Giornate di Ginecologia ed Ostetricia:
fertilità, contraccezione, endometriosi
e menopausa

"Stress ossidativo e deterioramento cognitivo nell'anziano"

Carlo Cervellati, PhD
Università di Ferrara

Claude Bernard (1813-1878)

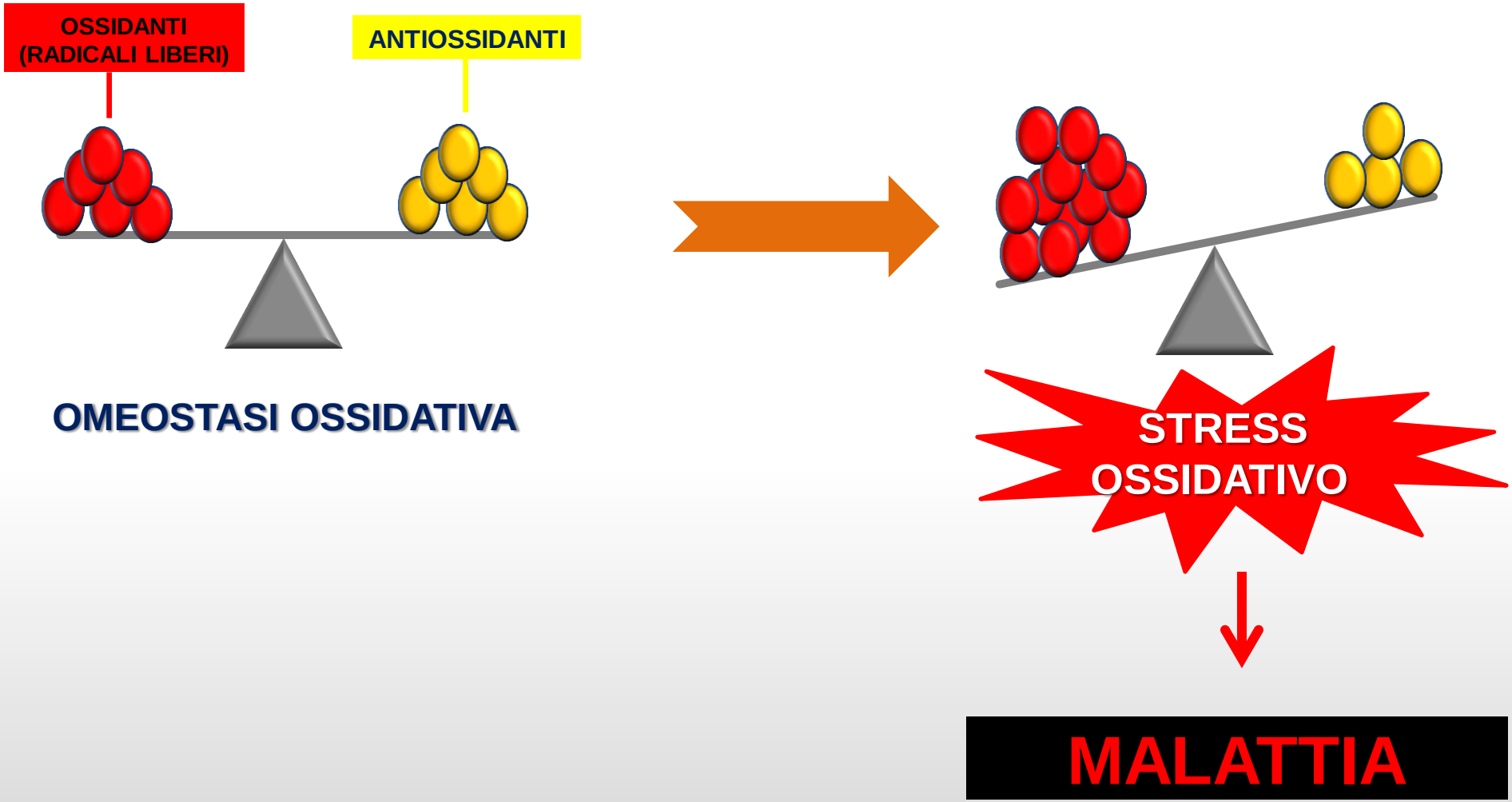
Primo a definire il concetto di «milieu intérieur» (omeostasi) in fisiologia

"è la tendenza naturale al raggiungimento e al mantenimento di una relativa stabilità interna delle proprietà chimico-fisiche, anche al variare delle condizioni esterne….."

Omeostasi del calcio, del sodio, del potassio, del glucosio e…..

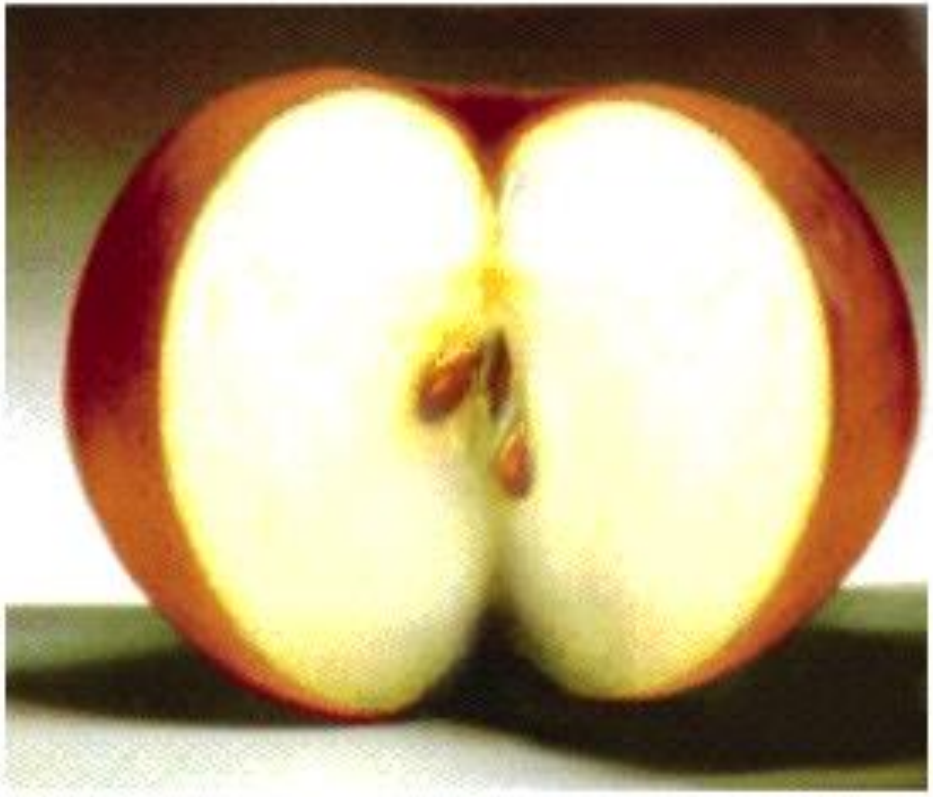
“LO STRESS OSSIDATIVO E’ IL RISULTATO DI UNA DEVIAZIONE DELL’ EQUILIBRIO TRA OSSIDANTI ED ANTIOSSIDANTI”

Sies H. Experimental Physiology, 1997;82:291-295.

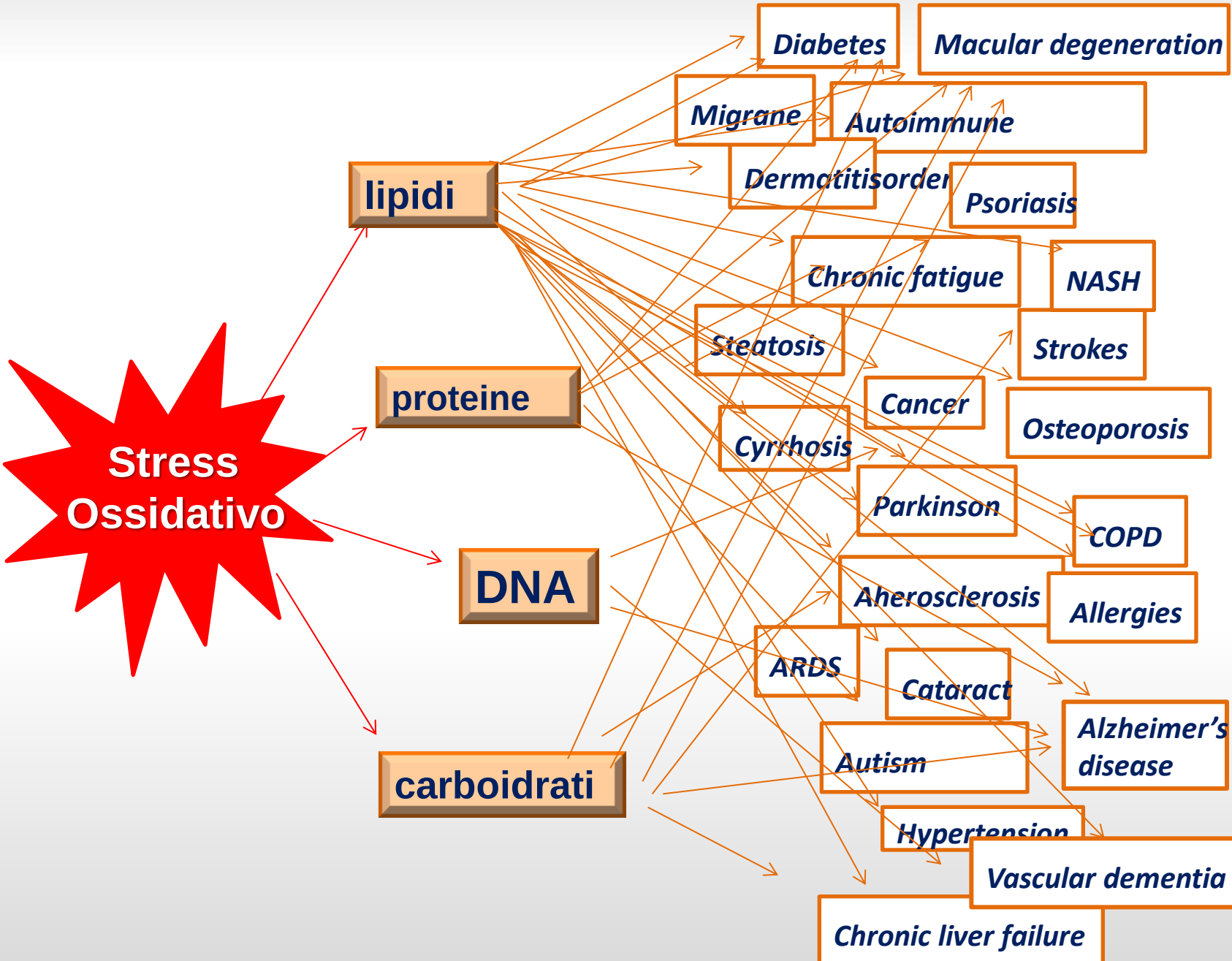


Perché lo stress ossidativo comporta un danno biologico?

OSSIDAZIONE = TRASFORMAZIONE



STRESS OSSIDATIVO: CAUSE & EFFETTI



STRESS OSSIDATIVO: CAUSE & EFFETTI





Stress Ossidativo

AGING

- **lipidi**
- **proteine**
- **DNA**
- **carboidrati**

- Diabetes
- Macular degeneration
- Migrane
- Autoimmune
- Dermatitisorder
- Psoriasis
- Chronic fatigue
- NASH
- Steatosis
- Strokes
- Cancer
- Osteoporosis
- Cyrrhosis
- Parkinson
- COPD
- Aherosclerosis
- Allergies
- ARDS
- Cataract
- Alzheimer's disease
- Autism
- Hypertension
- Vascular dementia
- Chronic liver failure

Le specie ossidanti sono (soprattutto) radicali liberi

Specie Reattive dell'Ossigeno (ROS)

Specie Reattive dell'Azoto (RNS)

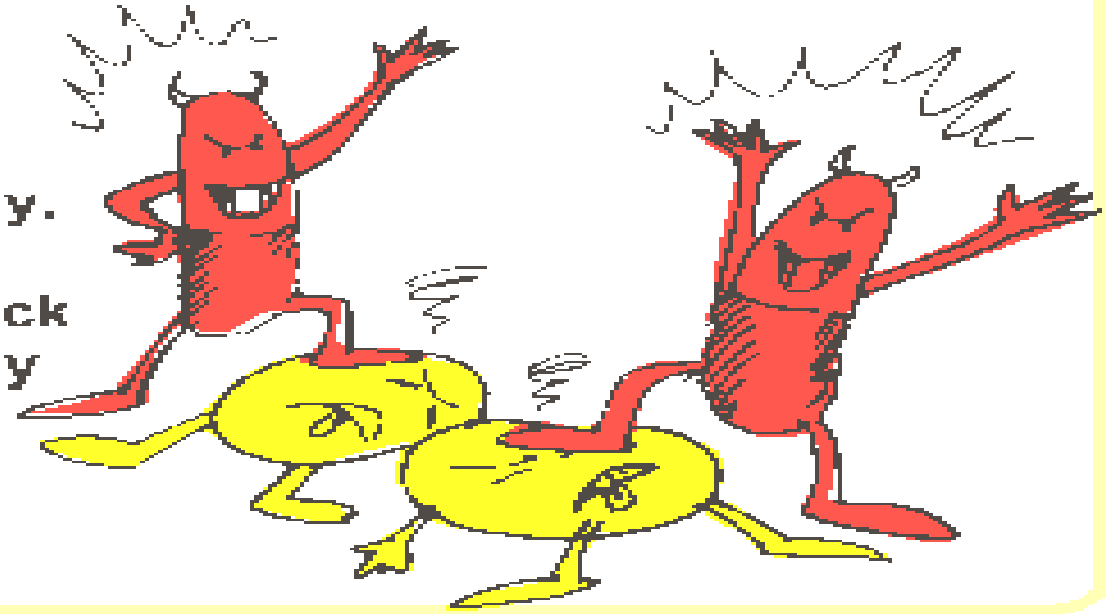
Es: H_2O_2 → **Radicale ossidrile**

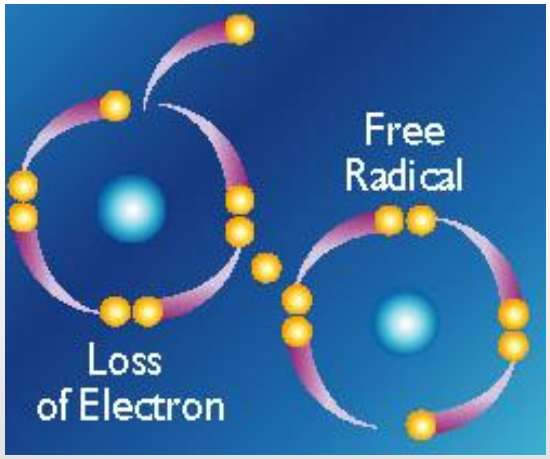
Fe^{2+}

NO → **Radicale perossinitrito**

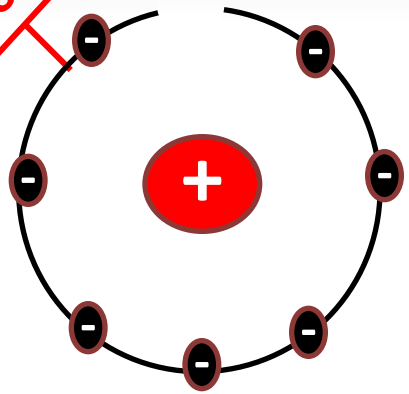
What are Free radicals ?

- Free radicals are like robbers which are deficient in energy.
- Free radicals attack and snatch energy from the other cells to satisfy themselves.





Radicale libero



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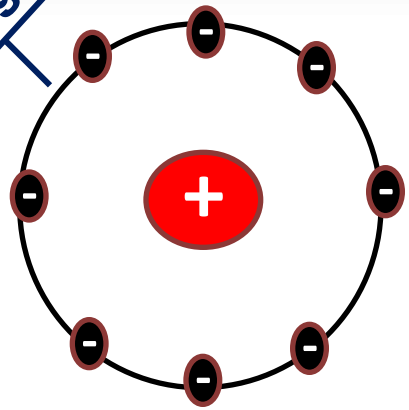
Molecola biologica



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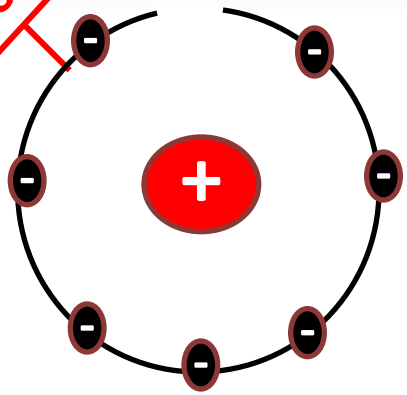

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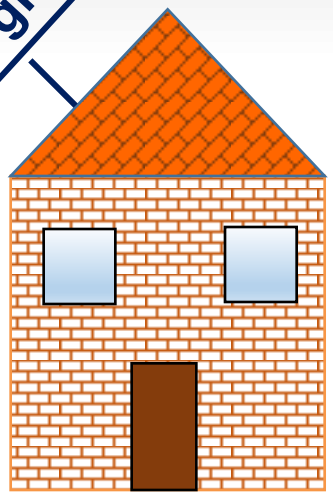

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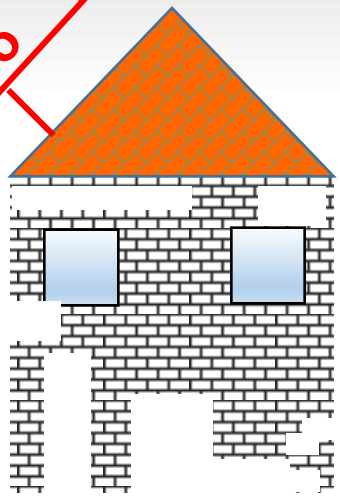

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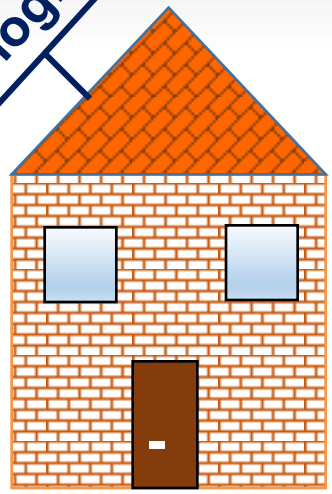
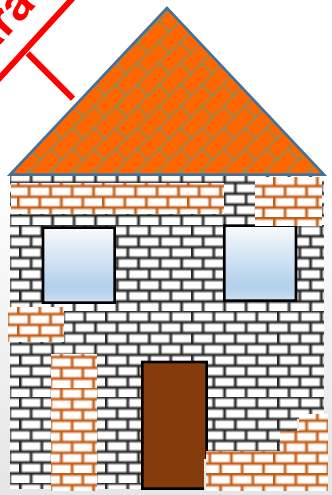


OSSIDAZIONE

Radicale «riparato»



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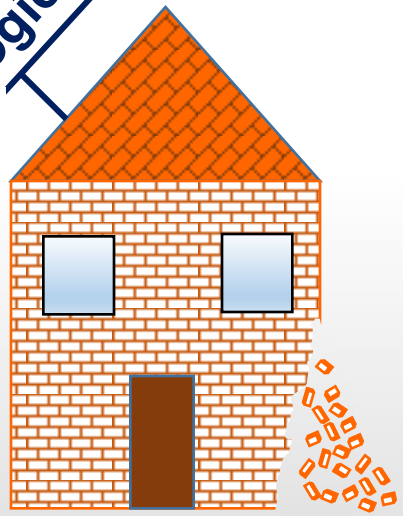
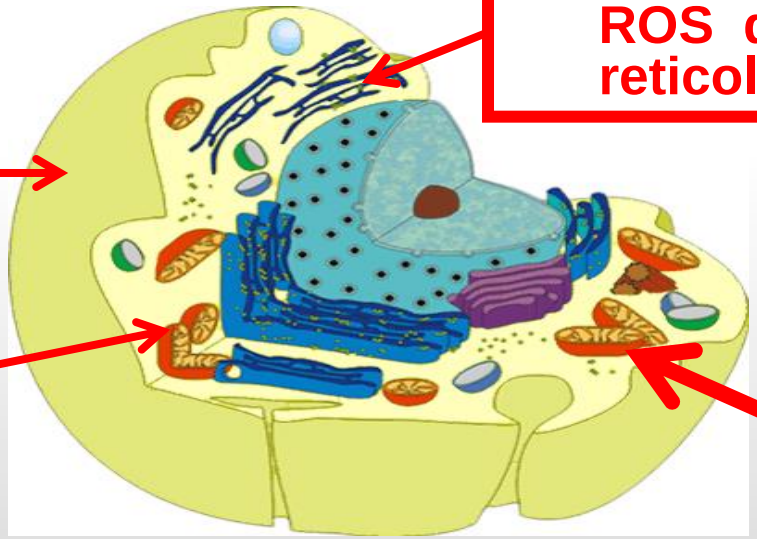
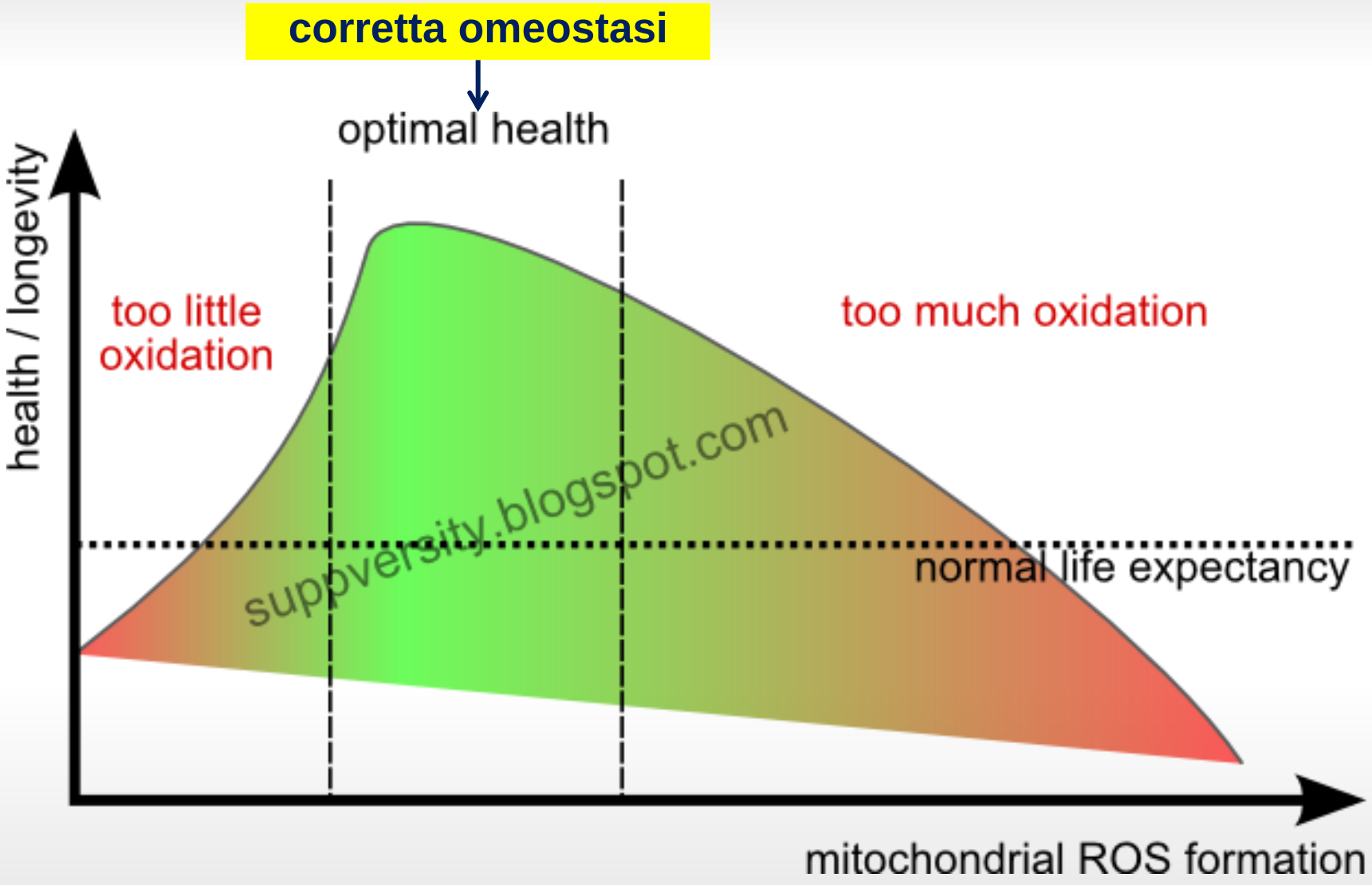


Un soggetto sano di 30 anni

trasforma ogni giorno il 2-3 % dell'ossigeno che respira in radicali liberi

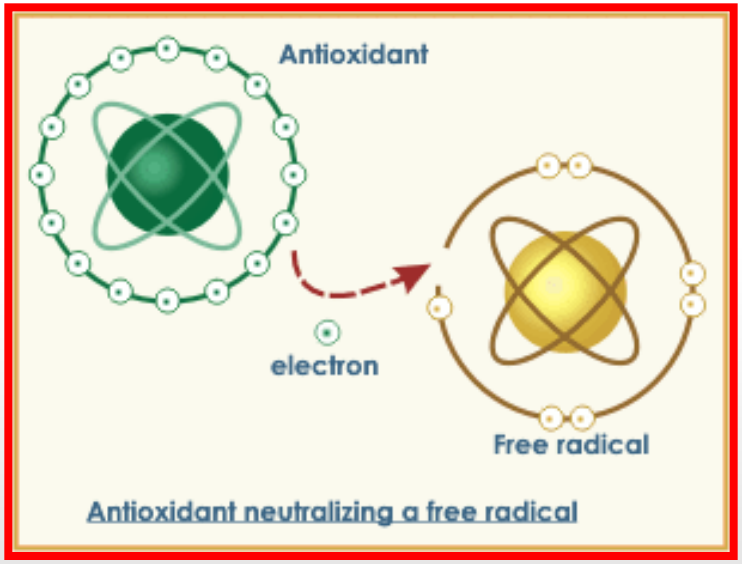
INVECCHIAMENTO



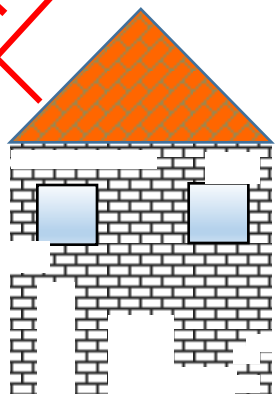

corretta omeostasi
optimal health
health / longevity
too little oxidation
too much oxidation
normal life expectancy
suppversity.blogspot.com
mitochondrial ROS formation

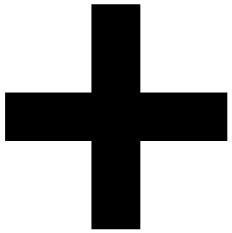
ANTIOSSIDANTI

Proteggono la cellula/organismo dal danno ossidativo



Radicale libero





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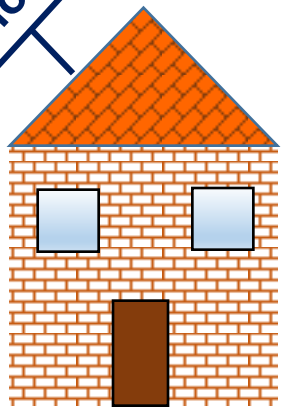
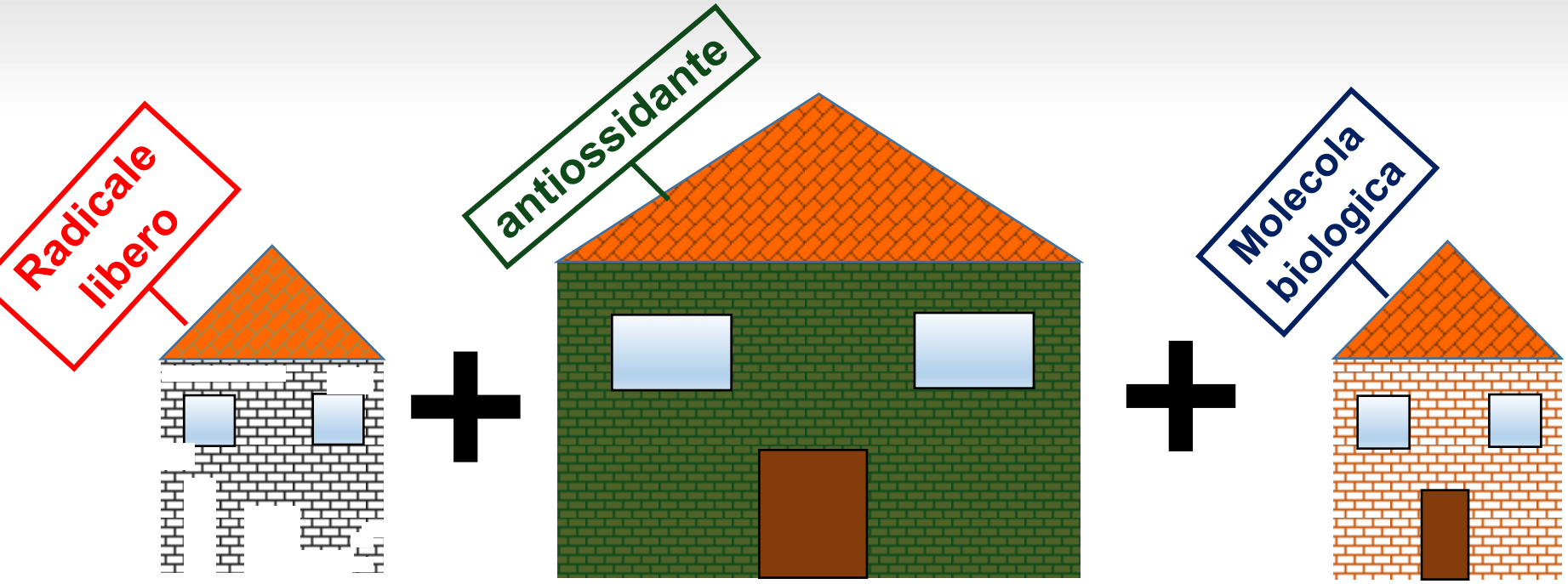
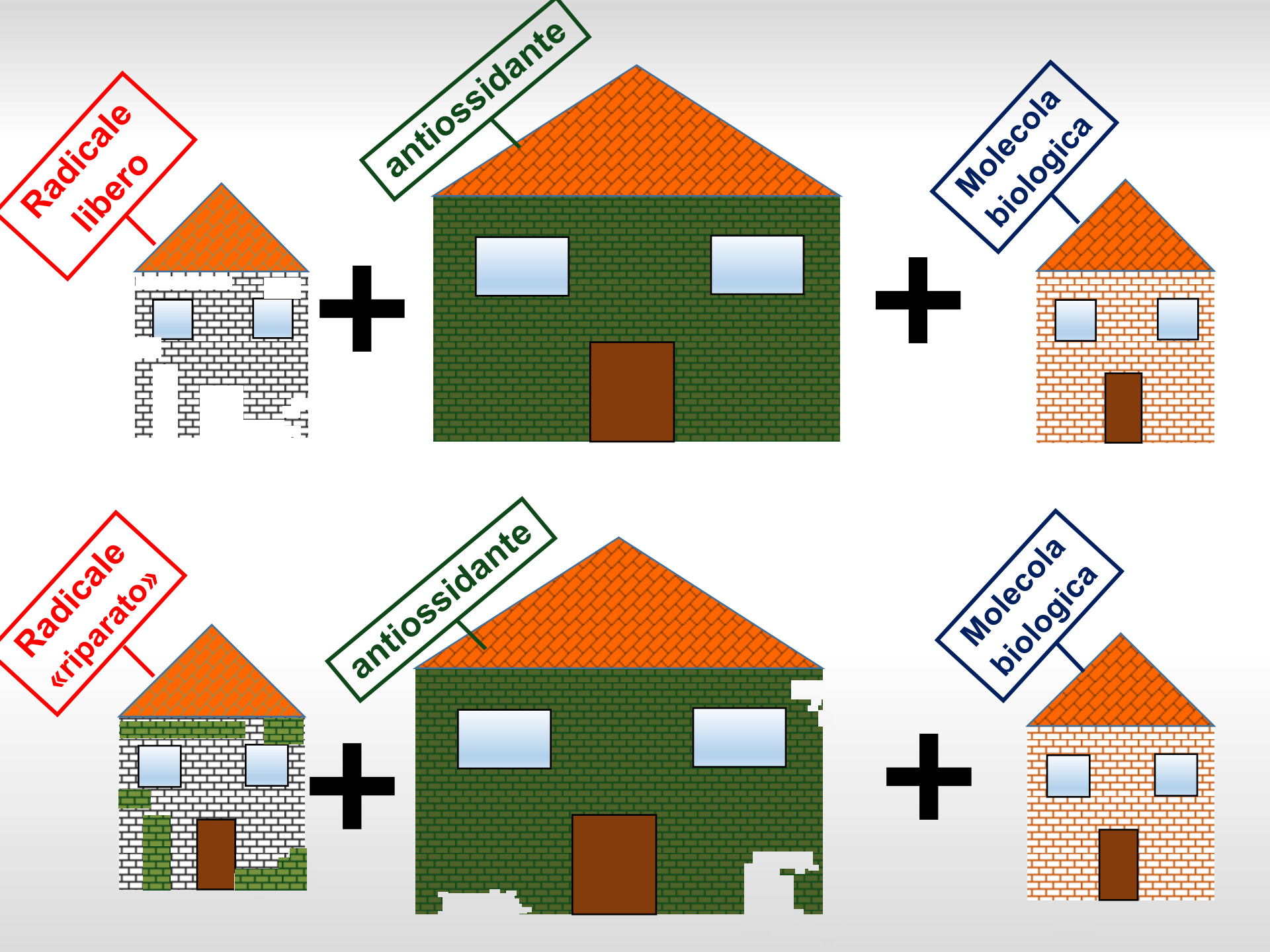



Radicale libero
antiossidante
Molecola biologica


Radicale libero
antiossidante
Molecola biologica
Radicale «riparato»
antiossidante
Molecola biologica

DIFESA ANTIOSSIDANTE

DIFESA ACQUISITA

Vitamina E

Vitamina C

Beta-carotene

Flavonoidi

PUFA

DIFESA INNATA

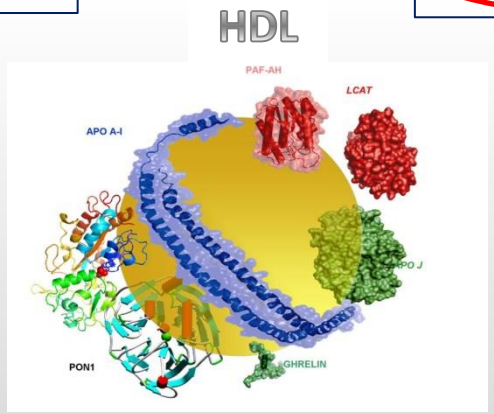
Enzimi intracellulari

Glutatione

Acido urico

Ceruloplasmina

Paraossonasi



STRESS OSSIDATIVO: CAUSE & EFFETTI





Stress Ossidativo

lipidi

proteine

DNA

carboidrati

Diabetes

Macular degeneration

Migrane

Autoimmune

Dermatitisorder

Psoriasis

Chronic fatigue

NASH

Steatosis

Strokes

Cancer

Osteoporosis

Cyrrhosis

Parkinson

COPD

Aherosclerosis

Allergies

ARDS

Cataract

Alzheimer's disease

Autism

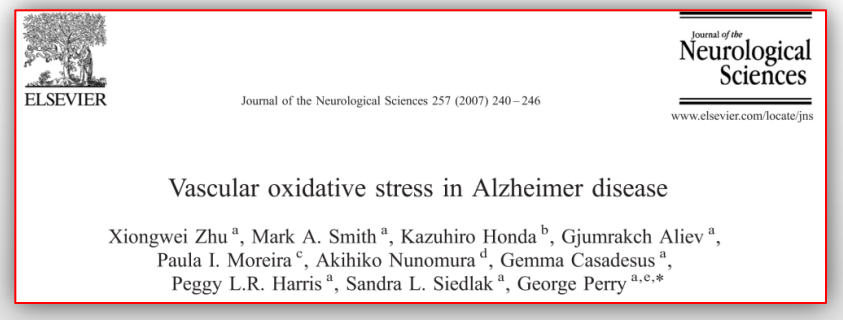
Hypertension

Vascular dementia

Chronic liver failure

ALZHEIMER (AD) & DEMENZA VASCOLARE (VAD)
caratteristiche in comune:

- Fattori di rischio
- Alterazione e danneggiamento dei vasi cerebrali
- Disfunzione dei mitocondri neuronali
- Neuro-infiammazione
- **Stress ossidativo** ⟷



ELSEVIER

Journal of the Neurological Sciences 257 (2007) 240–246

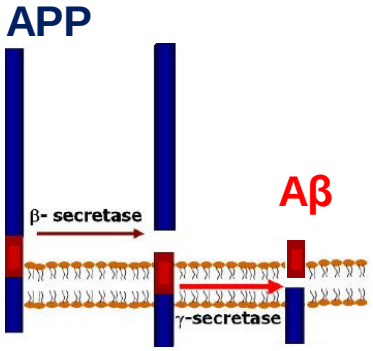
Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Vascular oxidative stress in Alzheimer disease

Xiongwei Zhu [a], Mark A. Smith [a], Kazuhiro Honda [b], Gjumrakch Aliev [a], Paula I. Moreira [c], Akihiko Nunomura [d], Gemma Casadesus [a], Peggy L.R. Harris [a], Sandra L. Siedlak [a], George Perry [a,e,*]

Stress ossidativo in AD



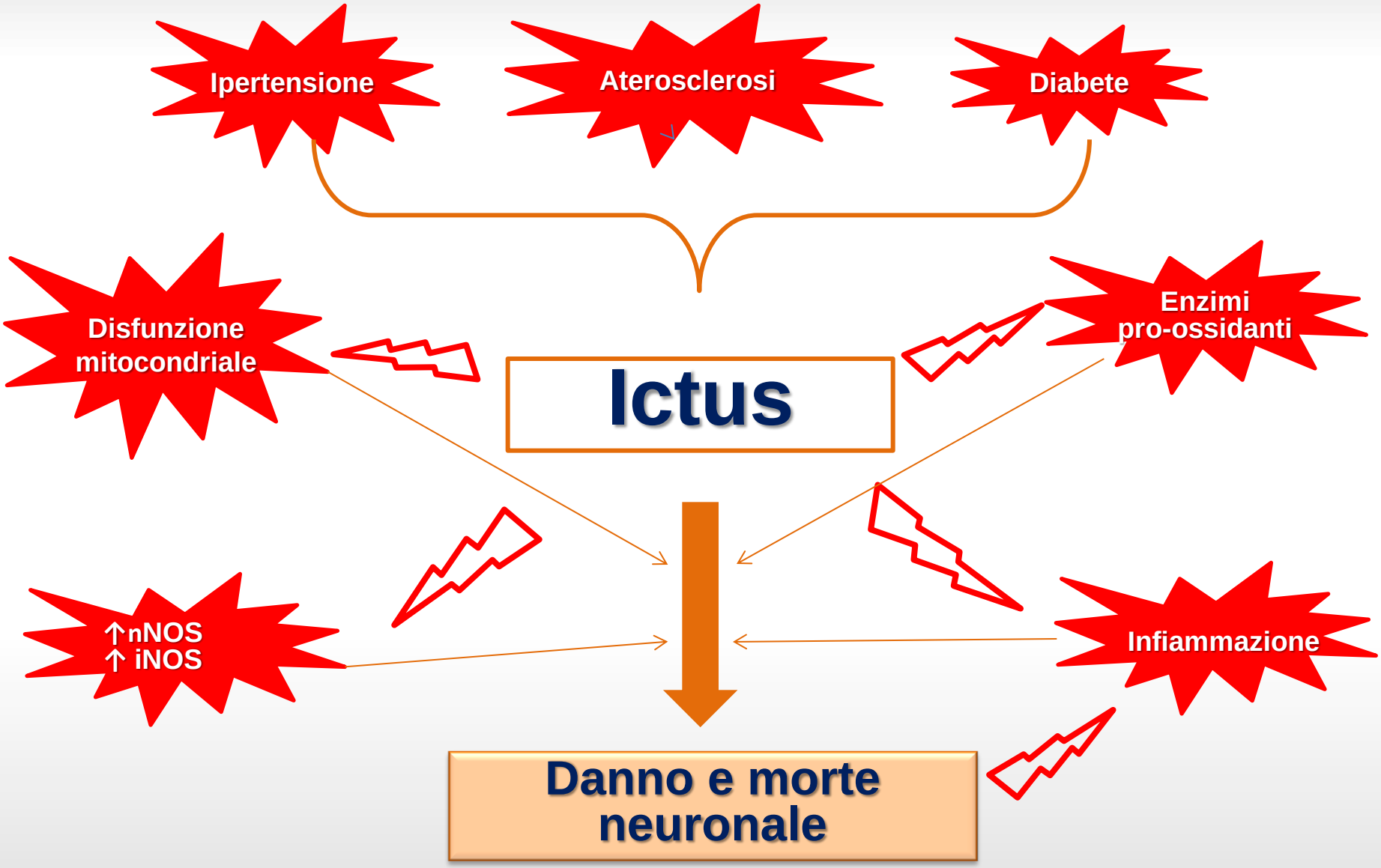
oligomeri
Aß solubili

- Attività enzimatica pro-ossidante
- Induzione di neuroinfiammazione mediante attivazioni cellule gliali
- Inibizione attività enzimi del mitocondrio (disfuzione mitocondriale)

Inoltre il cervello è costitutivamente:

- **Ricco di PUFA**
- **Povero di antiossidanti endogeni**
- **Uno dei tessuti a maggiore consumo di O_2**
- **Ricco di ferro**

Stress ossidativo in VAD

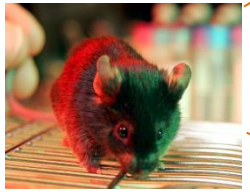


STRESS OSSIDATIVO vs AD & VAD: prove sperimentali

Opazo C. et all. **Metalloenzyme-like activity of Alzheimer's disease beta-amyloid. Cu-dependent catalytic** conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H(2)O(2)., AIJ Biol Chem. 2002 ;277(43):40302-8.

Abramov AY. et al. The role of **an astrocytic NADPH oxidase in the neurotoxicity of amyloid beta peptides**. Philos Trans R Soc Lond B Biol Sci. 2005;360(1464):2309-14

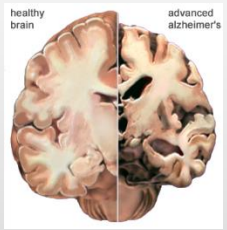
. Smith MA et al. **Amyloid-beta deposition in Alzheimer transgenic mice is associated with oxidative stress**. J Neurochem. 1998;70(5):2212-5



Conte V et al. **Vitamin E reduces amyloidosis and improves cognitive function** in **Tg2576** mice following repetitive concussive brain injury. J Neurochem. 2004;90(3):758-64.

Yan SD et al. Mitochondrial dysfunction and Alzheimer's disease: **role of amyloid-beta peptide alcohol dehydrogenase (ABAD)**. Int J Exp Pathol. 2005 ;86(3):161-71.

Park L et al. **NADPH-oxidase-derived reactive oxygen** species mediate the cerebrovascular dysfunction induced by the amyloid beta peptide. J Neurosci. 2005 16;25(7):1769-77



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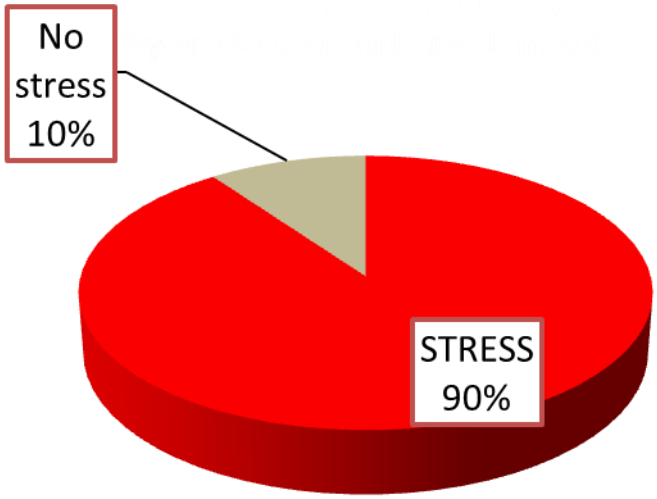
Mecocci, U. et al. Oxidative damage to **mitochondrial DNA** is increased in Alzheimer's disease, Ann. Neurol.1994;36:747–751

…e gli studi di popolazione??

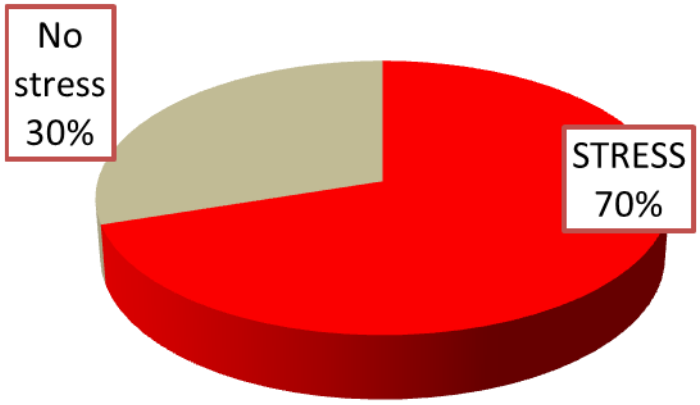
% di studi *in vitro* (e *postmortem*) o *in vivo* (su uomo) che riportano un associazione tra stress ossidativo e AD/VAD

stress ossidativo in AD or VAD > controlli

stress ossidativo in AD or VAD = controlli



STUDI *IN VITRO* O *POSTMORTEM*



STUDI *IN VIVO*

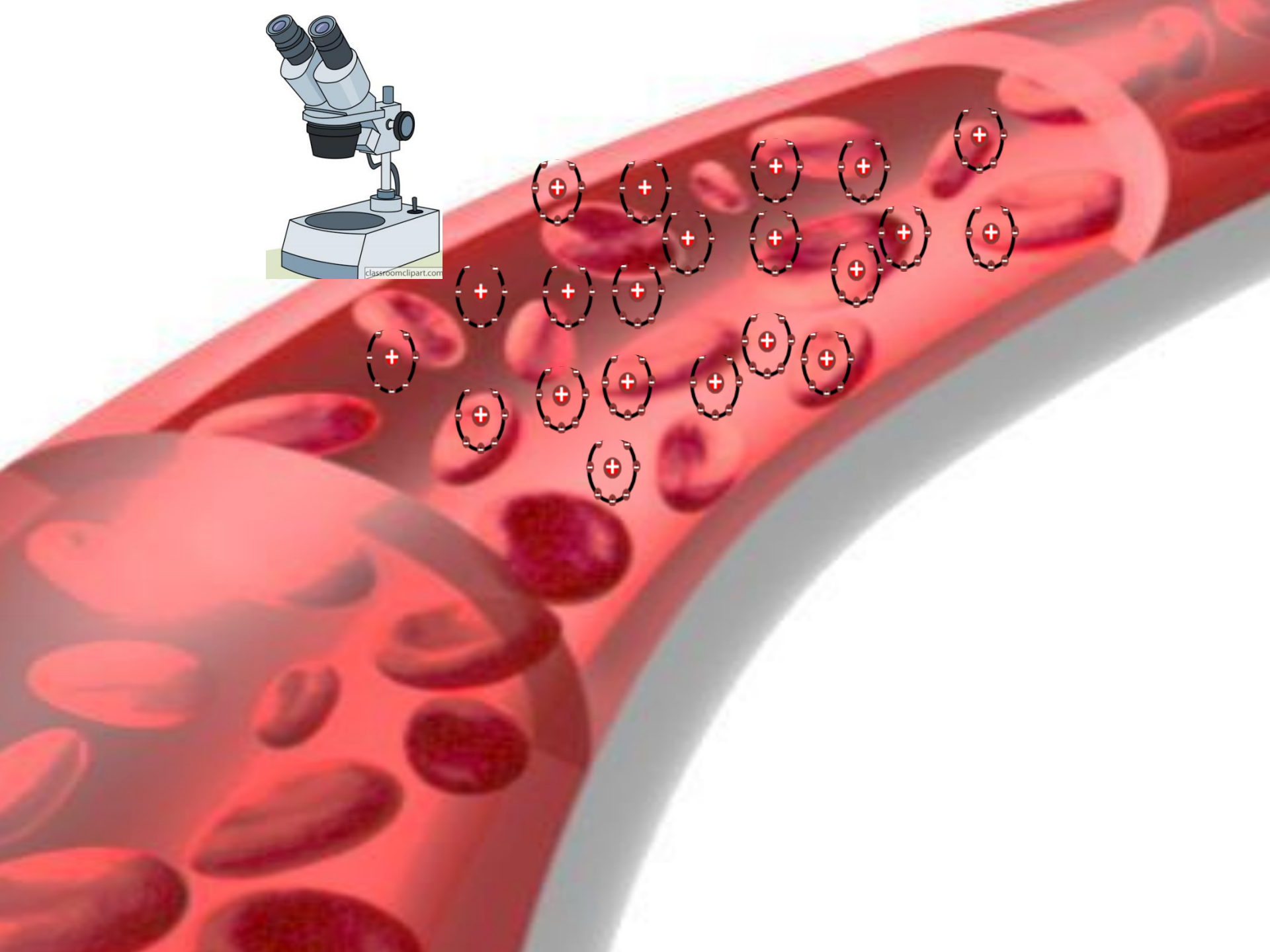
I RISULTATI DEGLI STUDI DI POPOLAZIONE FINORA CONDOTTI SONO CONTRASTANTI…..PERCHE'?

1) PROBLEMI «TECNICI» NEL DOSAGGIO DELLO STRESS OSSIDATIVO NEI FLUIDI PERIFERICI

- **La valutazione *in vivo* dei radicali liberi è impraticabile**
- **Vi sono tanti marcatori dello stress ossidativo e nessuno di essi è stato ancora validato né clinicamente né analiticamente**

2) LIMITAZIONI DEGLI STUDI FINORA PUBBLICATI

- **La misura del marcatore del danno ossidativo è stato solo raramente accompagnato dal dosaggio della componente antiossidante**
- **Bassa numerosità del campione**
- **Mancato controllo per potenziali fattori interferenti**
- **Mancanza di studi longitudinali**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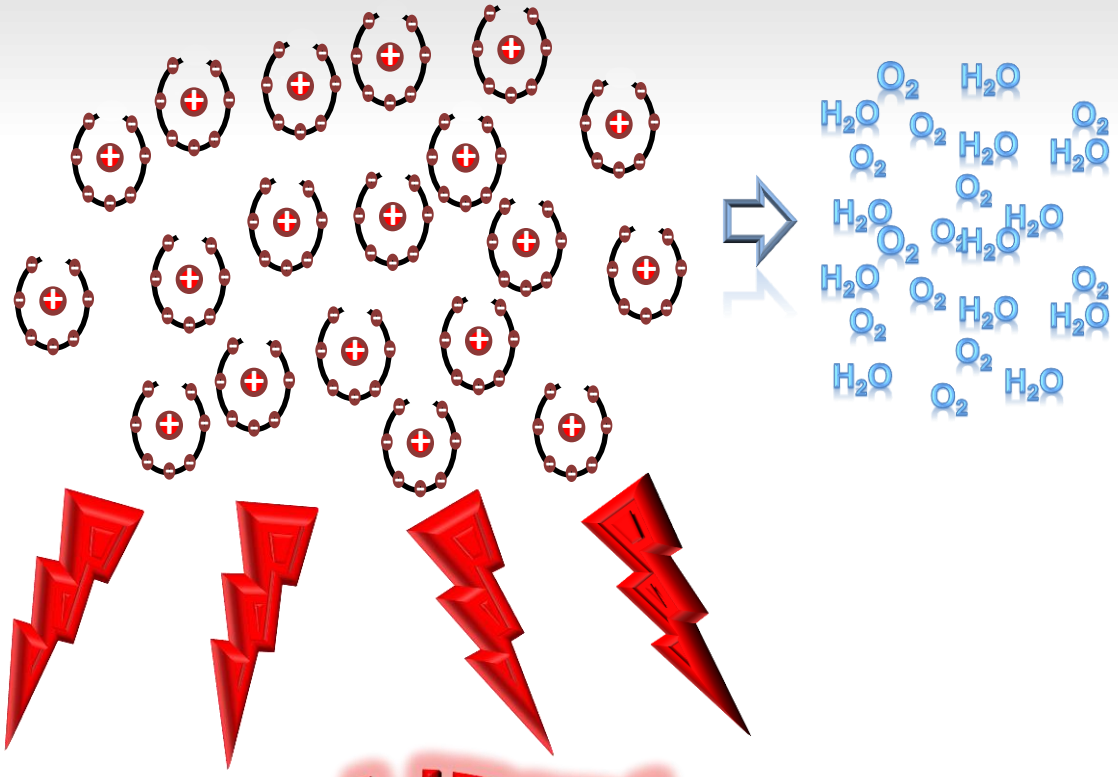
RADICALI LIBERI



OSSIDAZIONE

MOLECOLE BIOLOGICHE

PROTEINE

DNA

LIPIDI

CARBOIDRATI

PRODOTTI OSSIDAZIONE

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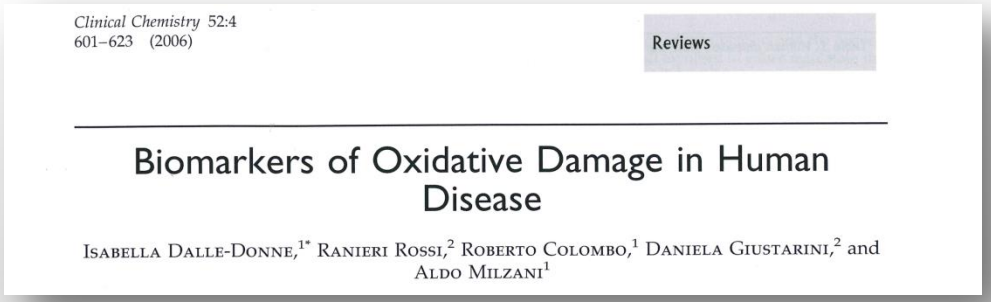
Ad oggi nessuno dei marcatori dello stress ossidativo si è dimostrato essere:

«è una caratteristica oggettivamente misurabile e valutabile come indicatore di un normale processo biologico, un processo patogenico o una risposta farmacologica ad una terapia»

Soprattutto perchè :

Nessun marcatore è stato ancora inserito in un TRIAL clinico interventistico basato sull'uso di antiossidanti

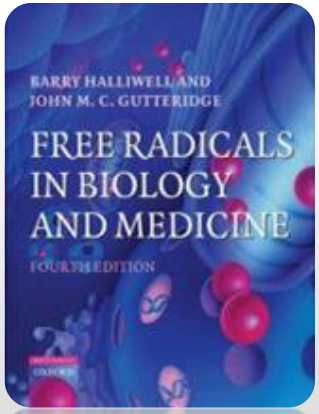

Clinical Chemistry 52:4
601–623 (2006)

Reviews

Biomarkers of Oxidative Damage in Human Disease

Isabella Dalle-Donne,[1*] Ranieri Rossi,[2] Roberto Colombo,[1] Daniela Giustarini,[2] and Aldo Milzani[1]

&



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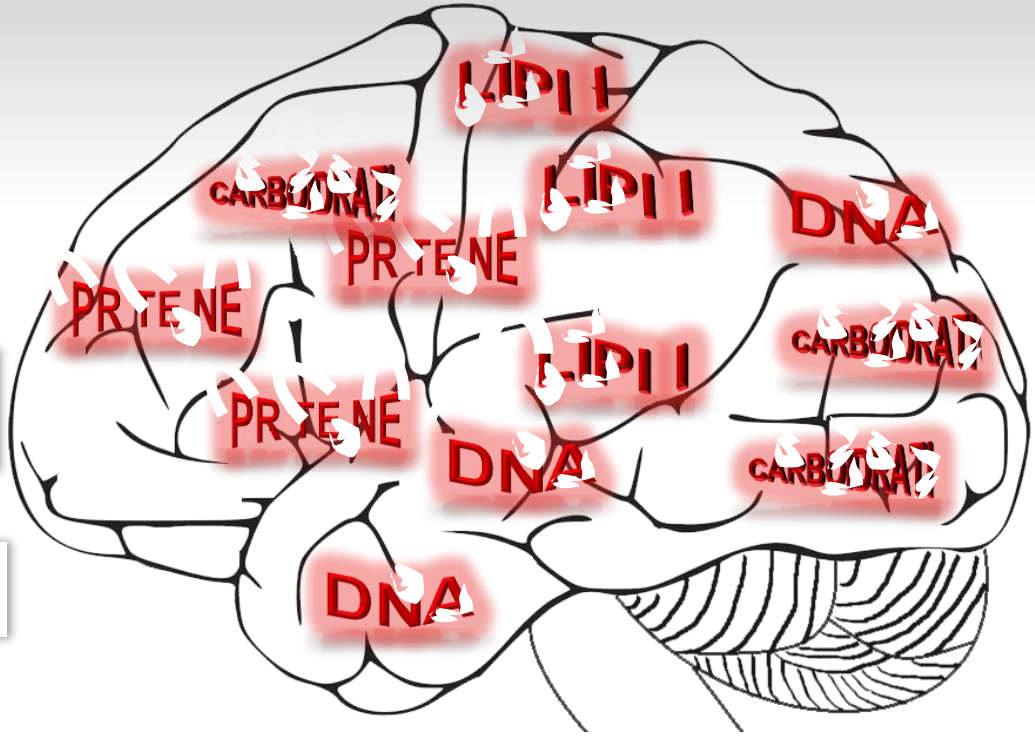

C.E. Teunissen, et al. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiogy of aging. 2002

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Marksbery WR et al. Lipid peroxidation is an early event in the brain in amnestic mild cognitive impairment. Ann Neurol. 2005.

Circolo sistemico

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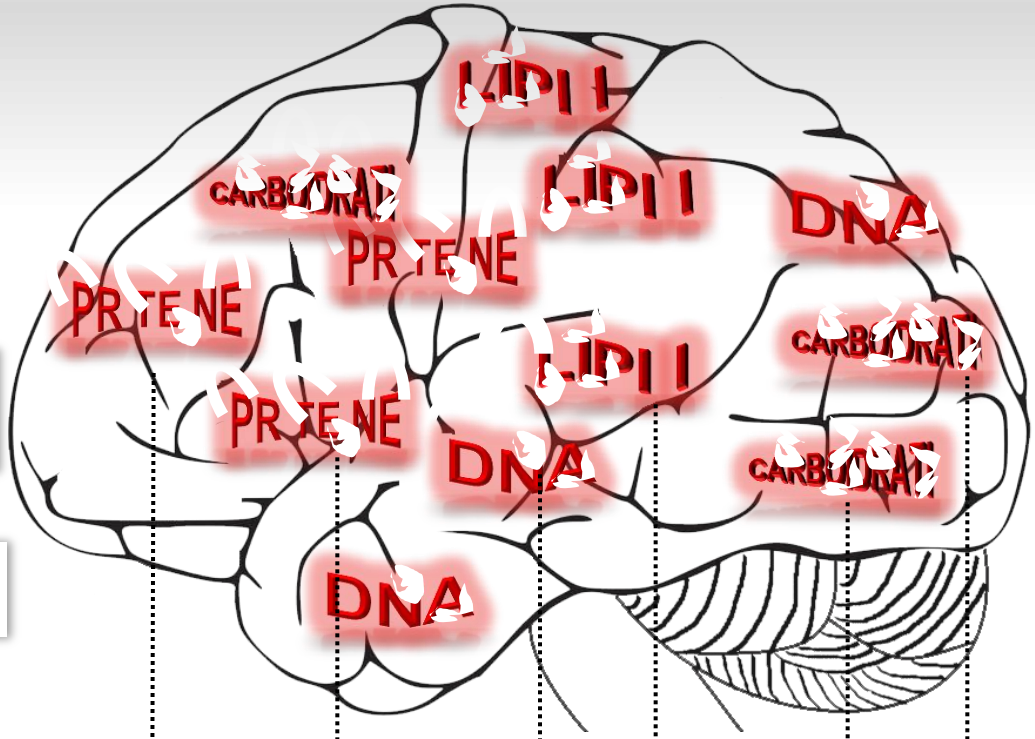

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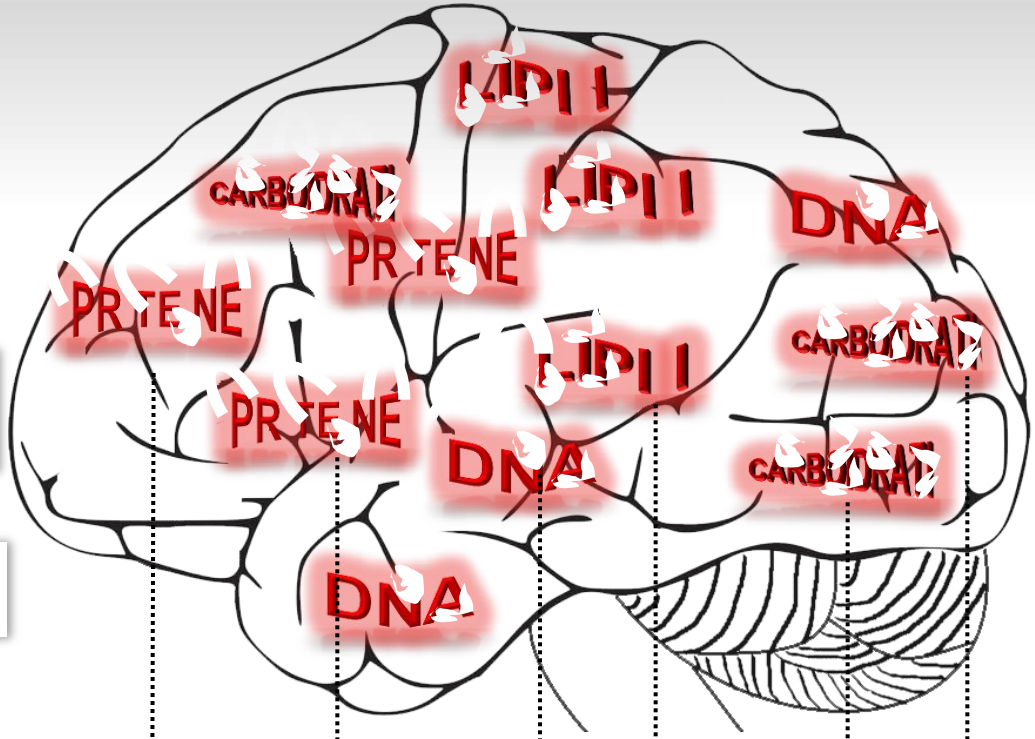

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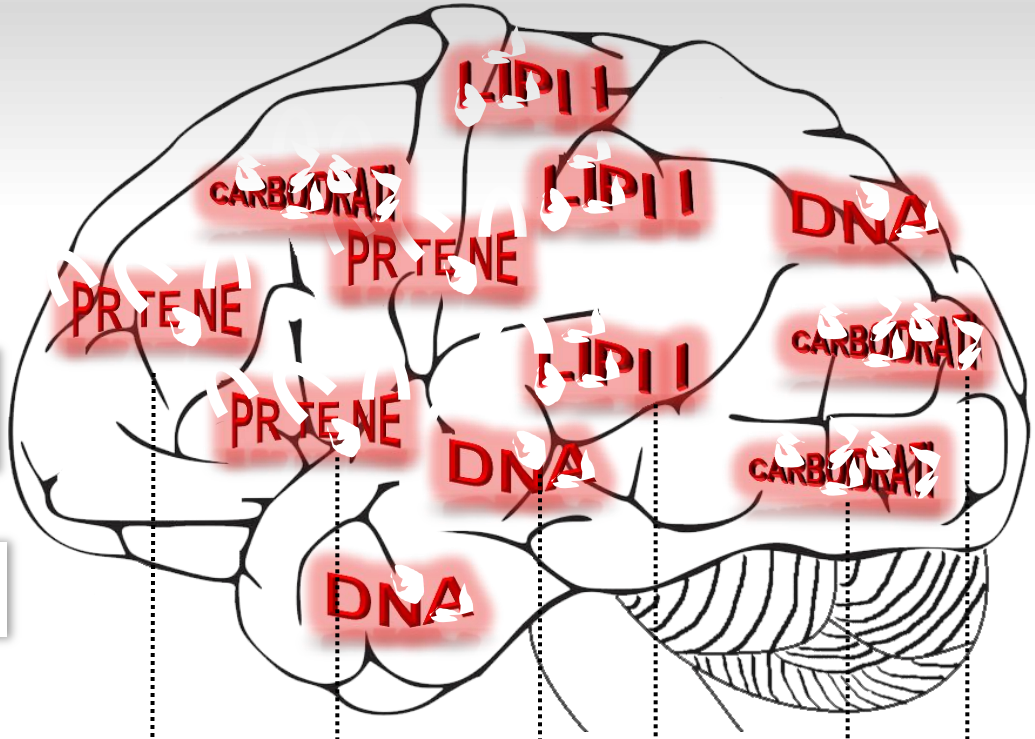

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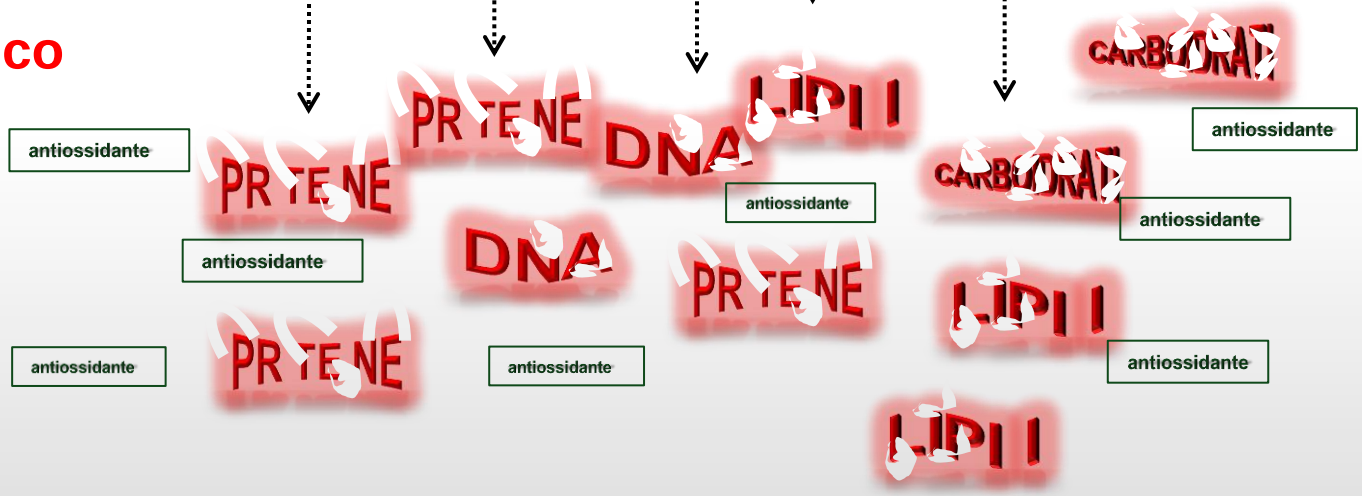


I RISULTATI DEGLI STUDI DI POPOLAZIONE FINORA CONDOTTI SONO CONTRASTANTI…..PERCHE'?

1) PROBLEMI «TECNICI» NEL DOSAGGIO DELLO STRESS OSSIDATIVO NEI FLUIDI PERIFERICI

- La valutazione *in vivo* dei radicali liberi è impraticabile
- Vi sono tanti marcatori dello stress ossidativo e nessuno di essi è stato ancora validato né clinicamente né analiticamente

2) LIMITAZIONI DEGLI STUDI FINORA PUBBLICATI

- La misura del marcatore del danno ossidativo è stato solo raramente accompagnato dal dosaggio della componente antiossidante
- Bassa numerosità del campione
- Mancato controllo per potenziali fattori interferenti
- Mancanza di studi longitudinali

1. RECLUTAMENTO
&
ESAMI CLINICI
(test neuropsichiatrici, CT, chimica clinica)

- Laboratorio di Geriatria e Gerontologia , IRCCS Casa Sollievo della Sofferenza, Foggia
- Dipartimento di Scienze Mediche, Sezione di Medicina Interna e Cardiorespiratoria, Università di Ferrara

Studio Trasversale

143 HEALTHY
223 MCI
162 AD (LOAD)
65 VAD

476 Soggetti

Studio Longitudinale (follow-up: 2 anni)

92 MCI-MCI
39 MCI-AD
21 MCI-VAD

152 Soggetti

2. Misurazione dei marcatori dello stress ossidativo

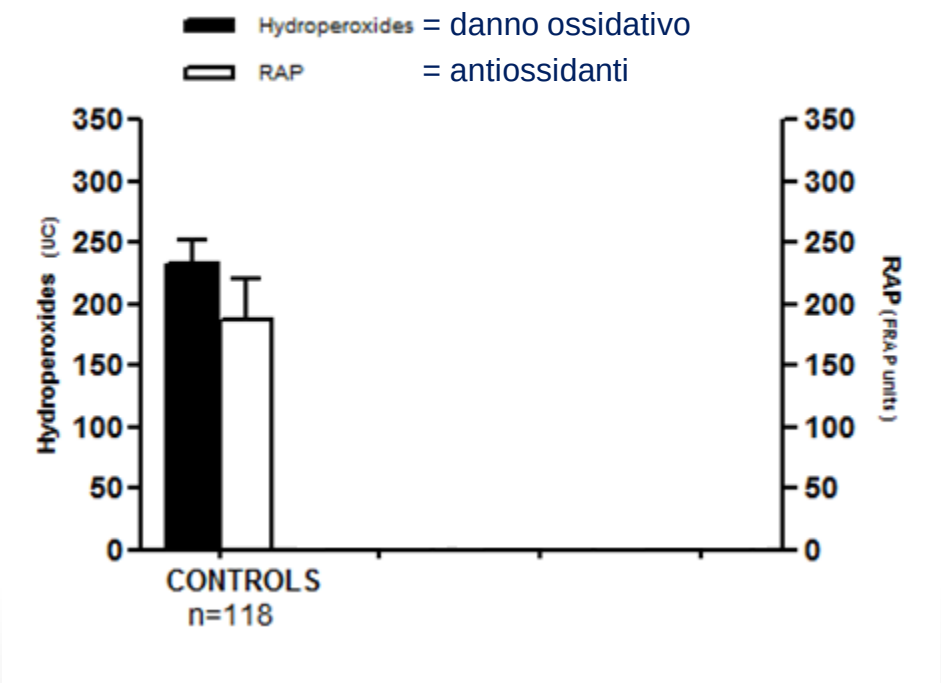
Dipartimento di Scienze Biomediche e Chirurgo Specialistiche, Università di Ferrara

- Idroperossidi
- Omocisteina
- AOPP
- Tioli
- Ferrossidasi
- PON-1
- Acido urico
- Residual antioxidant power (RAP)

CARATTERISTICHE DEL CAMPIONE

	CONTROLS (n=143)	MCI (n=223)	VAD (n=65)	LOAD (n=162)
Age (years)*	68.8 ± 9.3	76.4 ± 6.3[a]	77.7 ± 7.0[a]	78.6 ± 5.6 [a]
Gender (females, %)*	76.9	60.0[a]	54.2[a]	70.4[b]
Education (years)	8 (5-13)	5 (5-8)	5 (4-8)	5 (3-5)
MMSE score**	26.7 (25.2-28.3)	24.4 (22.2-26.7)	24.5 (18.7-23.4)	21.0 (18.4-23.7)
Hypertension (%)*	47.1	58.1[a]	68.5[a]	63.5[a]
Smoking (%)	7.1	8.8	8.5	6.0
Diabetes (%)*	11.0	16.1[a]	32.1[a,b]	13.2[c]
CVD (%)*	10.2	25.5[a]	35.6[a]	14.2[c]
Tot. Chol. (mmol/L)	5.4 (4.7-6.1)	5.3 (4.5-6.0)	5.1 (4.7-5.8)	5.4 (4.8-6.1)
Triglycerides (mmol/L)	1.3 ± 0.7	1.4 ± 0.7	1.3 ± 0.8	1.3 ± 0.5
LDL-C (mmol/L)	3.2 (2.6-3.8)	3.10 (2.6-3.6)	3.4 (2.5-4.4)	3.3 (2.8-4.2)
HDL-C (mmol/L)	1.6 ± 0.5	1.5 ± 0.4	1.5 ± 0.4	1.6 ± 0.4
Hs.CRP (mg/dL)**	0.28 (0.10-0.59)	0.19 (0.10-0.47)	0.30 (0.11-0.61)	0.17 (0.08 -0.04)
Haemoglobin (g/dL)	137 (126-145)	134 (124-143)	133 (120-143)	131 (124-142)
Albumin (g/L)	41.0 (38.2-43.2)	40.0 (38.3-43.4)	40.4 (38.9-43.7)	41.3(38.5-43.3)

DATI TRASVERSALI



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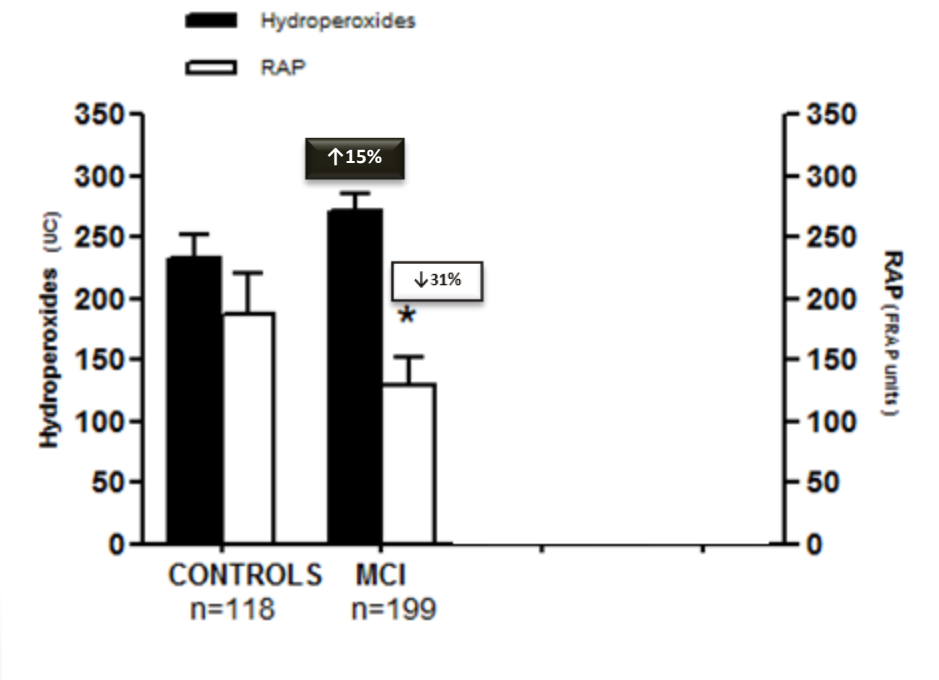
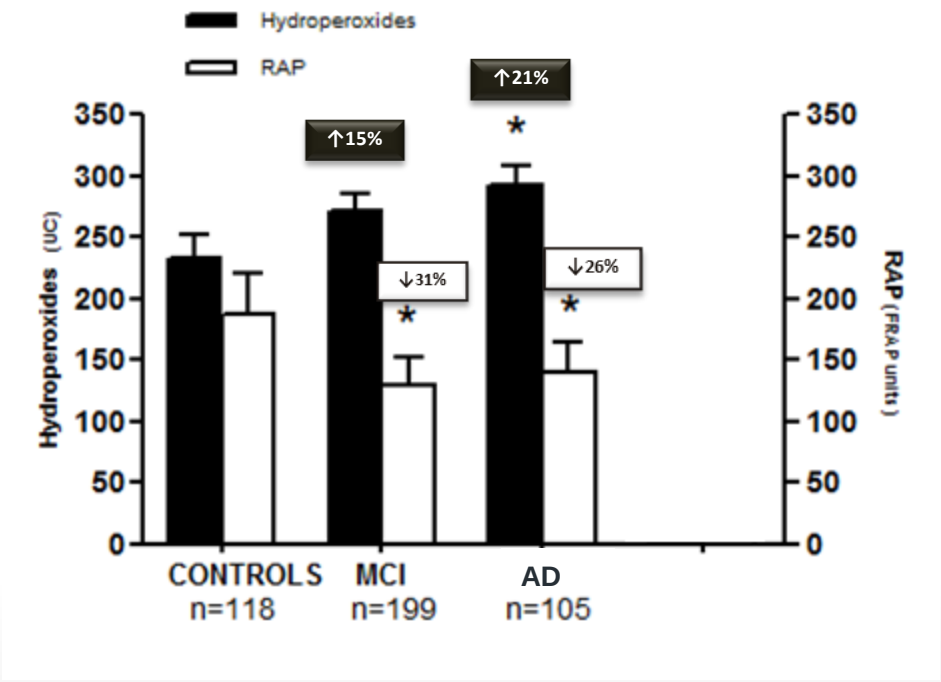


P<0.05 compared to controls
After adjustement for age, smoking and comorbidites

DATI TRASVERSALI



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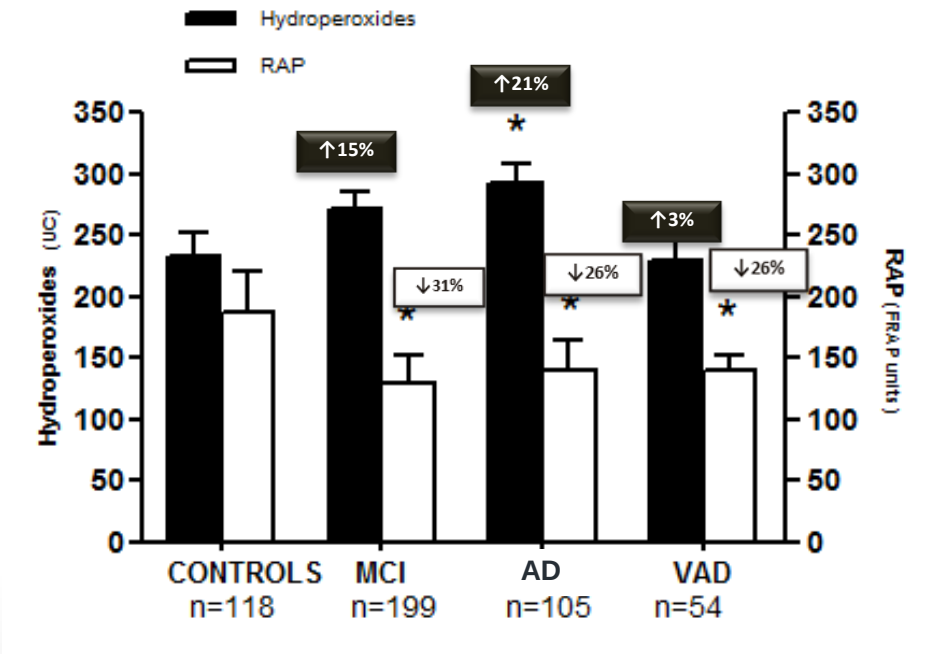


P<0.05 compared to controls
After adjustement for age, smoking and comorbidites

Cervellati C…and Zuliani G. Biomed Research International (2014)

Cervellati C…and Zuliani G. The Journal of Neurological Sciences (2014)

A) Idroperossidi	CONTROLS (OR,95%C.I.)	MCI (OR,95%C.I.)
MCI	2.59 (1.08-6.21)	-
AD	4.09 (1.36-11.81)	1.71 (0.89-3.25)

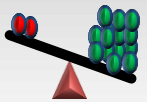
Alti livelli di idroperossidi sono associati ad un progressivo aumento della probabilità di avere MCI or AD rispetto ai controlli
(Dopo aggiustamento per fattori interferenti)

B) RAP	CONTROLS (OR,95%C.I.)	MCI (OR,95%C.I.)
MCI	3.97 (1.62-9.72)	-
AD	2.31 (0.83-6.63)	0.70 (0.35-1.38)

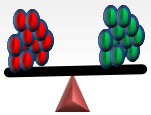
Bassi livelli di antiossidanti sono associati ad un aumento della probabilità di avere MCI o AD, ma solo per MCI questa associazione è significativa
(Dopo aggiustamento per fattori interferenti)

Cervellati C…and Zuliani G. Current Alzheimer Research (2013)

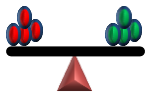
- GROUP I: idroperossidi (danno ossidativo):bassi & ANTIOSSIDANTI:ALTI (ref. group)



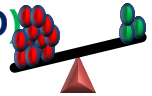
- GROUP II: IDROPEROSSIDI: ALTI & ANTIOSSIDANTI: ALTI



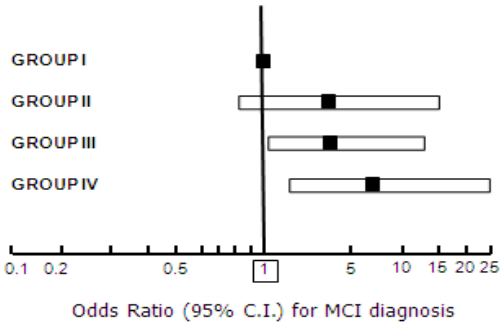
- GROUP III: idroperossidi: bassi & antiossidanti: bassi



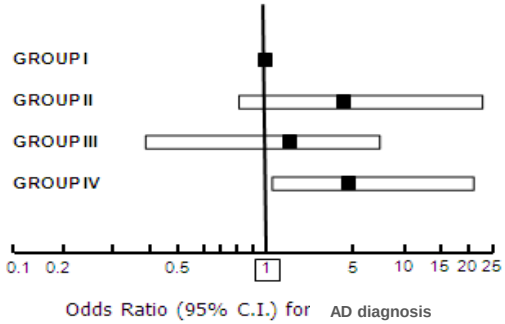
- GROUP IV: IDROPEROSSIDI: ALTI & antiossidanti: bassi (STRESS OSSIDATIVO CONCLAMATO)



A)



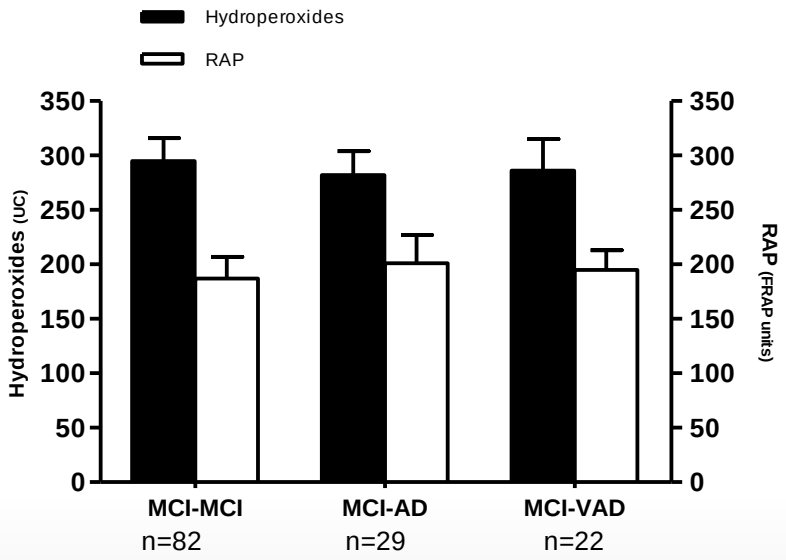
B)



Il rischio per MCI e AD aumenta quando il livello di antiossidanti e prodotti del danno ossidativo cambiano contemporaneamente da un bilancio ossidativo favorevole
(alti antiossidanti -bassi idroperossidi)
verso uno stress ossidativo conclamato
(bassi antiossidanti- idroperossidi alti)

Cervellati C…and Zuliani G. Current Alzheimer Research (2013)

DATI LONGITUDINALI



I livelli "baseline" di stress ossidativo sistemico non sono predittivi della progressione da MCI a AD o VAD

Cervellati C…and Zuliani G. Biomed Research International (2014)

IN CONCLUSIONE…..

- **Il danno da Stress Ossidativo svolge un ruolo importante nella patogenesi di AD e VAD**
- **Tale danno non si limita ai «confini» del CNS ma si riflette, PRECOCEMENTE, a livello periferico**

Journal of Neuropathology and Experimental Neurology
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Vol. 60, No. 8
August, 2001
pp. 759–767

Oxidative Damage Is the Earliest Event in Alzheimer Disease

AKIHIKO NUNOMURA, MD, PHD, GEORGE PERRY, PHD, GJUMRAKCH ALIEV, MD, PHD, KEISUKE HIRAI, PHD, ATSUSHI TAKEDA, MD, PHD, ELIZABETH K. BALRAJ, MD, PAUL K. JONES, PHD, HOSSEIN GHANBARI, PHD, TAKAFUMI WATAYA, MD, SHUN SHIMOHAMA, MD, PHD, SHIGERU CHIBA, MD, PHD, CRAIG S. ATWOOD, PHD, ROBERT B. PETERSEN, PHD, AND MARK A. SMITH, PHD

- **RAP e idroperossidi potrebbero essere marcatori promettenti per la DIAGNOSI di AD (e MCI) e VAD**

TERAPIE CON ANTIOSSIDANTI: CONSIGLI PER GLI ACQUISTI

gli antiossidanti prevengono (raramente riparano) il danno da Stress Ossidativo

- ***Siccome il bilancio ossidativo è già compromesso nei pazienti con MCI, un intervento terapeutico con antiossidanti potrebbe non essere efficacie in questi soggetti***


The NEW ENGLAND JOURNAL of MEDICINE

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

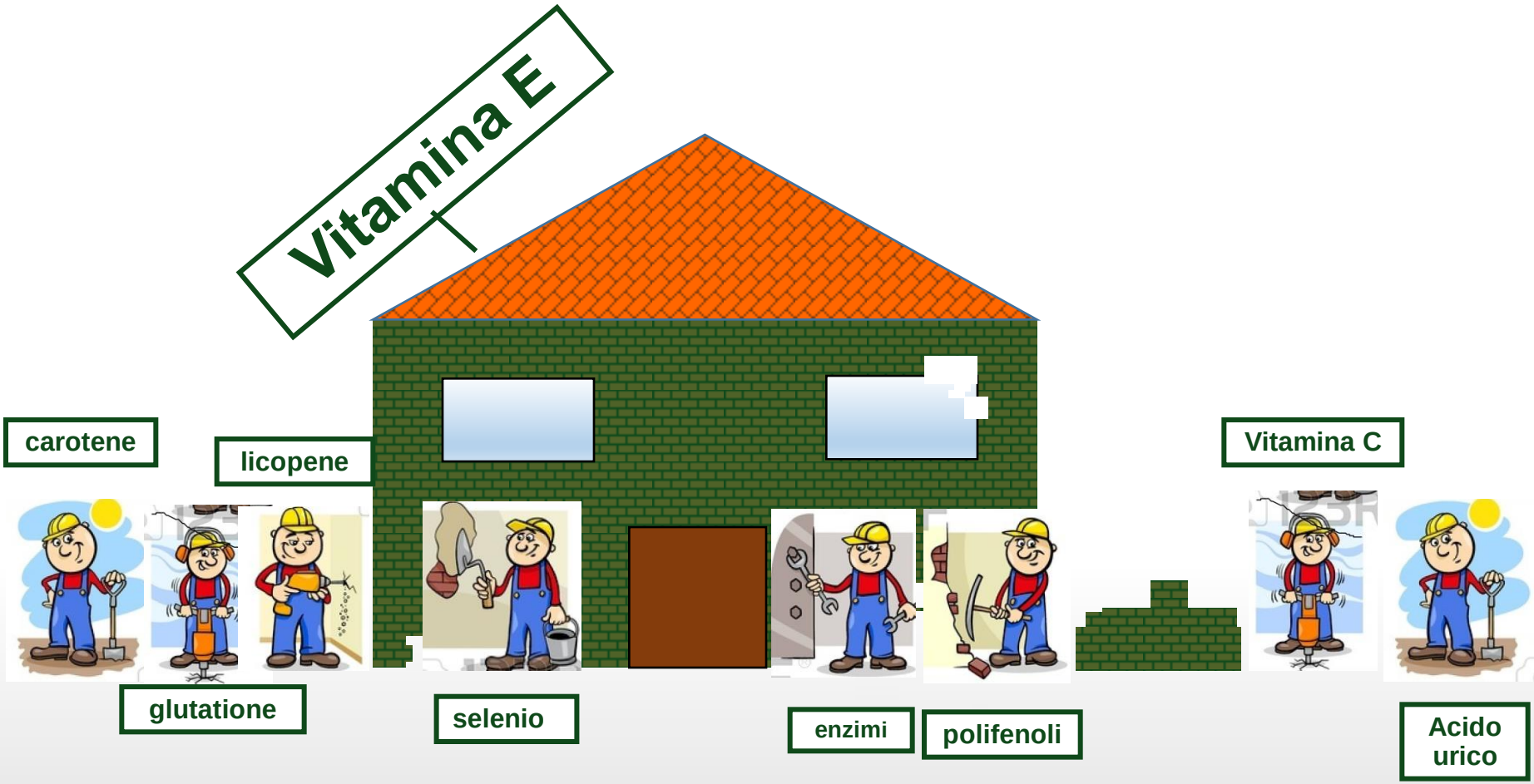
Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

- ***L'intervento con antiossidanti potrebbe essere invece più efficace sui soggetti sani***

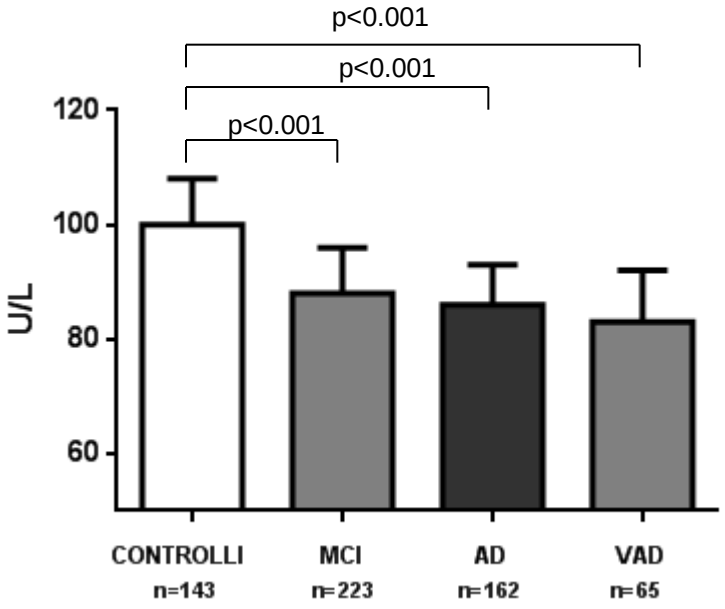
  - individuando le criticità («sbilancio ossidativo», apporto antiossidanti da dieta inadeguato)

  - Tenendo presente gli antiossidanti lavorano in network

Sinergia tra antiossidanti



INOLTRE…..VI SONO CERTI ANTIOSSIDANTI CHE NON SI POSSONO CORREGGERE INTERVENENDO DALL'ESTERNO, ES: PARAOSSONASI



Cervellati C…and Zuliani G. CCLM, under revision

I livelli di Paraossonasi sono più bassi (del 10-15%) nei pazienti con MCI, VAD e AD rispetto ai sani

AKNOWLEDGEMENTS:

My Group:

Prof. Carlo Bergamini

Eleonora Cremonini

Arianna Romani

Monica Squerzanti

Clinicians:

Prof. Giovanni Zuliani

Dr. Davide Seripa

Cristina Bosi

THANKS FOR THE ATTENTION

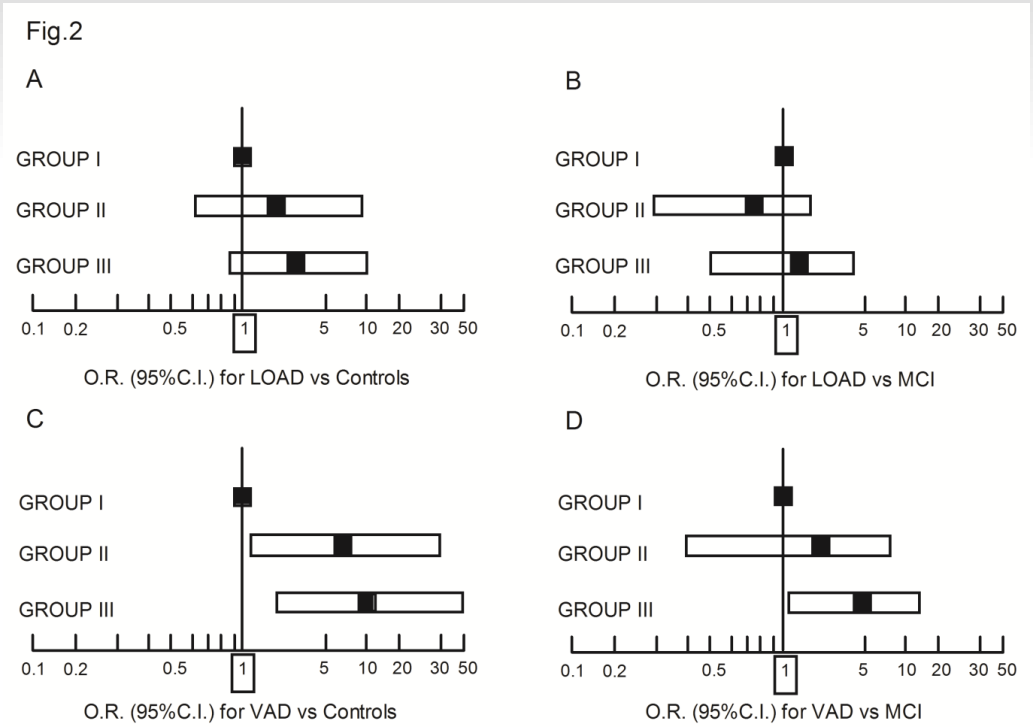


Fig. 2**.** Adjusted odds Ratio (95%C.I.) for the diagnosis of LOAD or VAD compared with CONTROLS or MCI in subjects with: low homocysteine AND uric acid (reference; GROUP I); high uric acid OR homocysteine (GROUP II); high homocysteine AND uric acid (GROUP III). Adjusting covariates: CVD, hypertension, diabetes, smoking, and gender.

Caratteristiche del campione

	CONTROLS (n=143)	MCI (n=223)	VAD (n=65)	LOAD (n=162)
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Triglycerides (mmol/L)	1.3 ± 0.7	1.4 ± 0.7	1.3 ± 0.8	1.3 ± 0.5
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Albumin (g/L)	41.0 (38.2-43.2)	40.0 (38.3-43.4)	40.4 (38.9-43.7)	41.3(38.5-43.3)
Creatinine (µmol/L)	79.2 (70.4-96.8)	79.2 (70.4-96.8)	96.8 (79.2-140.8)	79.2 (61.6-96.8)

* $p<0.05$ ANOVA or *Chi-squared* test (*post-hoc* test: a: $p<0.05$ vs Controls; b: $p<0.05$ vs MCI; c: $p<0.05$ vs VAD)

** $p<0.05$ Kruskal-Wallis

TRIALS WITH ANTIOXIDANTS

diet better than supplements

Priemé H, et al. **No effect of supplementation with vitamin E, ascorbic acid, or coenzyme Q10 on oxidative DNA damag**e estimated by 8-oxo-7,8-dihydro-2'-deoxyguanosine excretion in smokers. Am J Clin Nutr. 1997;65(2):503-7.

VS

Verhagen H et al. **Reduction of oxidative DNA-damage in humans by brussels sprouts.** Carcinogenesis. 1995 ;16(4):969-70

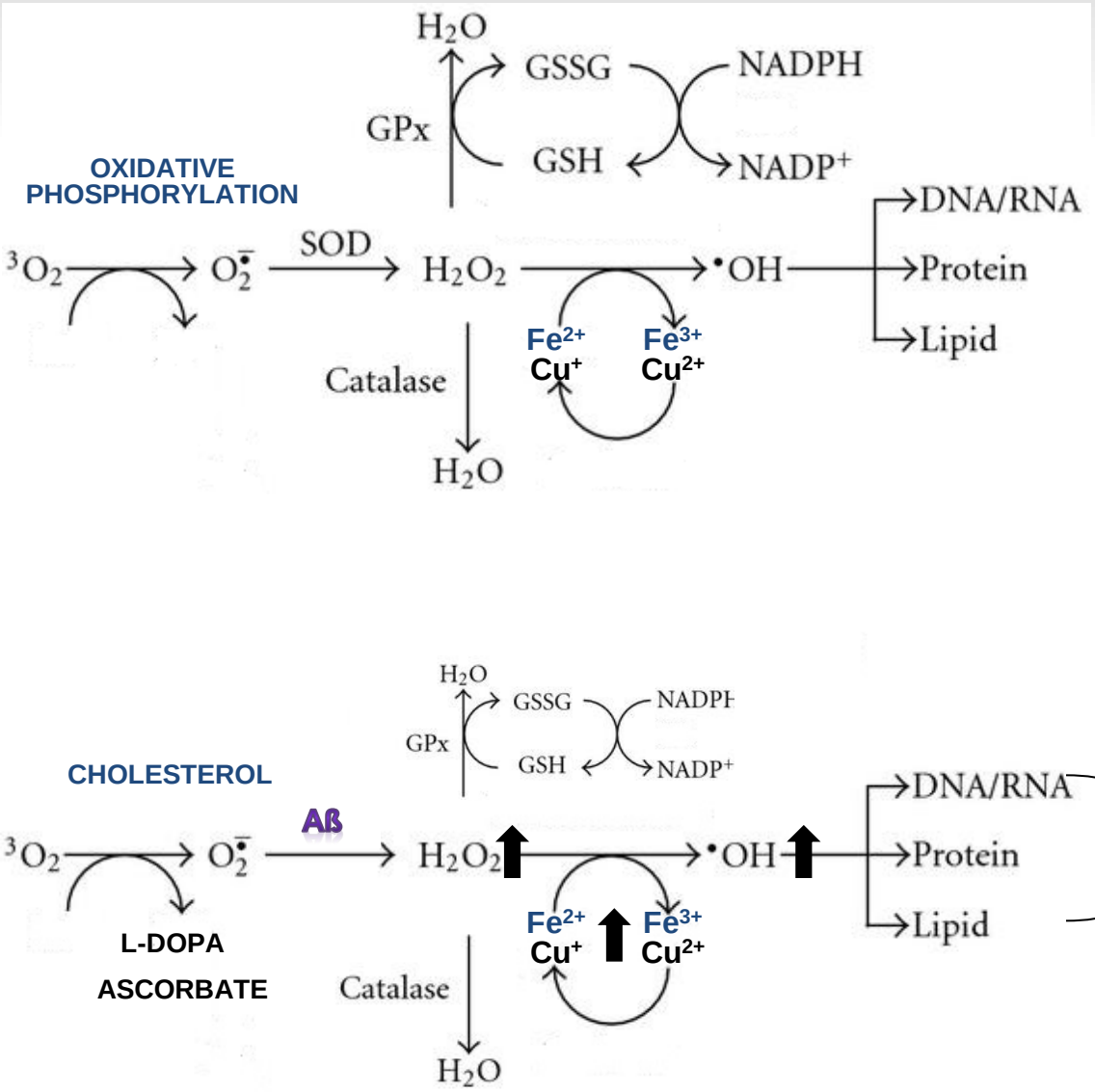
Intervention trials with antioxidants
«a state of CHAOS»

Stephens NG et al. **Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS).** Lancet. 1996 23;347(9004):781-6

Gey KF. **Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology.** Am J Clin Nutr. 1991;53:326S-334S

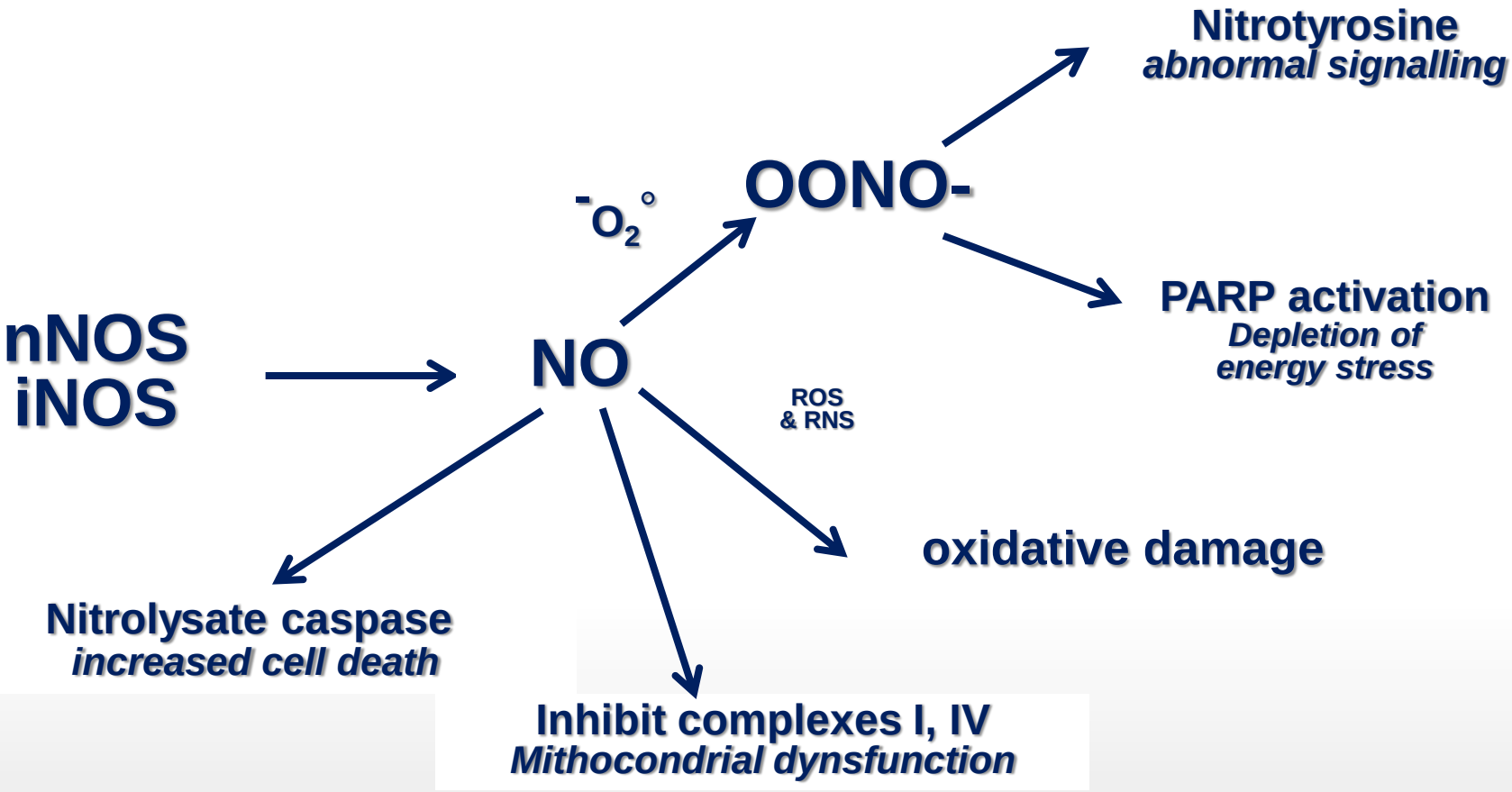
Galasko DR. et al. **Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures.** Arch Neurol. 2012 Jul;69(7):836-41

Sano M. et al. **A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. .** N Engl J Med. 1997 Apr 24;336(17):1216-22



INSIDE THE MITHOCONDRIA IN A NORMALLY FUNCTIONINIG CELLS

Toxic effects of NO following ischemia



Montine TJ, Quinn JF, Milatovic D, Silbert LC, Dang T, Sanchez S, Terry E, Roberts LJ 2nd, Kaye JA, Morrow JD.
***Peripheral F2-isoprostanes and F4-neuroprostanes are not increased in Alzheimer's disease**.*
Ann Neurol. 2002;52(2):175-9

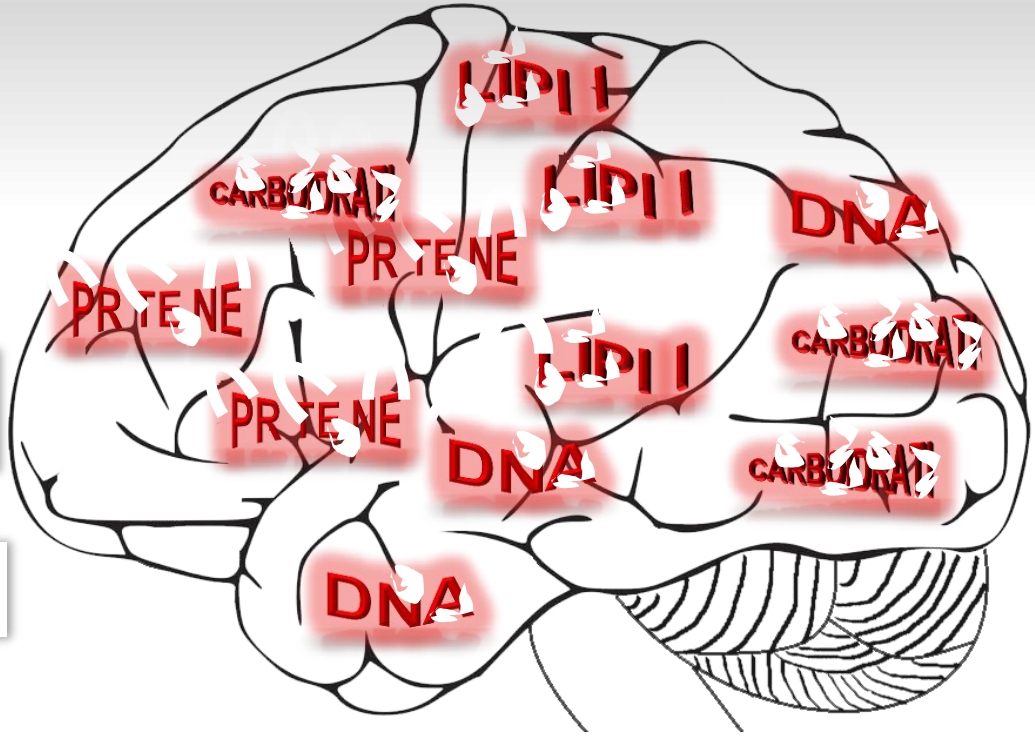
Praticò D, Clark CM, Lee VM, Trojanowski JQ, Rokach J, FitzGerald GA.
***Increased 8,12-iso-iPF2alpha-VI in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity**.*
Ann Neurol. 2000;48(5):809-12.

Ipotesi di partenza

Bradley MA et al. Increased levels of **4-hydroxynonenal and acrolein** in the brain in preclinical Alzheimer disease. Free Radic Biol Med 2010

Yao Y et al. Enhanced brain levels of **8,12-iso-iPF2alpha-VI** differentiate AD from frontotemporal dementia. Neurology. 2003

Mecocci, U. et al. Oxidative damage to **mitochondrial DNA** is increased in Alzheimer's disease, Ann. Neurol.1994;



C.E. Teunissen, et al. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiogy of aging. 2002

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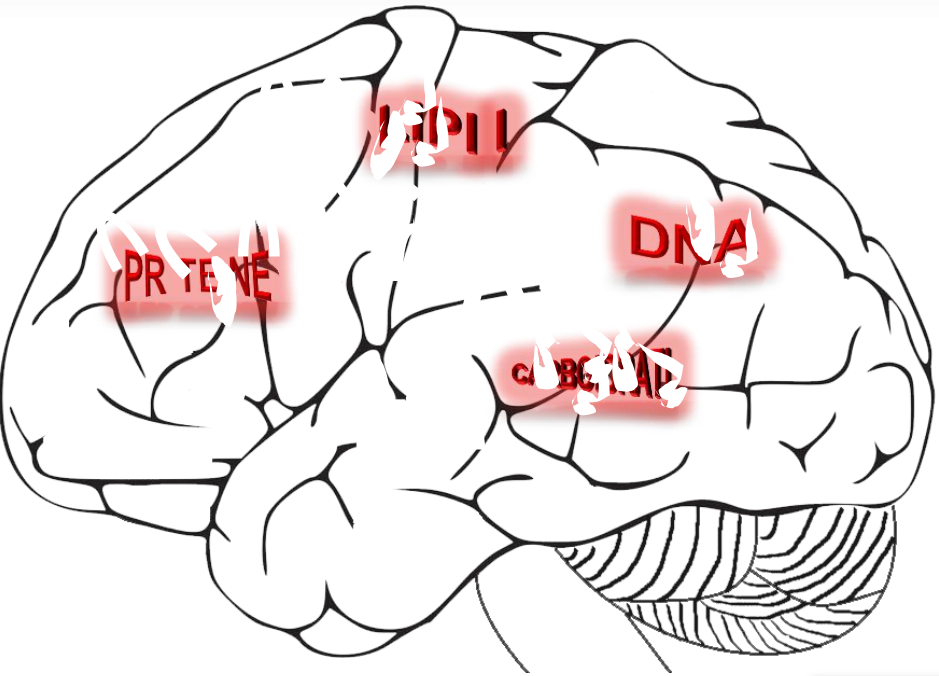
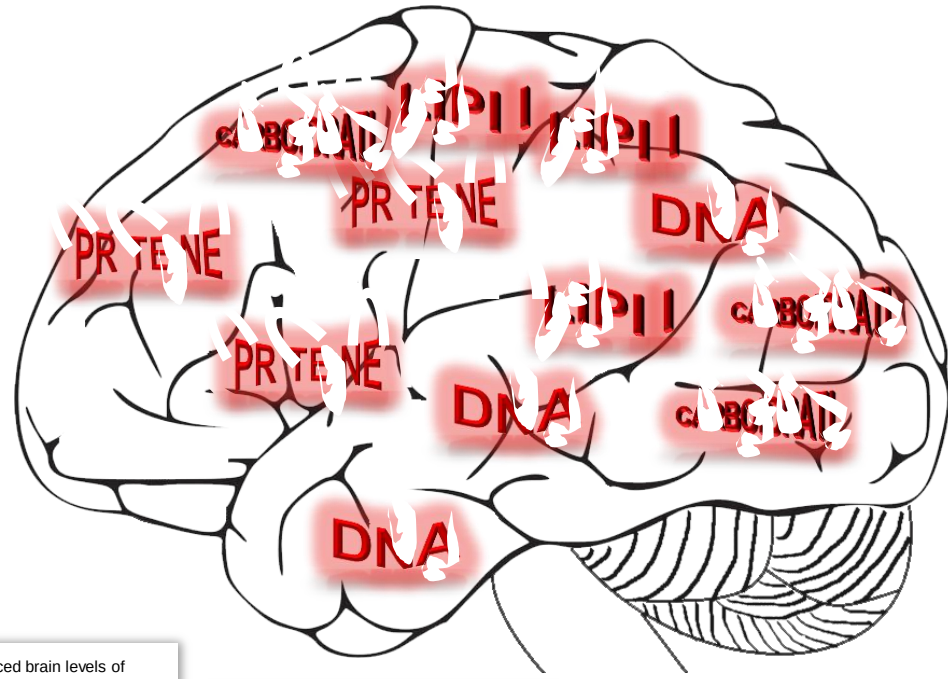
Marksbery WR et al. Lipid peroxidation is an early event in the brain in amnestic mild cognitive impairment. Ann Neurol. 2005.

Circolo sistemico

SANO

AD (o MCI)





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Yao Y et al. Enhanced brain levels of **8,12-iso-iPF2alpha-VI** differentiate AD from frontotemporal dementia. Neurology. 2003

C.E. Teunissen, et al. Biochemical markers related to Alzheimer's dementia in serum and cerebrospinal fluid. Neurobiogy of aging. 2002

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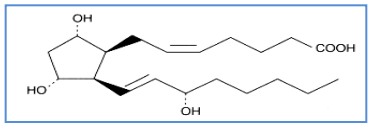
MISURA DELLO STRESS OSSIDATIVO MEDIANTE QUANTIFICAZIONE PRODOTTI DEL DANNO OSSIDATIVO

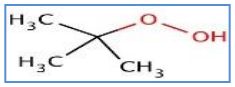
A. DANNO AI LIPIDI

- **Malondialdehyde** (MDA)

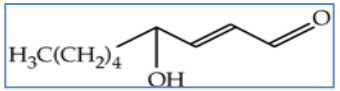
- **Isoprostanes**



- **hydroperoxides**

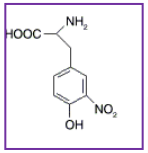


- **HNE**

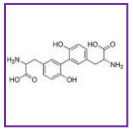


B. DANNO ALLE PROTEINE

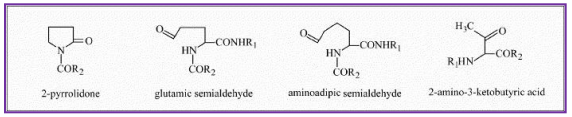
- **3-Nitrotyrosine**



- **dityrosine**

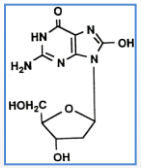


- **carbonyles**

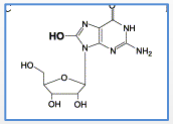


C. DANNO AGLI ACIDI NUCLEICI

- **8OHDg**

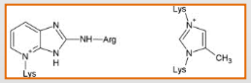


- **8OHDg**

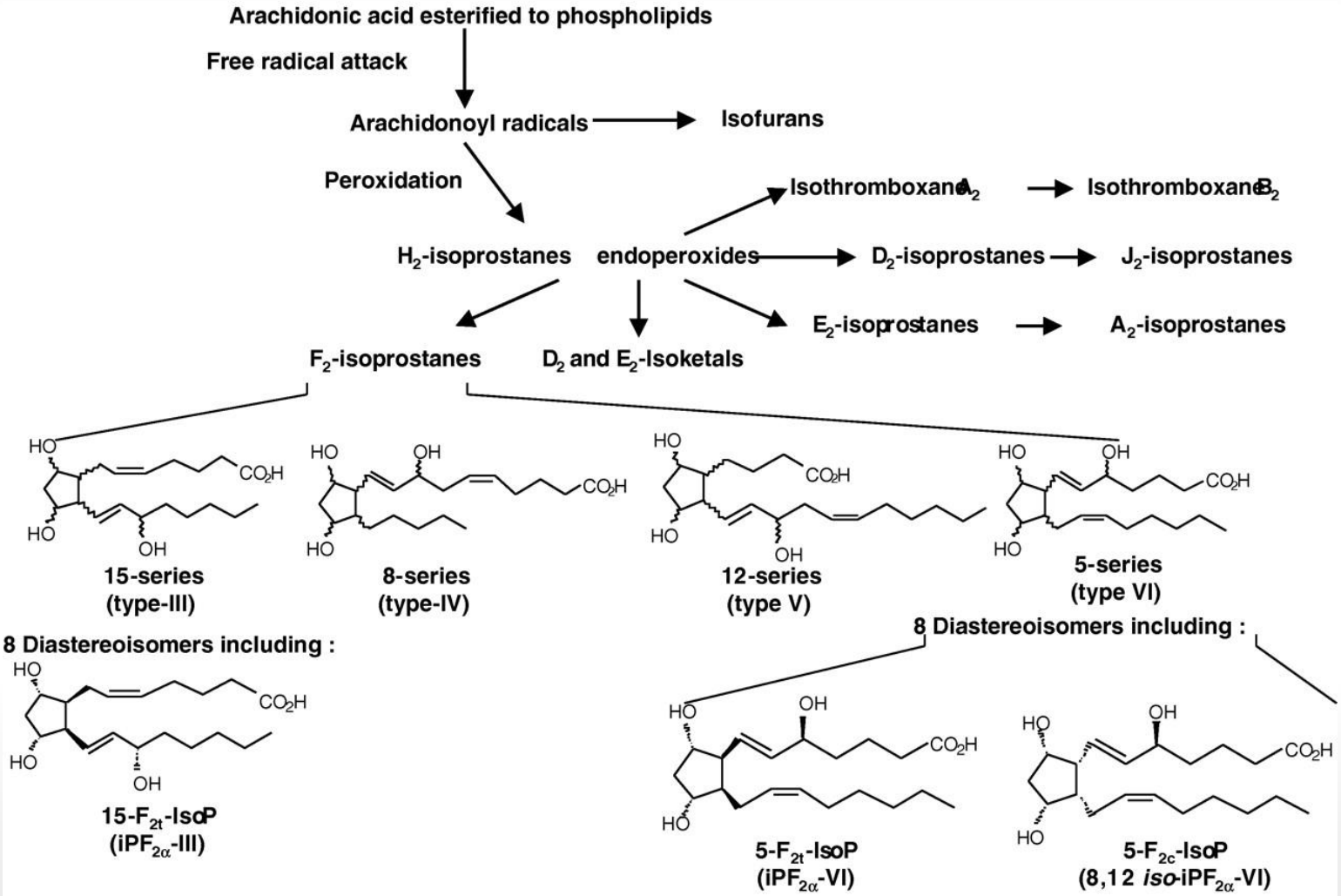


D. DANNO AI CARBOIDRATI

- **AGE**



THE ISOPROSTANE PATHWAY



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