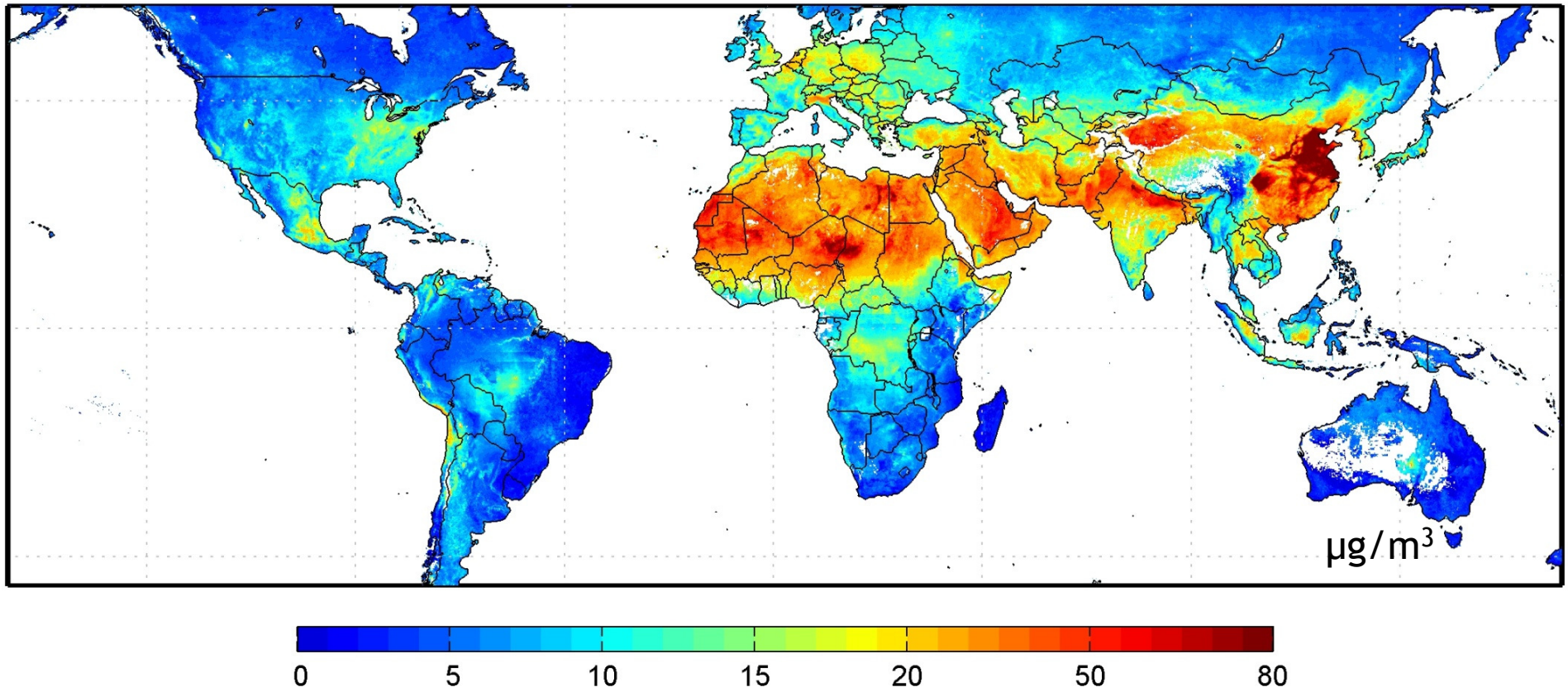
Age is the only proven risk factor for AD



Global satellite-derived PM2.5 averaged over 2001-06



Environ Health Perspect 2010;118:847
http://www.nasa.gov/topics/earth/features/health-sapping.html

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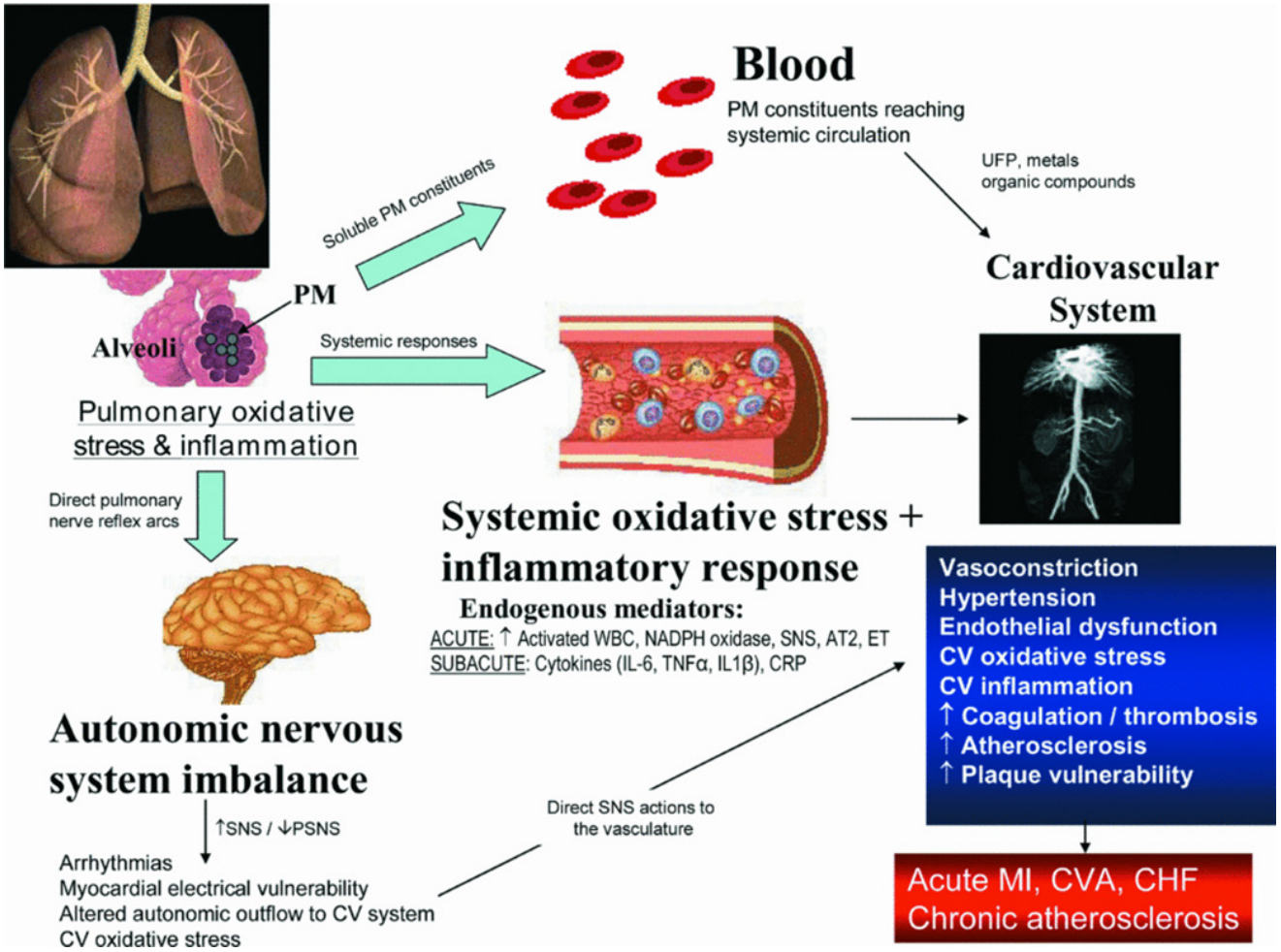
PM exposure is associated with an increased risk of CV morbidity and mortality



Brook et al. 2008

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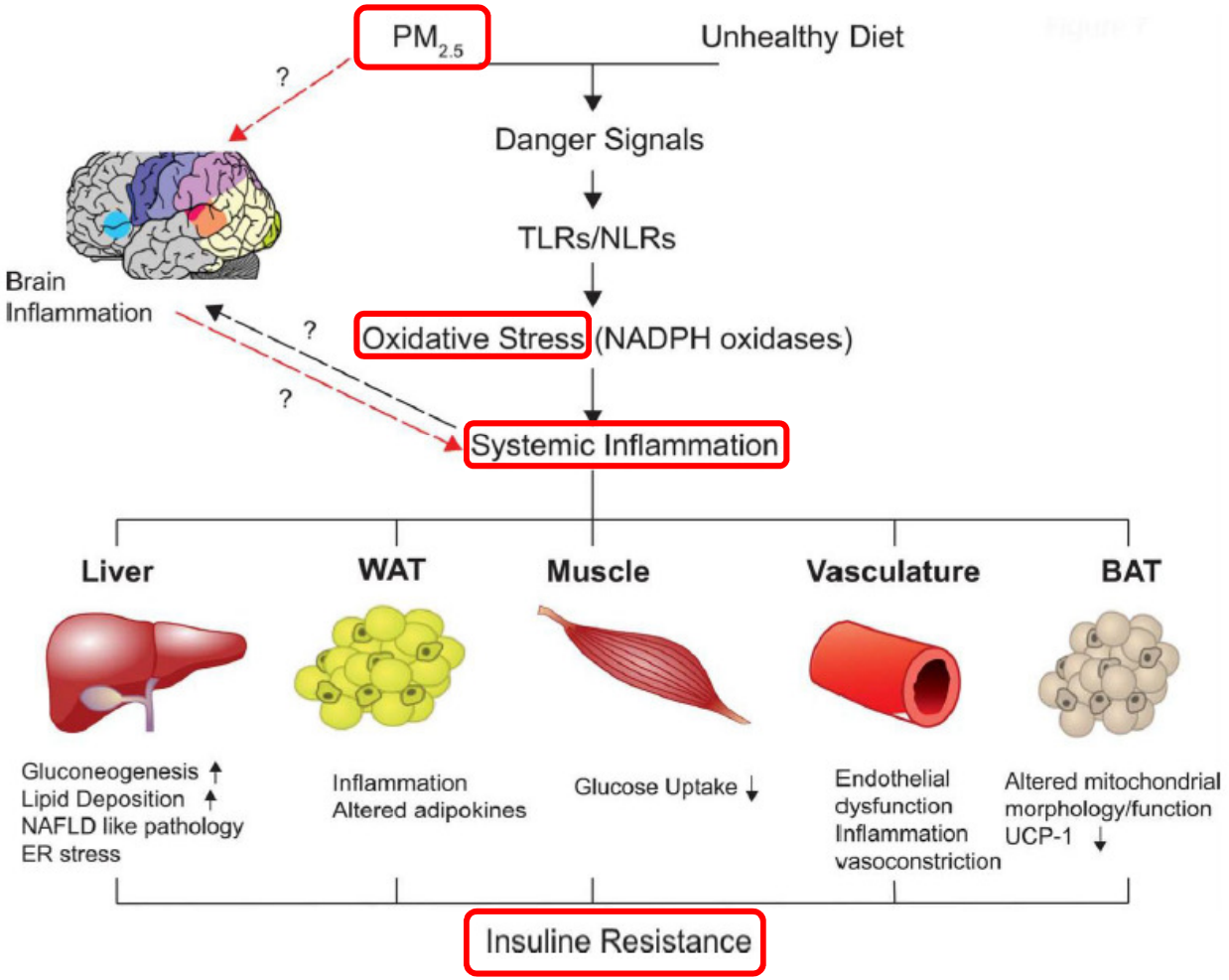
Mechanisms linking air-pollution & type 2 diabetes / insulin resistance



Liu et al. 2013

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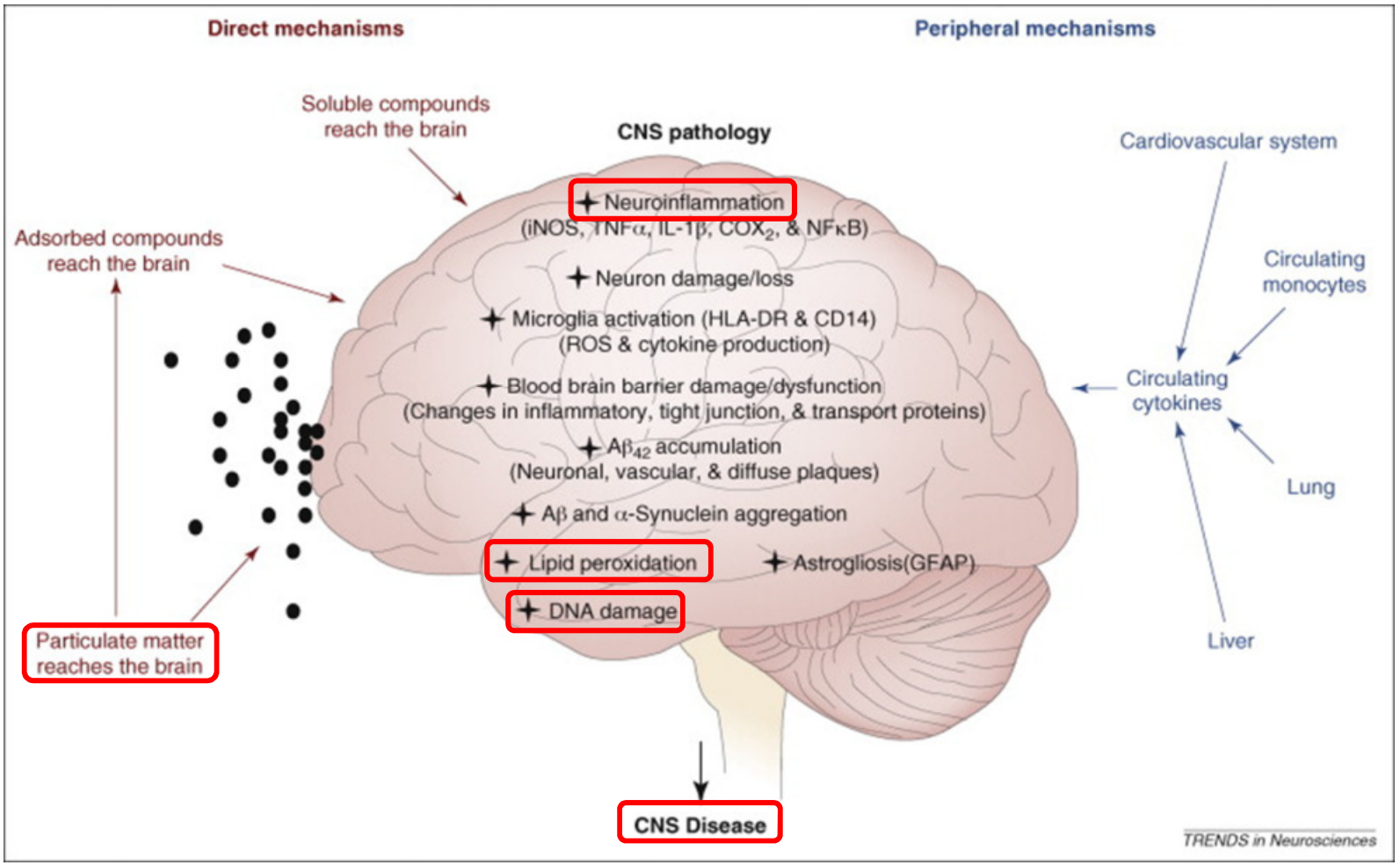
Air pollution, neuro-inflammation & brain function



Block et al. 2009

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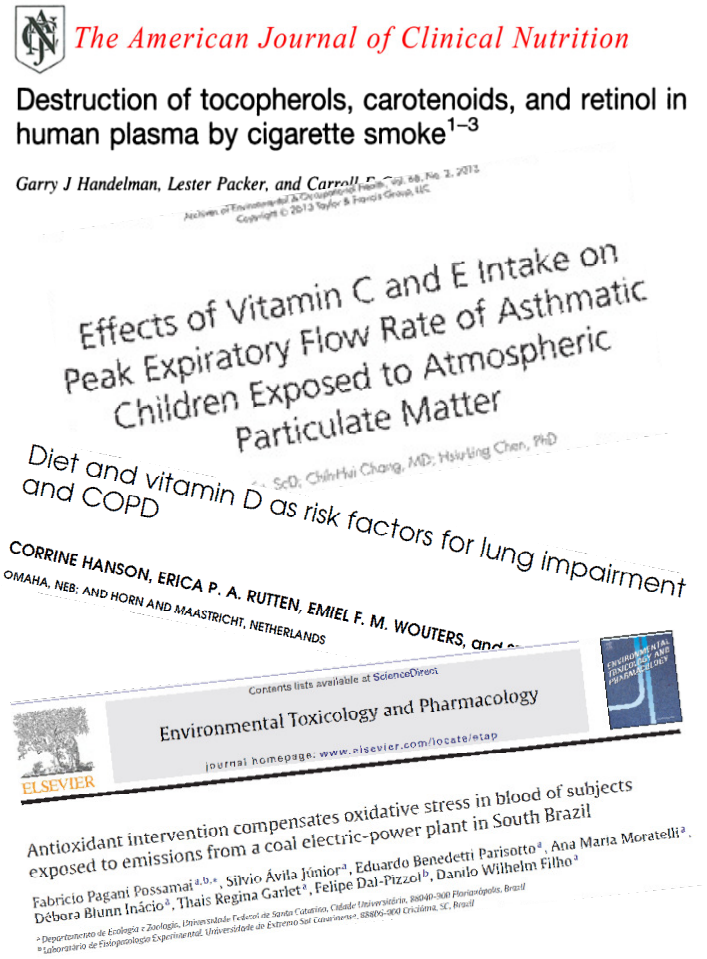
Combination of PUFAs and vitamins as solution to counteract negative impact of air pollution

- PM enters respiratory (lung) system when we inhale
- PM 2.5 travels all the way to alveoli and causes local and systematic harm including:
  - Increased oxidative stress
  - Increased inflammation
  - Systemic effects on complete human system

Antioxidants, vitamins and PUFAs reduce negative impact of PM 2.5

New concept for combination of PUFAs and antioxidants in development which requires further evaluation and substantiation



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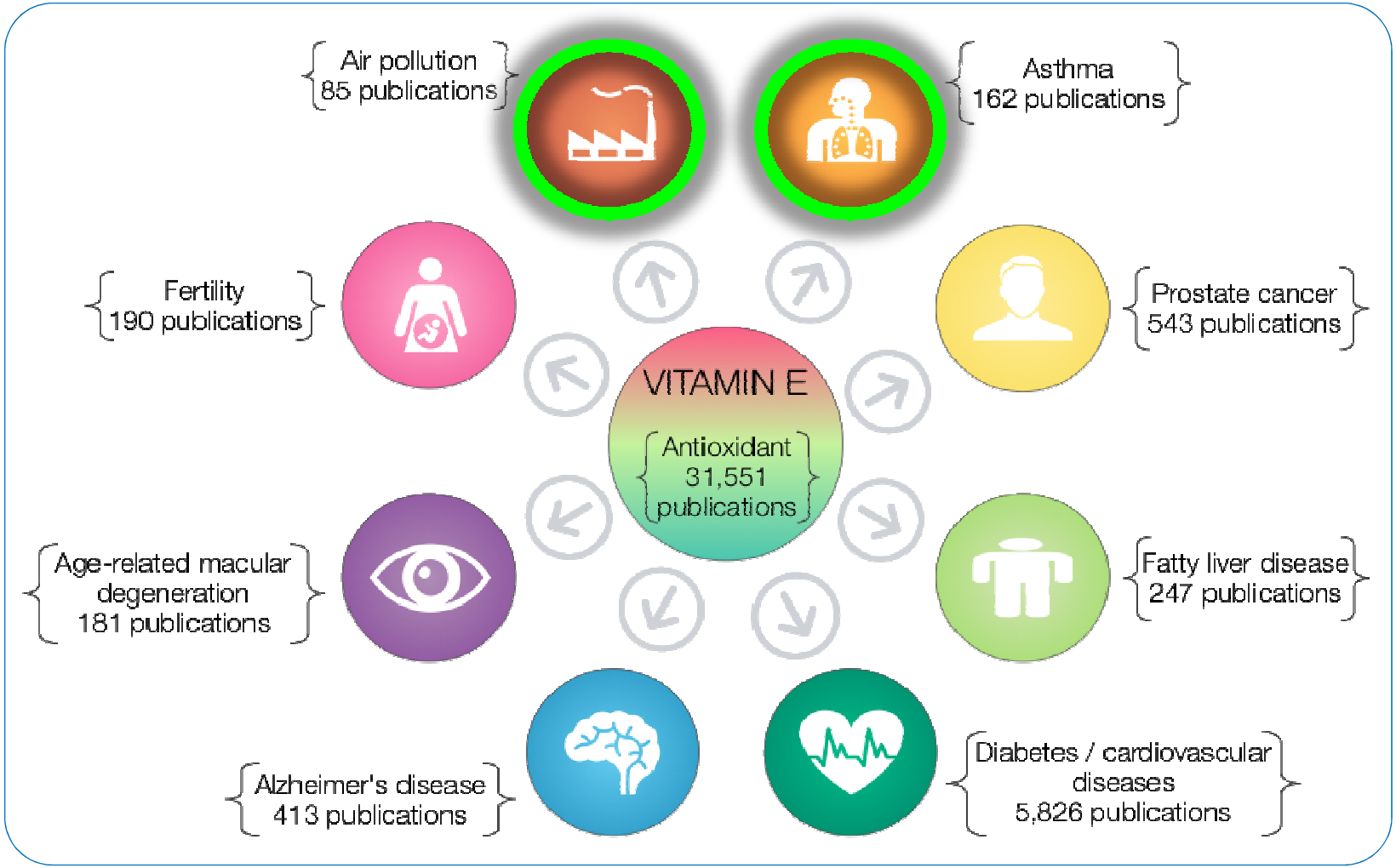
Demonstrated benefits of Vitamin E go beyond essentiality



No. of publications based on general search in PubMed with the indicated keywords (Status: June 30, 2014)

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