

Mistakes to Avoid in the Management of Children's Respiratory Diseases to Plan Long Term Health



Attilio Boner
University of
Verona, Italy

attilio.boner@univr.it



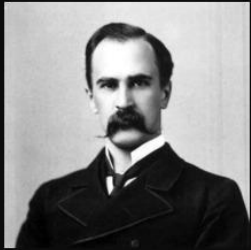
335 6274799

- ✓ **Introduction**
- ✓ **Why is avoiding mistakes important?**
The long-term consequences of early respiratory diseases
- ✓ **Early respiratory diseases: "a canary in the mine"**
- ✓ **10 Mistakes to avoid**
- ✓ **Summary & Conclusions**

Conflitto di interessi: Envicon medical srl

Contextual Errors in Medical Decision Making: Overlooked and Understudied.

Weiner SJ, Acad Med. 2016 May;91(5):657-62.



The good physician treats the disease; the great physician treats the patient who has the disease.

~ William Osler

AZ QUOTES

- inattention to patient context is an underrecognized cause of medical error
("a contextual error" was found in 41% of visits"),



- detecting its presence usually requires listening in on the visit, and that it has significant implications for quality of care.

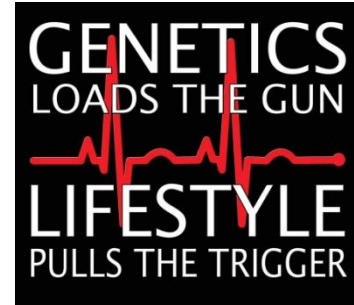
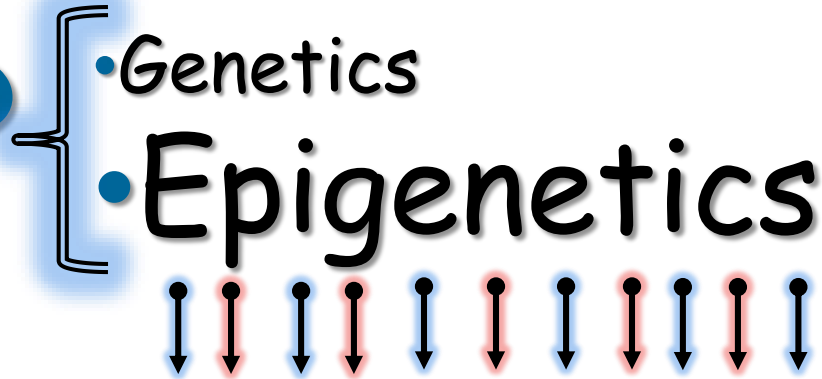


Not to consider the pathogenesis is a frequent error

What

-
-
-
-
-
-
-
- $\geq 10,000$

Why ?



Few biological systems:

- chronic inflammation
- oxidative stress
- immune hypo/hyperactivity
- dysbiosis
- mental detoxification



Mistakes to Avoid in the Management of Children's Respiratory Diseases to Plan Long Term Health



Attilio Boner
University of
Verona, Italy

attilio.boner@univr.it



335 6274799

- ✓ Introduction
- ✓ Why is avoiding mistakes important?
The long-term consequences of early respiratory diseases
- ✓ Early respiratory diseases: "a canary in the mine"
- ✓ 10 Mistakes to avoid
- ✓ Summary & Conclusions

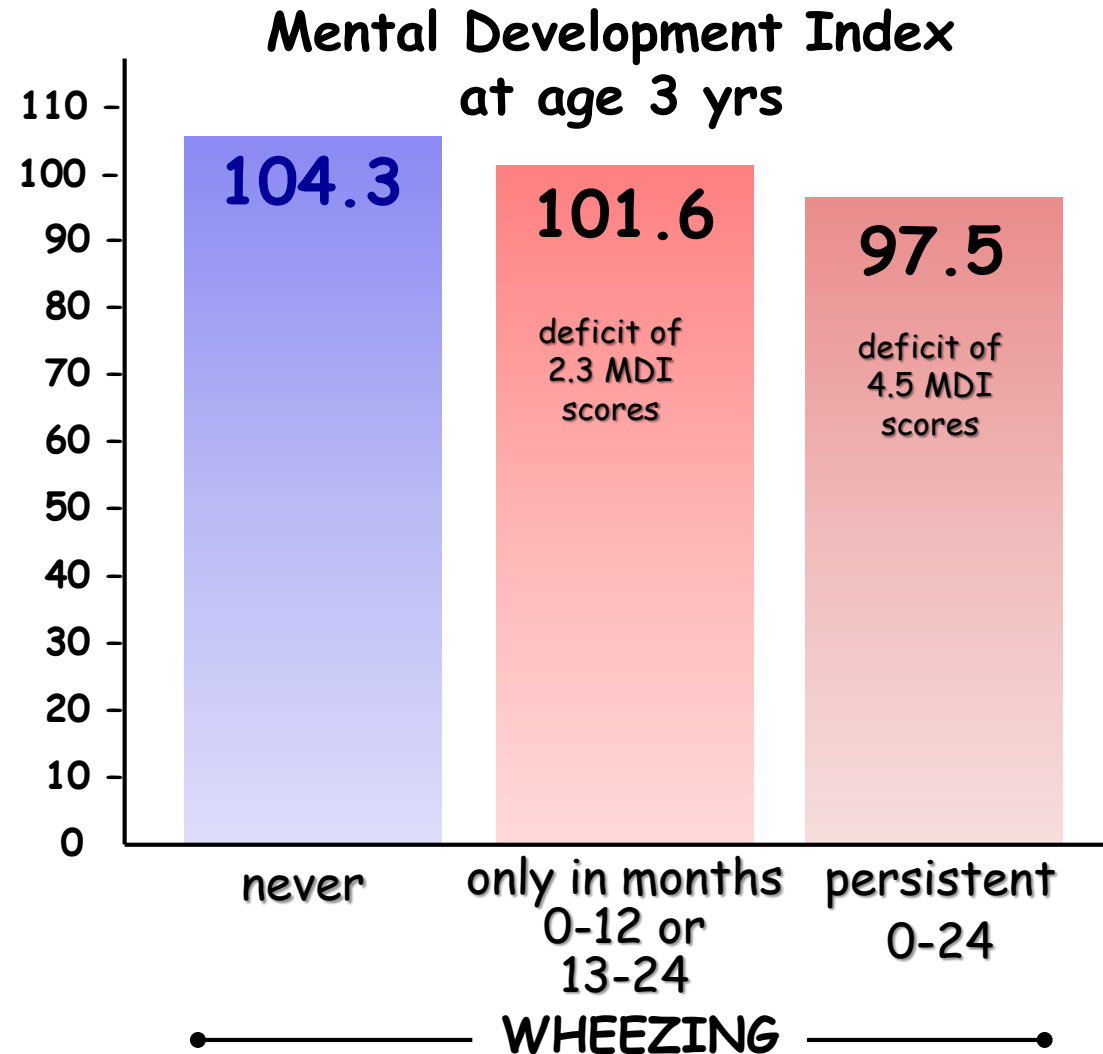
Early wheezing phenotypes and cognitive development of 3-yr-olds. Community-recruited birth cohort study

Jedrychowski W. Pediatr Allergy Immunol. 2010;21:550-6

✓ Birth cohort (n=468).

✓ Wheezing symptoms over first 2 years.

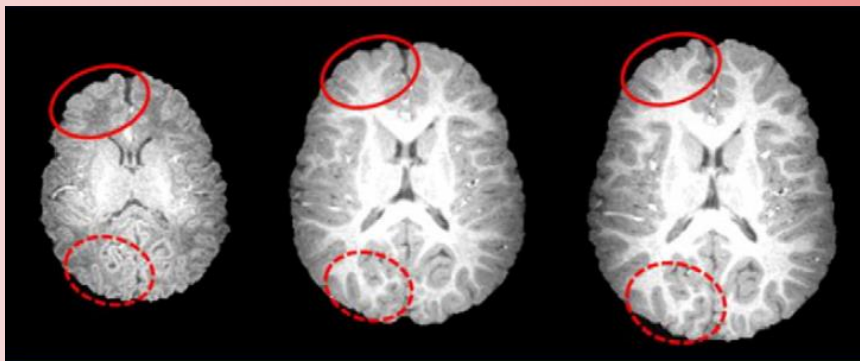
✓ Cognitive status of children at the age of 3 yr with the Bayley Mental Development Index (MDI).



Early wheezing phenotypes and cognitive development of 3-yr-olds. Community-recruited birth cohort study

Jedrychowski W. *Pediatr Allergy Immunol.* 2010;21:550-6

Cognitive deficit in very young children may be related to lower lung function attributed to persistent wheezing, which reducing oxygen supply would affect rapidly developing brain.

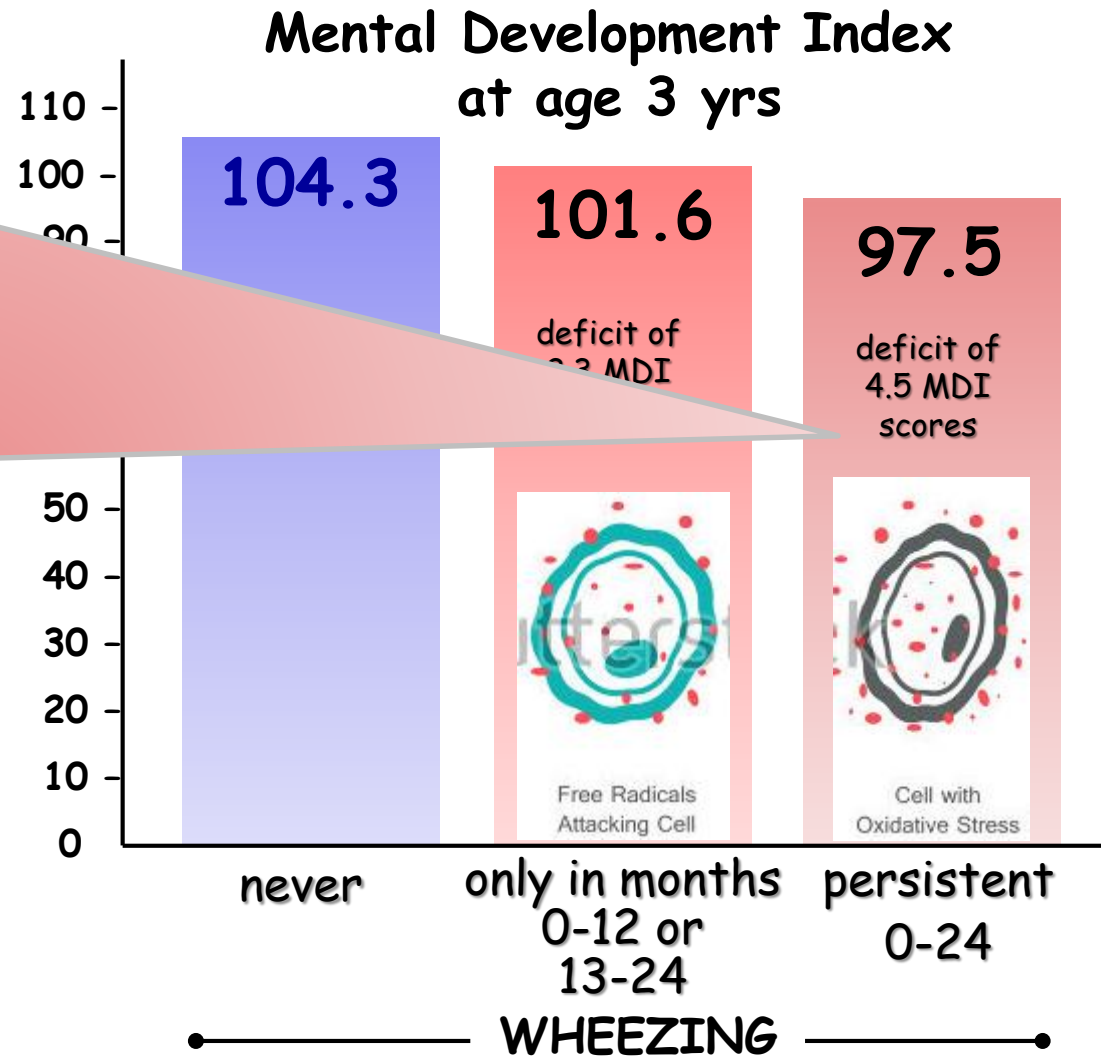


Two weeks

One year

Two years

Selenium may be protective



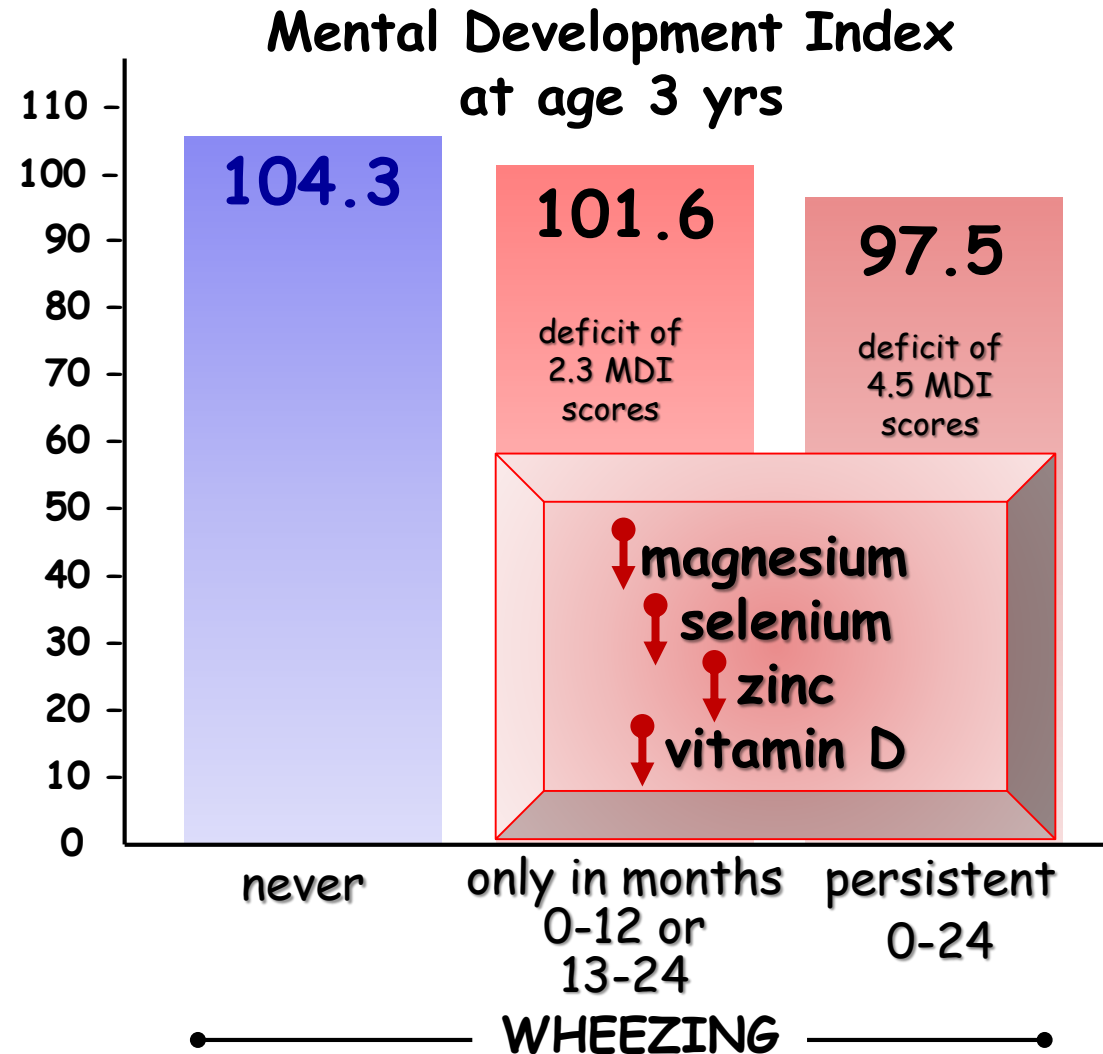
Early wheezing phenotypes and cognitive development of 3-yr-olds. Community-recruited birth cohort study

Jedrychowski W. *Pediatr Allergy Immunol.* 2010;21:550-6

✓ Birth cohort (n=468).

✓ Wheezing symptoms over first 2 years.

✓ Cognitive status of children at the age of 3 yr with the Bayley Mental Development Index (MDI).



3-yr-olds. Community-recruited birth cohort study

Jedrychowski W. Pediatr Allergy Immunol. 2010;21:550-6

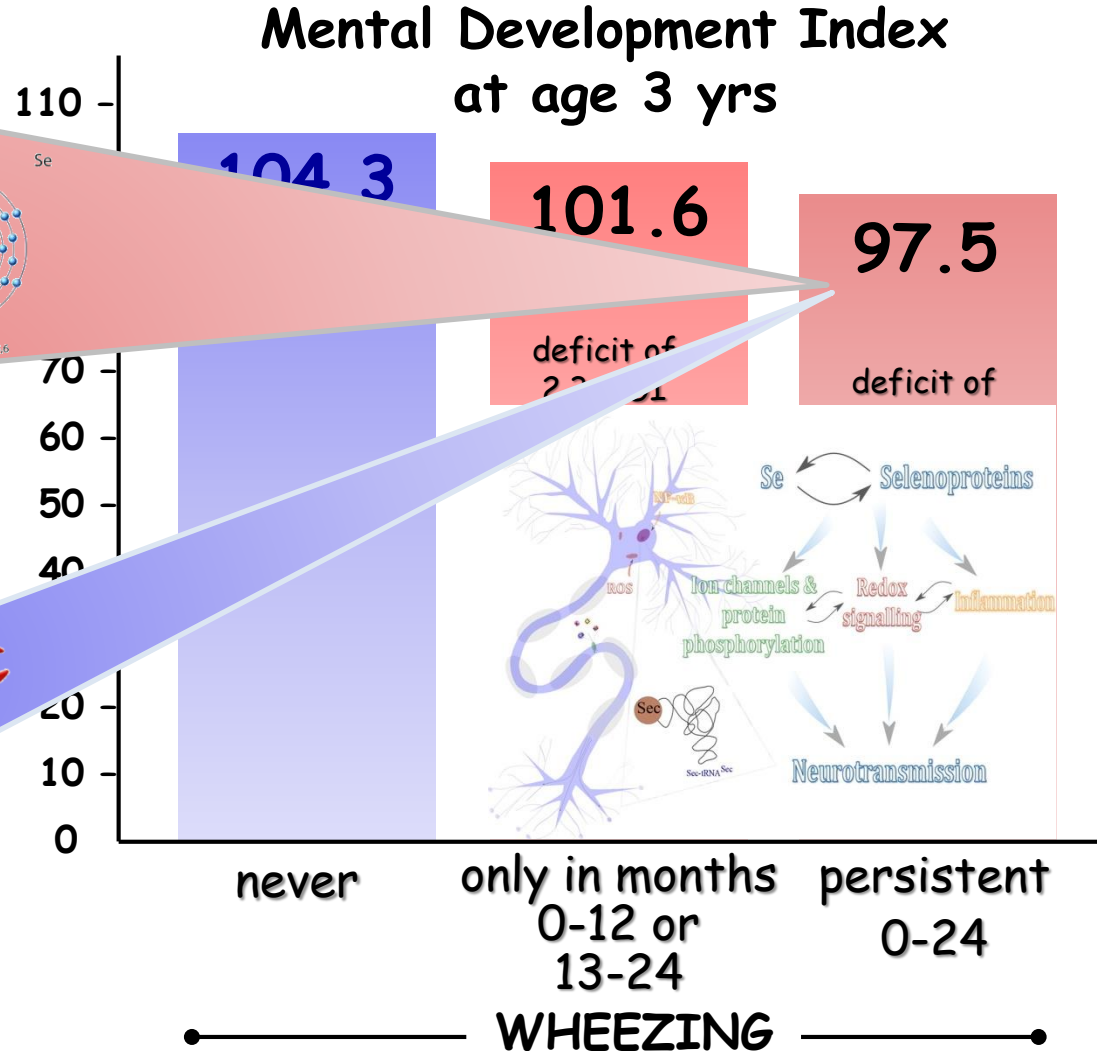
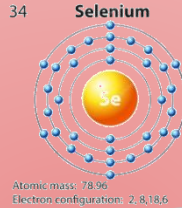
Selenium status in pregnancy influences children's cognitive function at 1.5 years of age.

Skröder HM, Clin Nutr. 2015;34(5):923-30.

Low prenatal selenium status is disadvantageous for children's psychomotor and language development.

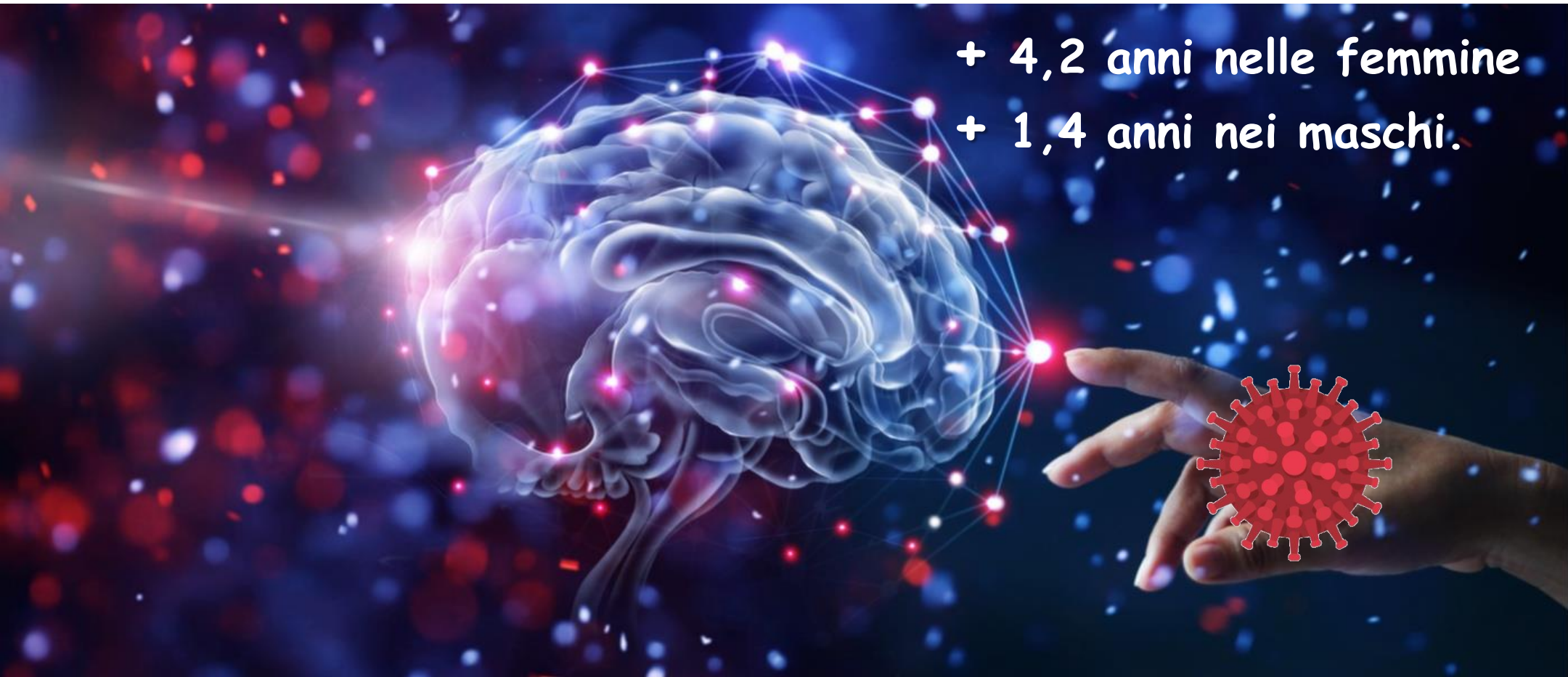
Optimal selenium levels decrease the host's susceptibility to viral infections.

- Arthur J, J Nutr 2003; 133:1457S-1459S.
- Beck M, Proc Nutr Soc 1999; 58:707-711.
- Beck M, J Nutr 2003; 133:1463S-7S.
- Gill H, Nutr Diet 2008; 65 (S3):S41-S47.
- Kiremidjian-Schumacher L, Biol Trace Elem Res 1992; 33:23-35.



Il COVID-19 ha "invecchiato" il cervello degli adolescenti

09.09.2024 | Popular Science



+ 4,2 anni nelle femmine
+ 1,4 anni nei maschi.

- La corteccia cerebrale, che si assottiglia normalmente con l'età, anche negli adolescenti.
- Stress cronico e difficoltà quotidiane accelerano l'assottigliamento della corteccia, aumentando il rischio di sviluppo di disturbi neuropsichiatrici e comportamentali.

Corrigan NM, COVID-19 lockdown effects on adolescent brain structure suggest accelerated maturation that is more pronounced in females than in males. Proc Natl Acad Sci U S A. 2024 Sep 17;121(38):e2403200121.

Incidence of cognitive impairment and dementia after hospitalisation for pneumonia:

a UK population-based matched cohort study.

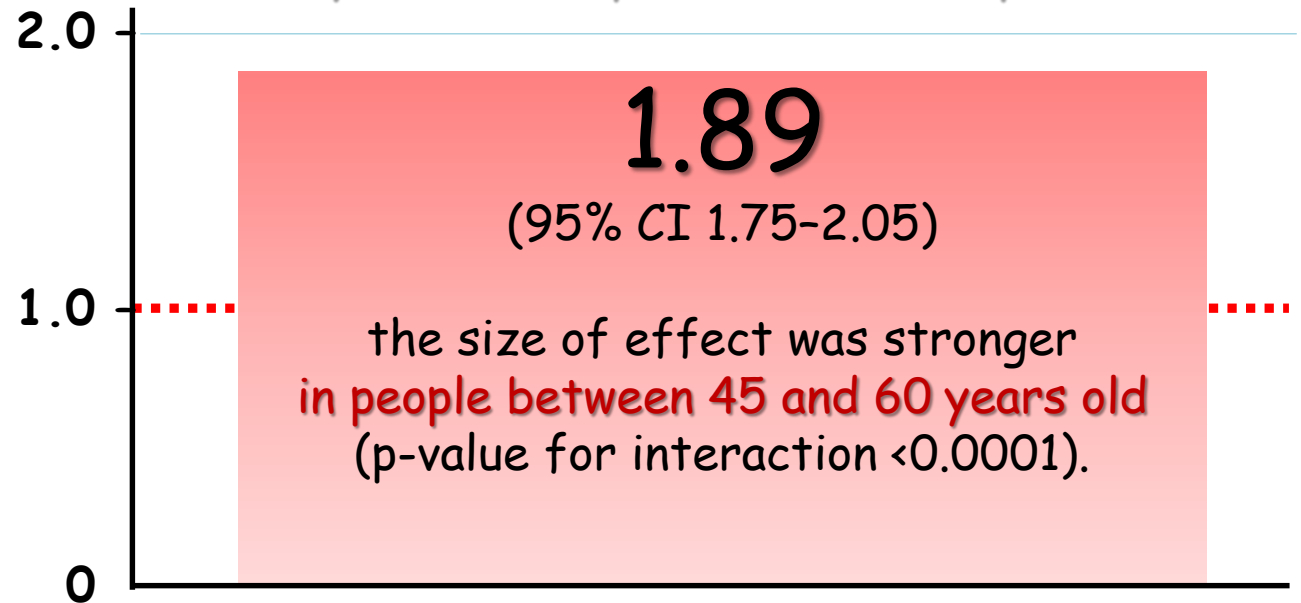
Chalitsios CV, ERJ Open Res. 2023 May 9;9(3):00328-2022.

✓ 55 808 persons hospitalised with pneumonia pneumonia between 1 July 2002 and 30 June 2017



✓ 206 168 controls matched by sex, age and practice.

aHR of cognitive impairment and dementia within 1 year of hospitalisation for pneumonia



Incidence of cognitive impairment and dementia after hospitalisation for pneumonia:

a UK population-based matched cohort study.

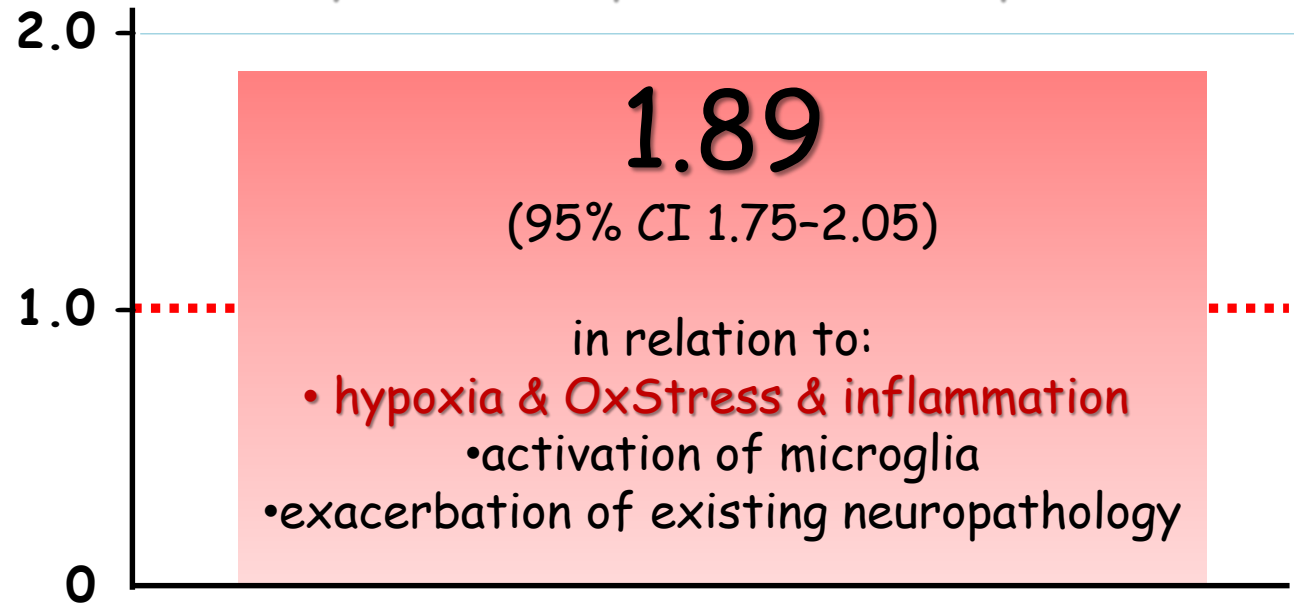
Chalitsios CV, ERJ Open Res. 2023 May 9;9(3):00328-2022.

✓ 55 808 persons hospitalised with pneumonia pneumonia between 1 July 2002 and 30 June 2017



✓ 206 168 controls matched by sex, age and practice.

aHR of cognitive impairment and dementia within 1 year of hospitalisation for pneumonia

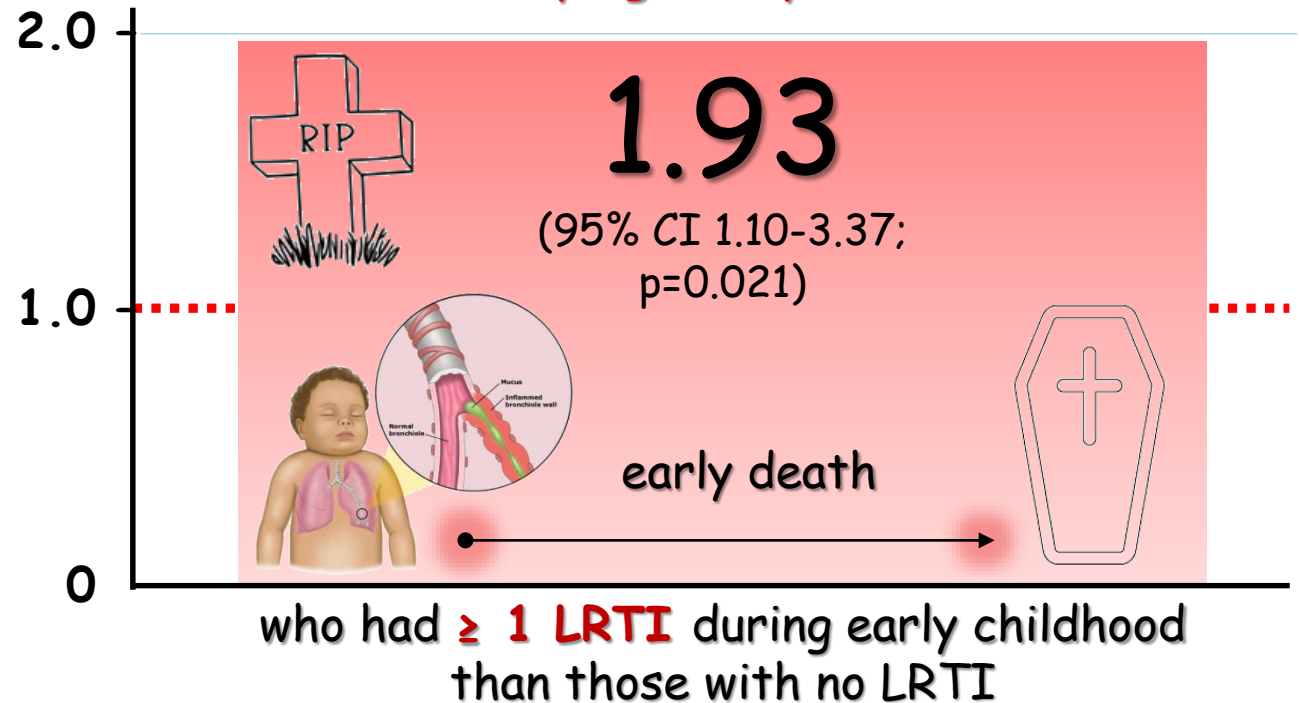


Early childhood lower respiratory tract infection and premature adult death from respiratory disease in Great Britain: a national birth cohort study.

Allinson JP, Lancet. 2023;401:1183-1193.

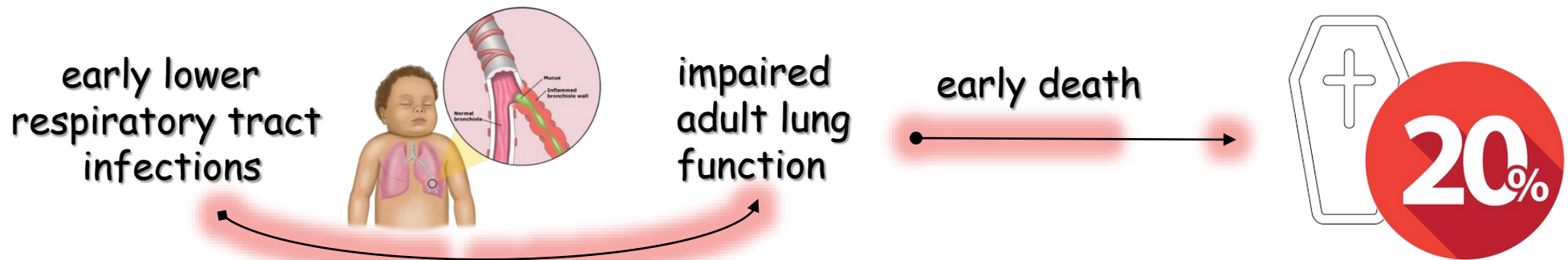
- ✓ association between LRTI during early childhood (age <2 years, n= 5362)
- and
- ✓ death from respiratory disease from age 26 through 73 years

aHR of DYING from respiratory disease by age 73 years

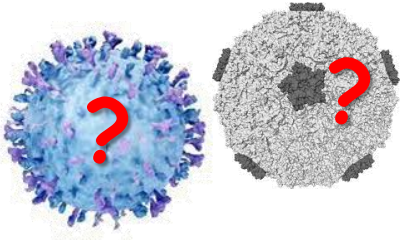


Early childhood lower respiratory tract infection and premature adult death from respiratory disease in Great Britain: a national birth cohort study.

Allinson JP, Lancet. 2023;401:1183-1193.



- Identifying young children with LRTIs and actively optimising their health as they and their lungs grow into adulthood

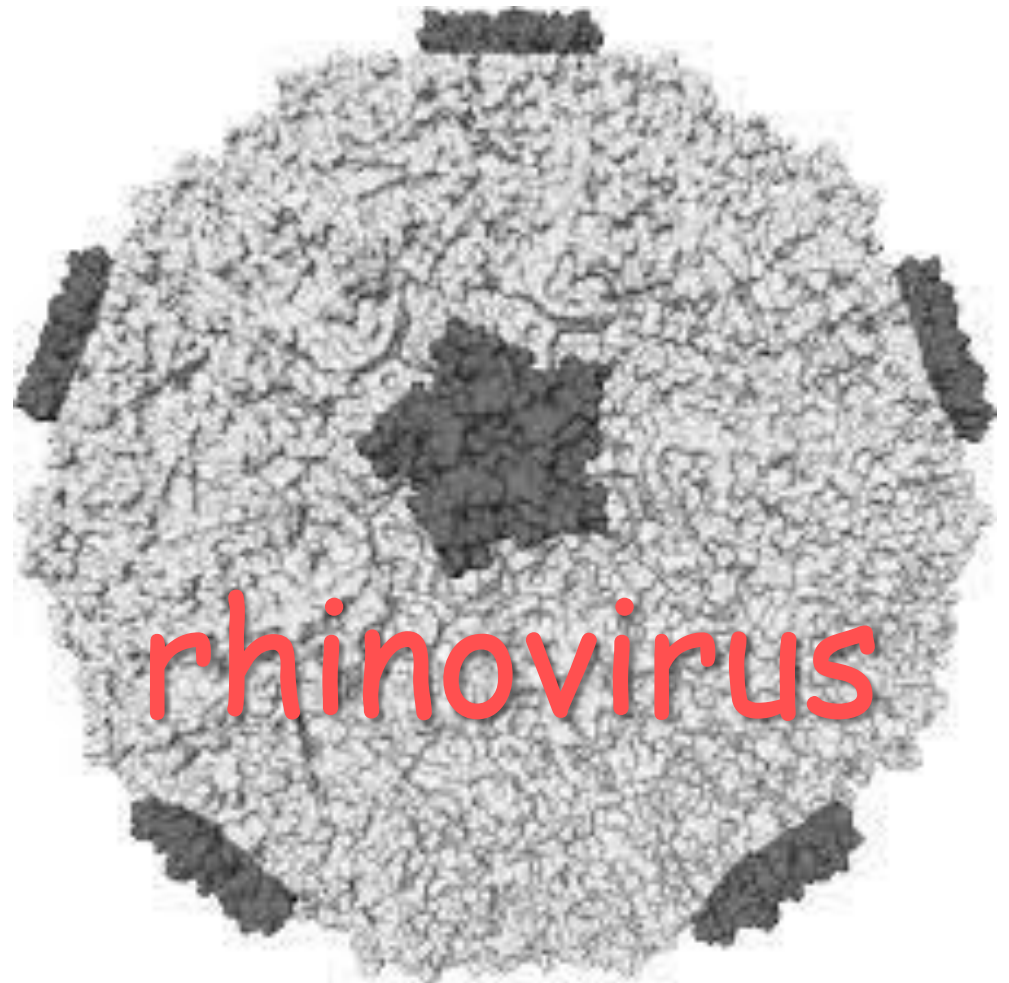


- might be one way to break the connection between poor respiratory health in childhood and adulthood.



cortesia dr. Martino Barretta

Which is worse ?



Mistakes to Avoid in the Management of Children's Respiratory Diseases to Plan Long Term Health



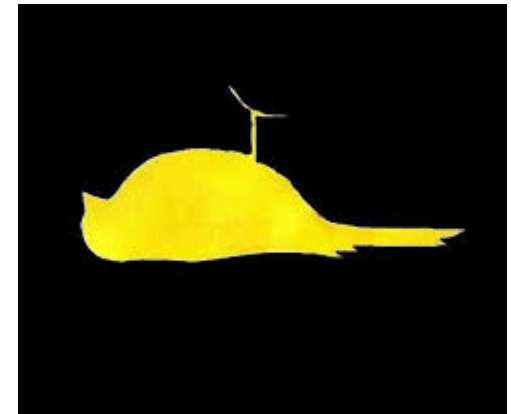
Attilio Boner
University of
Verona, Italy

attilio.boner@univr.it



335 6274799

- ✓ Introduction
- ✓ Why is avoiding mistakes important?
The long-term consequences of early respiratory diseases
- ✓ Early respiratory diseases: "a canary in the mine"
- ✓ 10 Mistakes to avoid
- ✓ Summary & Conclusions



The role of **respiratory syncytial virus-** and **rhinovirus-** induced bronchiolitis in recurrent wheeze and asthma- A systematic review and meta-analysis.

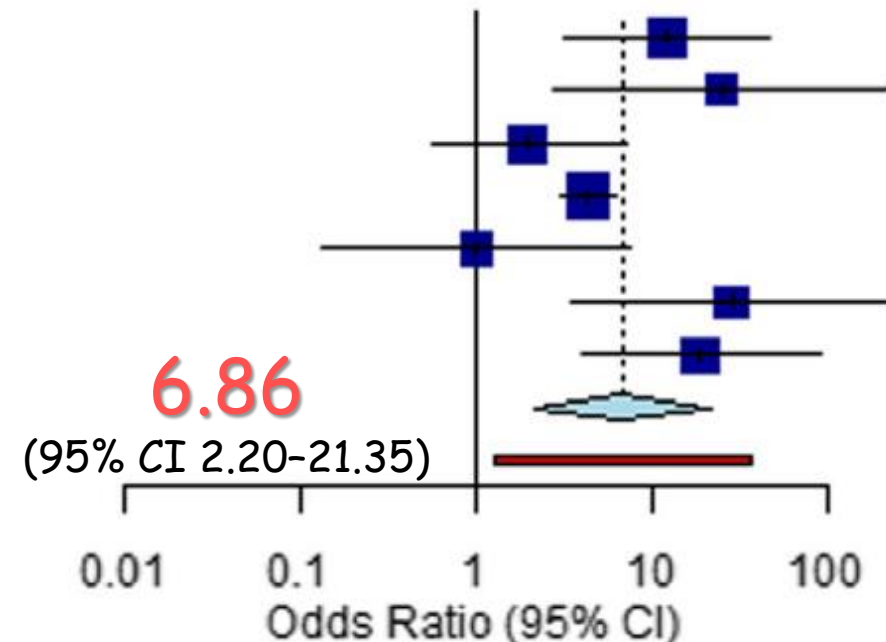
Makrinioti H, Pediatr Allergy Immunol. 2022 Mar;33(3):e13741.

- ✓ 38 cohort studies
- ✓ infants with bronchiolitis

Source	OR (95% CI)
Schauer et al.	12.10 [3.22; 45.54]
Chung et al.	24.75 [2.69; 227.61]
Kristjansson et al.	1.99 [0.56; 7.05]
Tian M et al.	4.33 [2.98; 6.31]
Bertrand P. et al.	1.00 [0.13; 7.45]
Sigurs et al.	28.11 [3.50; 225.70]
Bont L. et al.	18.75 [3.94; 89.13]
Total	6.86 [2.20; 21.35]
Prediction interval (80%-PI)	[1.27; 37.01]
Heterogeneity: $\chi^2_6 = 14.15$ ($P = .03$), $I^2 = 58\%$	



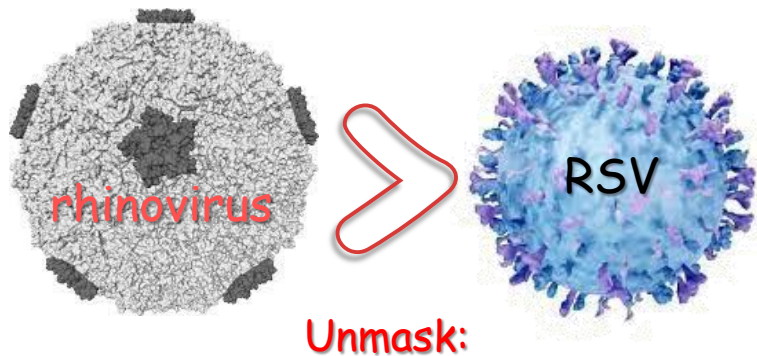
**OR of recurrent wheeze
post RSV-bronchiolitis**



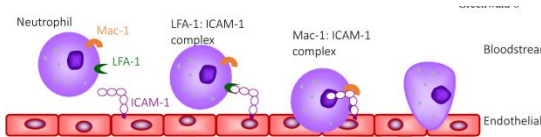
The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma- A systematic review and meta-analysis.

Makrinioti H, Pediatr Allergy Immunol. 2022 Mar;33(3):e13741.

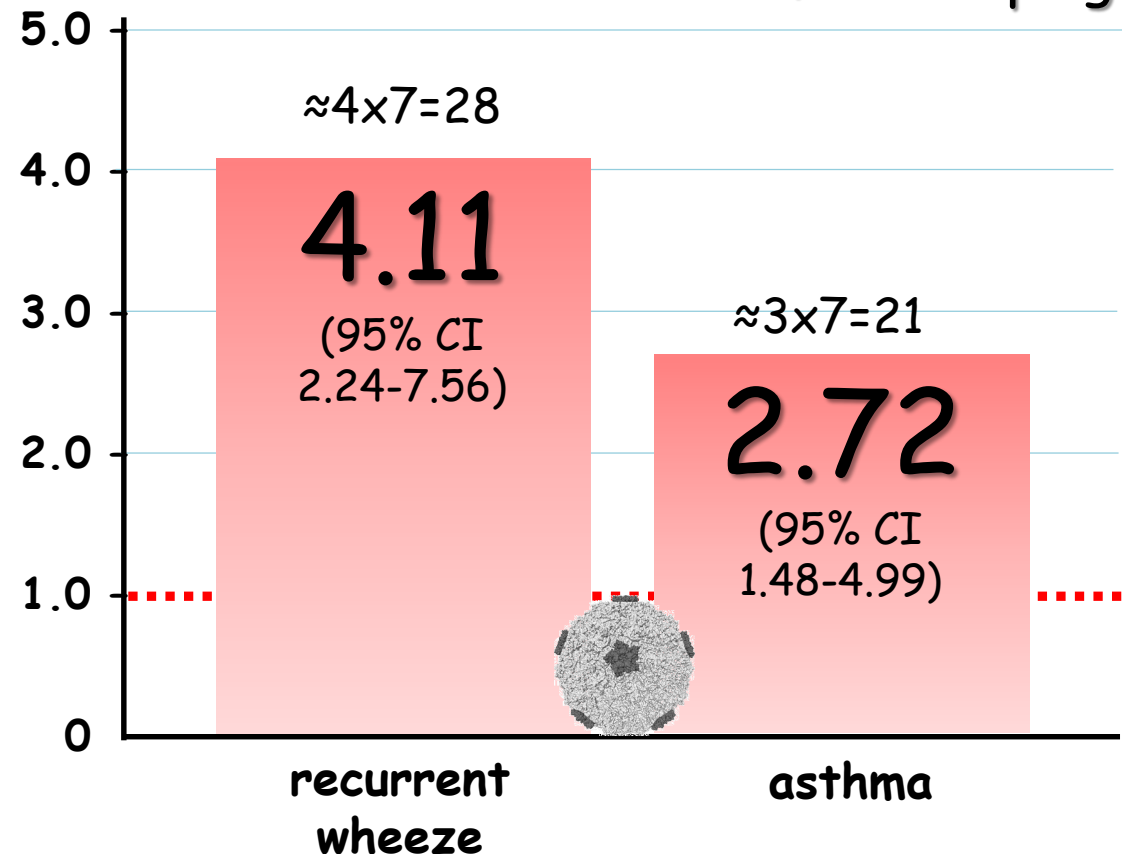
- ✓ 38 cohort studies
- ✓ infants with bronchiolitis



- ✓ - small airways ✓
- ✓ - oxidative stress ✓
- ✓ - ICAM-1 adhesion receptor



in RV-bronchiolitis compared to
RSV-bronchiolitis OR of developing



Assessing the strength of evidence for a **causal effect** of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis.

Brunwasser SM, Lancet Respir Med. 2020 Aug;8(8):795-806.

THE LANCET
Respiratory Medicine

✓ 35 studies estimated the direct effect of RSV-LRTI on wheezing illnesses (exposure studies)

✓ 8 studies evaluated the effect of RSV immunoprophylaxis (immunoprophylaxis studies).



❖ Infants who were not protected with **RSV immunoprophylaxis** tended to have higher odds of subsequent wheezing illness, as we would expect if RSV-LRTI were causal, but the effect was **not significant** (OR₊ 1.21, 95% CI 0.73-1.99).

❖ Our findings do not support basing policy decisions on an assumption that prevention of RSV-LRTI will **reduce recurrent chronic wheezing illnesses**.

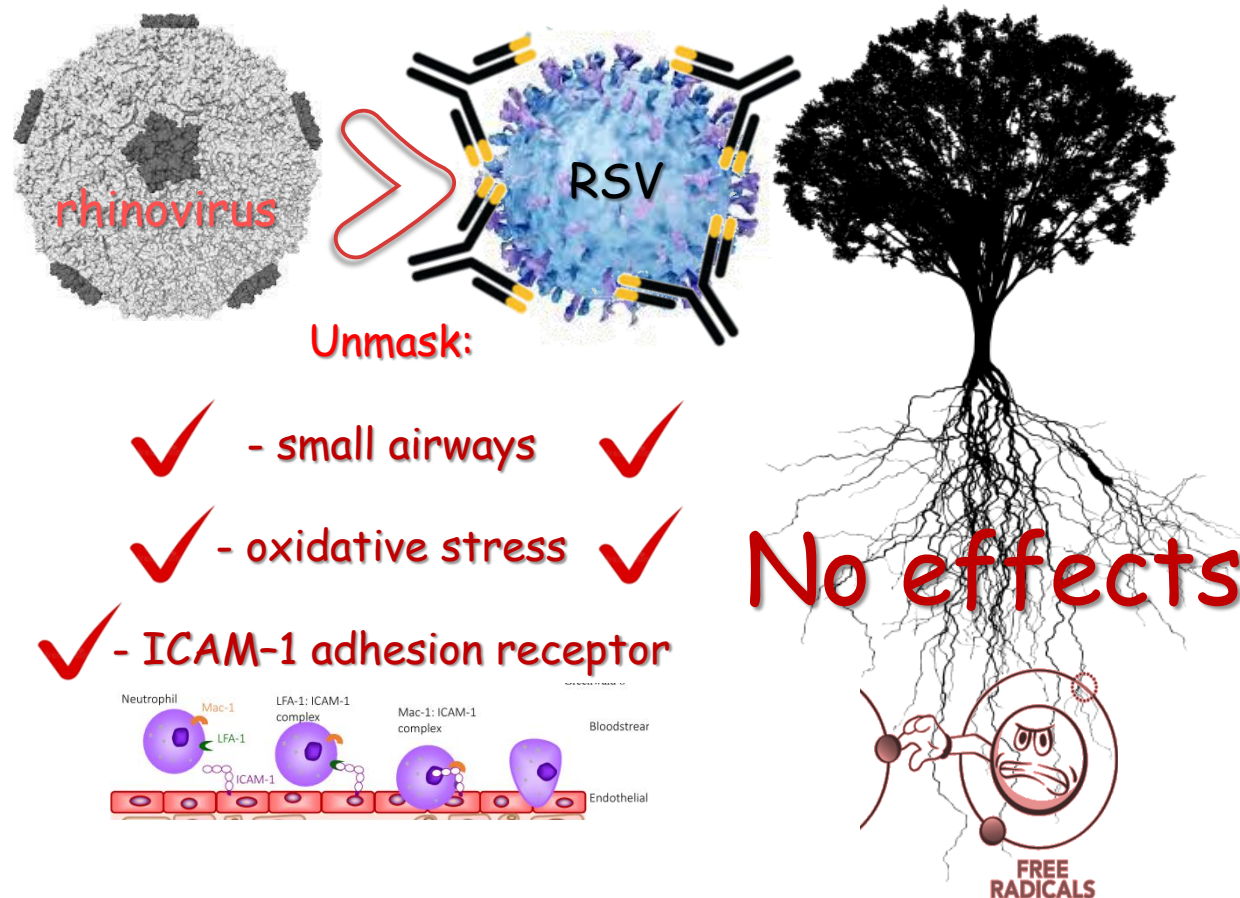
Assessing the strength of evidence for a **causal effect** of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis.

Brunwasser SM, Lancet Respir Med. 2020 Aug;8(8):795-806.

THE LANCET
Respiratory Medicine

✓ 35 studies estimated the direct effect of RSV-LRTI on wheezing illnesses (exposure studies)

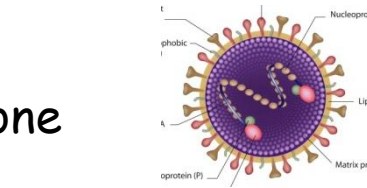
✓ 8 studies evaluated the effect of RSV immunoprophylaxis (immunoprophylaxis studies).



Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis.

Hosakote YM, Am J Respir Crit Care Med. 2011 Jun 1;183(11):1550-60.

- ✓ Superoxide dismutase 1 (SOD 1), SOD 2, SOD 3, catalase, glutathione peroxidase, and glutathione S-transferase, as well as NF-E2-related factor 2 (Nrf2) expression, measured in murine bronchoalveolar lavage, cell extracts of conductive airways, and/or in human nasopharyngeal secretions.



❖ RSV infection induced a significant **decrease** in the expression and/or activity of:

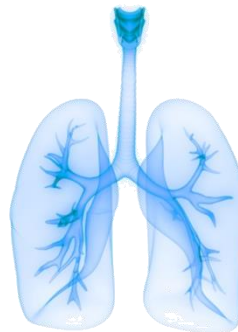
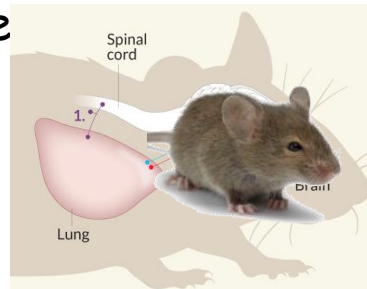
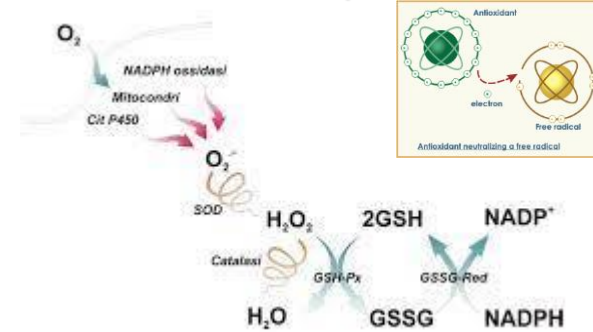
↓ **SOD**,

↓ **catalase**,

↓ **glutathione S-transferase**,

↓ **glutathione peroxidase**
in murine lungs

and
in the airways of children
with severe bronchiolitis.



- ✓ Antioxidant enzyme activity and markers of oxidative cell injury were measured in either murine bronchoalveolar lavage or nasopharyngeal secretions.

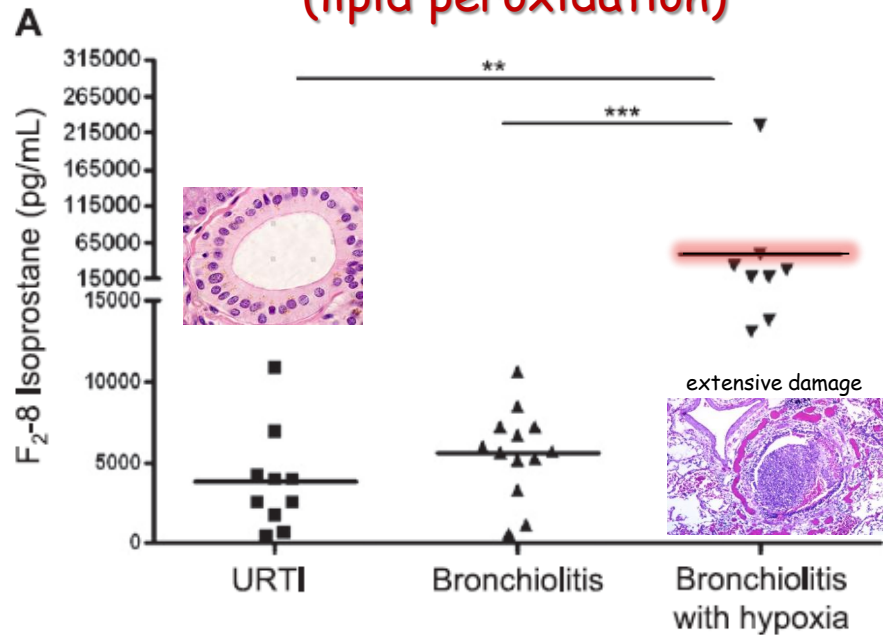
Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis.

Hosakote YM, Am J Respir Crit Care Med. 2011 Jun 1;183(11):1550-60.

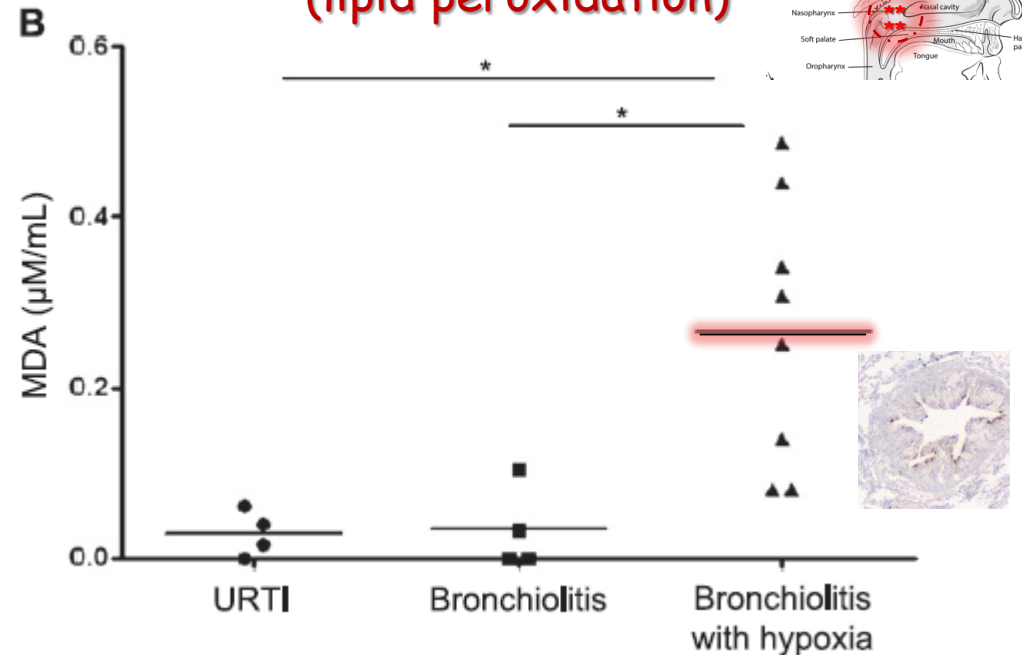
Concentrations of the oxidative stress markers in nasopharyngeal secretions (NPS) of infants with naturally acquired respiratory syncytial virus (RSV) infections.



F2-isoprostane concentration
(lipid peroxidation)



Malondialdehyde concentration
(lipid peroxidation)



** $p < 0.01$ and *** $p < 0.001$ compared with upper respiratory tract infection

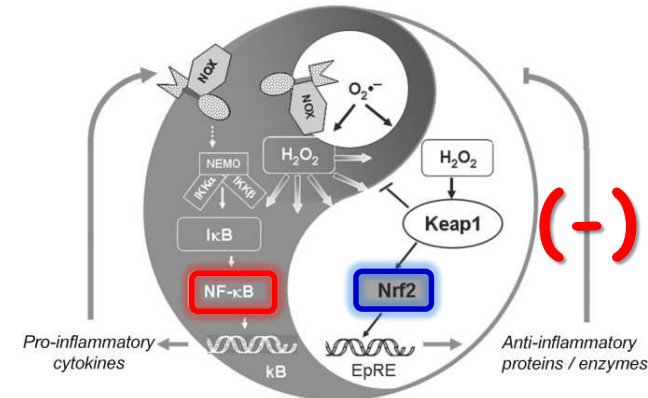
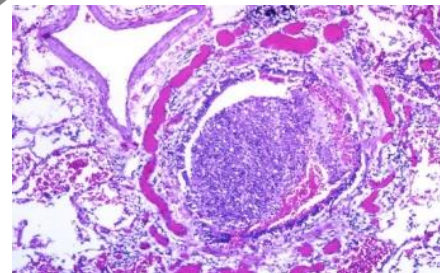
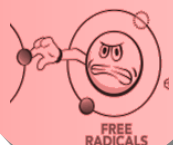
Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis.

Hosakote YM, Am J Respir Crit Care Med. 2011 Jun 1;183(11):1550-60.

RSV infection induces significant down-regulation of the airway antioxidant system in vivo, likely resulting in lung oxidative damage.

Markers of oxidative damage correlated with severity of clinical illness in RSV infected infants.

Nrf2 expression was also significantly reduced in the lungs of viral-infected mice.



Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis.

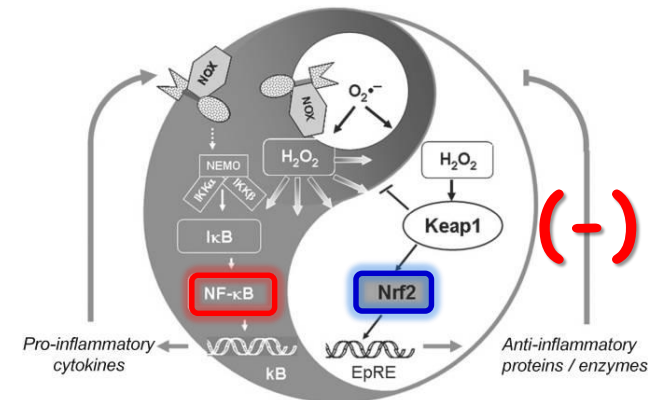
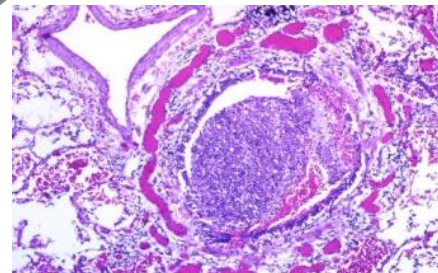
Hosakote YM, et al. *J Child Care Med*. 2011 Jun 1;183(11):1550-60.

Modulation of oxidative stress may pave the way toward important advances in the therapeutic approach of RSV-induced acute lung disease.

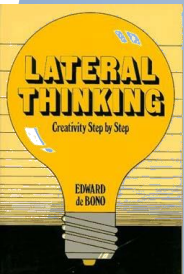
Markers of oxidative damage correlated with severity of clinical illness in RSV infected infants.



Nrf2 expression was also significantly reduced in the lungs of viral-infected mice.



✓ Super
SO
per
S-
c



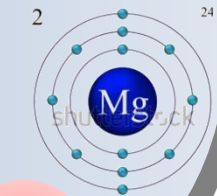
✓ I
we
bronc
nasophar



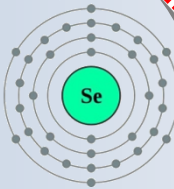
Polyphenols



Vitamin K2



Vitamin E



ANTIOXIDANTS

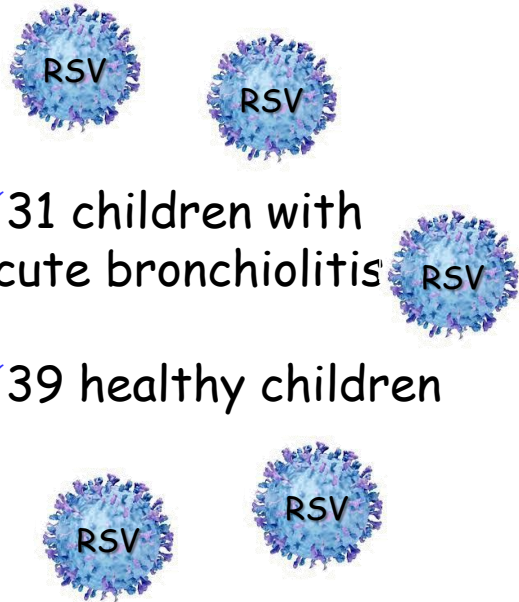


ANTIOXIDANTS



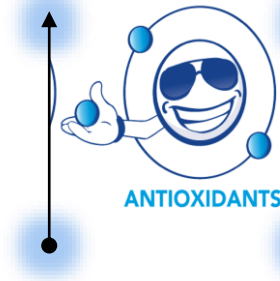
Oxidative and antioxidative status of children with acute bronchiolitis.

Dundaroz R, J Pediatr (Rio J). 2013 Jul-Aug;89(4):407-11.

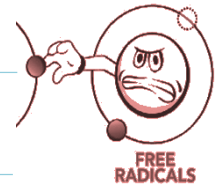
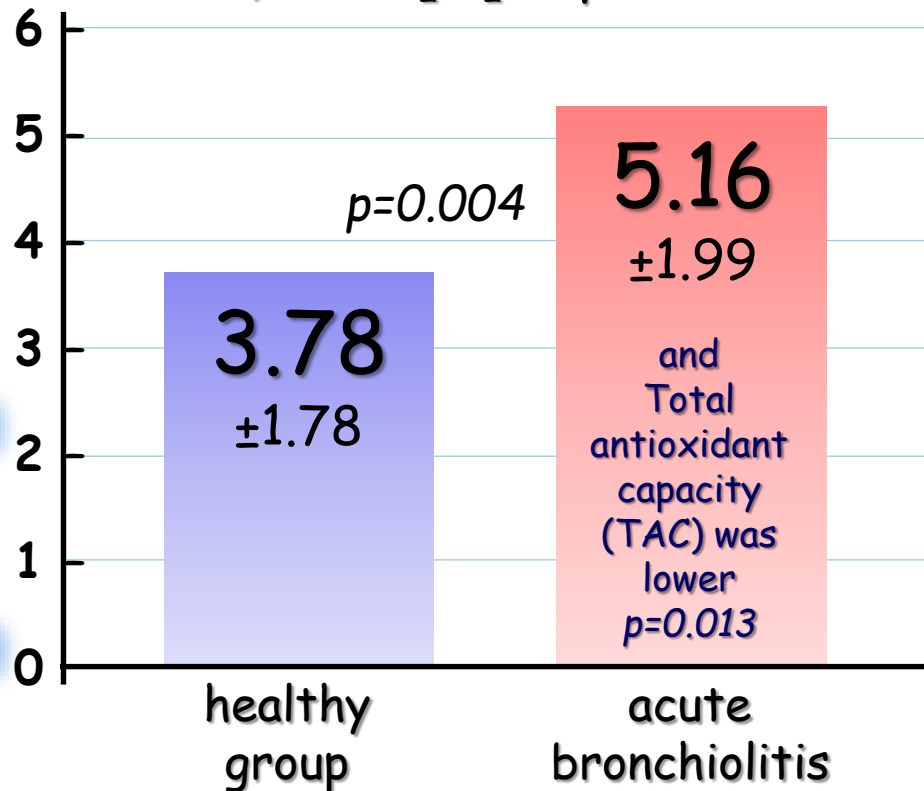


✓ 31 children with acute bronchiolitis

✓ 39 healthy children



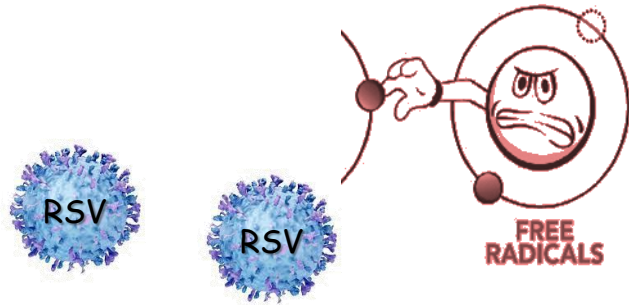
Total Oxidative Status (TOS)
 $\mu\text{mol H}_2\text{O}_2$ in plasma



Oxidative and antioxidative status of children with acute bronchiolitis.

Dundaroz R, J Pediatr (Rio J). 2013 Jul-Aug;89(4):407-11.

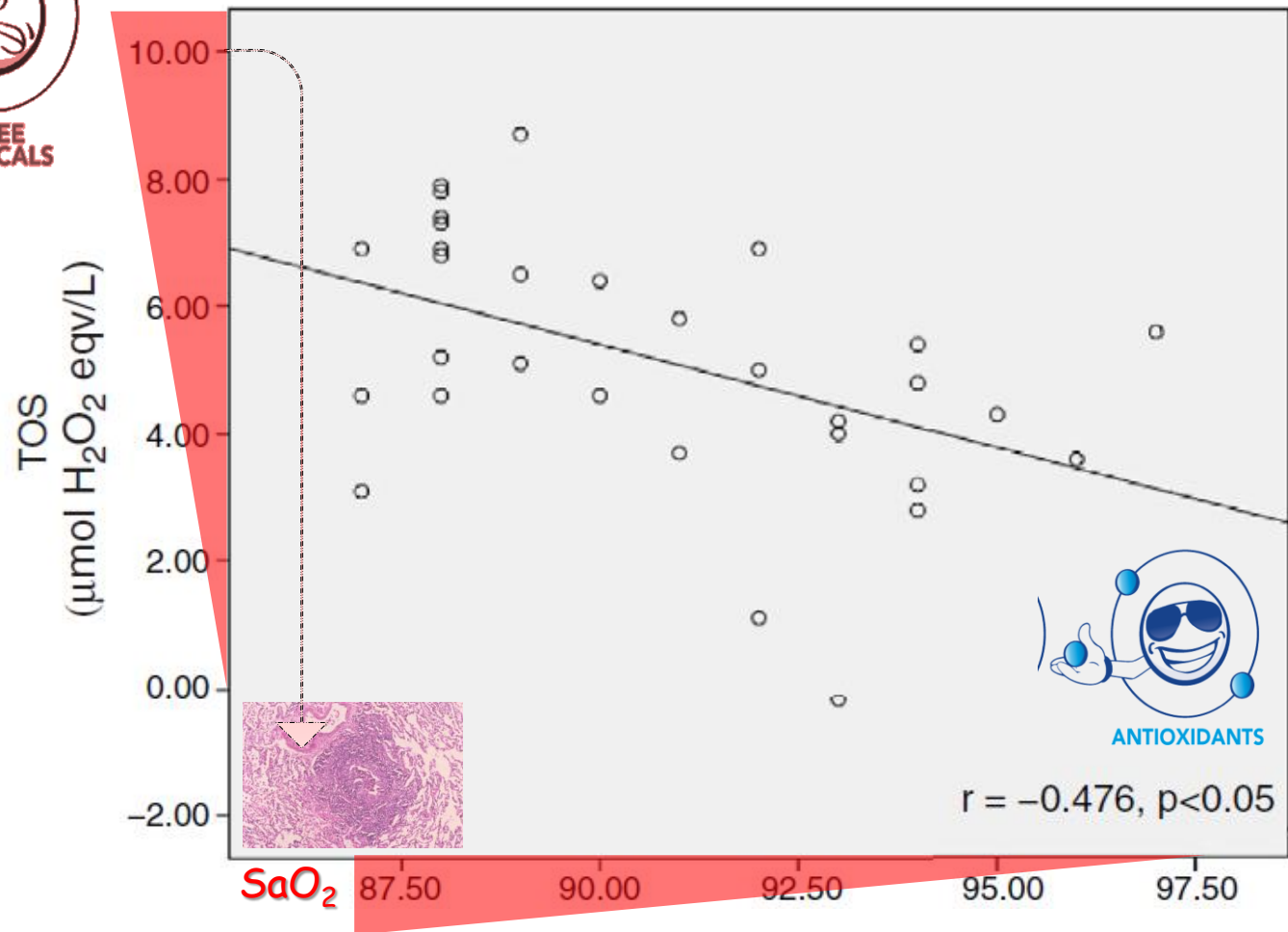
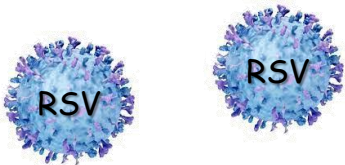
SaO₂ was inversely correlated with Total Oxidative Status (TOS) H₂O₂



✓ 31 children with acute bronchiolitis

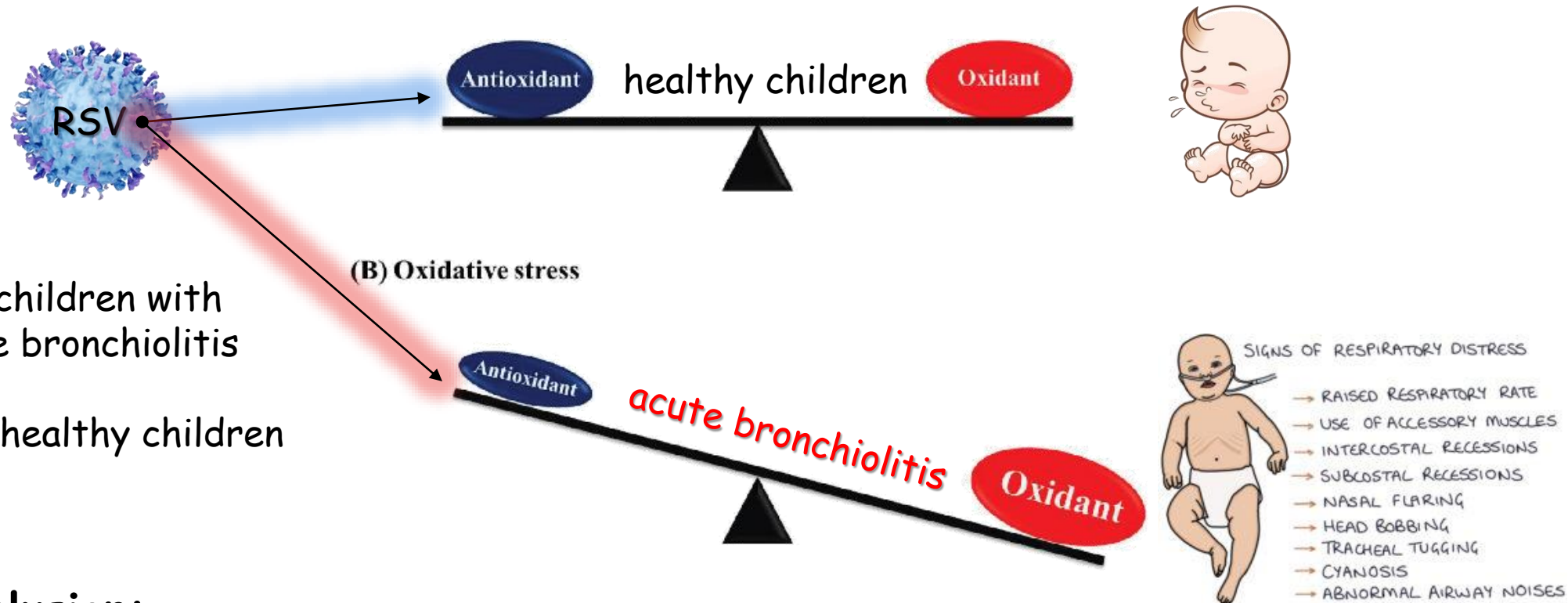


✓ 39 healthy children



Oxidative and antioxidative status of children with acute bronchiolitis.

Dundaroz R, J Pediatr (Rio J). 2013 Jul-Aug;89(4):407-11.



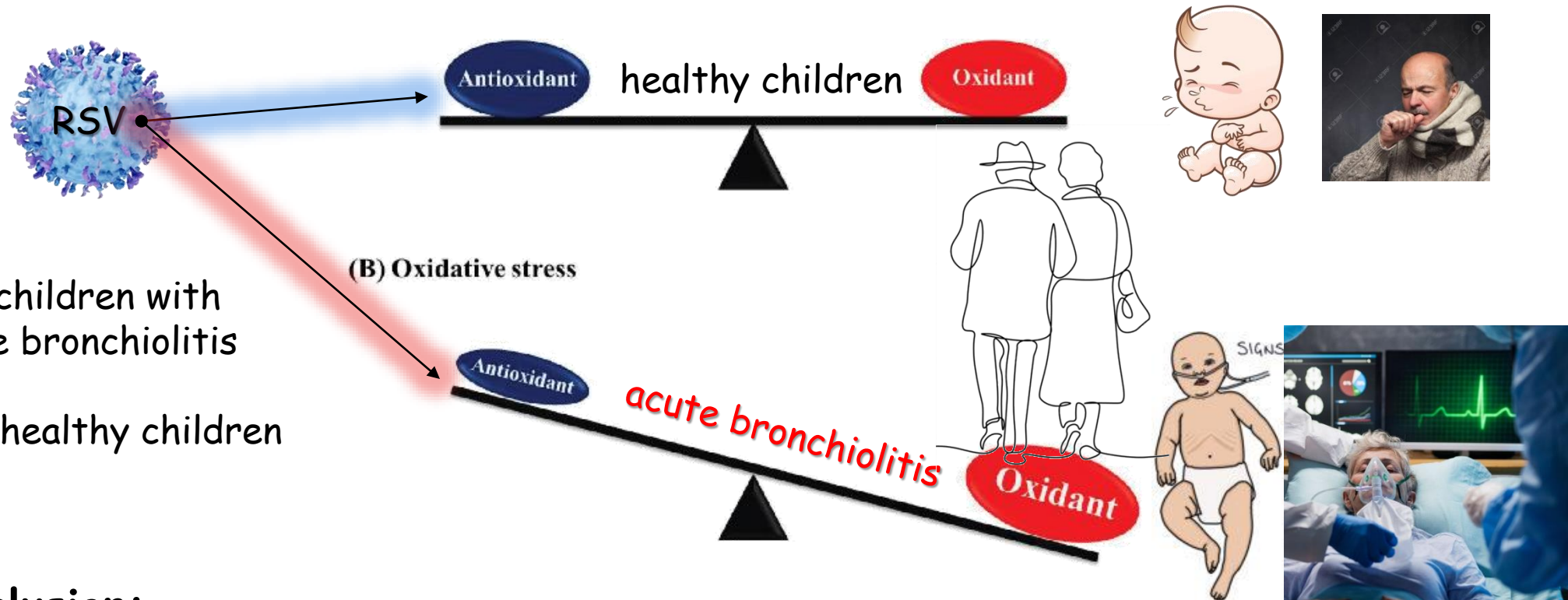
- ✓ 31 children with acute bronchiolitis
- ✓ 39 healthy children

Conclusion:

The balance between oxidant and antioxidant systems is disrupted in children with moderate bronchiolitis, which indicates that this stress factor may have a role in the pathogenesis of the disease.

Oxidative and antioxidative status of children with acute bronchiolitis.

Dundaroz R, J Pediatr (Rio J). 2013 Jul-Aug;89(4):407-11.



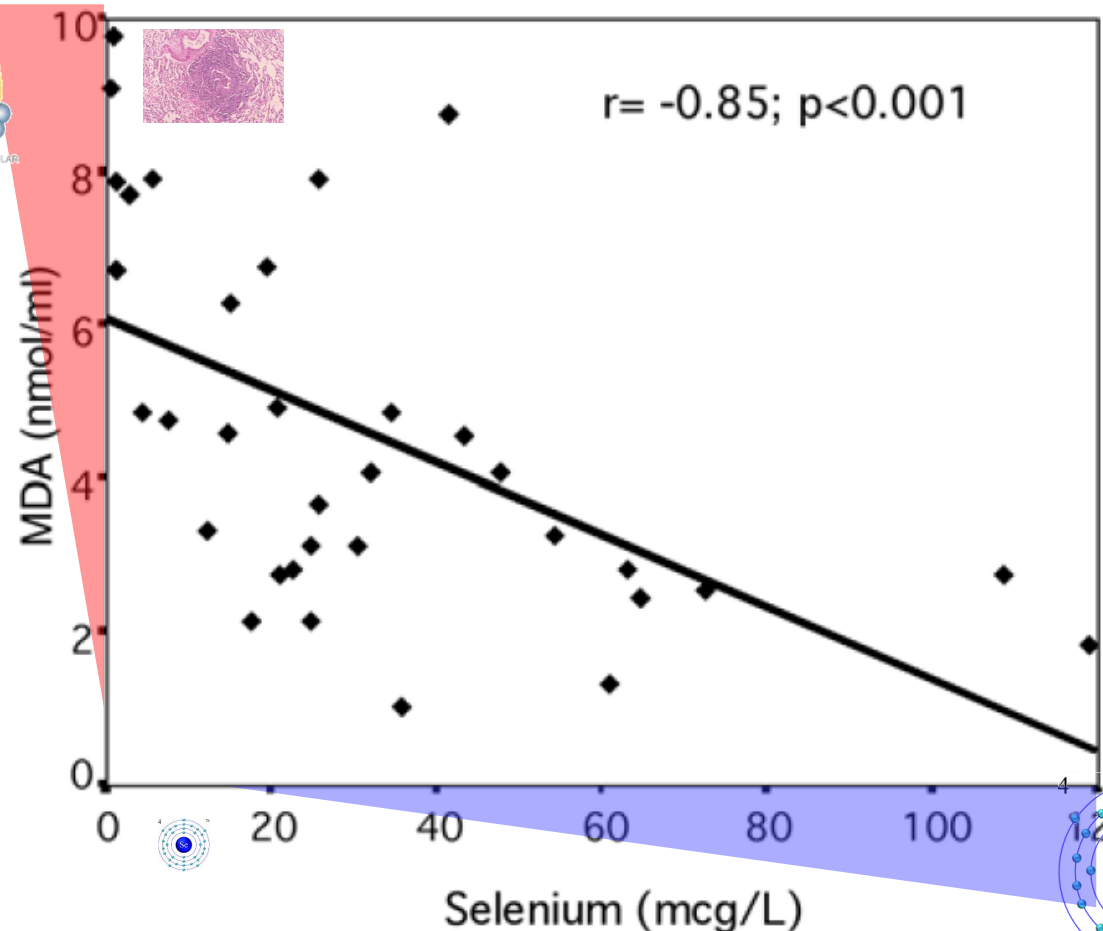
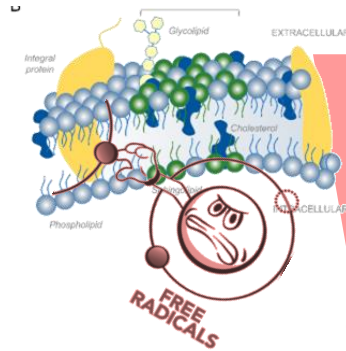
Conclusion:

The balance between oxidant and antioxidant systems is disrupted in children with moderate bronchiolitis, which indicates that this stress factor may have a role in the pathogenesis of the disease.

Relationship among serum selenium levels, lipid peroxidation, and acute bronchiolitis in infancy.

Gurkan F, Biol Trace Elem Res. 2004 Aug;100(2):97-104.

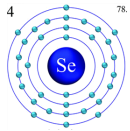
Correlation between serum Se and MDA levels in children with acute bronchiolitis.



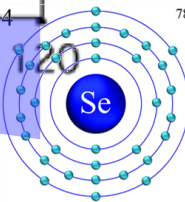
✓ 34 infants with acute bronchiolitis

✓ 25 age-matched healthy controls

✓ serum malondialdehyde (MDA) and selenium (Se) levels

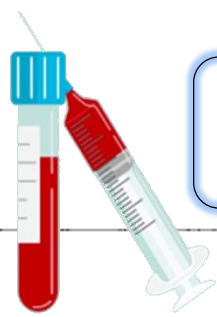


✓ occurrence and severity of acute bronchiolitis in children.



Relationship among serum selenium levels, lipid peroxidation, and acute bronchiolitis in infancy.

Gurkan F, Biol Trace Elem Res. 2004 Aug;100(2):97-104.



Blood was taken again from the children with bronchiolitis at 2 mo after discharge from the hospital.

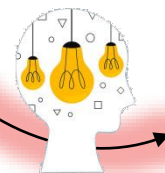


	Acute Bronchiolitis (n=34)	Postbronchiolitis Stage (n=34)	Control (n=25)	P
Male/female ratio	22/12	22/12	16/9	NS
Age (months)	9.0±6.8	9.0±6.8	11.5±8.9	NS
Se (mcg/L)	31.7±28.9	68.4±26.4	145±21.9	<0.001 ^a , <0.001 ^b
MDA (nmol/ml)	4.2±2.5	1.4±0.8	0.7±0.2	<0.001 ^a , <0.001 ^b
Clinical score	6.8±1.8	0	0	<0.001

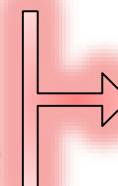
Note: Age, Se, MDA, and score values are expressed as mean±SD. NS = not significant.

^a Between acute and postbronchiolitis stages.

^b Between acute bronchiolitis and controls.



Recurrent
Wheezing
Bronchitis



ASTHMA & COPD

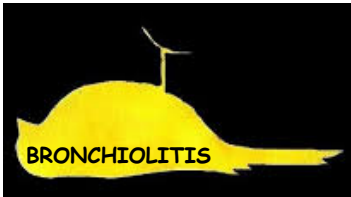


< 73 yrs ?

Early-life respiratory infection: How do we react to this red flag?



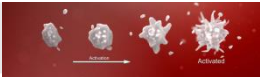

Bush A, Pediatr Pulmonol. 2024 Jun;59(6):1817-1819.



We suggest the following should at least be considered:

- 1. Measure micronutrient status in all babies at high risk (e.g., preterm delivery) and supplement those who are deficient.
- 2. Measure micronutrient status and supplement as above in all babies and infants admitted to hospital with bronchiolitis.

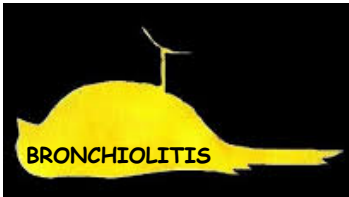
TABLE 1 Biological effects of different nutritional components.

	Vitamin B	Vitamin C	Vitamin D	Vitamin E	Magnesium	Selenium	Zinc	Phytochemicals
Antiviral activity			✓			✓	✓	✓
Immune modulation	✓	✓	✓	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	✓	✓	✓	✓	✓
Auto-immunity prevention		?	✓	?	?	✓	✓	✓
Antioxidant effect	✓	✓	✓	✓	✓	✓	✓	✓
Anti-thrombotic effect			✓	✓	✓	✓		✓
Endothelial protective	✓		✓	✓	✓	✓	✓	✓
Cytoprotective & organ damage prevention	✓		✓	✓	✓	✓		✓
Antiarrhythmic effect			✓		✓	?		✓
Antidepression effect	✓		✓		?	?	✓	✓
Microbiome	✓		✓	✓		?	?	✓

Early-life respiratory infection: How do we react to this red flag?



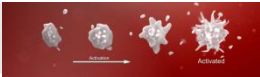
Bush A, Pediatr Pulmonol. 2024 Jun;59(6):1817-1819.



We suggest the following should at least be considered:

- 1. Measure micronutrient status in all babies at high risk (e.g., preterm delivery) and supplement those who are deficient.
- 2. Measure micronutrient status and supplement as above in all babies and infants admitted to hospital with bronchiolitis.

TABLE 1 Biological effects of different nutritional components.

	Vitamin B	Vitamin C	Vitamin D	Vitamin E	Magnesium	Selenium	Zinc	Phytochemicals
Antiviral activity			✓			✓	✓	✓
Immune modulation	✓	✓	✓	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	✓	✓	✓	✓	✓
Auto-immunity prevention		?	✓	?	?	✓	✓	✓
Antioxidant effect	✓	✓	✓	✓	✓	✓	✓	✓
Anti-thrombotic effect				✓	✓	✓	✓	✓
Endothelial protective	✓		✓	✓	✓	✓	✓	✓
Cytoprotective & organ damage prevention	✓		✓	✓	✓	✓	✓	✓
Antiarrhythmic effect			✓	✓	✓	✓	✓	✓
Antidepression effect	✓		✓	✓	✓	✓	✓	✓
Microbiome	✓		✓	✓		?	?	✓

Sinergistic Effect



National Library of Medicine
National Center for Biotechnology Information

Log in

Why supplementing the nursing mother & older siblings?

PubMed.gov

October 2nd 2024

virus inhibition and

Search

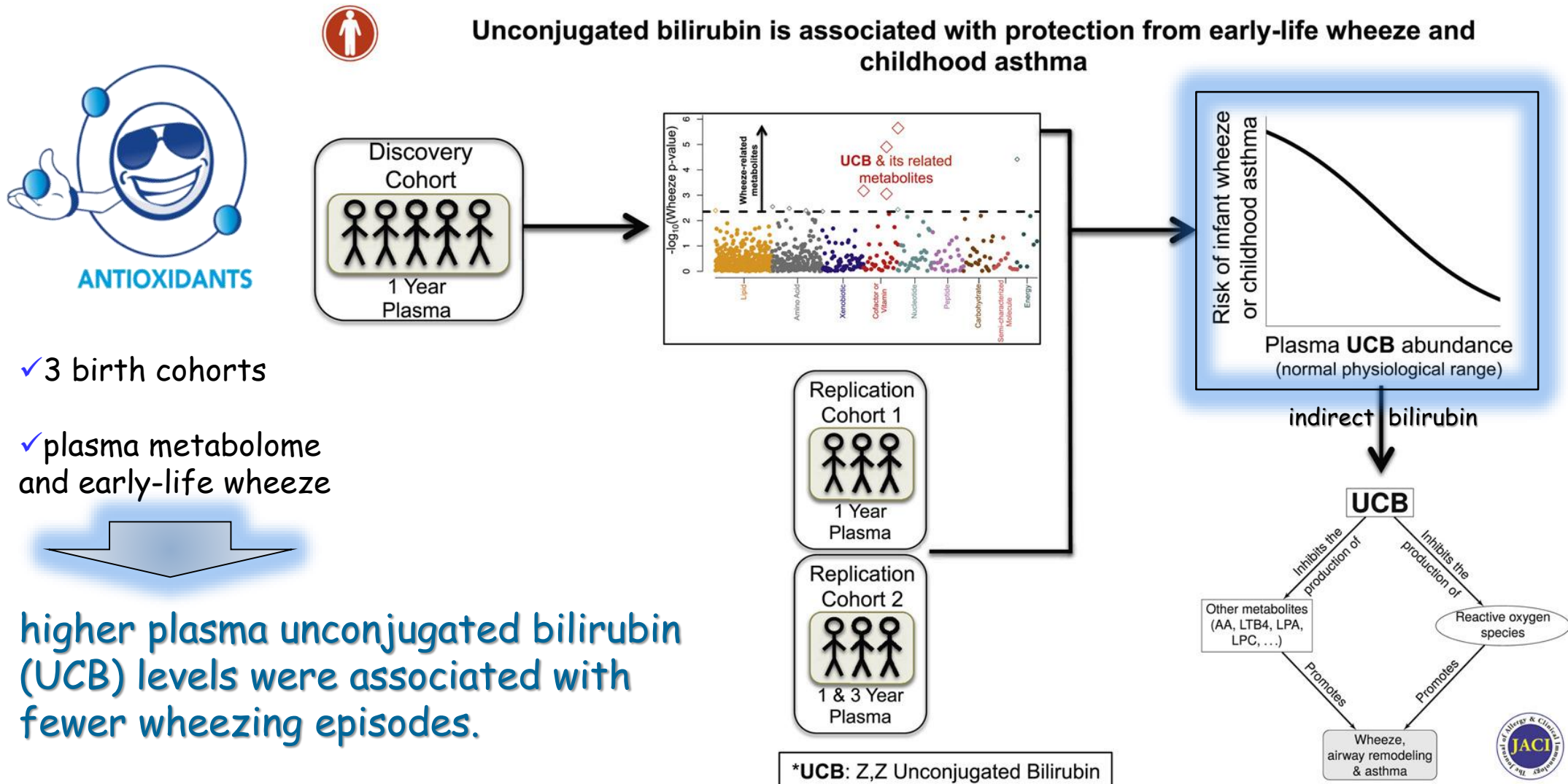
Advanced

PubMed® comprises more than 32 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full text content from PubMed Central and publisher web sites.

- virus inhibition and magnesium: 496 results
- virus inhibition and selenium: 149 results
- virus inhibition and zinc: 1259 results
- virus inhibition and polyphenols: 554 results

Unconjugated bilirubin is associated with protection from early-life wheeze and childhood asthma.

Turi KN, *J Allergy Clin Immunol*. 2021 Jul;148(1):128-138.



Bilirubin: The yellow hormone?

Vítek L, *J Hepatol.* 2021 Dec;75(6):1485-1490.

❖ lower incidence of diseases of civilisation:

- ❖ cardiovascular diseases,
- ❖ arterial hypertension,
- ❖ diabetes,
- ❖ obesity,
- ❖ metabolic syndrome,
- ❖ certain cancers,
- ❖ autoimmune diseases,
- ❖ neurodegenerative diseases.



ANTIOXIDANTS

Non-Communicable Diseases



Cardiovascular
Diseases



Diabetes



Chronic Respiratory
Diseases



Cancer

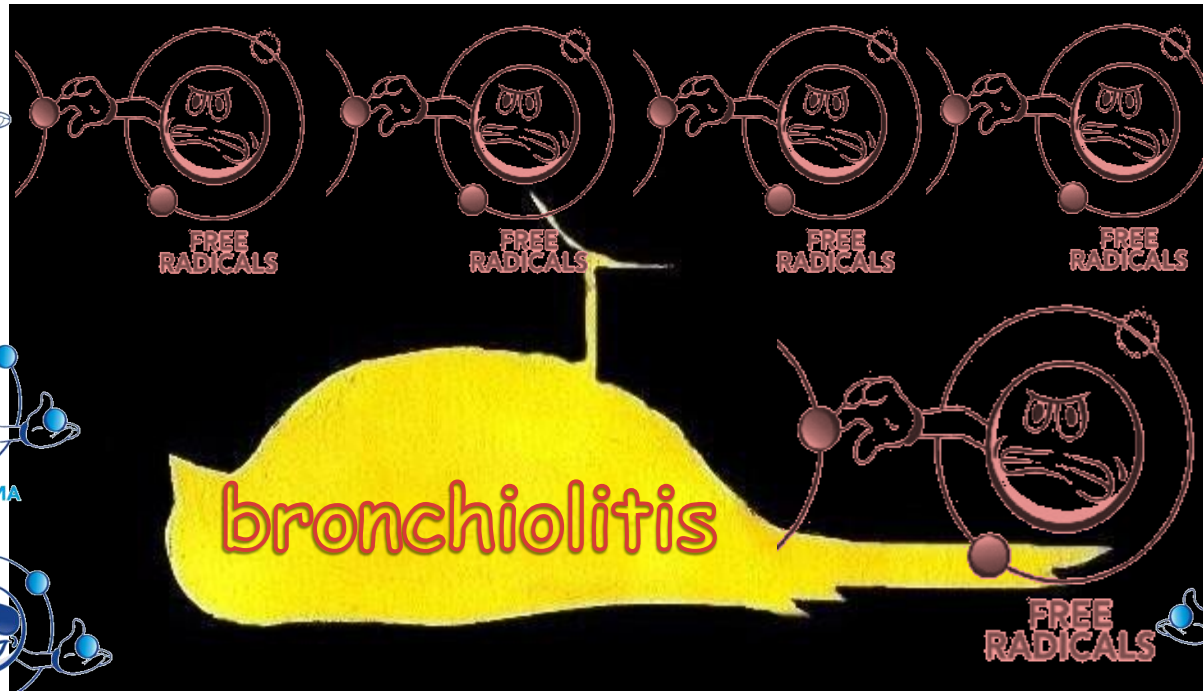
➤ individuals with a chronic mild unconjugated hyperbilirubinemia, a typical sign of Gilbert's syndrome.



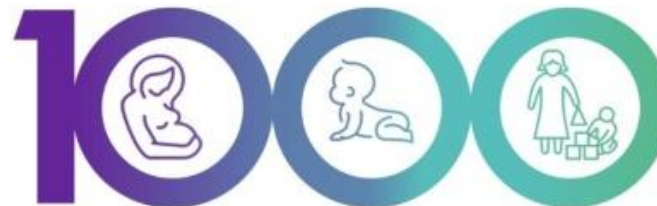
Take home message



ANTIOXIDANTS



ANTIOXIDANTS

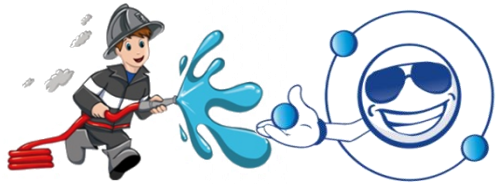


PREGNANCY
270 DAYS

YEAR 1
365 DAYS

YEAR 2
365 DAYS

Oligoelements & Polyphenols as non-specific antivirals and in general health



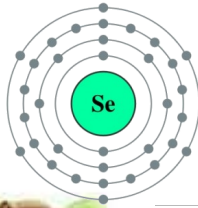
ANTIOXIDANTS



curcumin



sulforaphane



Vitamin E



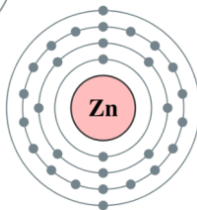
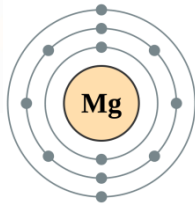
quercetin



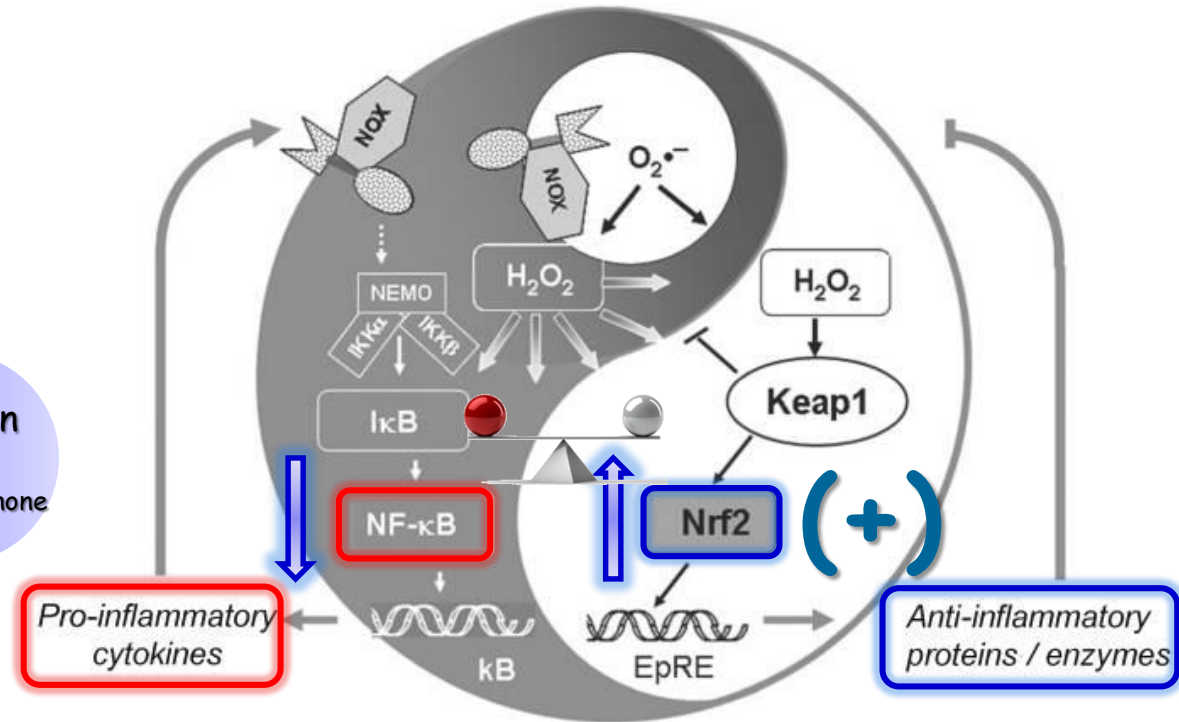
Vitamin K2
7-metakinone



resveratrol



Transcription factors involved in the process of converting, or transcribing, DNA into RNA.



MULTIPLE MICRONUTRIENTS
Multiple advantages not only on immunity

Mistakes to Avoid in the Management of Children's Respiratory Diseases to Plan Long Term Health



Attilio Boner
University of
Verona, Italy

attilio.boner@univr.it



335 6274799

- ✓ Introduction
- ✓ Why is avoiding mistakes important?
The long-term consequences of early respiratory diseases
- ✓ Early respiratory diseases: "a canary in the mine"
- ✓ 10 Mistakes to avoid
- ✓ Summary & Conclusions



1° errore: Non rispettare l'ambiente

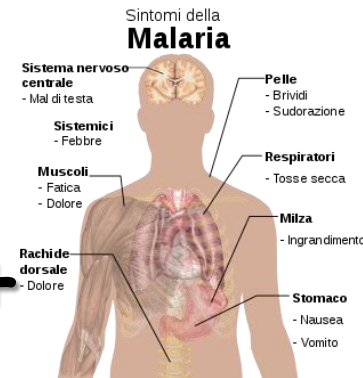
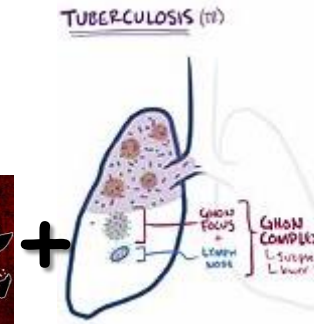


❖ **Pollution** is the largest environmental cause of disease and premature death in the world today.

❖ Diseases caused by pollution were responsible for an estimated:

■ **9 million premature deaths in 2015—**

- 16% of all deaths worldwide— **>3X**
- 3 times more deaths than from AIDS, tuberculosis, and malaria combined
- 15 times more than from all wars and other forms of violence.



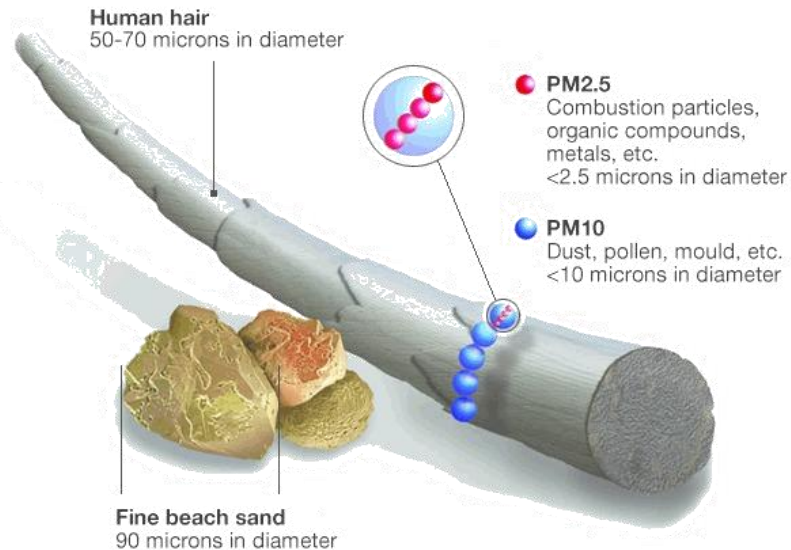
How Much Pollution Do We Breathe Every Day?

we breathe between 4.5-42.5L
of air per minute
(depending on the activity we're doing)

we're breath around:

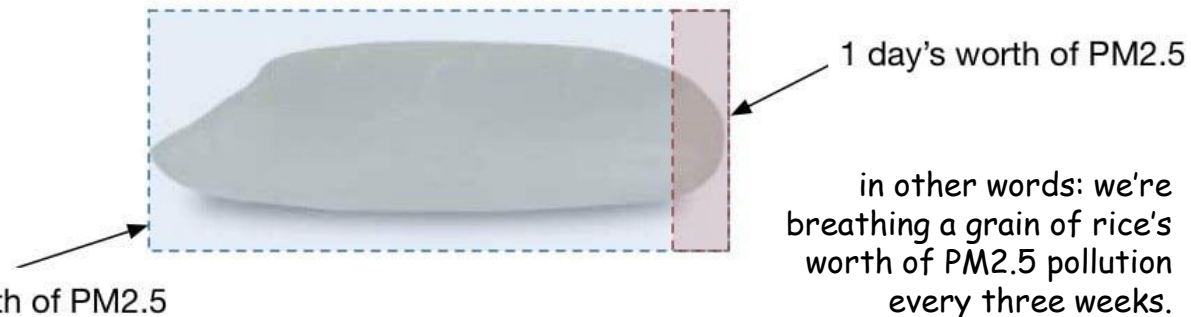
220 million tiny PM_{2.5}
particles every day,

just over 2,500 per second.



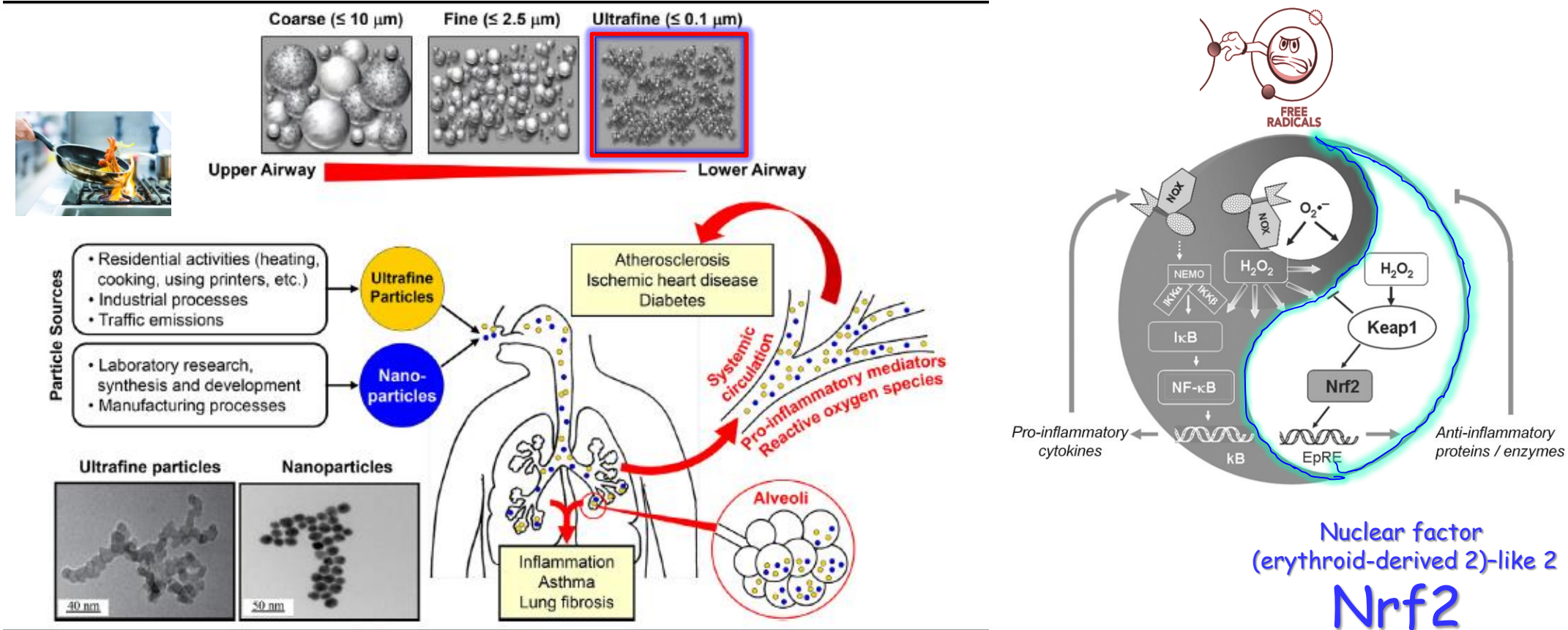
Source: US EPA

Looking at their weight, in one day we're breathing 622 micrograms
of PM_{2.5}! about the equivalent of 1/20th of a grain of rice.



A work group report on **ultrafine particles** (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects.

Li N, J Allergy Clin Immunol. 2016;138(2):386-96.



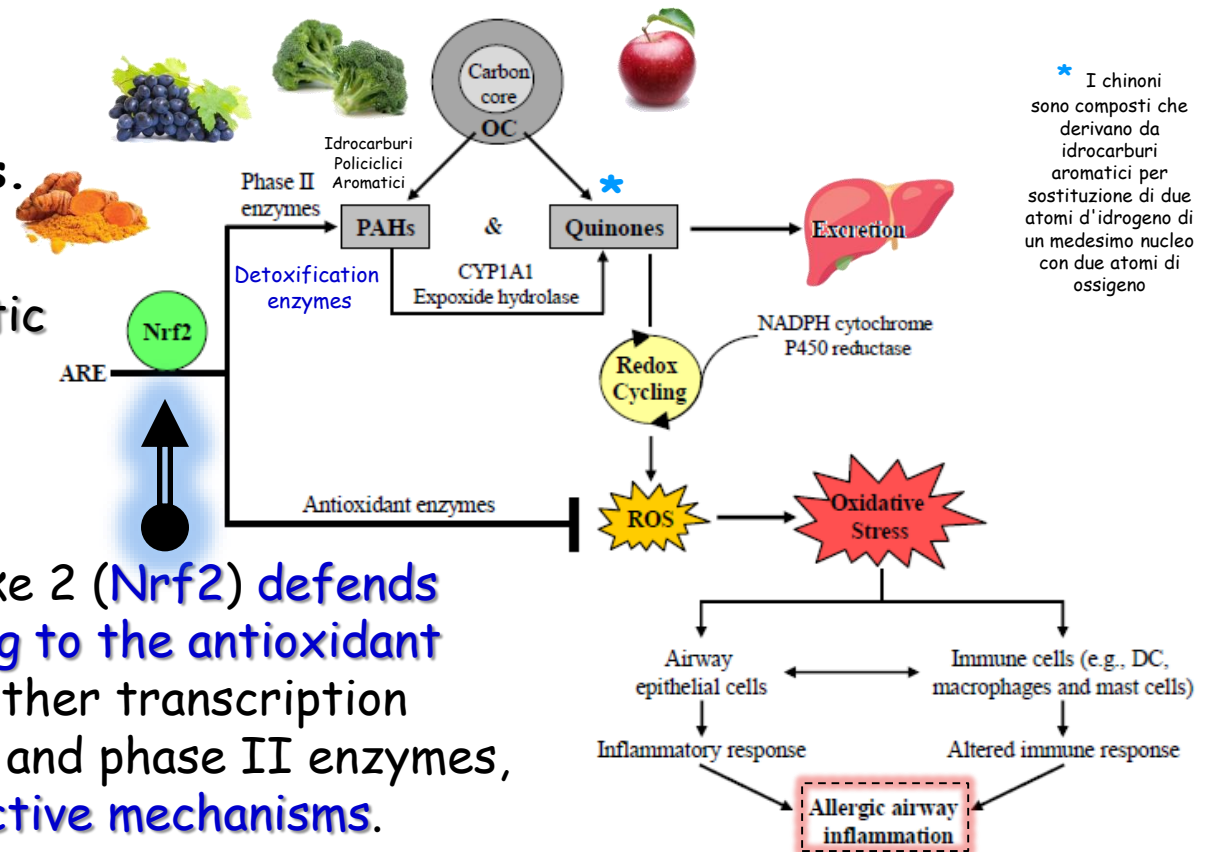
A work group report on **ultrafine particles** (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects.

Li N, J Allergy Clin Immunol. 2016;138(2):386-96.

Generation of oxidative stress by
ambient UFPs and its role in allergic
airway inflammation and aging diseases.

UFPs carry a large amount of **Organic Carbon (OC)**, including **Polycyclic Aromatic Hydrocarbons (PAHs)** which stimulates **ROS production** and are transformed by **Phase II enzymes** in **Quinones**.

Nuclear factor (erythroid-derived 2)-like 2 (**Nrf2**) defends cells against oxidative injuries by binding to the antioxidant response element (**ARE**) together with other transcription factors in the promoters of antioxidant and phase II enzymes, leading to activation of effective protective mechanisms.



coronary heart disease- cancer - non communicable diseases

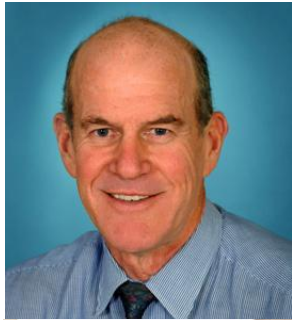
Incluso l'ambiente intrauterino

Thorax 2000;55:1063–1067



Paediatric origins of adult lung diseases • 4

Series editors 



Tobacco related lung diseases begin in childhood

P N Le Souëf

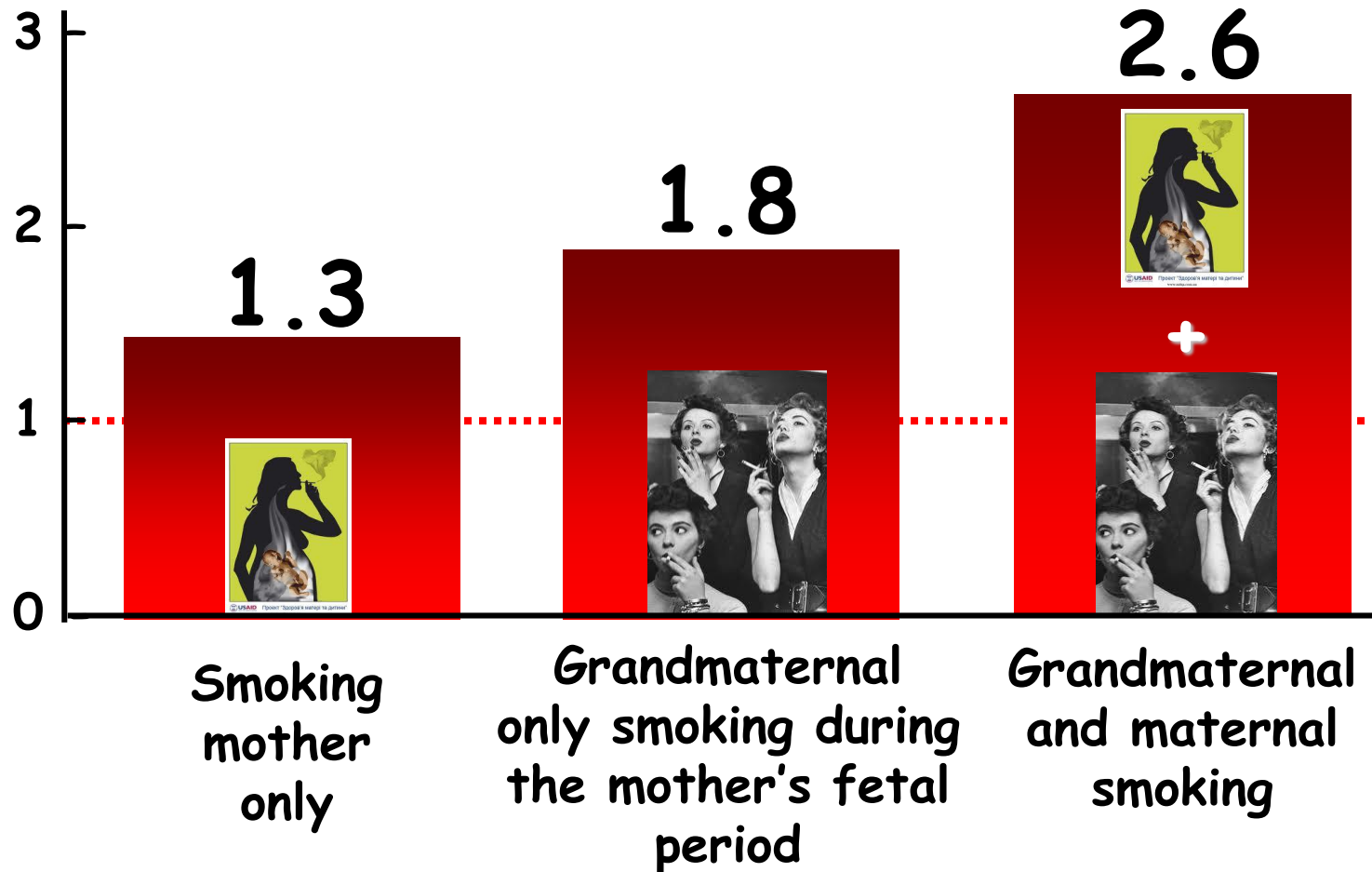


- prematurity
- low birthweight
- worse lung function
- respiratory infections
- asthma
- chronic obstructive pulmonary disease

Maternal and grandmaternal smoking patterns are associated with early childhood asthma.

Li YF, Chest. 2005;127(4):1232-41.

OR for asthma in the first 5 years of life



✓ 338 children with asthma diagnosed in the first 5 years of life

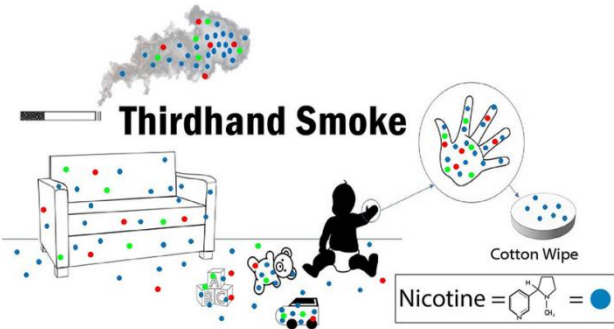
✓ 570 control subjects

Long-term exposure to third-hand smoke could accelerate biological aging via mitochondrial dysfunction: Evidence from population and animal studies.

Jiang W, J Hazard Mater. 2024 Oct 4;480:136061.

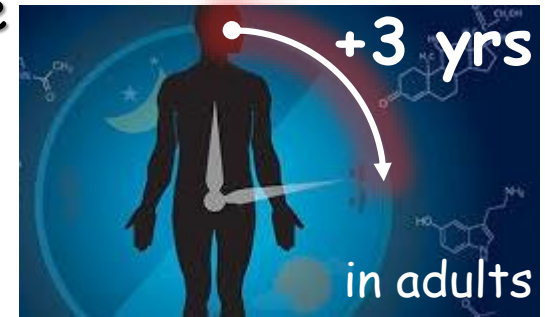
✓ third-hand smoke (THS) exposure

residual tobacco smoke pollutants that adhere to surfaces such as walls, furniture, and clothing.

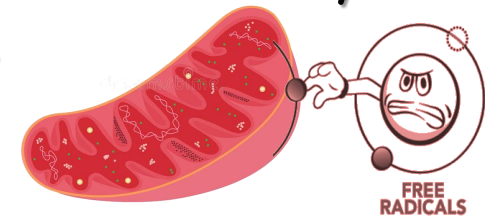


➤ **Biological Age** in 986 non-smoking participants mean age 40 ± 8 yrs

➤ exposed individuals exhibiting an average increase in biological age of 3.04 years compared to their unexposed counterparts ($p < 0.05$).



➤ Proteomic analyses identified MRPL2 as a pivotal protein in THS-induced aging, linking its expression to mitochondrial dysfunction and oxidative stress.

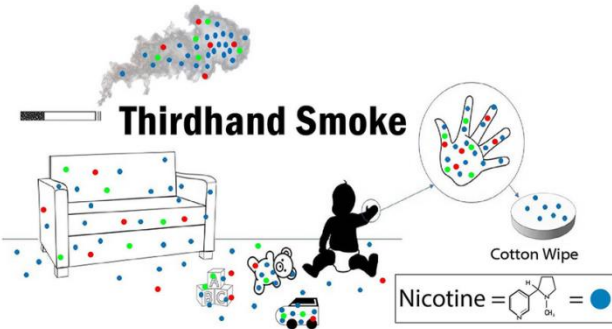


Long-term exposure to third-hand smoke could accelerate biological aging via mitochondrial dysfunction: Evidence from population and animal studies.

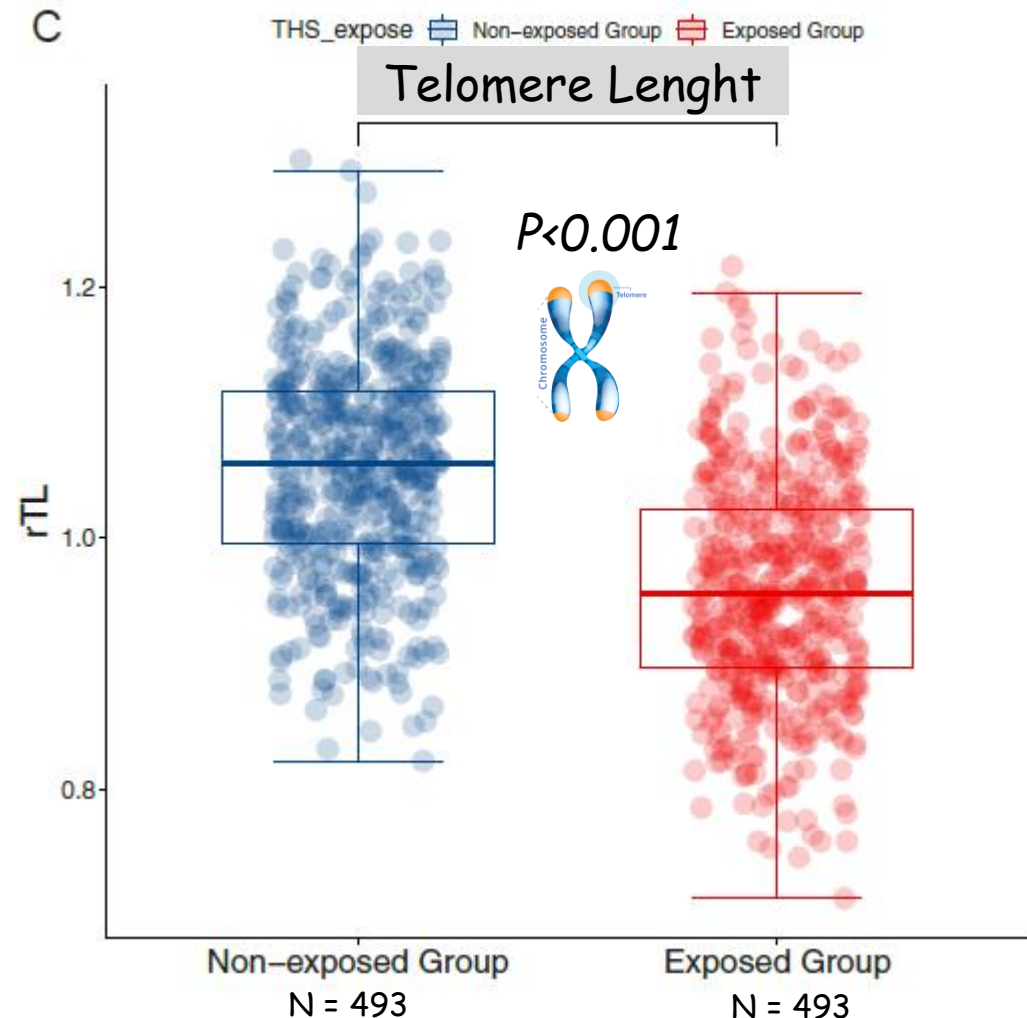
Jiang W, J Hazard Mater. 2024 Oct 4;480:136061.

✓ third-hand smoke (THS) exposure

residual tobacco smoke pollutants that adhere to surfaces such as walls, furniture, and clothing.

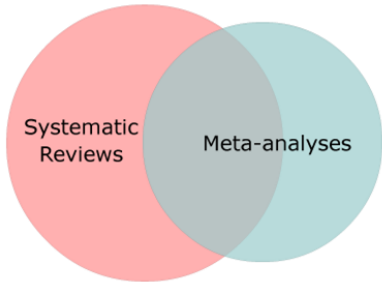


➤ **Biological Age** in 986 non-smoking participants mean age 40.22 (8.29) yrs



Courtesy of Dr. Luigi Terracciano

2° errore: Non utilizzare tutti i sistemi di comunicazione e di educazione per favorire l'allattamento al seno nei primi mesi di vita



❖ Non-breastfeeding practices are a significant risk factor for RSV hospitalization.

❖ Exclusive breastfeeding for >4-6 months significantly lowered:

1. admission rates,
2. length of stay
3. supplemental oxygen use,
4. unscheduled GP visits,
5. emergency department presentation.

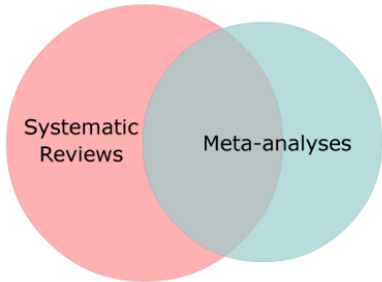


✓ 29 articles on impact of breastfeeding on the incidence and severity of RSV bronchiolitis in infants.



Mineva G. Impact of breastfeeding on the incidence and severity of respiratory syncytial virus bronchiolitis in infants: systematic review. Rural Remote Health. 2023 Jan;23(1):8088.

2° errore: Non utilizzare tutti i sistemi di comunicazione e di educazione per favorire l'allattamento al seno nei primi mesi di vita



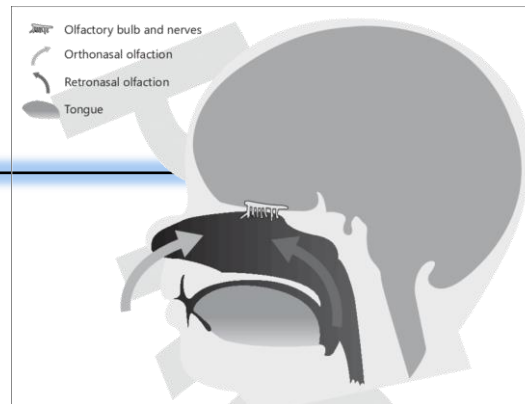
✓ 29 articles on impact of breastfeeding on the incidence and severity of RSV bronchiolitis in infants.



Mineva G. Impact of breastfeeding on the incidence and severity of respiratory syncytial virus bronchiolitis in infants: systematic review. Rural Remote Health. 2023 Jan;23(1):8088.

3°: Non incoraggiare la madre nutrice, ma ancor prima durante la gravidanza, ad assumere tutti i tipi di verdura e frutta di stagione.

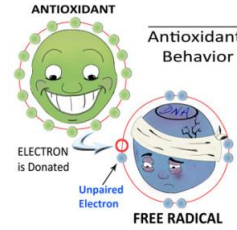
- Chemosensory systems (taste and olfaction) are functional before birth and continue to mature throughout childhood.
- Children live in their own flavor world, preferring foods that are high in sugar and salt over those that are sour (aciduli) and bitter tasting, such as fruits and vegetables.
- Flavor preferences can be 'fine tuned' by sensory experiences beginning prenatally.
- Through exposure to the flavors of amniotic fluid and breast milk, which reflect the foods within the mother's diet, infants become more accepting of foods within their culture



Forestell CA. The Development of Flavor Perception and Acceptance: The Roles of Nature and Nurture. Nestle Nutr Inst Workshop Ser. 2016;85:135-43.

Dietary total antioxidant capacity in early school age and subsequent allergic disease.

Gref A, Clin Exp Allergy. 2017;47(6):751-759



aOR of
allergic asthma
by adolescence



TAC of the diet for the 3rd
compared to the 1st tertile
at age 8 years

- ✓ 2359 children from the Swedish birth cohort BAMSE
- ✓ Dietary total antioxidant capacity (TAC) at age 8 years estimated by combining information on the child's diet the past 12 months from a food frequency questionnaire with a database of common foods analysed with the oxygen radical absorbance capacity method.
- ✓ asthma and rhinitis was based on questionnaires, and serum IgE antibodies were measured at 8 and 16 years.

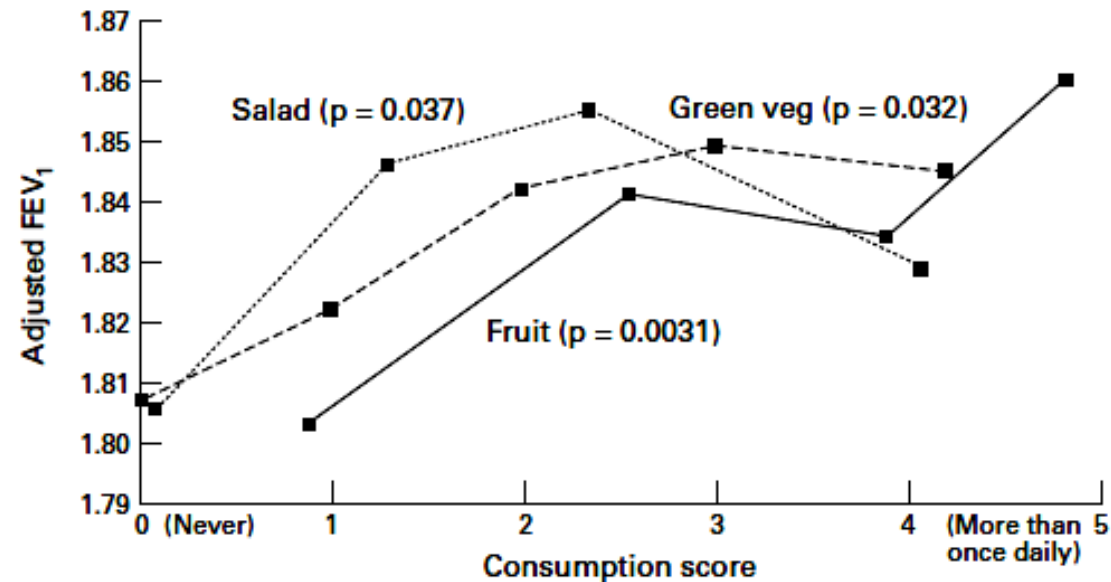
Effect of fresh fruit consumption on lung function and wheeze in children

Cook DG, Thorax 1997;52:628-633



Relationship between frequency of consumption of fresh fruit, salad, and green vegetables and FEV₁

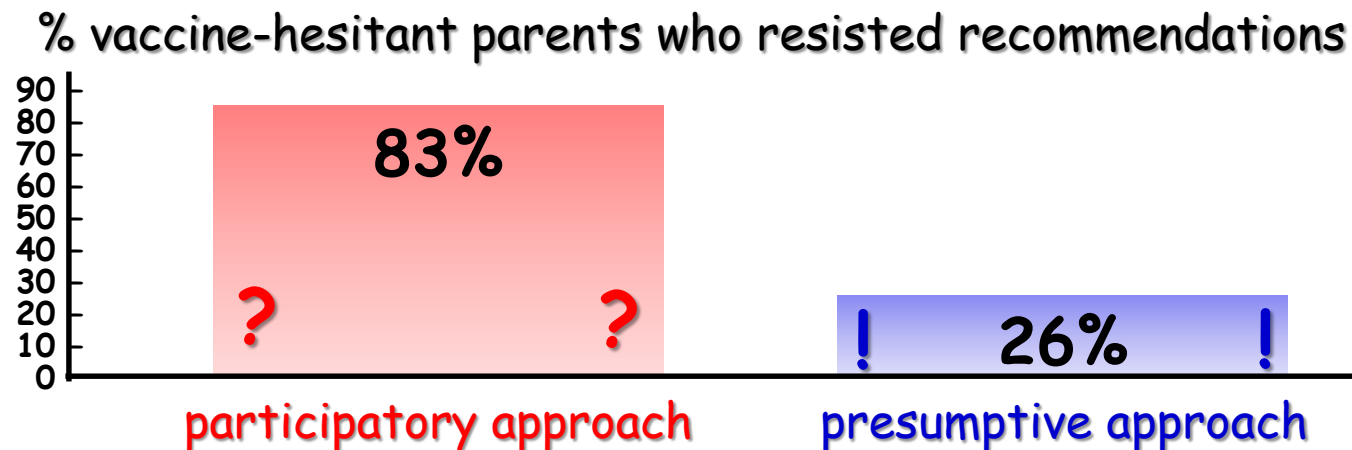
- ✓ 2650 children aged 8-11 yrs from 10 towns in England and Wales
- ✓ FEV₁
- ✓ A food frequency questionnaire



4° errore :Discutere l'importanza delle vaccinazioni con un approccio partecipativo invece che presuntivo

Give a Strong Recommendation

Opening the immunization conversation with a **presumptive approach** (approccio presuntivo) rather than a **participatory approach** (approccio partecipativo) (e.g., saying "We have to do some shots," rather than asking, "What do you want to do about shots?") can dramatically decrease resistance to vaccine recommendations. *Opel DJ, JAMA Pediatr. 2013;167(11):1065-1071.*



4° errore :Discutere l'importanza delle vaccinazioni con un approccio partecipativo invece che presuntivo

Give a Strong Recommendation

Opening the immunization conversation with a **presumptive approach** (approccio presuntivo) rather than a **participatory approach** (approccio partecipativo) (e.g., saying "We have to do some shots," rather than asking, "What do you want to do about shots?") can dramatically decrease resistance to vaccine recommendations. *Opel DJ, JAMA Pediatr. 2013;167(11):1065-1071.*

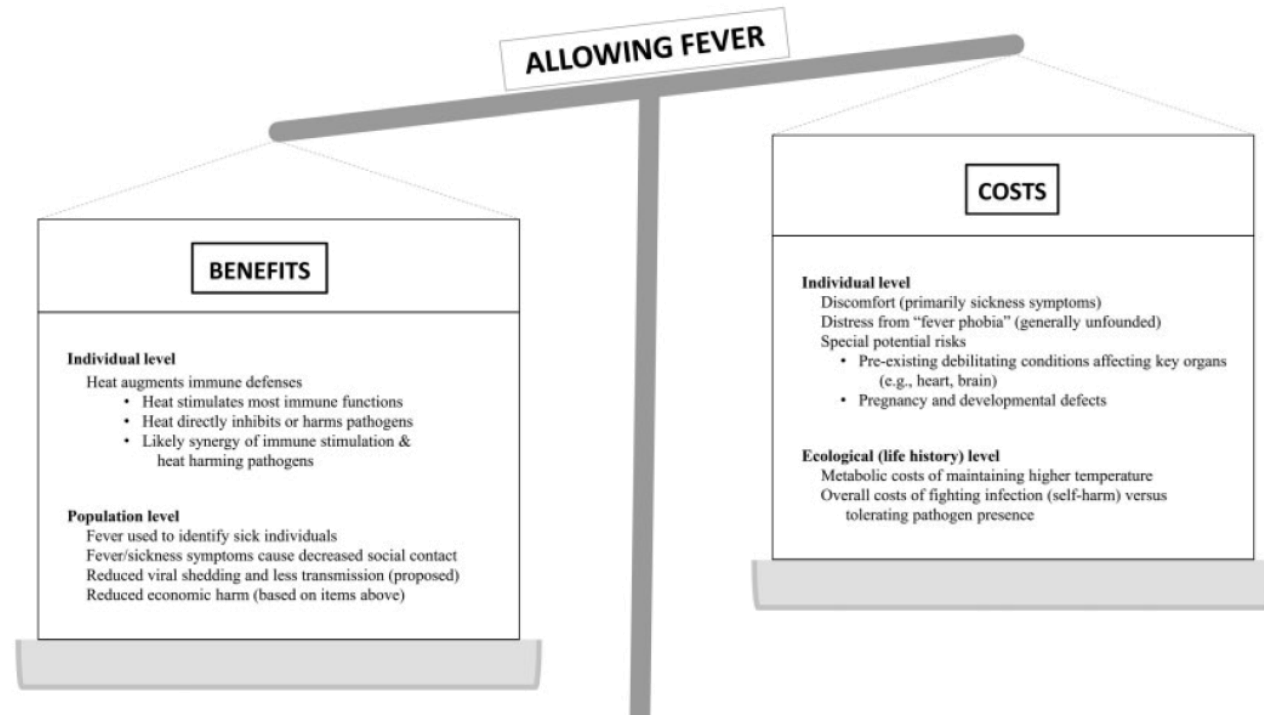


5° errore: Istruire i genitori ad usare sempre il paracetamolo quando la febbre supera i 38,5°C.

• Questa informazione, nota ad ogni genitore, dimentica che la **FEBBRE**, oltre ad essere un importante **segnale di malattia** che evita al medico importanti errori diagnostici, *Najaf-Zadeh A, Epidemiology and aetiology of paediatric malpractice claims in France. Arch Dis Child 2011; 96(2): 127-30.*

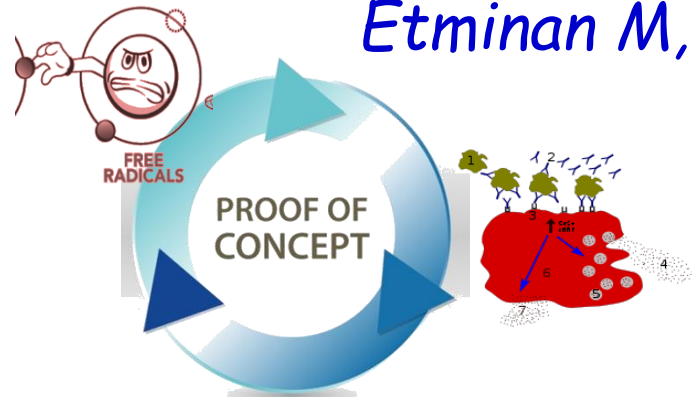


• è il piu prezioso **alleato** contro le infezioni virali. *Wrotek S, Let fever do its job: The meaning of fever in the pandemic era. Evol Med Public Health 2021; 9(1): 26-35.*

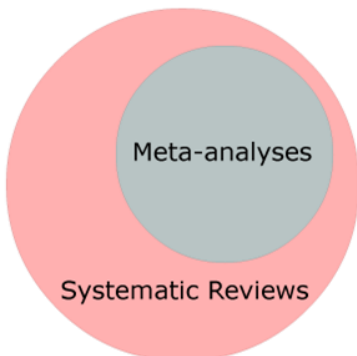


Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis.

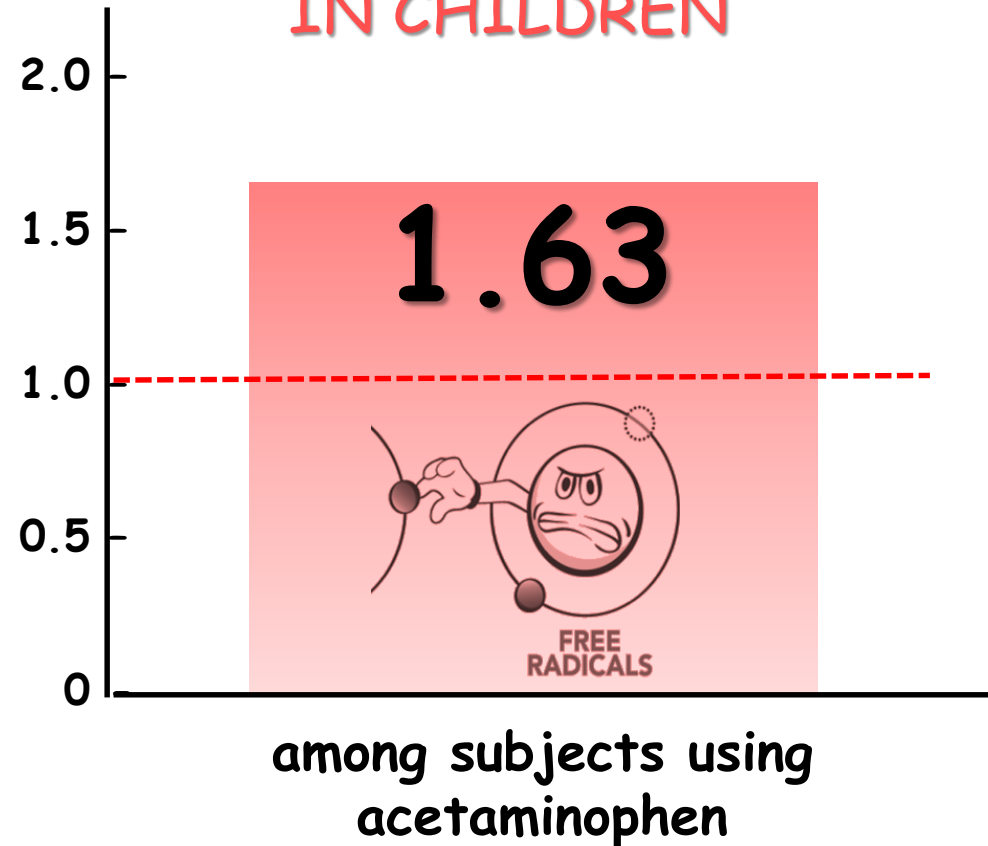
Etminan M, Chest. 2009 Nov;136(5):1316-1323.



- ✓ 13 cross-sectional studies
- ✓ 4 cohort studies
- ✓ 2 case-control studies
- ✓ 425,140 subjects



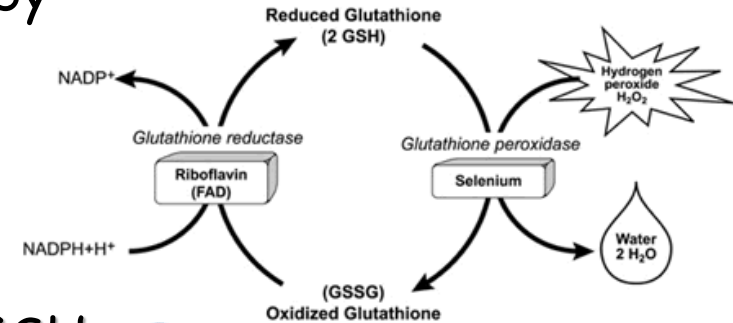
**OR FOR ASTHMA
IN CHILDREN**



The acetaminophen (APAP or paracetamol) enigma in asthma.

Holgate ST. Am J Respir Crit Care Med. 2011 Jan 15;183(2):147-8.

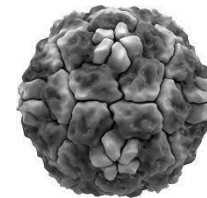
- APAP metabolite decreases glutathione[GSH], thereby augmenting oxidative damage and airway inflammatory responses either directly or by enhancing Th2 cell polarization.



- It is important to maintain high concentrations of GSH in the airways as a powerful anti-oxidant.



- APAP has been shown to reduce the immune response to, and to prolong, rhinovirus infection, a strong risk factor for developing asthma at age 6 years .

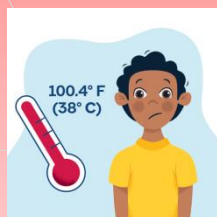


- APAP inhibits the transcriptional response to IFN- β and λ provides a further link to virus infection.

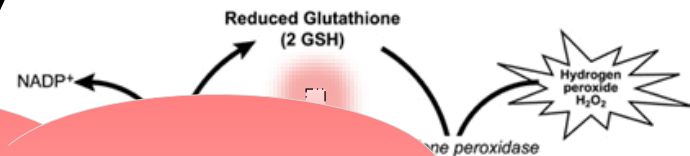
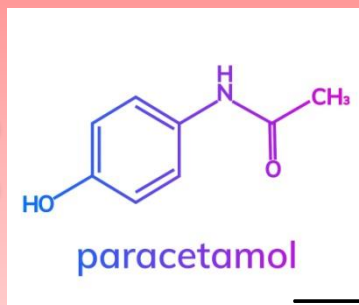


Infections = Fever = Acetaminophen

- APAP metabolite decreases glutathione [GSH], thereby augmenting oxidative damage and airway inflammatory responses either directly or by enhancing the effect of oxidants.



=



PubMed.gov

October 3rd 2024

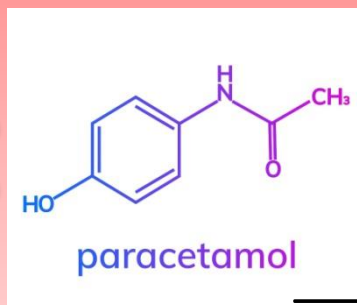
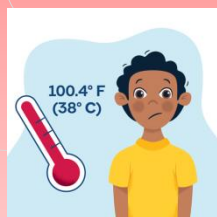
acetaminophen and oxidative stress = 1,635 results
acetaminophen and allergy development = 278 results

Search

PubMed® comprises more than 32 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full text content from PubMed Central and publisher web sites.

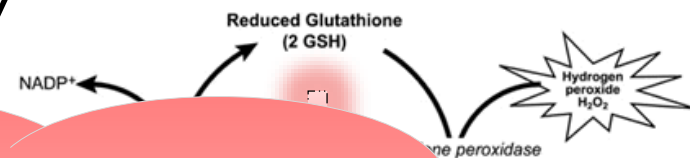
Infections = Fever = Acetaminophen

- APAP metabolite decreases glutathione [GSH], thereby augmenting oxidative damage and airway inflammatory responses either directly or by enhancing the effect of



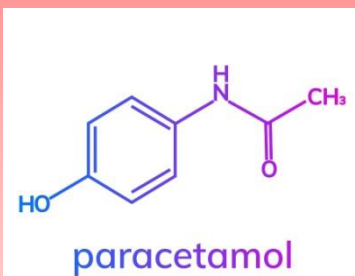
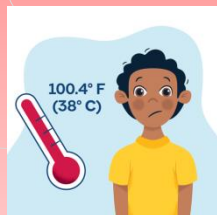
oxidative stress

balance



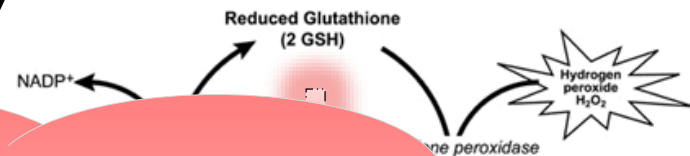
Infections = Fever = Acetaminophen

- APAP metabolite decreases glutathione [GSH], thereby augmenting oxidative damage and airway inflammatory responses either directly or by enhancing the effect of oxidants



oxidative stress

balance

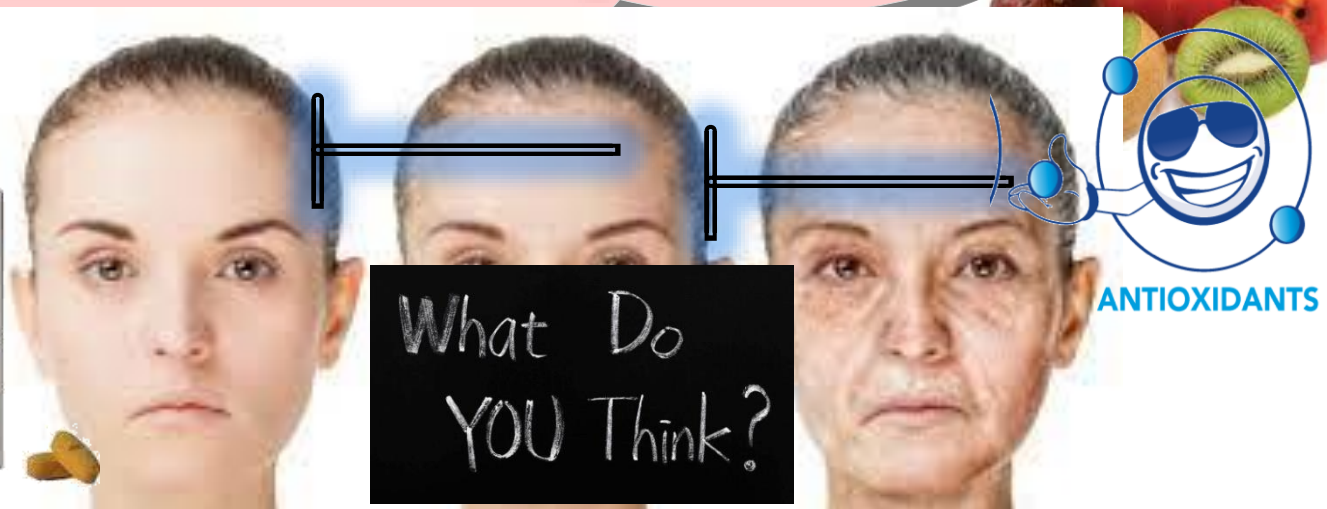


- APAP metabolite

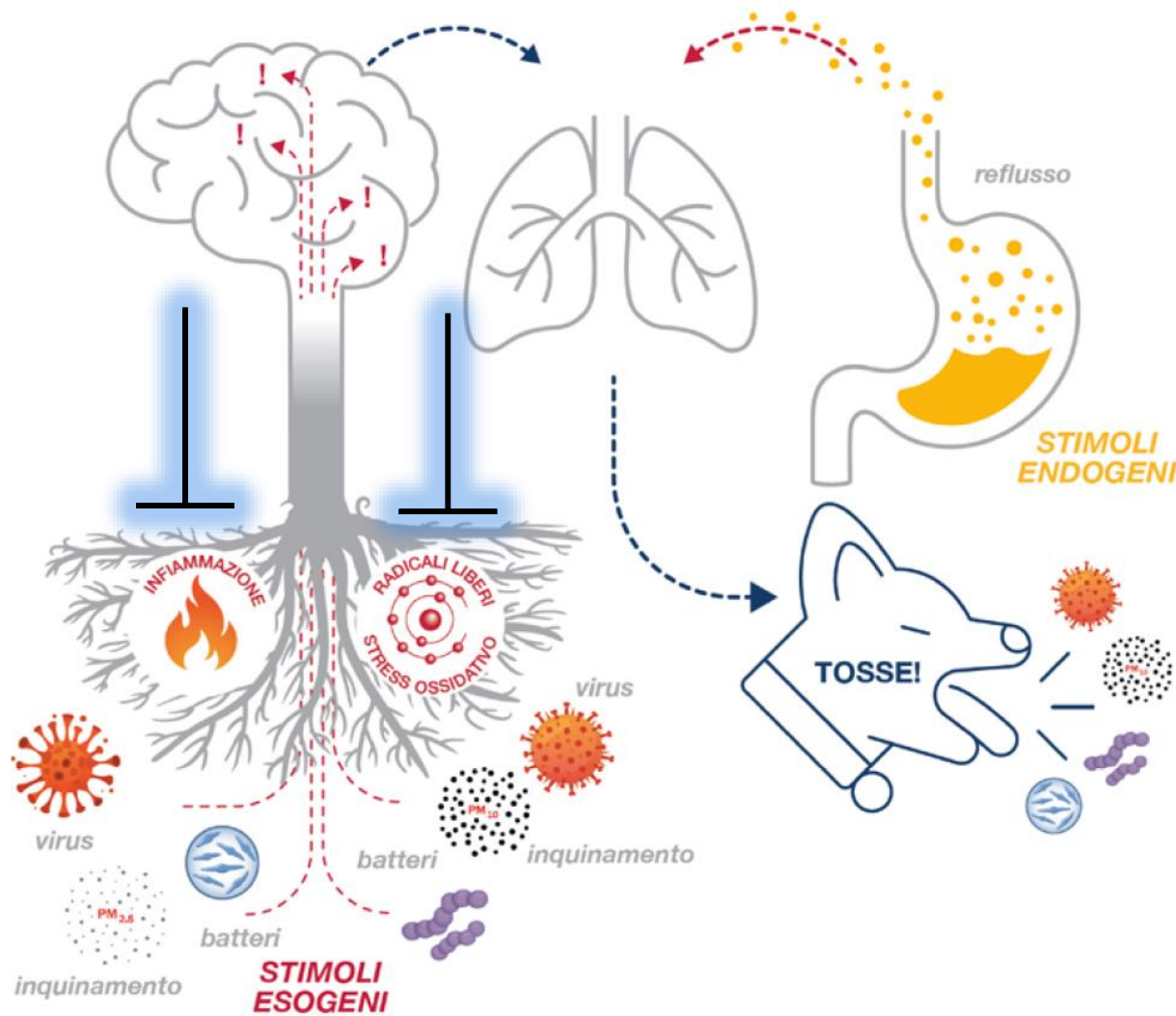
an
fo



- Al
pr



6° errore: Bloccare il riflesso della tosse.



❖ La tosse è
“il cane da guardia
delle vie aeree”,
pertanto
non dovrebbe essere **sedata**,
MA
si dovrebbe piuttosto
cercare di attenuare
gli stimoli che la evocano
intervenedo sulle
“radici profonde”
del problema.



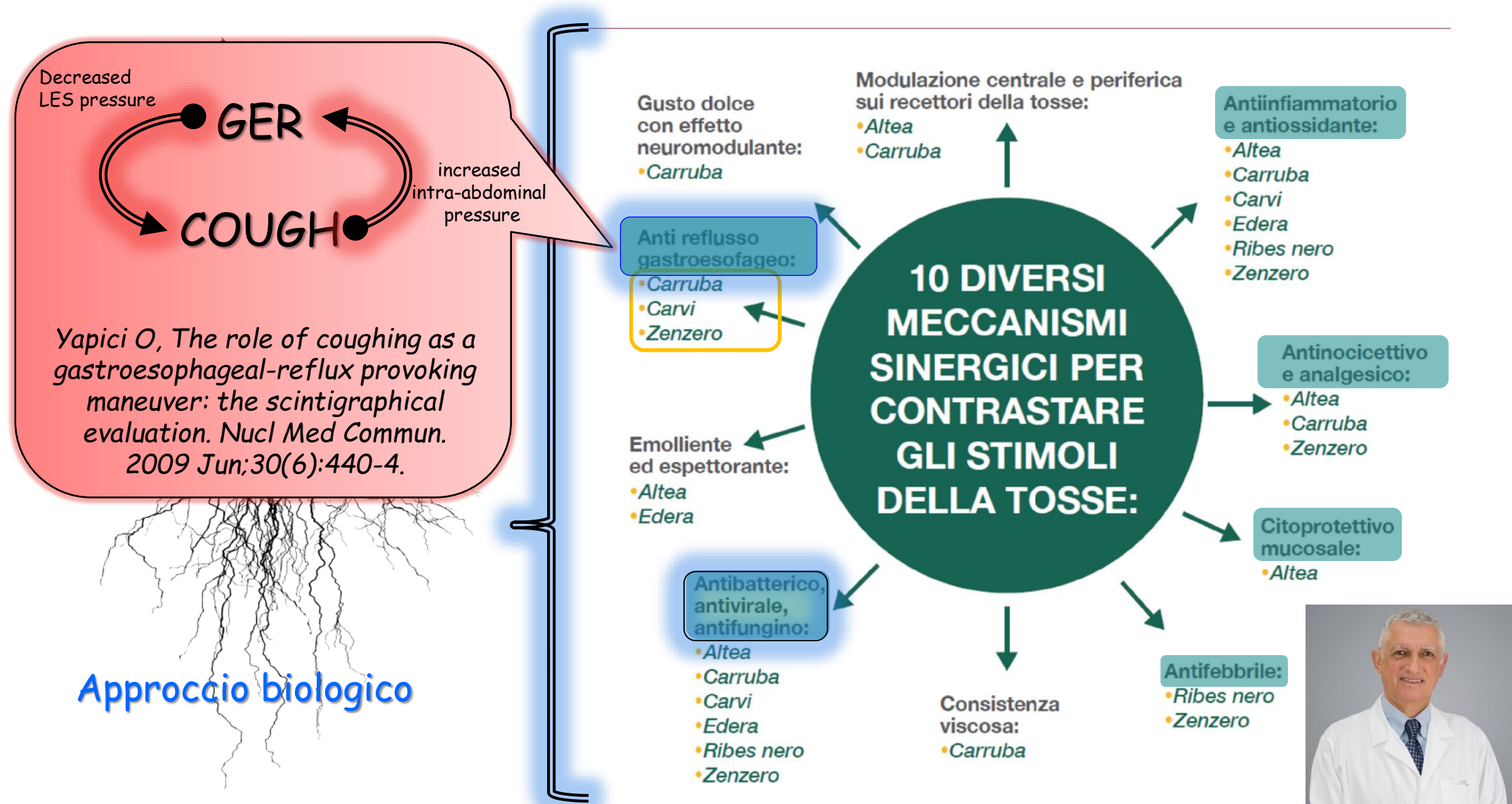
❖ La tosse viene utilizzata da
virus e batteri per infettare
nuovi ospiti

6° errore: Bloccare il riflesso della tosse.



Kantar A , Prodotti naturali di origine vegetale che attenuano il riflesso della tosse durante l'infezione acuta virale. *Il Medico Pediatra* 2024;33(1):26-35.

6° errore: Bloccare il riflesso della tosse.



Kantar A. Well-Established and Traditional Use of Vegetal Extracts as an Approach to the "Deep Roots" of Cough. Children (Basel). 2024 May 11;11(5):584.

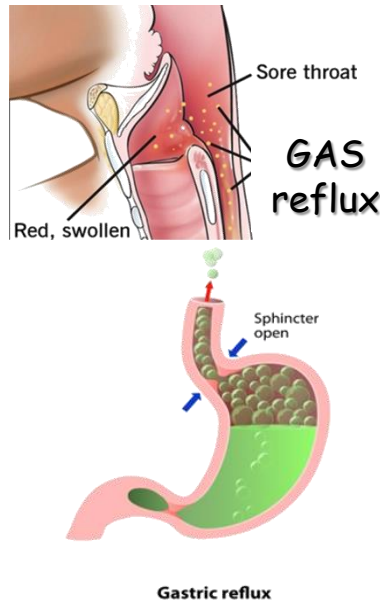
Allergic rhinitis, asthma and laryngopharyngeal reflux disease: a cross-sectional study on their reciprocal relations. Kakaje A, Sci Rep. 2021 Feb 3;11(1):2870.

✓ cross-sectional study

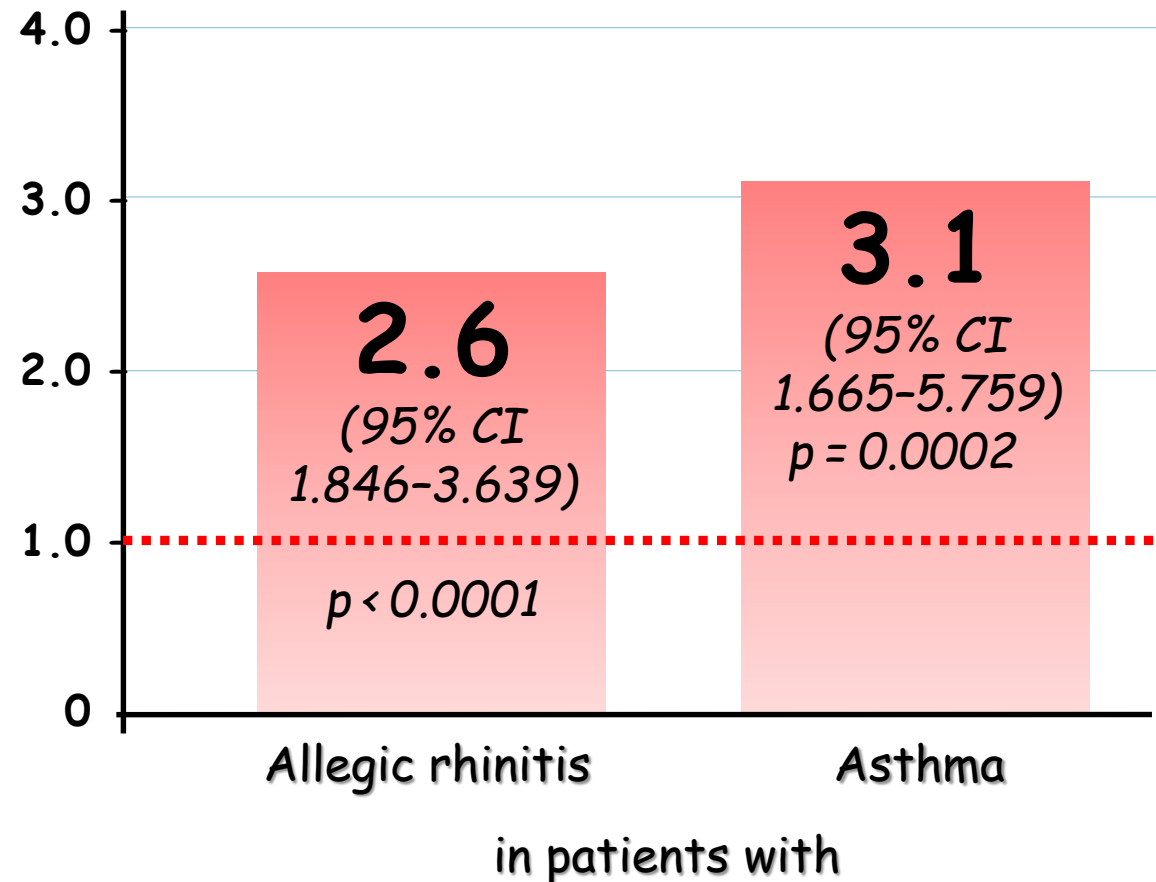
✓ 673 subjects,
mean age of
 23.9 ± 6.6 years

✓ self-administered
questionnaire for
laryngopharyngeal
reflux

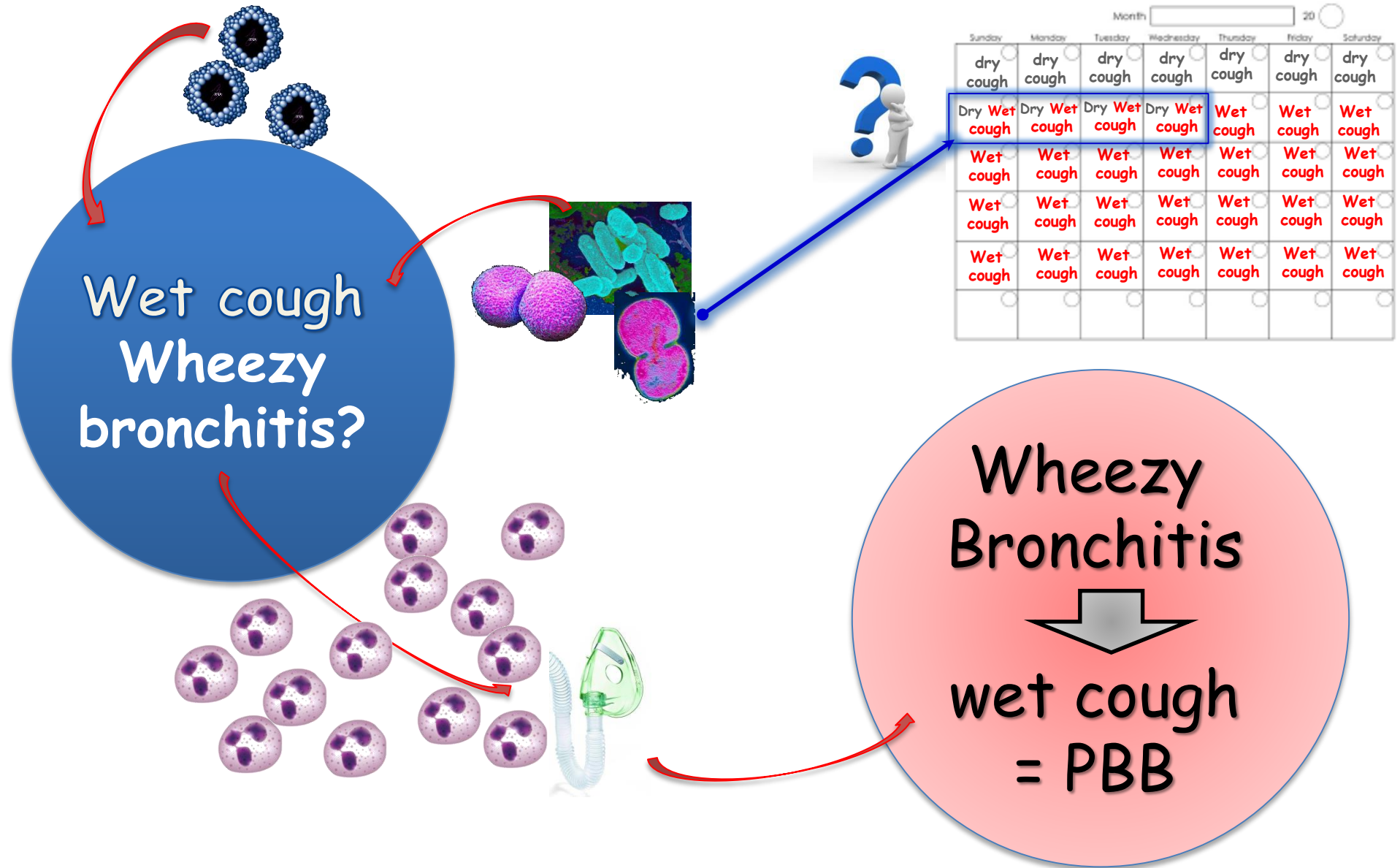
✓ Reported doctor -
-diagnosis of allergic
rhinitis - asthma



OR for laryngopharyngeal reflux



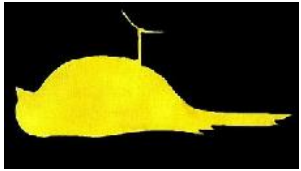
The Wheezy Bronchitis & Protracted Bacterial Bronchitis Vicious Circle in Young Children:



Respiratory health outcomes 1 year after admission with severe lower respiratory tract infection.

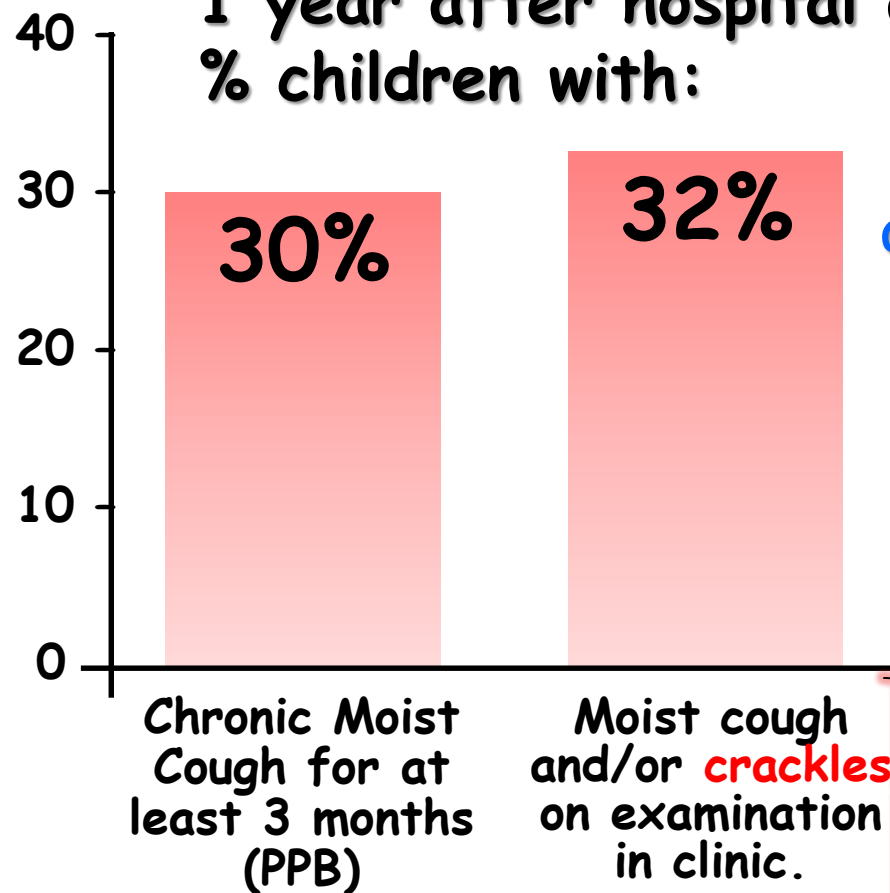
Trenholme AA, Pediatr Pulmonol. 2013 Aug;48(8):772-9.

- ✓ 94 children aged < 2 years hospitalized for severe bronchiolitis or pneumonia with no co-morbidities.

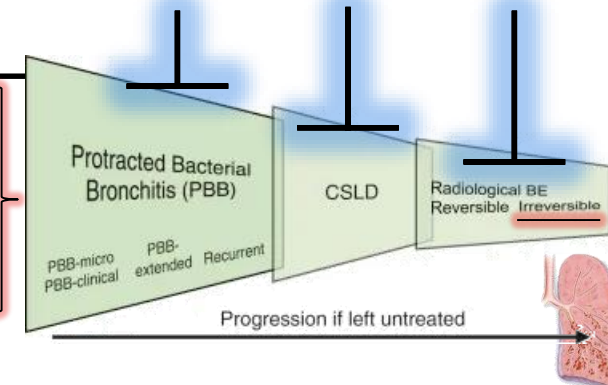


- ✓ Assessed 1 year post index admission.
- ✓ Examination, pulse oximetry, and chest X-ray (CXR).

1 year after hospital admission
% children with:



Early appropriate
antibiotic treatment
+
Antioxidants
&
Immune Modulation



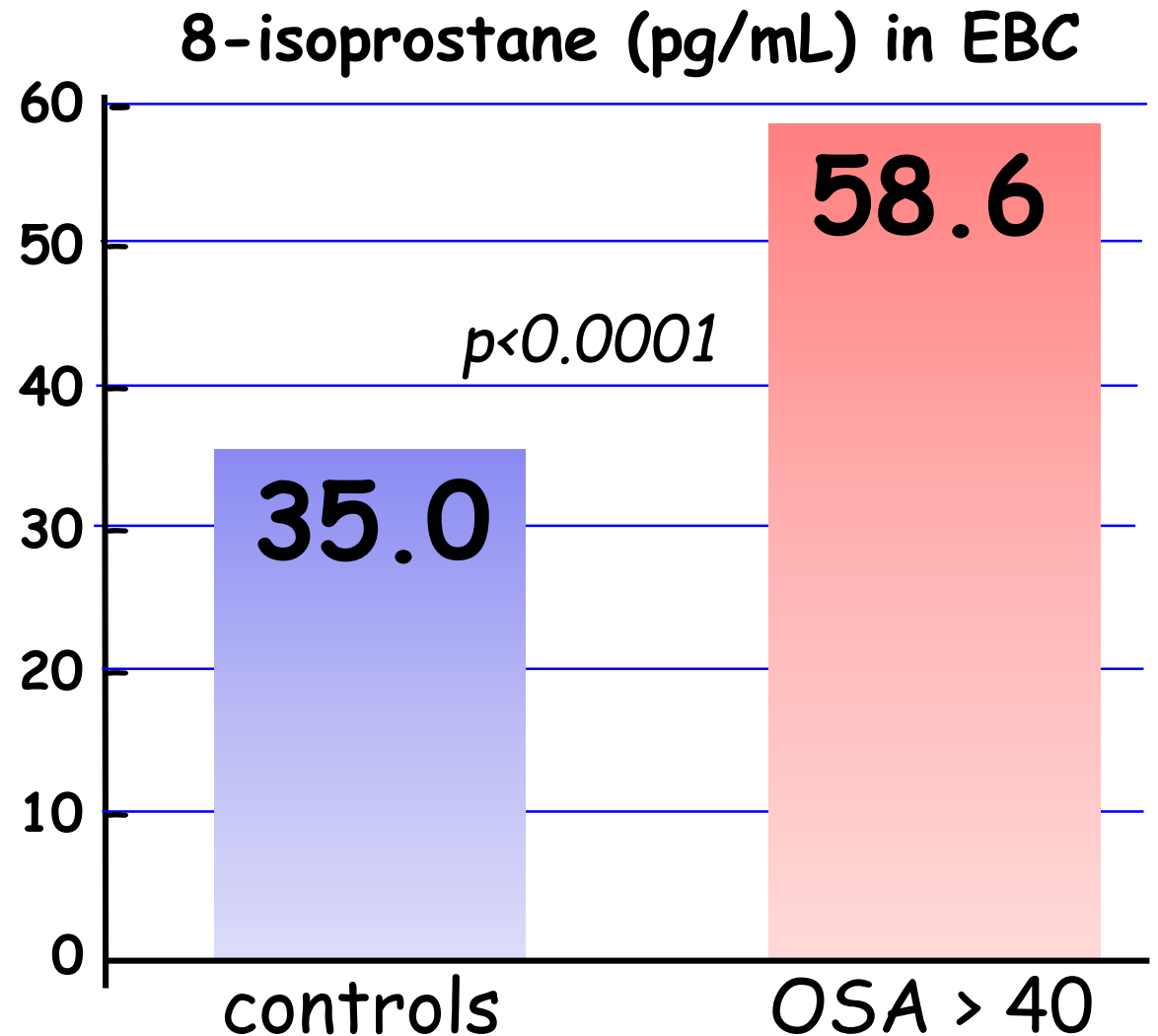
**7° Non prendere in seria considerazione
il bambino con naso chiuso**



Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea. Biltagi MA. *Acta Paediatr.* 2008;97:1397-405.



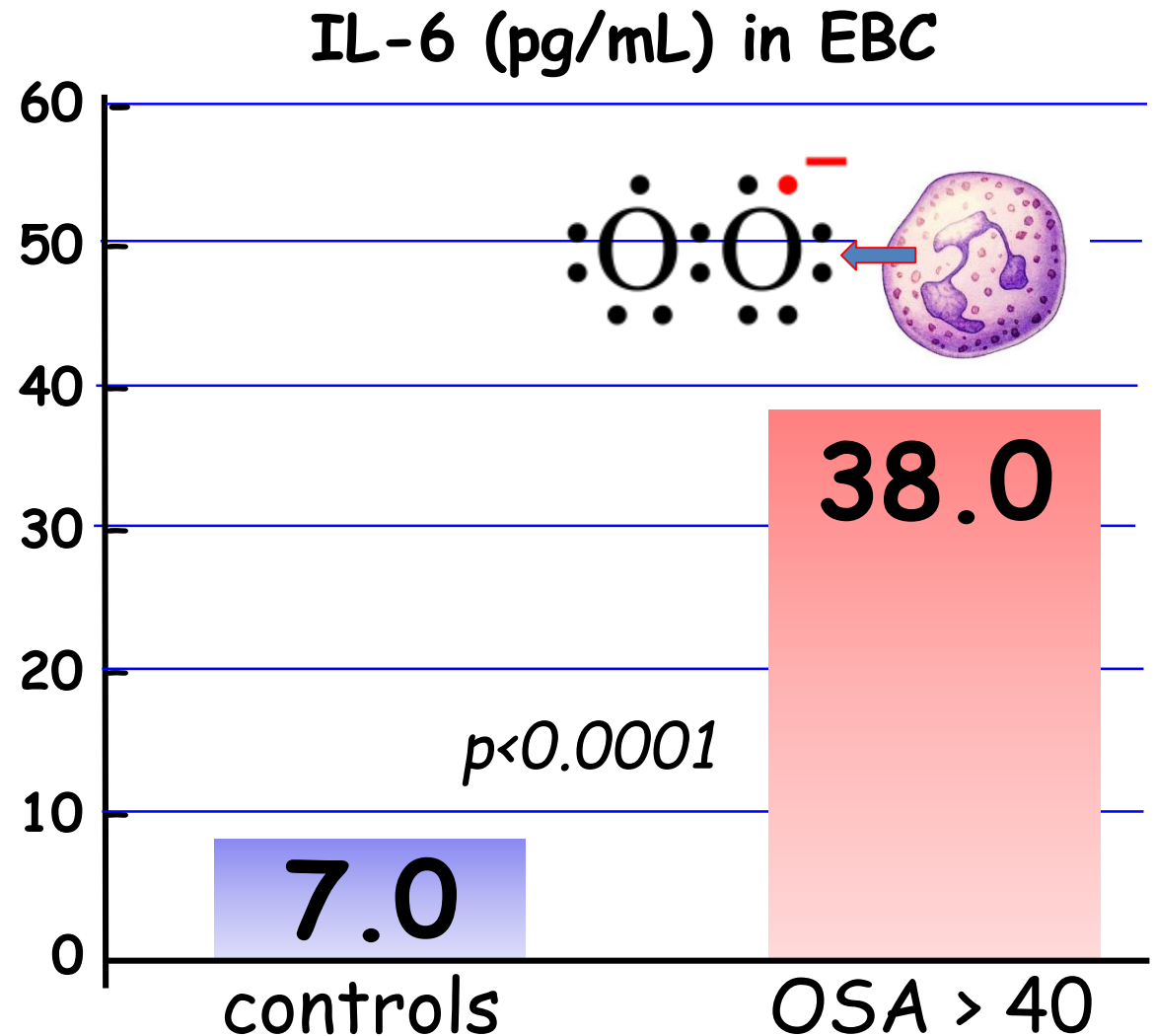
- ✓ 40 children with adenoidal hypertrophy and 20 controls
- ✓ OSA clinical score
- ✓ IL-6 and 8-isoprostane in exhaled breath condensate.
- ✓ Echocardiography



Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea. Biltagi MA. Acta Paediatr. 2008;97:1397-405.



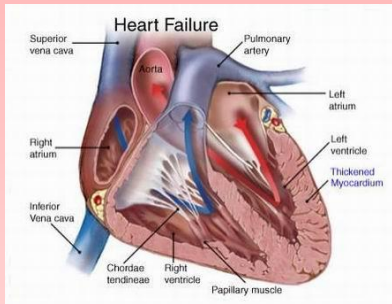
- ✓ 40 children with adenoidal hypertrophy and 20 controls
- ✓ OSA clinical score
- ✓ IL-6 and 8-isoprostane in exhaled breath condensate.
- ✓ Echocardiography



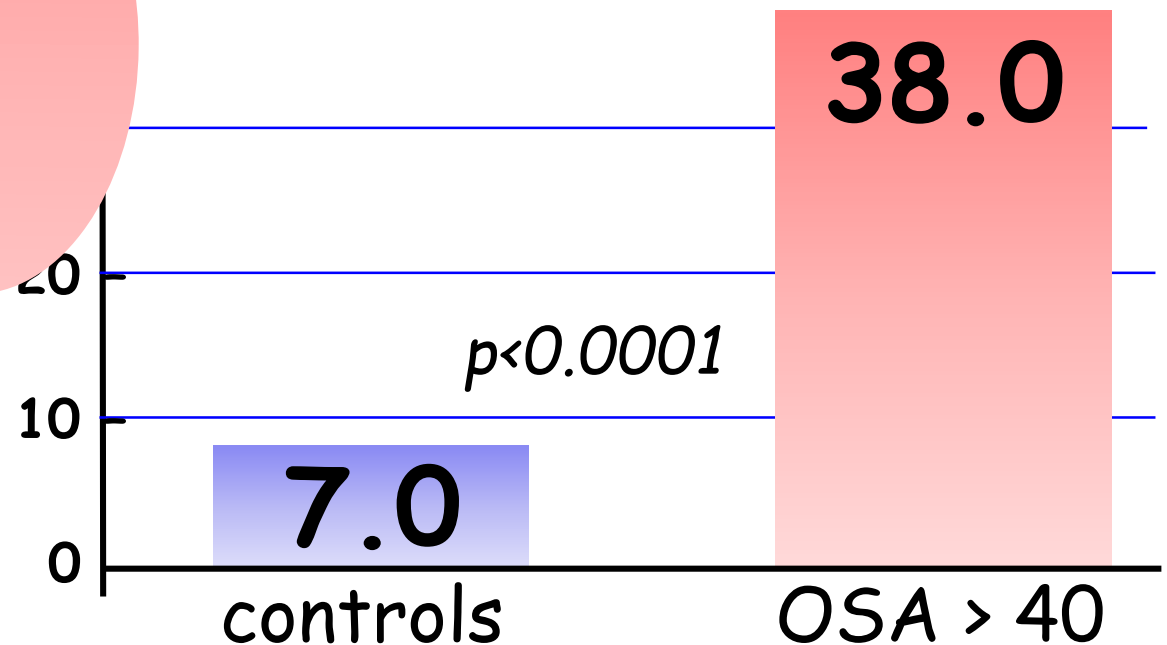
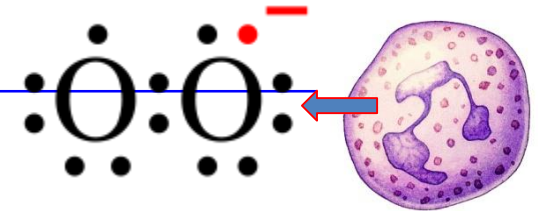
Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea

Pilto MA. *Acta Paediatr.* 2008;97:1397-405.

IL-6 level has a positive correlation with the degree of right heart diastolic dysfunction in children with OSA



IL-6 (pg/mL) in EBC



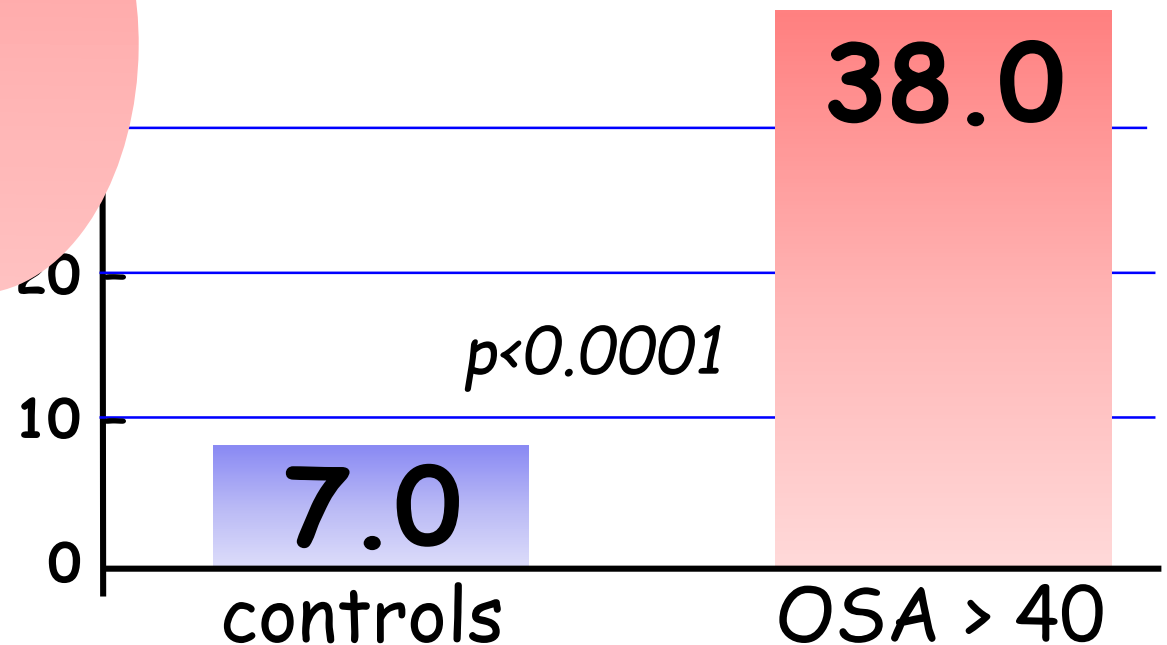
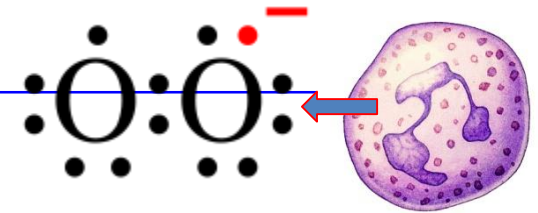
Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea

Pilto J MA. *Acta Paediatr.* 2008;97:1397-405.

a significant positive correlation between IL-6 production in the lung and the pulmonary vascular resistance has been previously demonstrated

Naoko M
Chest 2002;121:1195.

IL-6 (pg/mL) in EBC



Cardiovascular risks of children with primary snoring: A 5-year follow-up study.

Au CT, Respirology. 2021 Aug;26(8):796-803.



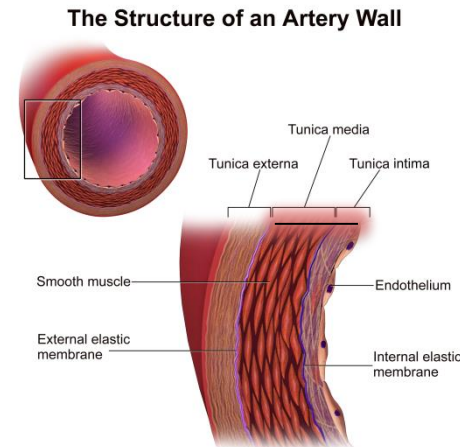
✓ 55 children with primary snoring: defined as the presence of snoring on most nights, when the number of apnoeas and hypopnoeas detected by sleep testing is below the diagnostic cut-off for obstructive sleep apnoea (OSA) at baseline

✓ followed for 5 years

✓ matched with 55 control subjects with normal sleep study

➤ compared to matched controls children with snoring at follow-up showed:

1. Lower flow-mediated dilation ($p=0.001$) (INCREASED endothelial dysfunction),
2. Greater carotid intima-media thickness ($p=0.005$)
3. Higher systolic blood pressure



Cardiovascular risks of children with primary snoring: A 5-year follow-up study.

Am J CT Respirology. 2021 Aug;26(8):796-803.

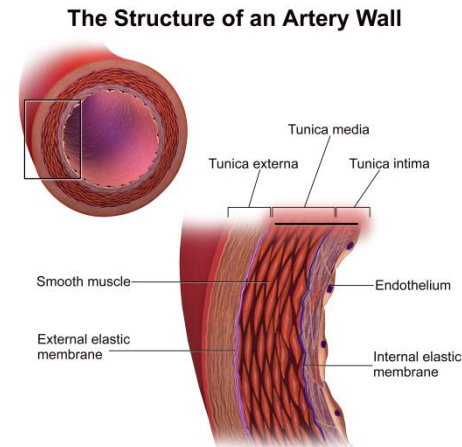


In relation to an epigenetic effect of Oxidative Stress with the induction of microRNA targeting IL-6.

Chen YC, Long non-coding RNA FKSG29 regulates oxidative stress and endothelial dysfunction in obstructive sleep apnea. Mol Cell Biochem. 2023 Nov 2.

➤ compared to matched controls children with snoring at follow-up showed:

1. Lower flow-mediated dilation ($p=0.001$) (**INCREASED endothelial dysfunction**),
2. Greater carotid intima-media thickness ($p=0.005$)
3. Higher systolic blood pressure



Childhood snoring has long-term adverse effects on cardiovascular health. Editorial

Horne RSC. *Respirology*. 2021 Aug;26(8):725-726.



- ❖ Over a third of pre-school children snore often or always

- ❖ \approx 15% of older children snore

- ❖ **Primary snoring**, defined as the presence of snoring on most nights, when the number of apnoeas and hypopnoeas detected by sleep testing is below the diagnostic cut-off for obstructive sleep apnoea (OSA), an obstructive apnoea-hypopnoea index (OAHI) $< 1/\text{h}$ as confirmed by overnight polysomnography, has been considered as benign, and something that does not need to be treated.

- ❖ However, there is mounting evidence that primary snoring is also associated with significant adverse consequences for both

- **daytime performance**

- Biggs SN, The conundrum of primary snoring in children: what are we missing in regards to cognitive and behavioural morbidity? Sleep Med Rev. 2014;18:463-75.*

- and the

- **cardiovascular system.**

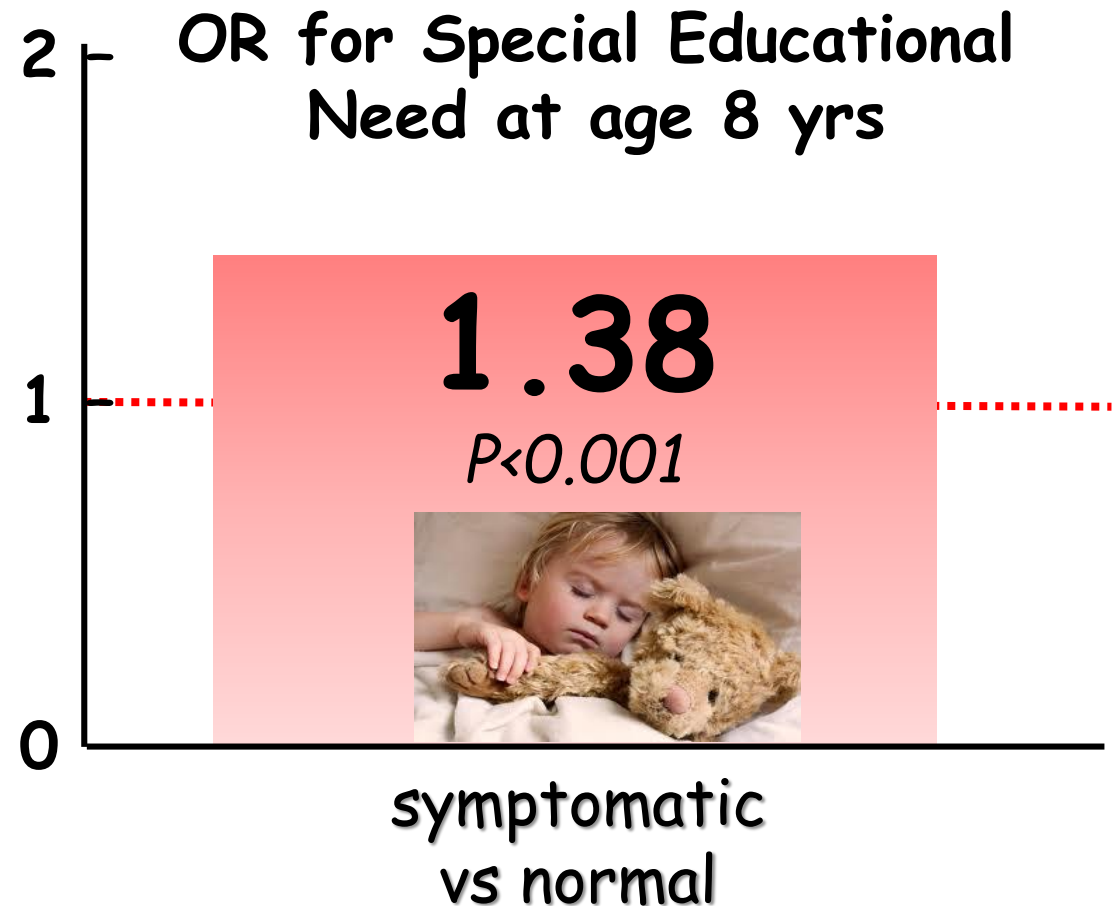
- Nisbet LC, Blood pressure regulation, autonomic control and sleep disordered breathing in children. Sleep Med Rev. 2014; 18:179-89.*



Pediatric Sleep Disorders and Special Educational Need at 8 Years: A Population-Based Cohort Study

Bonuck K. Pediatrics 2012;130:634-42.

- ✓ Sleep disordered breathing (SDB) through 5 years of age (11 049 children).
- ✓ Special educational need (SEN) at 8 years.
- ✓ Parents reported on children's snoring, witnessed apnea, and mouth-breathing at 6, 18, 30, 42, and 57 months.



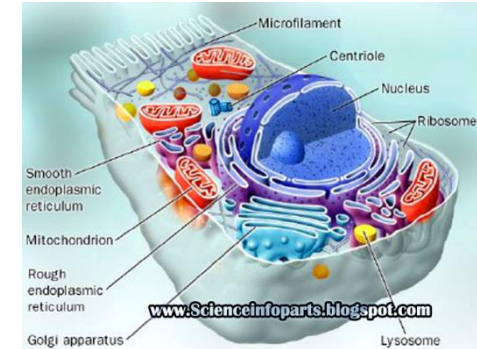
Role of Oxidative Stress in the Neurocognitive Dysfunction of Obstructive Sleep Apnea Syndrome.

Zhou L, *Oxid Med Cell Longev*. 2016;2016:9626831.

repetitive hypoxia
and reoxygenation

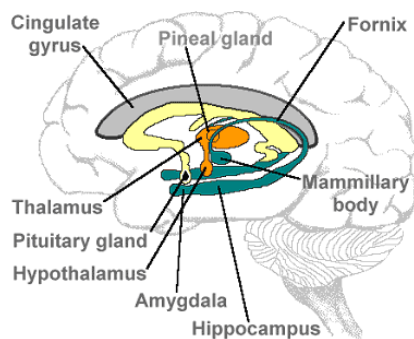


mitochondria and
endoplasmic reticulum
dysfunction



oxidative stress (OS) responses, such as:
protein oxidation, lipid peroxidation, and DNA oxidation

neuron injury especially in the hippocampus* * primarily associated with
memory and spatial navigation.
and cerebral cortex regions.



cognitive dysfunction
(memory, executive function, attention/vigilance)

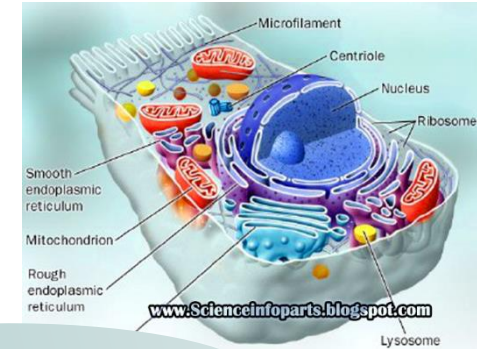
Role of Oxidative Stress in the Neurocognitive Dysfunction of Obstructive Sleep Apnea Syndrome.

Zhou L, *Oxid Med Cell Longev*. 2016;2016:9626831.

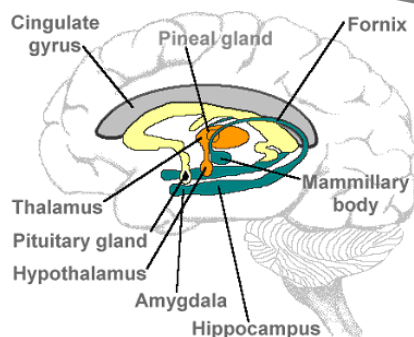
repetitive hypoxia
and reoxygenation



mitochondria and
endoplasmic reticulum
dysfunction



antioxidant may be a promising therapeutic method
to improve partially reversible neurocognitive function



neuron injury especially in the hippocampus* * primarily associated with memory and spatial navigation.
and cerebral cortex regions.

cognitive dysfunction

(memory, executive function, attention/vigilance)

Childhood snoring has long-term adverse effects on cardiovascular health. Editorial

Horne RSC. *Respirology*. 2021 Aug;26(8):725-726.



- ❖ Over a third of pre-school children snore often or always
- ❖ \approx 15% of older children snore
- ❖ **Primary snoring**, defined as the presence of snoring on most nights, when the number of apnoeas and hypopnoeas detected by sleep testing is below the diagnostic cut-off for obstructive sleep apnoea (OSA), an obstructive apnoea-hypopnoea index (OAHI) $< 1/h$ as confirmed by overnight polysomnography, has been considered as benign, and something that does not need to be treated.

❖ However, there is mounting evidence that primary snoring is also associated with significant adverse consequences for both

- daytime performance

Biggs SN, The conundrum of primary snoring in children: what are we missing in regards to cognitive and behavioural morbidity? Sleep Med Rev. 2014;18:463-75.

and the

- **cardiovascular system:** \uparrow endothelial dysfunction, \uparrow carotid intima-media thickness, \uparrow blood pressure.

Nisbet LC, Blood pressure regulation, autonomic control and sleep disordered breathing in children. Sleep Med Rev. 2014; 18:179-89.



Supportive treatment of vascular dysfunction in pediatric subjects with obesity: the OBELIX study.

Pecoraro L, Pietrobelli A. Nutr Diabetes. 2022 Jan 10;12(1):2.



✓ 48 obes subjects aged 6-17 years

✓ randomized in two groups (placebo Vs treatment)

✓ attended 3 visits at 0, 3 and 6 month (+/- 15 days)

INGREDIENTI, per una compressa:

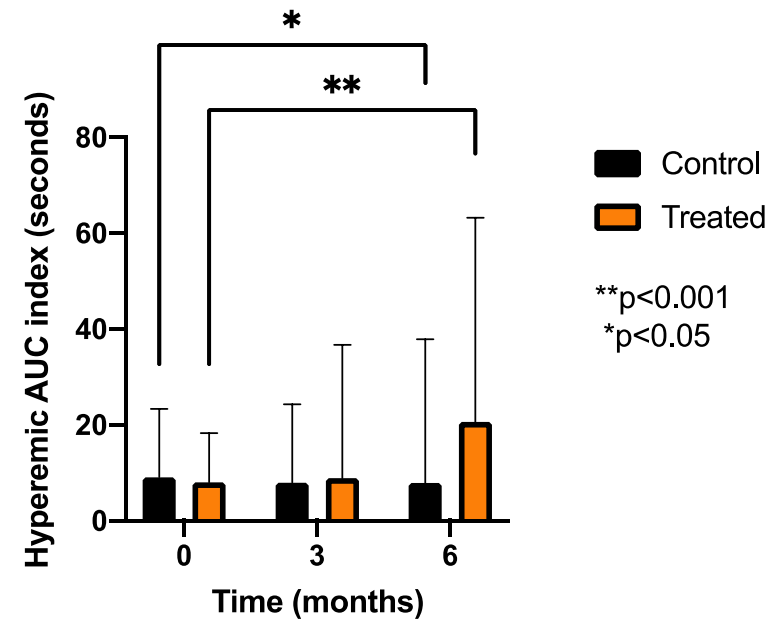
Contenuti medi	per 1 cpr	%VNR*
Magnesio	200,00 mg	55,00
Fitosoma di Curcuma (Meriva®)	100,00 mg	
Curcuminoidi apportati	18,00 mg	
Zinco	5,00 mg	50,00
Quercetina	150,00 mg	
Vitamina E	15,00 mg	125,00
Polygonum e.s.	20,41 mg	
Resveratrolo apportato	20,00 mg	
Selenio	55,00 mcg	100,00
Vitamina D3	20,00 mcg	400,00
Acido folico	90,00 mcg	45,00

SYNERGY
1+1>2



Hyperemic AUC index time trend variations was higher significance for treatment group ($p<0.001$).

Hyperemic AUC index time trend



curcumin, resveratrol, zinc, magnesium, selenium, Vitamin D and folic acid appear to be promising in enhancing endothelial function

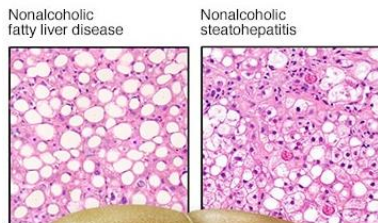
Nocturnal hypoxia-induced oxidative stress promotes progression of pediatric non-alcoholic fatty liver disease.

Sundaram SS, J Hepatol. 2016 Sep;65(3):560-9.



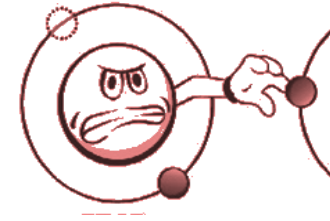
✓ 36 adolescents with
with biopsy proven
Non-Alcoholic
Fatty Liver Disease

✓ 14 lean controls



©2016
MAYO

The NAFLD subjects with OSA/hypoxia
compared to those without OSA/hypoxia
had:



•greatest 4-hydroxynonenal
(in situ hepatic lipid peroxidation) $p=0.03$

•more severe liver fibrosis $p=0.03$

Endothelial Dysfunction is present in several conditions

Oxidative stress

Inflammation

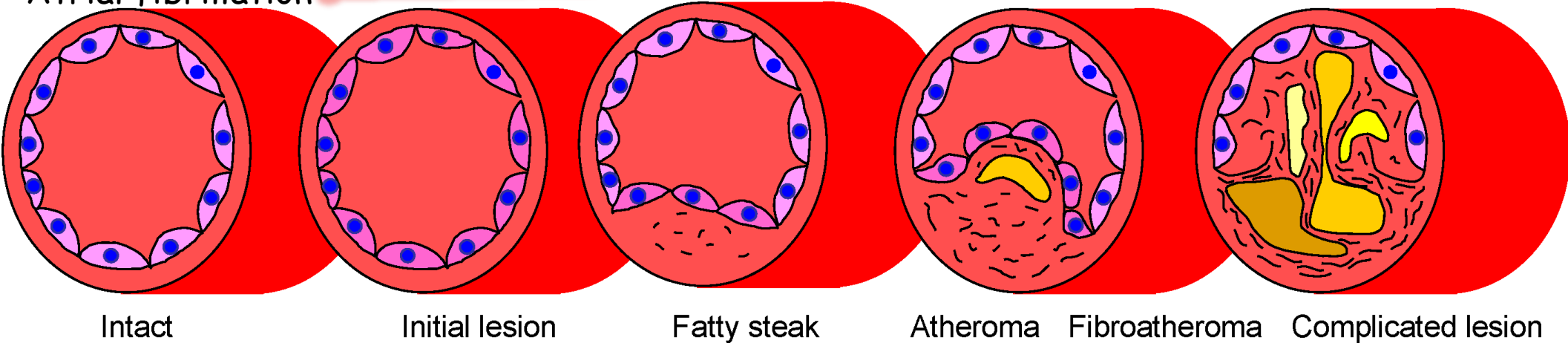
- * Snoring
- * Hypertension & chronic kidney disease
- * Dyslipidemia
- * Diabetes
- * Aging
- * Smoking
- * Obesity
- * Menopause & birth control pill
- * Atrial fibrillation

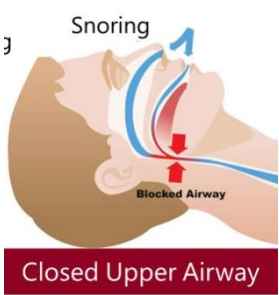
Endothelial dysfunction

Occurrence and development of atherosclerosis

Cardiovascular complications

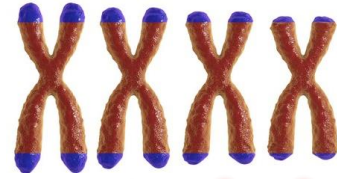
STROKE





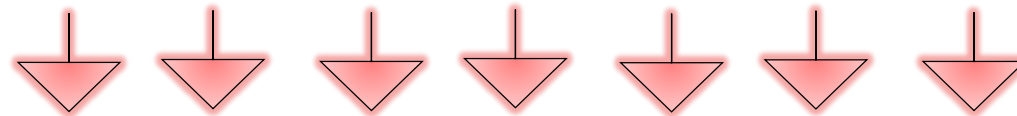
Impact of Snoring on Telomere Shortening in Adolescents with Atopic Diseases.

Tung KTS, Genes (Basel). 2021 May 18;12(5):766.



➤ **Shorter TL** was found in participants with a history of:

- snoring and atopic diseases ($\beta = -0.34, p = 0.002$) particularly for:
- asthma ($\beta = -0.21, p = 0.007$) and
- allergic rhinitis ($\beta = -0.22, p = 0.023$).



snoring in atopic patients has important implications for accelerated telomere shortening.



✓ **354 ADOLESCENTS** and their parents.

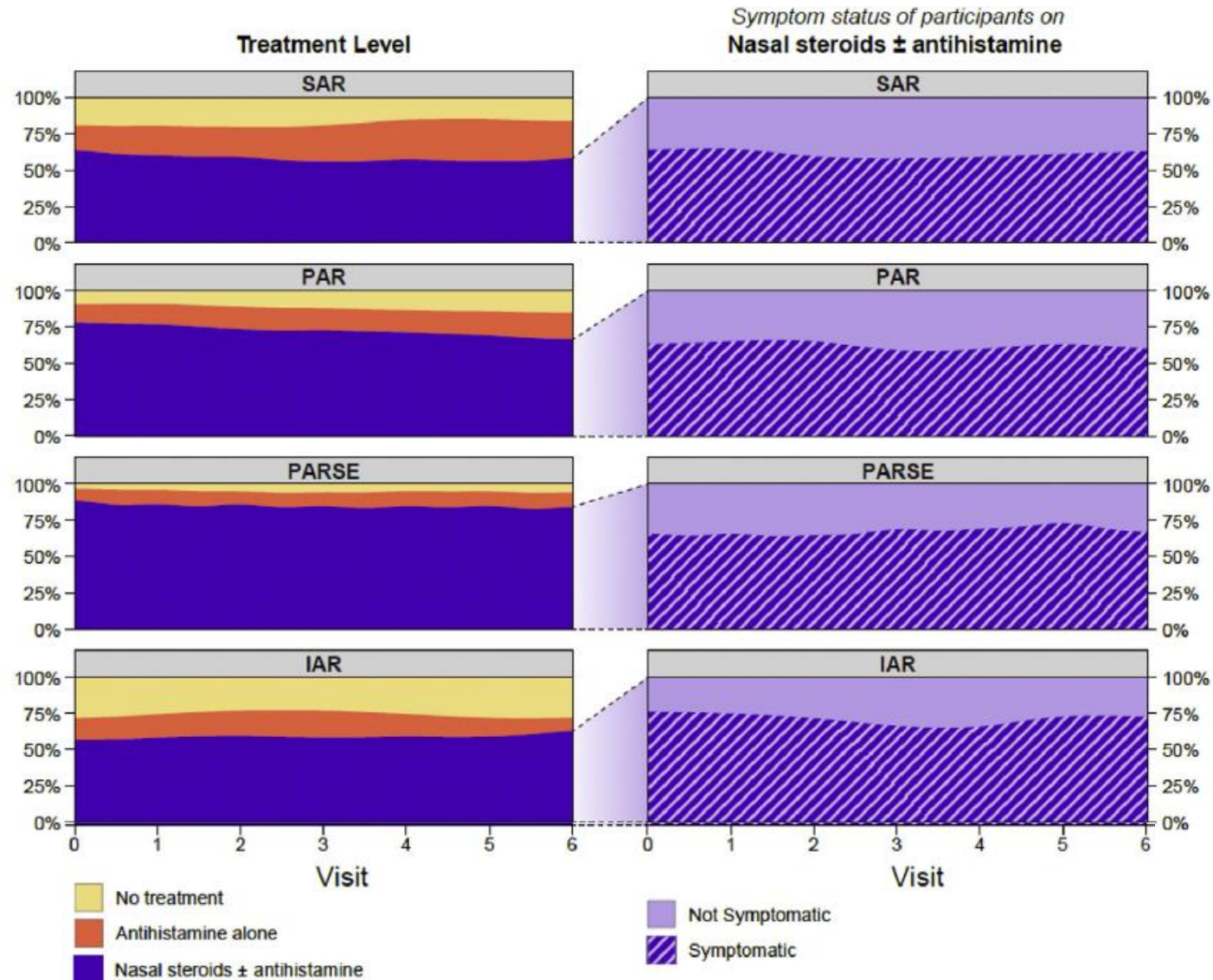
✓ Parents reported the adolescents' history of atopic diseases, recent snoring history

The majority of children with allergic rhinitis remain symptomatic despite the use of nasal corticosteroids ± oral antihistamines.

Courtesy MA Tosca

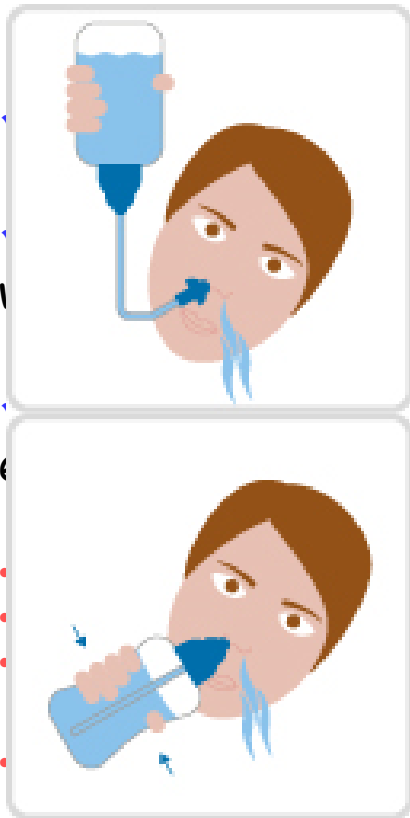
- ✓ 619 children with asthma,
- ✓ 93.5%, of whom (579) with allergic rhinitis
- ✓ managed for 1 year and evaluated bimonthly
- Seasonal Allergic Rhinitis (SAR)
- Perennial Allergic Rhinitis (PAR)
- Perennial Allergic Rhinitis with Seasonal Exacerbations (PARSE)
- Indeterminate Atopic Rhinitis (IAR)

≈ 60% of children with allergic rhinitis do NOT respond to nasal corticosteroids ± antihistamine



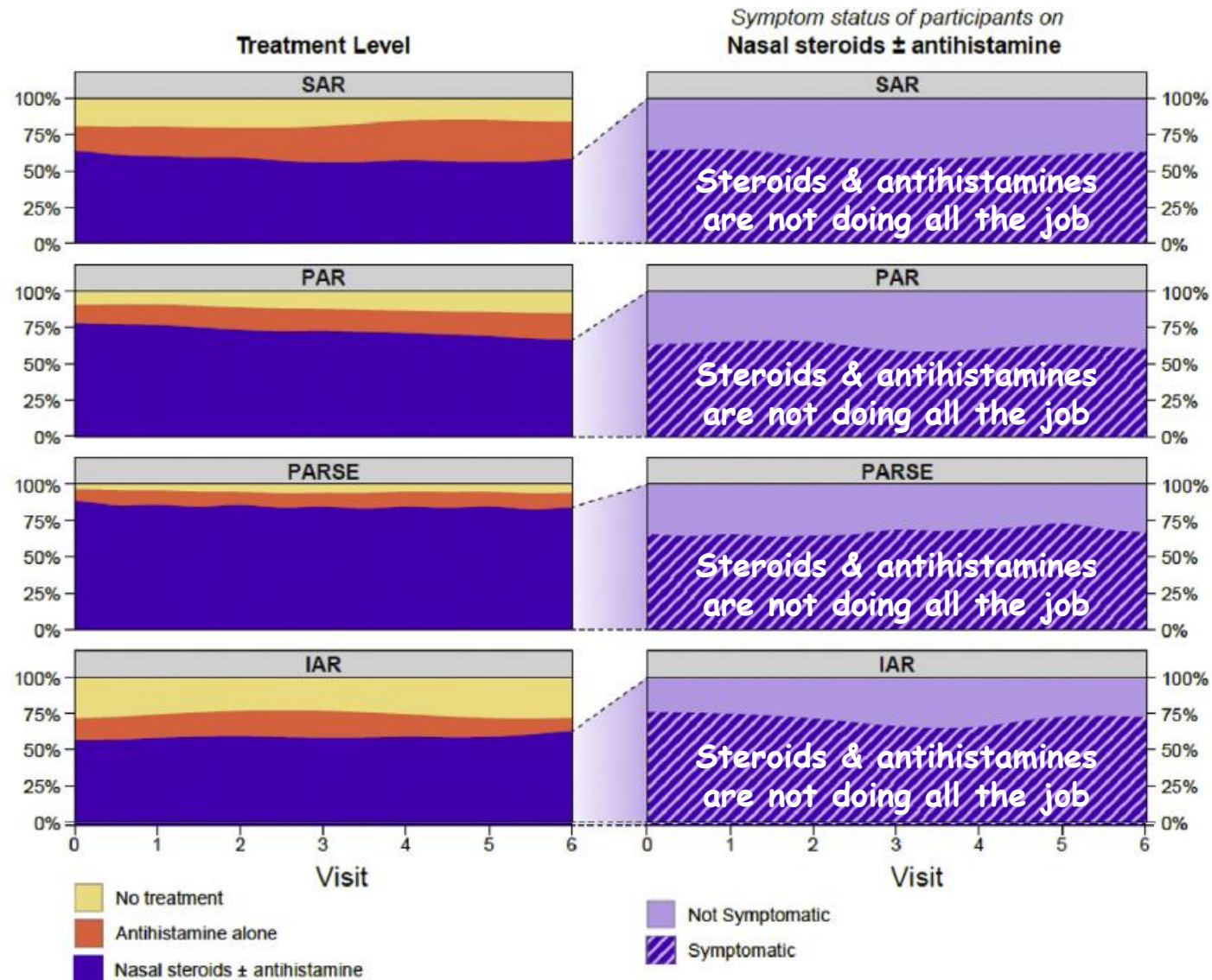
Togias A, Rhinitis in children and adolescents with asthma: Ubiquitous, difficult to control, and associated with asthma outcomes. *J Allergy Clin Immunol*. 2019 Mar;143(3):1003-1011.e10.

The majority of children with allergic rhinitis remain symptomatic despite the use of nasal corticosteroids ± oral antihistamines.



asthma,
(579)
is
ar and
y
tis (SAR)
tis (PAR)
tis
ations (PARSE)
rhinitis (IAR)

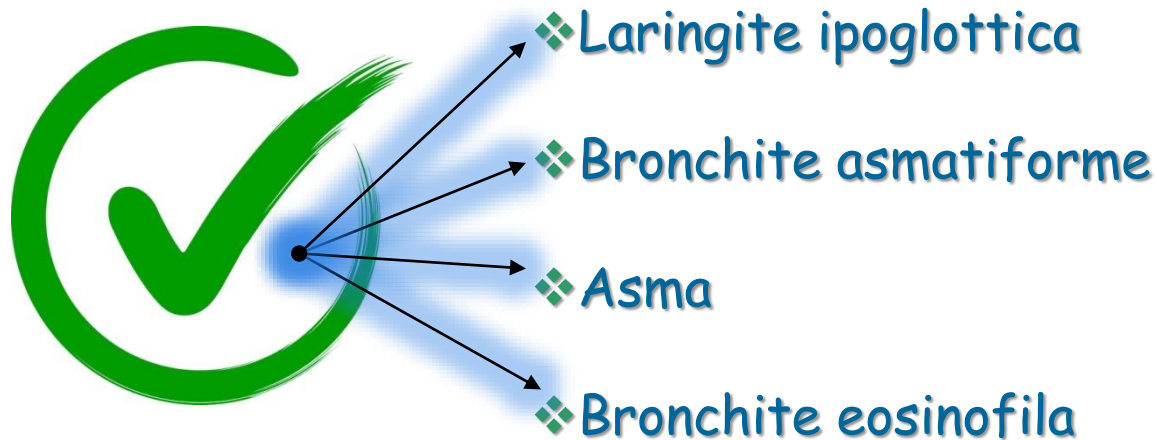
≈ 60% of children with allergic rhinitis do NOT respond to nasal corticosteroids ± antihistamine



Togias A, Rhinitis in children and adolescents with asthma: Ubiquitous, difficult to control, and associated with asthma outcomes. *J Allergy Clin Immunol*. 2019 Mar;143(3):1003-1011.e10.

8° errore: Considerare gli steroidi una panacea.

Non esiste **bambino con tosse** al quale non venga prescritto uno aerosol con steroidi più soluzione fisiologica, o broncodilatatori, o altre sostanze: almeno **l'80% di loro riceve una prescrizione di steroidi per inalazione**.
Dal Negro RW, Acute cough in Italian children: parents' beliefs, approach to treatment, and the family impact. Multidiscip Respir Med 2019; 14: 16.



8° errore: Considerare gli steroidi una panacea.

Duse et al. *Italian Journal of Pediatrics* (2021) 47:97
<https://doi.org/10.1186/s13052-021-01013-8>


Italian Journal of Pediatrics

RESEARCH

Open Access



Inter-society consensus for the use of inhaled corticosteroids in infants, children and adolescents with airway diseases

Marzia Duse^{1†}, Francesca Santamaria^{2*†} , Maria Carmen Verga³, Marcello Bergamini⁴, Giovanni Simeone⁵, Lucia Leonardi⁶, Giovanna Tezza⁷, Annamaria Bianchi⁸, Annalisa Capuano⁹, Fabio Cardinale¹⁰, Giovanni Cerimoniale¹¹, Massimo Landi¹², Monica Malventano⁴, Mariangela Tosca¹³, Attilio Varricchio¹⁴, Anna Maria Zicari¹⁵, Carlo Alfaro¹⁶, Salvatore Barberi¹⁷, Paolo Becherucci¹⁸, Roberto Bernardini¹⁹, Paolo Biasci²⁰, Carlo Caffarelli²¹, Valeria Caldarelli²², Carlo Capristo²³, Serenella Castronuovo²⁴, Elena Chiappini^{25,26}, Renato Cutrera²⁷, Giovanna De Castro¹⁵, Luca De Franciscis²⁸, Fabio Decimo²³, Iride Dello Iacono²⁹, Lucia Diaferio³⁰, Maria Elisa Di Cicco³¹, Caterina Di Mauro³², Cristina Di Mauro⁹, Dora Di Mauro³³, Francesco Di Mauro³⁴, Gabriella Di Mauro⁹, Mattia Doria³⁵, Raffaele Falsaperla³⁶, Valentina Ferraro³⁷, Vassilios Fanos³⁸, Elena Galli³⁹, Daniele Giovanni Ghiglioni⁴⁰, Luciana Indinnimeo¹, Ahmad Kantar⁴¹, Adima Lamborghini⁴², Amelia Licari⁴³, Riccardo Lubrano⁴⁴, Stefano Luciani⁴⁵, Francesco Macrì⁴⁶, Gianluigi Marseglia⁴³, Alberto Giuseppe Martelli⁴⁷, Luigi Masini⁴⁸, Fabio Midulla⁶, Domenico Minasi⁴⁹, Vito Leonardo Miniello⁵⁰, Michele Miraglia del Giudice²³, Sergio Renzo Morandini¹¹, Germana Nardini⁵¹, Agostino Nocerino⁵², Elio Novembre⁵³, Giovanni Battista Pajno⁵⁴, Francesco Paravati⁵⁵, Giorgio Piacentini⁵⁶, Cristina Piersantelli⁵⁷, Gabriella Pozzobon⁵⁸, Giampaolo Ricci⁵⁹, Valter Spanevello⁶⁰, Renato Turra⁶¹, Stefania Zanonato⁶², Melissa Borrelli², Alberto Villani⁶³, Giovanni Corsello⁶⁴, Giuseppe Di Mauro³⁴ and Diego Peroni⁶⁵

Even though

vs

Despite

una consensus di tutte le Società scientifiche e sindacali italiane, firmata da 65 esperti appartenenti a tutte le figure professionali pediatriche, abbia dichiarato che **gli steroidi inalatori NON sono utili nella terapia delle infezioni delle alte vie respiratorie**

Nutraceuticals and mitochondrial oxidative stress: bridging the gap in the management of bronchial asthma.

Allam VSRR, Allam VSRR, Paudel KR, Gupta G, Singh SK, Vishwas S, Gulati M,
Gupta S, Chaitanya MVNL, Jha NK, Gupta PK, Patel VK, Liu G, Kamal MA,
Hansbro PM, Oliver BGG, Chellappan DK, Dua K.

Environ Sci Pollut Res Int. 2022;29:62733.

17 Authors

23 Institutions



"The current treatment strategies for asthma mainly involve the use of anti-inflammatory agents and bronchodilators.



However, long-term usage of such medications is associated with severe adverse effects and complications.

Hence, there is an urgent need to develop newer, novel, and safe treatment modalities for the management of asthma."

Nutraceuticals and mitochondrial oxidative stress: bridging the gap in the management of bronchial asthma.

Allam VSRR, Allam VSRR, Paudel KR, Gupta G, Singh SK, Vishwas S, Gulati M,
Gupta S, Chaitanya MVNL, Jha NK, Gupta PK, Patel VK, Liu G, Kamal MA,
Hansbro PM, Oliver BGG, Chellappan DK, Dua K.

Environ Sci Pollut Res Int. 2022;29:62733.

17 Authors

23 Institutions



"The current treatment strategies for asthma mainly involve the use of anti-inflammatory agents and bronchodilators.

However, long-term usage of such medications is associated with severe adverse effects and complications.

Hence, there is an urgent need to develop newer, novel, and safe treatment modalities for the management of asthma."

MISSING

Nutraceuticals and mitochondrial oxidative stress: bridging the gap in the management of bronchial asthma.

Allam VSRR, Allam VSRR, Paudel KR, Gupta G, Singh SK, Vishwas S, Gulati M,
Gupta S, Chaitanya MVNL, Jha NK, Gupta PK, Patel VK, Liu G, Kamal MA,
Hansbro PM, Oliver BGG, Chellappan DK, Dua K.

Environ Sci Pollut Res Int. 2022;29:62733.

17 Authors

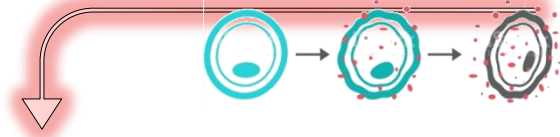
23 Institutions

*"In this review we provide a detailed insight into the therapeutic role of **nutraceuticals** as an effective strategy to attenuate the deleterious effects of oxidative stress and may be used in the mitigation of the cardinal features of bronchial asthma."*

as host directed therapy



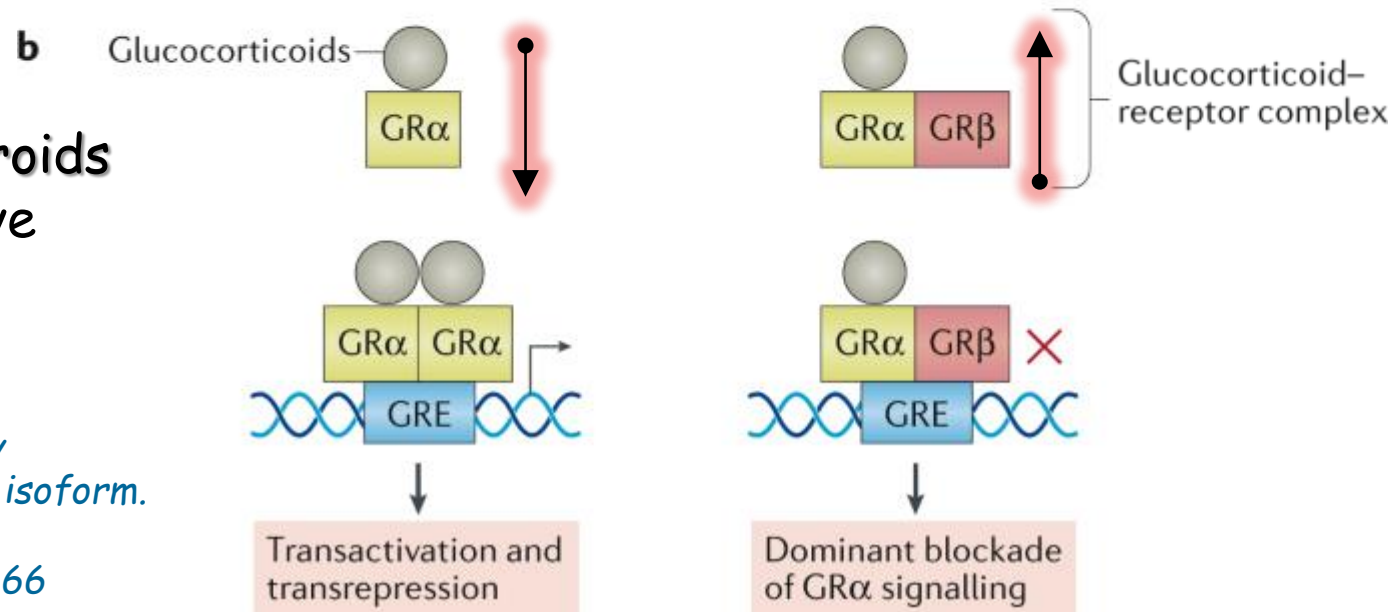
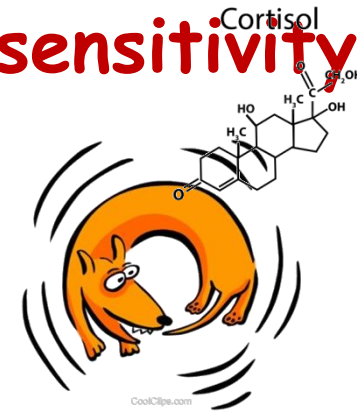
Oxidative Stress may induce Corticosteroids Insensitivity



- Oxidative stress is associated with impaired expression and function of the **glucocorticoid receptor-alfa** (GR- α), the classical glucocorticoid receptor isoform and induce
- **overexpression of GR- β** that does not bind corticosteroids and thus is a dominant-negative inhibitor of GR- α inducing corticosteroids resistance

• Oakley RH, The dominant negative activity of the human glucocorticoid receptor beta isoform. *Specificity and mechanisms of action.* *J Biol Chem.* 1999 Sep 24; 274(39):27857-66

• Enweasor C, *Ozone-Induced Oxidative Stress, Neutrophilic Airway Inflammation, and Glucocorticoid Resistance in Asthma.* *Front Immunol.* 2021 Feb 26;12:631092.



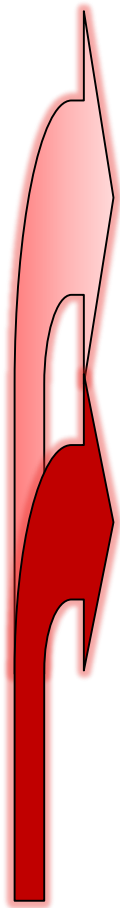
a | The structural domains of the glucocorticoid receptor isoforms glucocorticoid receptor- α (GR α) and GR β .

b | During glucocorticoid receptor binding, homodimers of GR α bind to the glucocorticoid response element (GRE) to regulate gene expression, whereas GR α -GR β heterodimers function as dominant-negative inhibitors, antagonizing the activity of GR α .

DBD, DNA binding domain; LBD, ligand binding domain.

Ambient air pollution, lung function, and airway responsiveness in asthmatic children.

Ierodiakonou D, *J Allergy Clin Immunol*. 2016 Feb;137(2):390-9.



✓ 1003 asthmatic children participating in a 4-year clinical trial (CAMP study)

✓ associations of lung function and methacholine responsiveness (PC20) with ozone, carbon monoxide (CO), nitrogen dioxide, and sulfur dioxide concentrations

➤ Long-term exposures to pollutants were associated with reduced methacholine PC20

(% change per interquartile range, -6% [95% CI, -11% to -1.5%] of sulfur dioxide).

➤ Treatment with budesonide and nedocromil augmented the negative short-term carbon monoxide effect on methacholine PC20.



Ambient air pollution, lung function, and airway responsiveness in asthmatic children.

Ierodiakonou D, *J Allergy Clin Immunol*. 2016 Feb;137(2):390-9.

✓ 100
part
clin

Anti-inflammatory treatment use may worsen the negative short-term effects of some pollutants on BHR.

1
o
(
c
cc

➤ Long-term exposures to pollutants were associated with reduced methacholine PC20
(% change per interquartile range, -6% [95% CI, -11% to -1.5%] of sulfur dioxide).

➤ Treatment with budesonide and nedocromil **attenuated** the negative carbon monoxide effect on methacholine PC20.



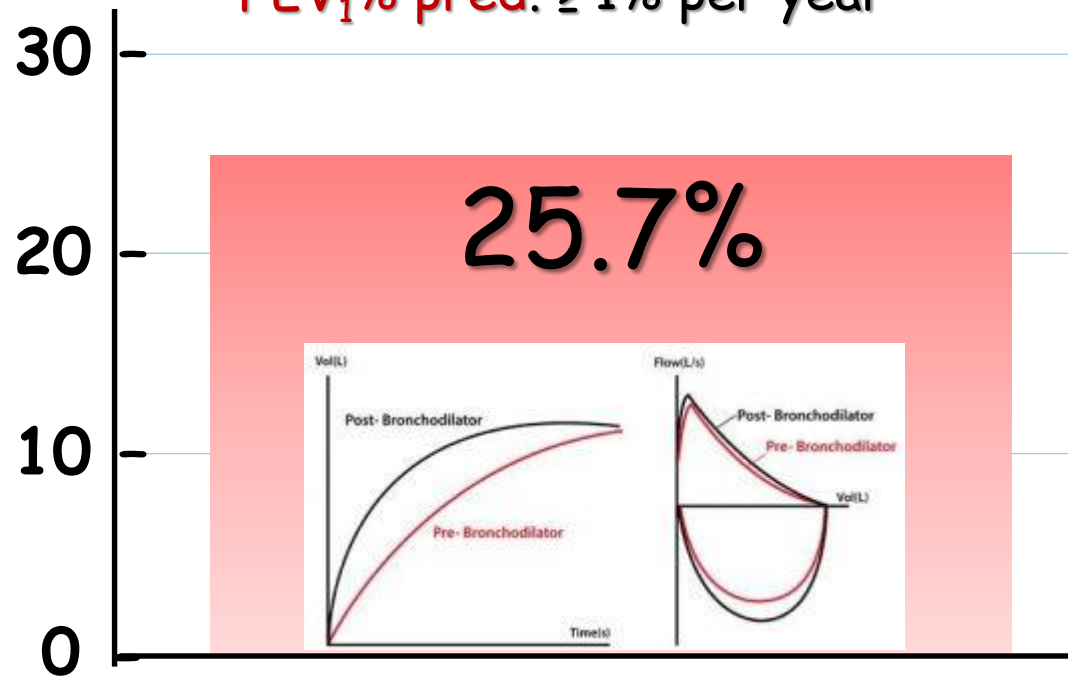
Progression of asthma measured by lung function in the childhood asthma management program.

Covar RA, Am J Respir Crit Care Med 2004;170:234-241.

✓CAMP cohort,
randomly assigned to
budesonide,
nedocromil,
or
placebo
for 4-6 years

✓prevalence of and factors
associated with $\geq 1\%$ per year
loss in postbronchodilator
FEV₁% predicted (SRP).

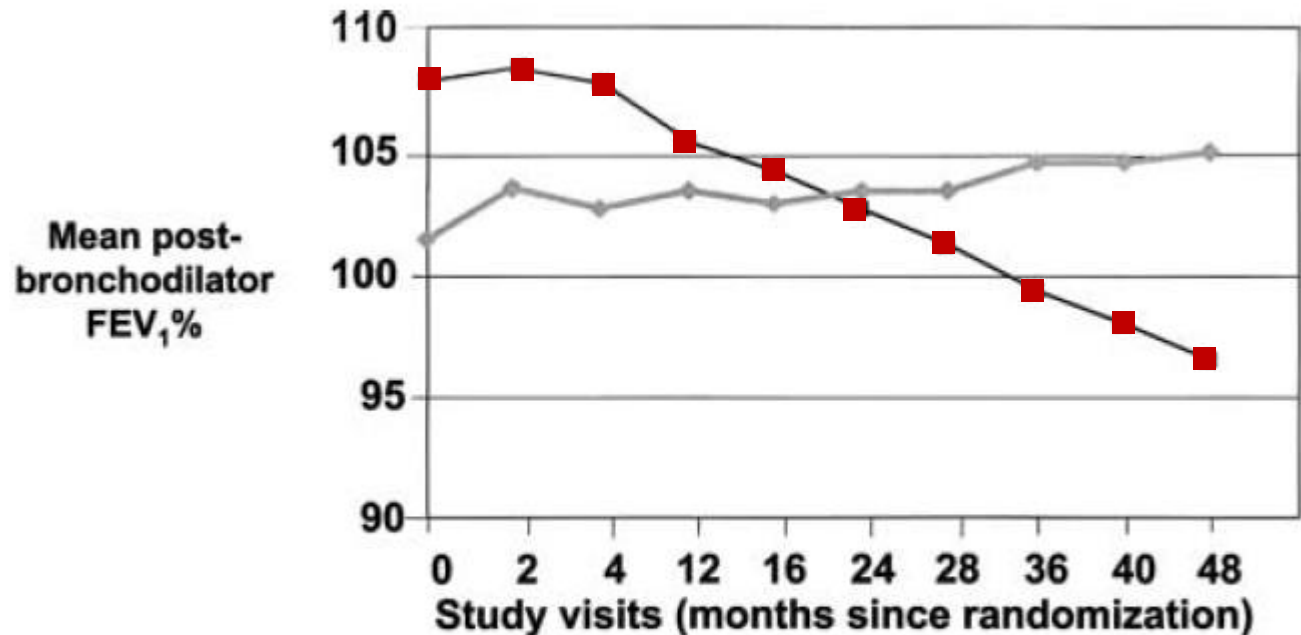
% participants with a significant reduction
(SRP) in **postbronchodilator**
FEV₁% pred. $\geq 1\%$ per year



Progression of asthma measured by lung function in the childhood asthma management program.

Covar RA, Am J Respir Crit Care Med 2004;170:234-241.

participants with (SRP) or without (NSRP)
reduction in postbronchodilator FEV₁% pred.



■ SRP (no.)
◆ NSRP (no.)

262	251	255	256	254	251	244	249	245	242
779	746	755	752	738	736	706	721	693	694

✓ CAMP cohort,
randomly assigned to
budesonide,
nedocromil,
or
placebo
for 4-6 years

✓ prevalence of and factors
associated with $\geq 1\%$ per year
loss in postbronchodilator
FEV₁% predicted (SRP).

Progression of asthma measured by lung function in the childhood asthma management program.

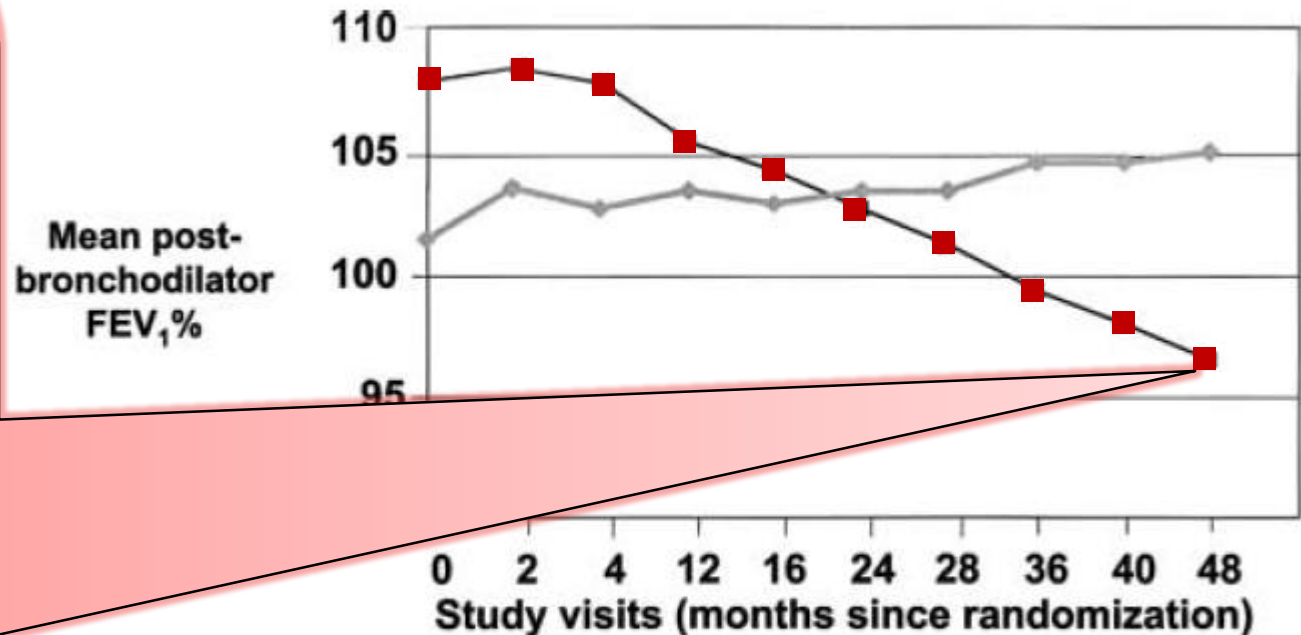
Covar RA, Am J Respir Crit Care Med 2004;170:234-241.

A similar proportion of SRPs was found in each treatment group.

ICS treatment does not do a complete job



participants with (SRP) or without (NSRP) reduction in postbronchodilator FEV₁% pred.



■ SRP (no.)
◆ NSRP (no.)

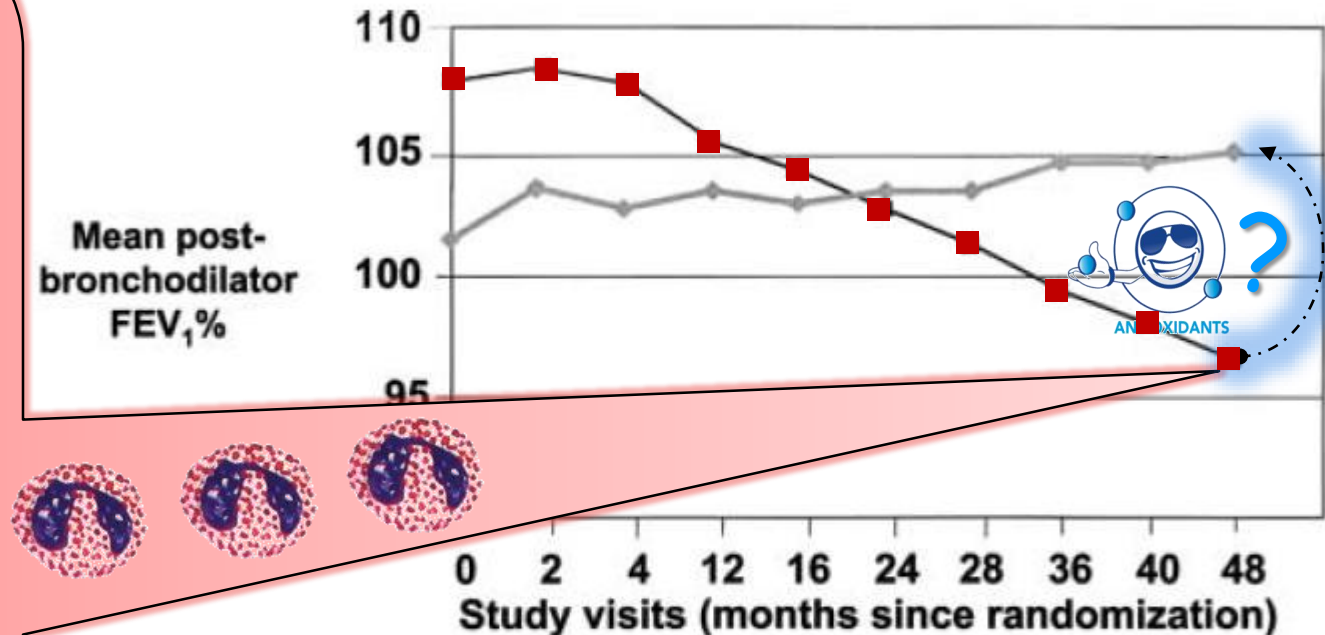
262	251	255	256	254	251	244	249	245	242
779	746	755	752	738	736	706	721	693	694

Progression of asthma measured by lung function in the childhood asthma management program.

Covar RA, Am J Respir Crit Care Med 2004;170:234-241.

participants with (SRP) or **without (NSRP)** reduction in postbronchodilator FEV₁% pred.

- Children in SRPs had more prominent eosinophilic inflammation.
- Eosinophils produce Free Radicals and this is **NOT** contrasted by ICS treatment!



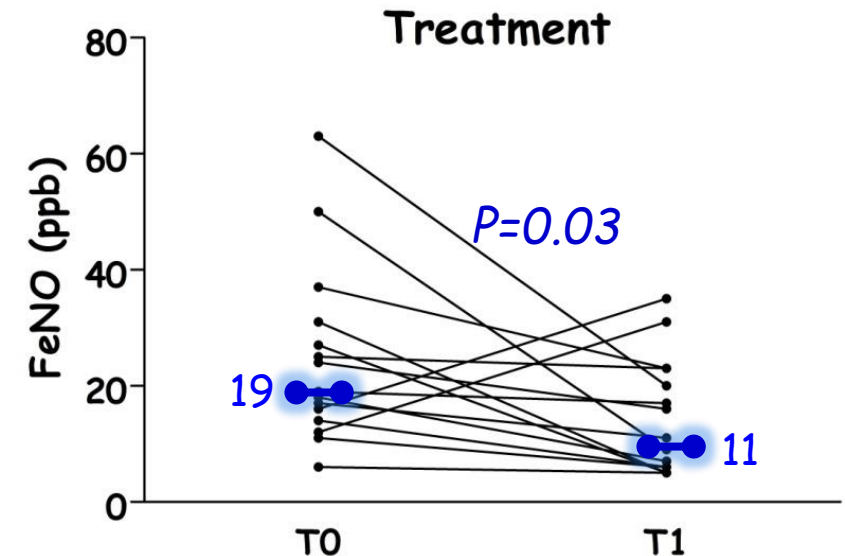
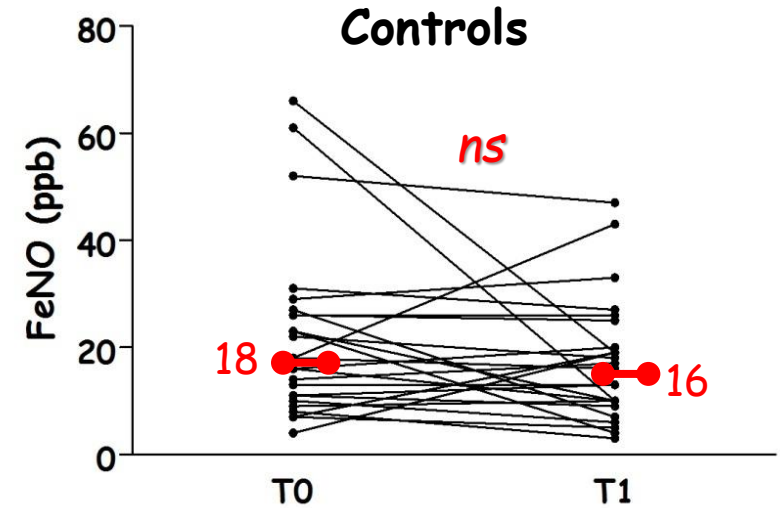
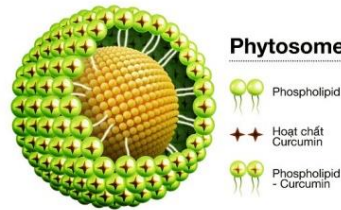
■ SRP (no.)
◆ NSRP (no.)

262	251	255	256	254	251	244	249	245	242
779	746	755	752	738	736	706	721	693	694

Anti-oxidants supplementation reduces FeNO in children with asthma.

Tenero L. Allergy Asthma Proc. 2016;37(1):8-13.

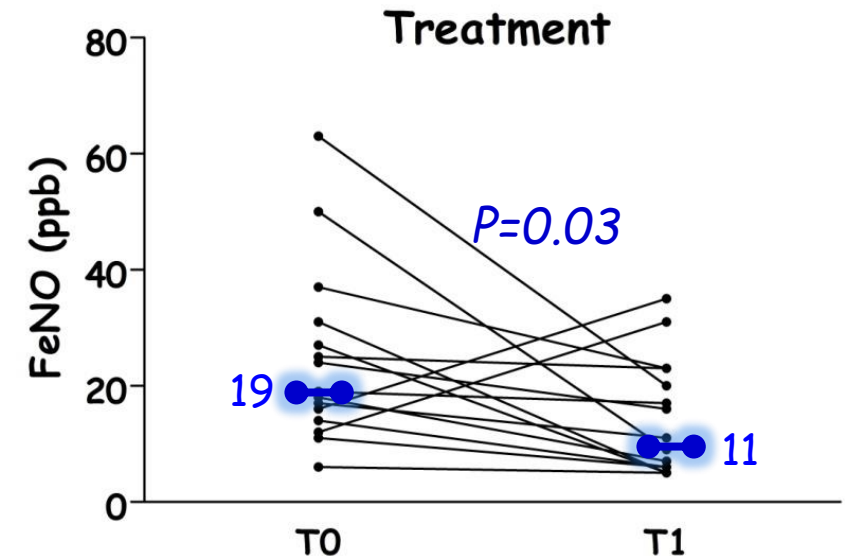
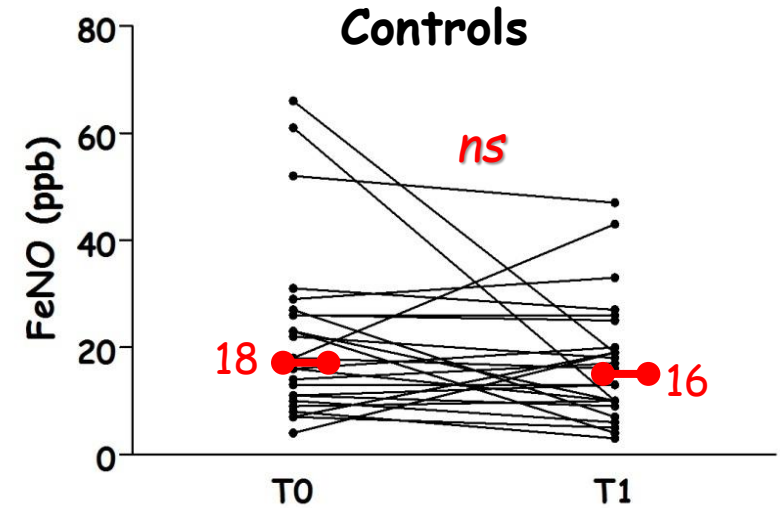
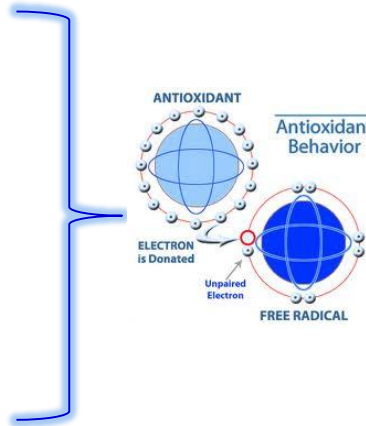
- ✓ 47 asthmatic children (moderate-severe GINA Guidelines) (12.01 ± 3.1 years) admitted to Istituto Pio XII, Misurina (m 1753)
- ✓ Supplementation for 1 mo with a mixture of nutraceuticals: soy genistein, curcumin Meriva, resveratrol, vitamin D, zinc, magnesium, selenium, folic acid (n=15) or controls (n=32)
- ✓ FeNO expressed as median values



Anti-oxidants supplementation reduces FeNO in children with asthma.

Tenero L. Allergy Asthma Proc. 2016;37(1):8-13.

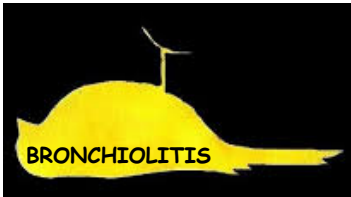
- ✓ 47 asthmatic children (moderate-severe GINA Guidelines) (12.01 ± 3.1 years) admitted to Istituto Pio XII, Misurina (m 1753)
- ✓ Supplementation for 1 mo with a mixture of nutraceuticals: soy genistein, curcumin Meriva, resveratrol, vitamin D, zinc, magnesium, selenium, folic acid (n=15) or controls (n=32)
- ✓ FeNO expressed as median values



Early-life respiratory infection: How do we react to this red flag?




Bush A, Pediatr Pulmonol. 2024 Jun;59(6):1817-1819.



We suggest the following should at least be considered:

- 1. Measure micronutrient status in all babies at high risk (e.g., preterm delivery) and supplement those who are deficient.
- 2. Measure micronutrient status and supplement as above in all babies and infants admitted to hospital with bronchiolitis.

TABLE 1 Biological effects of different nutritional components.

	Vitamin B	Vitamin C	Vitamin D	Vitamin E	Magnesium	Selenium	Zinc	Phytochemicals
Antiviral activity			✓			✓	✓	✓
Immune modulation	✓	✓	✓	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	✓	✓	✓	✓	✓
Auto-immunity prevention		?	✓	?	?	✓	✓	✓
Antioxidant effect	✓	✓	✓	✓	✓	✓	✓	✓
Anti-thrombotic effect				✓	✓	✓	✓	✓
Endothelial protective	✓		✓	✓	✓	✓	✓	✓
Cytoprotective & organ damage prevention	✓		✓	✓	✓	✓	✓	✓
Antiarrhythmic effect			✓	✓	✓	✓	✓	✓
Antidepression effect	✓		✓	✓	✓	✓	✓	✓
Microbiome	✓		✓	✓		?	?	✓

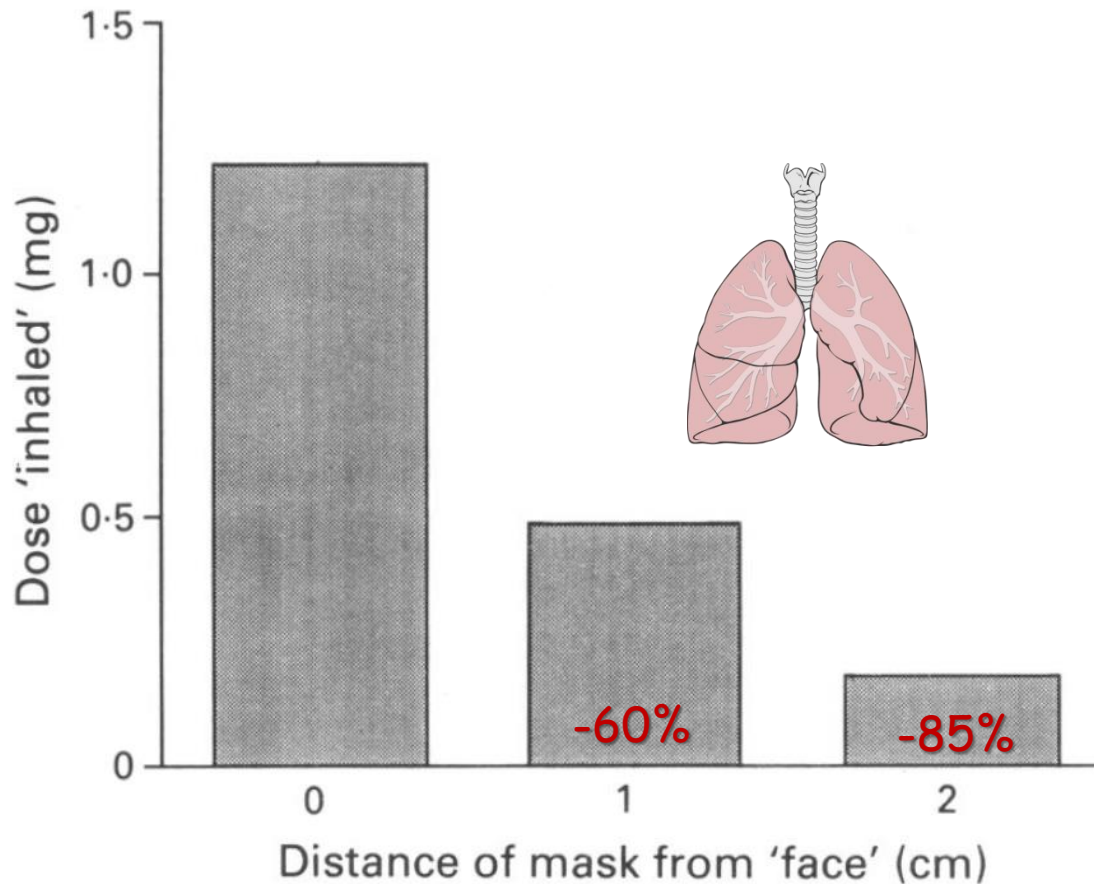
Sinergistic
Effect

9° errore: non istruire adeguatamente i genitori
quando si prescrive l'aerosol
(si da per scontato che sia intuitivo)
o lo spray con distanziatore



Drug delivery from jet nebulisers.

Everard ML, Arch Dis Child 1992;67:586-91.



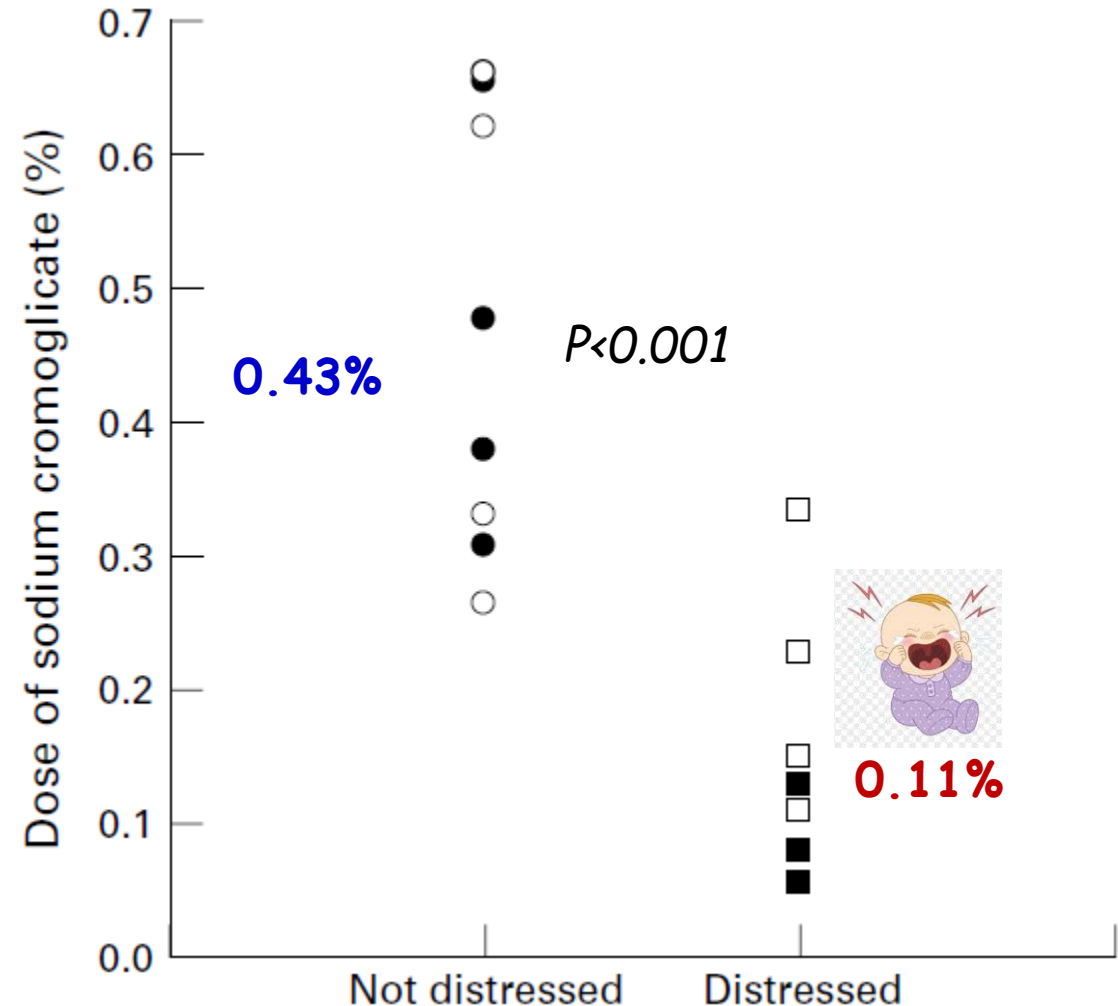
- At only 1 cm from the face while still directing the aerosol stream towards the filter the dose delivered was only 0.49 mg using a tidal volume of 50 ml and a DGF of 8 L/minute.
- At a distance of 2 cm the reduction was even greater with only 0.18 mg reaching the filter (15% of that when a closely fitting mask was used).

Figure 3 The dose deposited upon the filter in a five minute period of nebulisation with increasing distance between the nebuliser facemask and the 'face' of the model when using a DGF of 8 l/minute and a tidal volume of 50 ml.

Crying significantly reduces absorption of aerosolised drug in infants. *Iles R, Arch Dis Child 1999;81:163-5.*

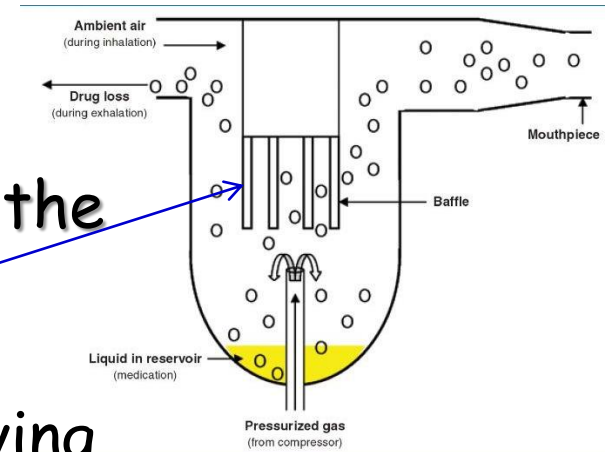
- ✓ 15 infants (mean age 12 months)
- ✓ a dose of 20 mg nebulised sodium cromoglicate via a Sidestream nebuliser (Sodium cromoglicate is absorbed by the respiratory epithelium, and undergoes renal (43%) and hepatic (57%) excretion).
- ✓ distress was graded as:
1, not distressed; 2, distressed.
- ✓ Infants were excluded if contact with the mask was lost for more than 10 seconds.
- ✓ Urine was collected for 8 hours and analysed for excreted drug by radioimmunoassay.

Individual data plot of estimated absorption plotted against the degree of infant distress.



Pneumatic or jet nebulisers

- Pneumatic or jet nebulisers use compressed gas flow to entrain liquid from a reservoir and break the liquid into small droplets by means of baffles.
- The particle size distribution of the aerosol leaving the device is determined by the design of the baffle and the flow through the device.



- These nebulisers are **relatively inefficient**, compared with the newer devices and their performance is dependent on the type of compressor.

Smith EC, Eur Respir J 1995;8: 1214-1221

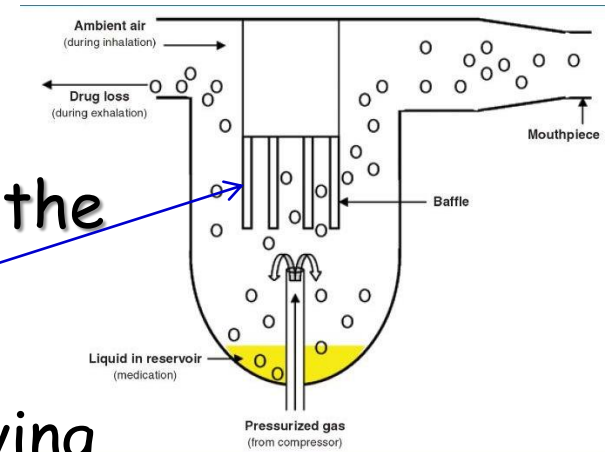
Kendrick AH, Thorax 1997; 52: S92-S101.



Laube BL, Eur Respir J 2011;37:1308-1331

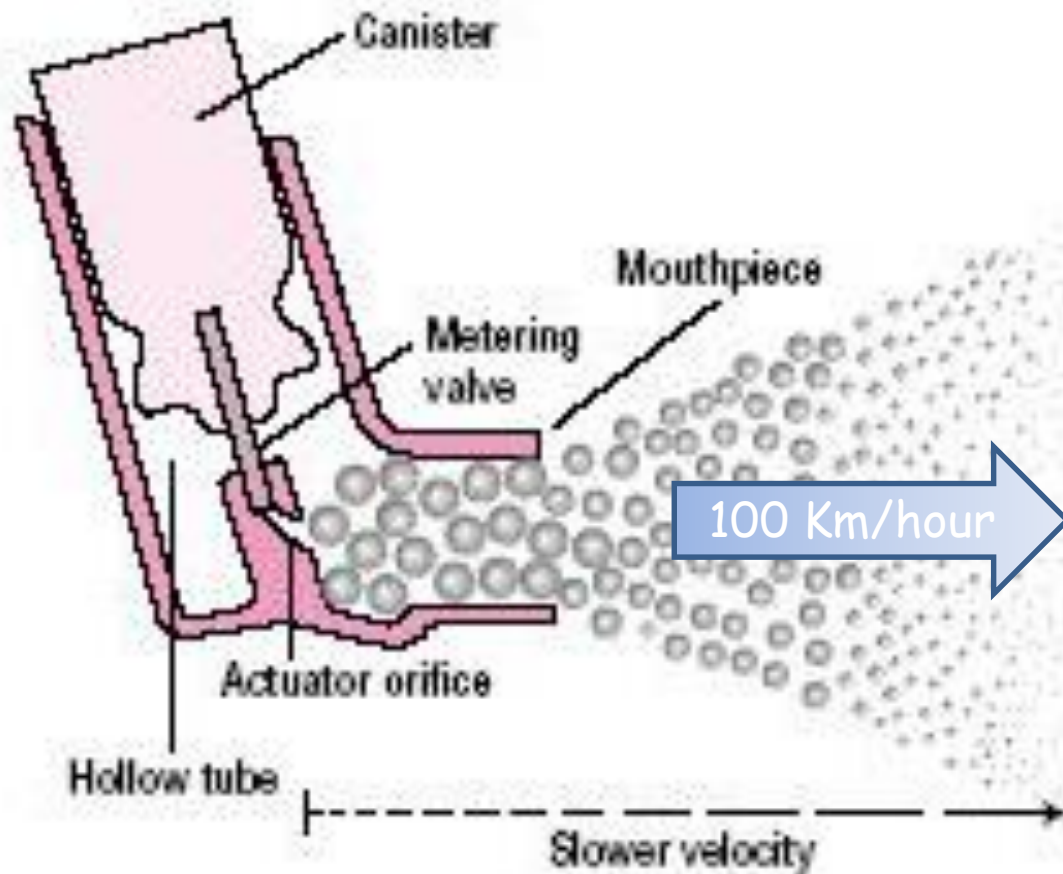
Pneumatic or jet nebulisers

- Pneumatic or jet nebulisers use compressed gas flow to entrain liquid from a reservoir and break the liquid into small droplets by means of baffles.
- The particle size distribution of the aerosol leaving the device is determined by the design of the baffle and the flow through the device.
- These nebulisers are **relatively inefficient**, compared with the newer devices and their performance is dependent on the type of compressor.



the efficiency with which drug is deposited in the lung by most jet nebulisers is 1-5%, whereas the efficiency of metered dose inhalers is 10-14%.

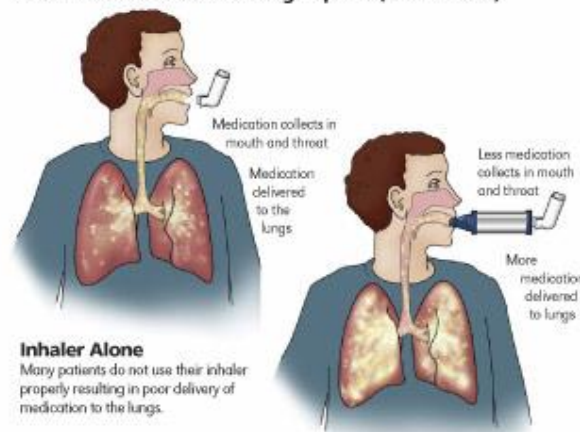
Metered Dose Inhaler



- When the metering chamber is opened to the air, the propellants start to boil, releasing large particles consisting of drug and propellant at high velocity (≈ 100 Km/h).

- The particles rapidly slow and the propellant evaporates producing small slow-moving particles ideal for inhalation.

Consider the benefits of using a spacer (air chamber)

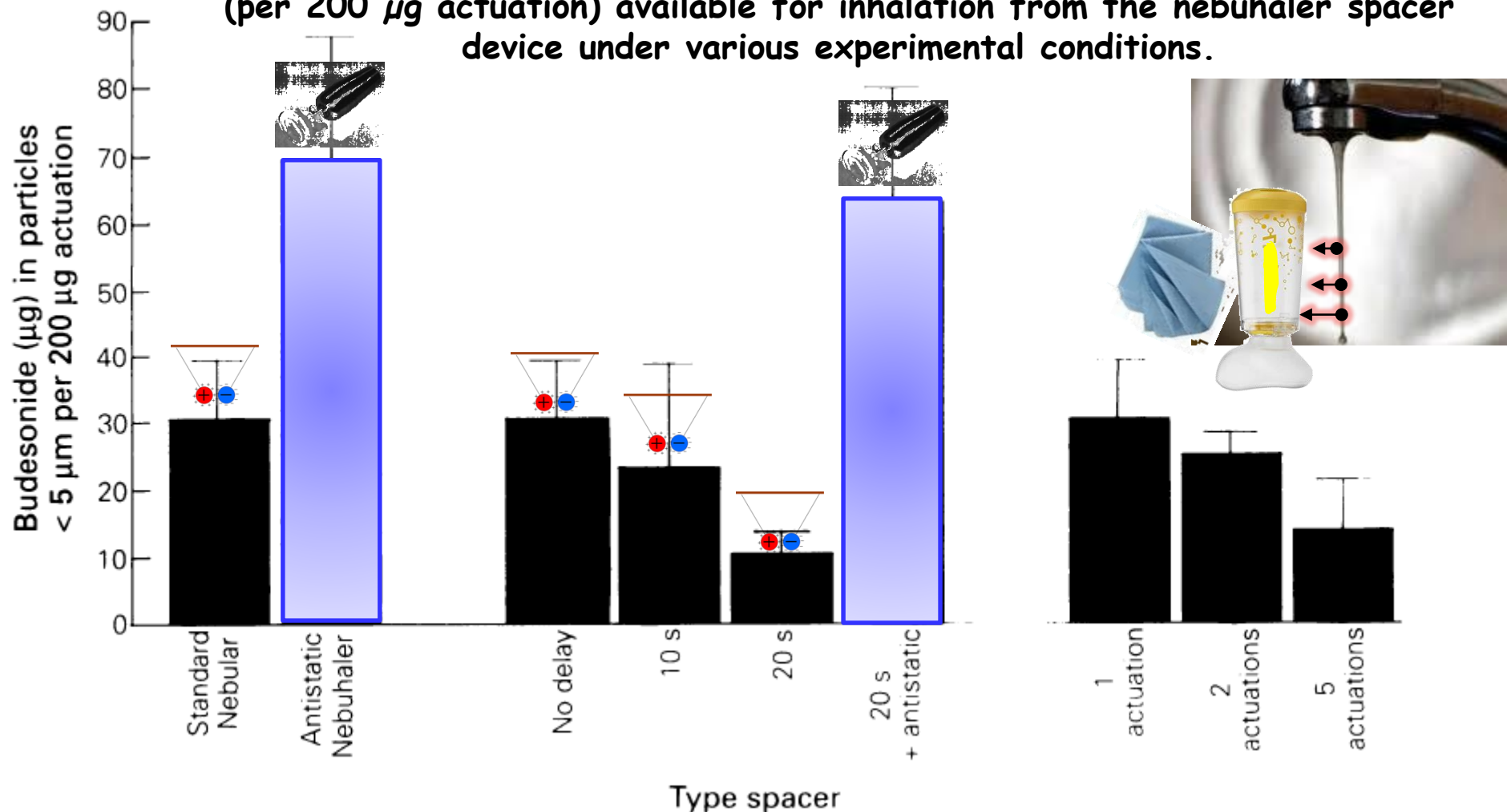


- Unfortunately, the distance between actuator and pharynx is such that much of the delivered dose is still too large and fast moving to reach the lungs, leading to very high upper airways deposition.

- This is reduced by the use of a spacer.

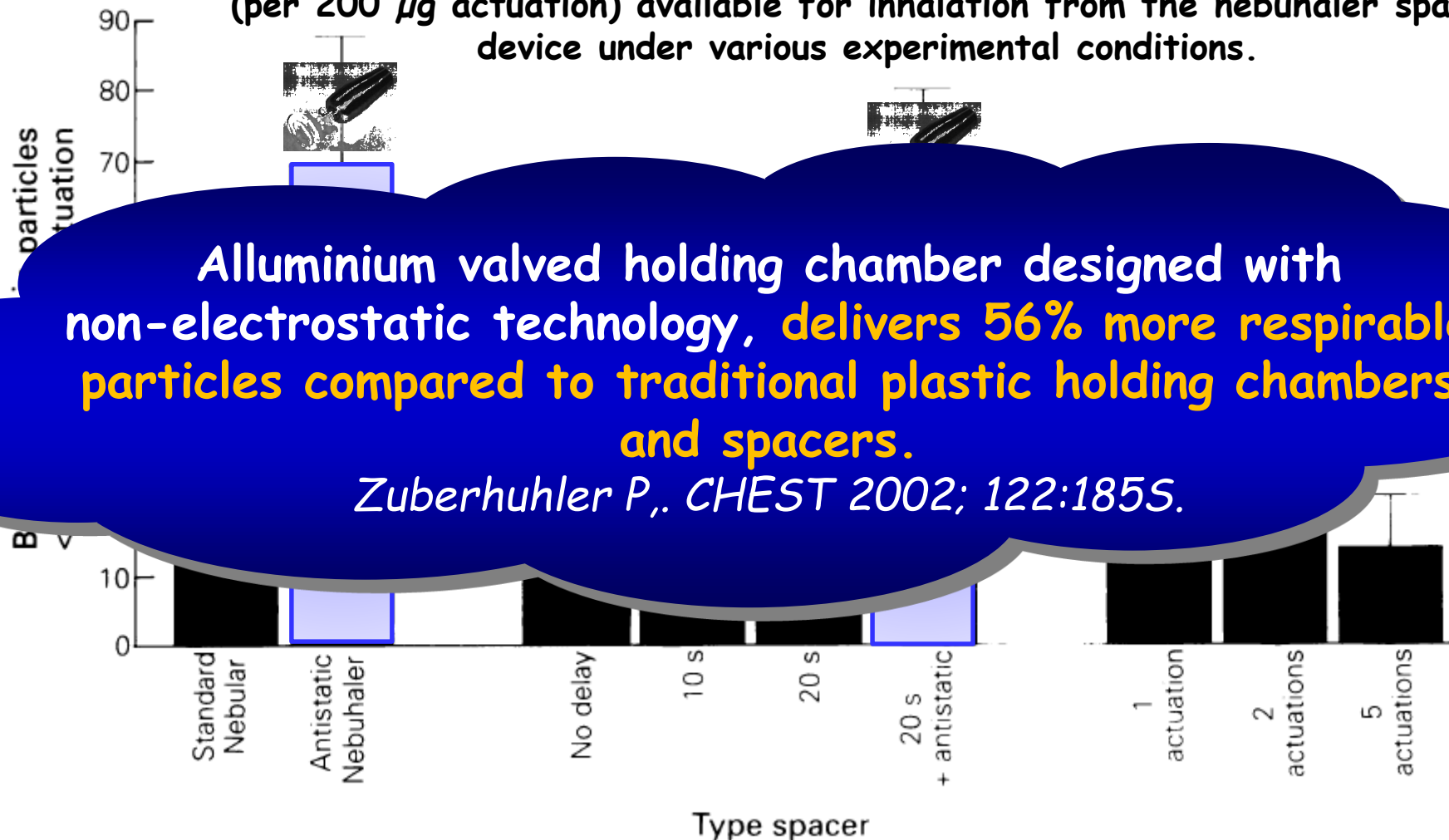
The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler . Barry PW , Br J Clin Pharmacol . 1995;40:76-78 .

The amount of budesonide (+ s.d.) contained in particles < 5 μm (per 200 μg actuation) available for inhalation from the nebuhaler spacer device under various experimental conditions.



The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler . Barry PW , Br J Clin Pharmacol . 1995;40:76-78 .

The amount of budesonide (+ s.d.) contained in particles < 5 μm (per 200 μg actuation) available for inhalation from the nebuhaler spacer device under various experimental conditions.



Alluminium valved holding chamber designed with non-electrostatic technology, **delivers 56% more respirable particles compared to traditional plastic holding chambers and spacers.**

Zuberhuhler P., CHEST 2002; 122:185S.

The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler . Barry PW , Br J Clin Pharmacol . 1995;40:76-78 .

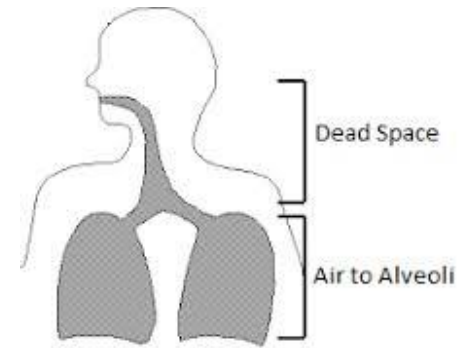
The amount of budesonide (+ s.d.) contained in particles $< 5 \mu\text{m}$ (per 200 μg actuation) available for inhalation from the neбуhaler spacer device under various experimental conditions.



Mask Use with Spacers/Valved Holding Chambers and Metered Dose Inhalers among Children with Asthma.

Volerman A, Ann Am Thorac Soc. 2021 Jan;18(1):17-22.

❖ Masks are most effective when there is a **tight seal around the child's face**.



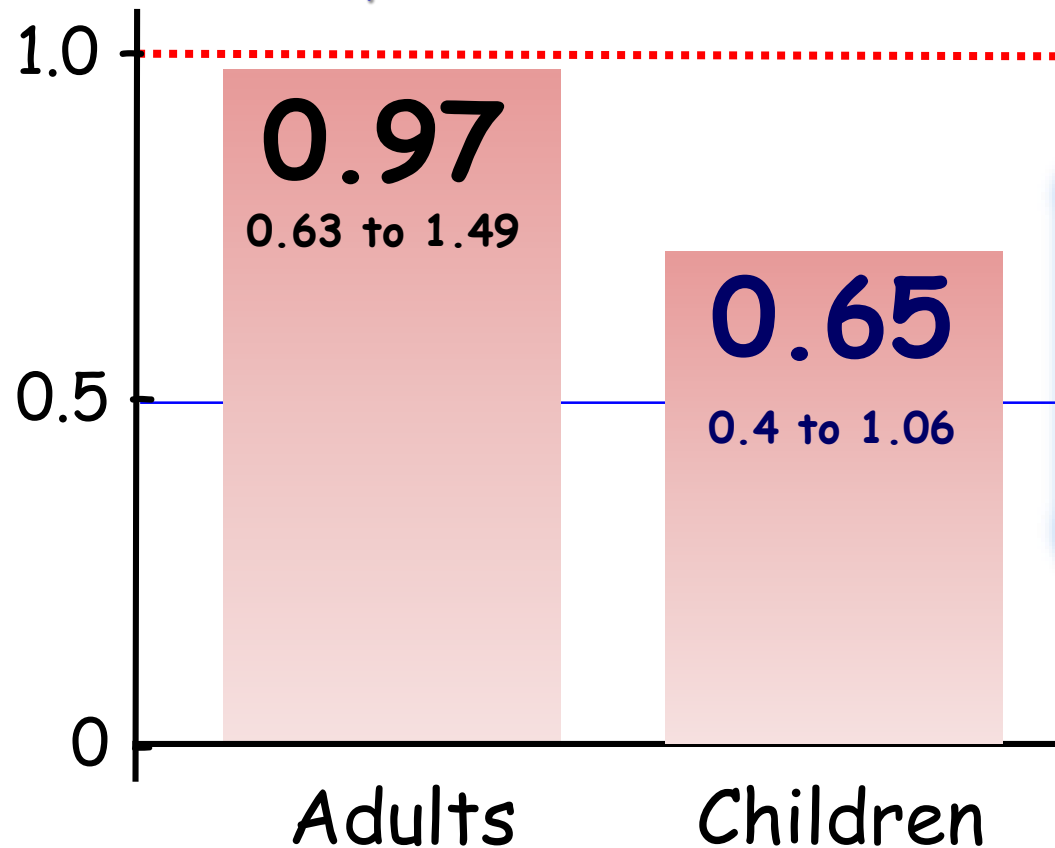
❖ This can be obtained with soft masks which also allow **reduction in dead space**



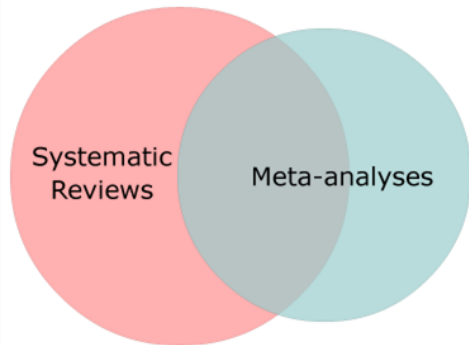
Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma.

Cates CJ, Cochrane Database Syst Rev. 2006;(2):CD000052.

Relative Risk of hospital admission
for spacer versus nebuliser



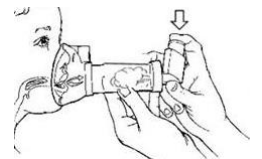
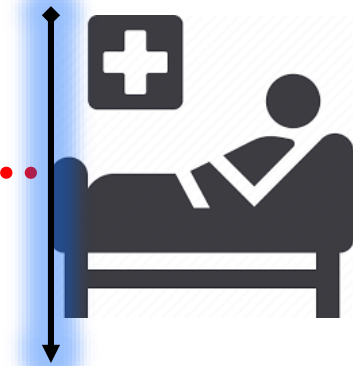
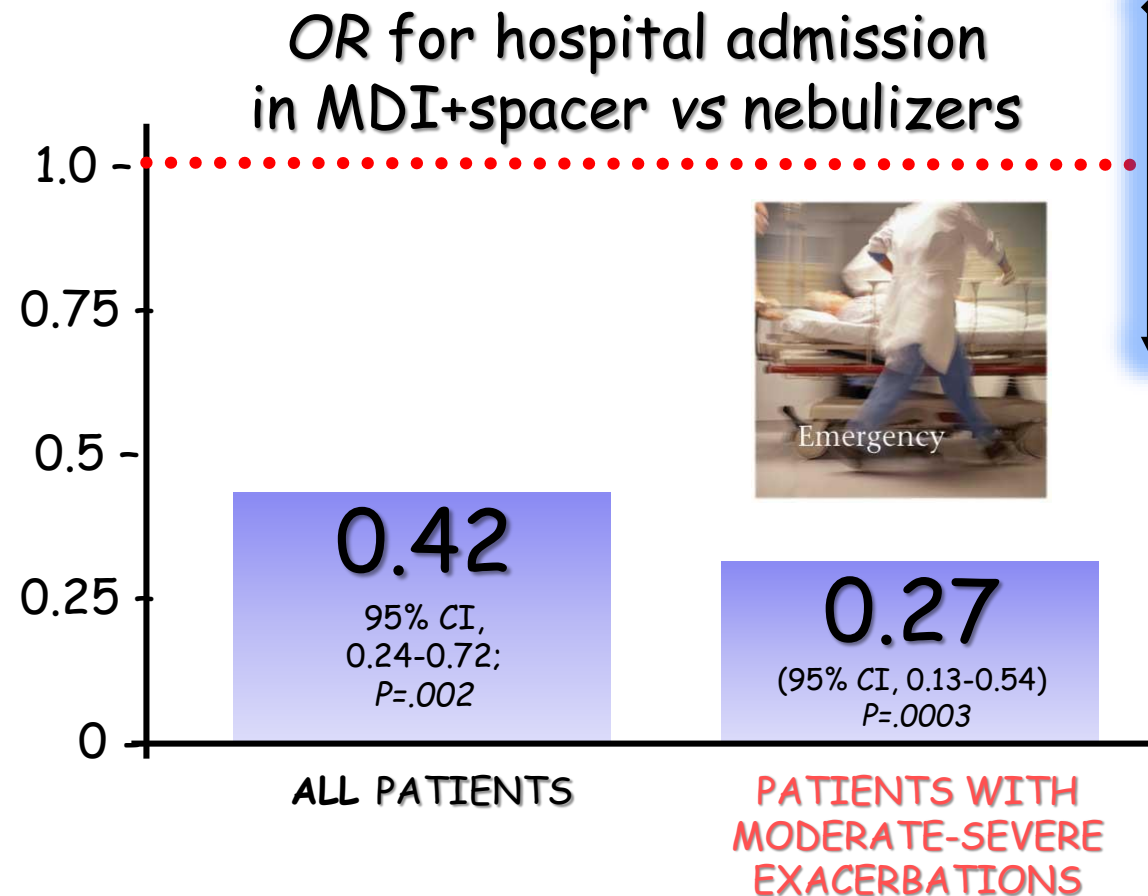
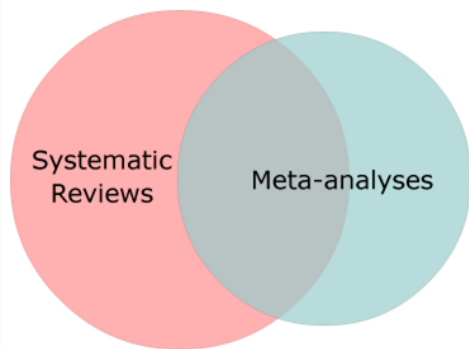
- ✓ 2279 children and 642 adults
- ✓ 31 trials from emergency room and community settings.



Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis.

Castro-Rodriguez JA, *J Pediatr*. 2004 Aug;145(2):172-7.

- ✓ 6 trials
- ✓ 491 children < 5 years of age



IL MIO PIANO D'AZIONE PER IL CONTROLLO DELL'ASMA:

L'uso di piani d'azione scritti per il controllo dell'asma sono associati ad una diminuzione delle crisi d'asma gravi che, se ripetute, si associano ad una progressiva perdita di funzionalità respiratoria e malattia più grave.

Nome: _____ Data: ____/____/____

Genitore: _____

Medico: _____

Numero di telefono per assistenza medica: _____

Numero di telefono di genitori o amici: _____

I colori del semaforo ti aiutano a riconoscere i sintomi dell'asma e a capire come controllarli.



ROSSO significa che **stai molto male:**
cerca subito aiuto.

GIALLO significa che **non stai molto bene:**
usa i farmaci ad azione rapida per sentirti meglio.

VERDE significa che **stai bene.**
usa i farmaci di controllo a lungo termine.

Action Plan for Asthma treatment



health
literacy
informed,
pictogram



MI SENTO BENE

- respiro facilmente,
- non ho tosse o respiro sibilante (broncospasmo),
- posso giocare e fare attività fisica normalmente,
- posso dormire bene.



Usare i farmaci per il controllo a lungo termine dell'asma.

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	_____ volte al giorno
_____	_____	_____	_____ volte al giorno
_____	_____	_____	_____ volte al giorno

20 minuti prima di fare sport o esercizi, prendere _____ dosi di questa medicina:

NON MI SENTO TANTO BENE

- ho preso un raffreddore
- **sono di malumore**
- tossisco di giorno e di notte,
- ho il respiro sibilante (broncospasmo),
- fatica a respirare,
- sento un senso di oppressione al petto,
- mi sveglio di notte,
- riesco a fare alcune, ma non tutte le attività.



Prendi N° _____ spruzzi di _____ anche ogni 20 minuti nella prima ora se non rientri subito nella zona verde. Poi continua con:

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	ogni _____ ore
_____	_____	_____	ogni _____ ore
_____	_____	_____	ogni _____ ore

CONTINUA ad utilizzare i farmaci per il controllo dell'asma a lungo termine:

Consultare il proprio medico se il medicinale ad effetto rapido non funziona OPPURE se i sintomi compaiono più di 1-2 volte alla settimana.

MI SENTO MALE

- i farmaci non funzionano più,
- respiro a fatica e velocemente e la tosse non si calma,
- **la gola viene tirata dentro e vedo le costole quando respiro,**
- faccio fatica a camminare,
- faccio fatica a parlare,
- ho molta paura.



CERCA SUBITO AIUTO!

Prendi questo farmaco ad effetto rapido finché non arrivano i soccorsi.

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

CHIAMA IL 118 se non riesci a camminare o a parlare perchè è troppo difficile respirare OPPURE se sei troppo stanco OPPURE se senti la pelle tesa intorno al collo e alle costole durante la respirazione OPPURE se le labbra e le punte delle dita sono grigie o blu.

IL MIO PIANO D'AZIONE PER IL CONTROLLO DELL'ASMA:

L'uso di piani d'azione scritti per il controllo dell'asma sono associati ad una diminuzione delle crisi d'asma gravi che, se ripetute, si associano ad una progressiva perdita di funzionalità respiratoria e malattia più grave.

Nome: _____ Data: ____/____/____

Genitore: _____

Medico: _____

Numero di telefono per assistenza medica: _____

Numero di telefono di genitori o amici: _____

I colori del semaforo ti aiutano a riconoscere i sintomi dell'asma e a capire come controllarli.



ROSSO significa che **stai molto male:**
cerca subito aiuto.

GIALLO significa che **non stai molto bene:**
usa i farmaci ad azione rapida per sentirti meglio.

VERDE significa che **stai bene.**
usa i farmaci di controllo a lungo termine.

Action Plan for Asthma treatment

se inizio la terapia
nelle fasi iniziali della
riacutizzazione mi
serve meno farmaco



MI SENTO BENE

- respiro facilmente,
- non ho tosse o respiro sibilante (broncospasmo),
- posso giocare e fare attività fisica normalmente,
- posso dormire bene.



Usare i farmaci per il controllo a lungo termine dell'asma.

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	_____ volte al giorno
_____	_____	_____	_____ volte al giorno
_____	_____	_____	_____ volte al giorno

20 minuti prima di fare sport o esercizi, prendere _____ dosi di questa medicina: _____

NON MI SENTO TANTO BENE

- ho preso un raffreddore
- **sono di malumore**
- tossisco di giorno e di notte,
- ho il respiro sibilante (broncospasmo),
- fatica a respirare,
- sento un senso di oppressione al petto,
- mi sveglio di notte,
- riesco a fare alcune, ma non tutte le attività.



Prendi N° _____ spruzzi di _____ anche ogni 20 minuti nella prima ora se non rientri subito nella zona verde. Poi continua con:

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	ogni _____ ore
_____	_____	_____	ogni _____ ore
_____	_____	_____	ogni _____ ore

CONTINUA ad utilizzare i farmaci per il controllo dell'asma a lungo termine:

Consultare il proprio medico se il medicinale ad effetto rapido non funziona OPPURE se i sintomi compaiono più di 1-2 volte alla settimana.

MI SENTO MALE

- i farmaci non funzionano più,
- respiro a fatica e velocemente e la tosse non si calma,
- **la gola viene tirata dentro e vedo le costole quando respiro,**
- faccio fatica a camminare,
- faccio fatica a parlare,
- ho molta paura.



CERCA SUBITO AIUTO!

Prendi questo farmaco ad effetto rapido finché non arrivano i soccorsi.

Farmaco:	Come:	Dose:	Quando:
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

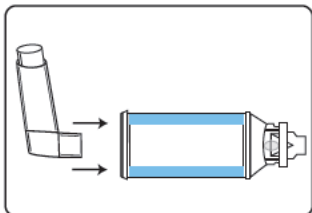
CHIAMA IL 118 se non riesci a camminare o a parlare perchè è troppo difficile respirare OPPURE se sei troppo stanco OPPURE se senti la pelle tesa intorno al collo e alle costole durante la respirazione OPPURE se le labbra e le punte delle dita sono grigie o blu.

How to use an MDI with a spacer

FASE 1:



Inserire lo spray nel distanziatore Respiro®



FASE 2:

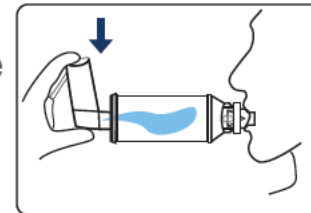
Agitare bene lo spray inserito nel distanziatore prima di ogni spruzzo.



FASE 3:

Espirare profondamente.

Mettere il boccaglio in bocca ed erogare nel distanziatore una sola dose di farmaco alla volta.



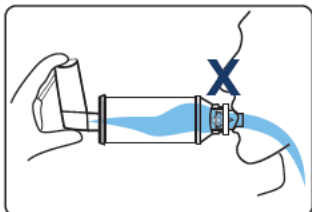
FASE 4:

FASE 5:

RIPETERE QUESTI PASSAGGI PER 2 VOLTE

Inspirare profondamente

e lentamente dalla bocca, tenendo le labbra chiuse sul boccaglio fino alla fine dell'inspirio.



Trattenere il respiro per 10 secondi

ed espirare lentamente dal naso per ridurre i sintomi della rinite con il farmaco che altrimenti andrebbe buttato. Sциquare bene la bocca.

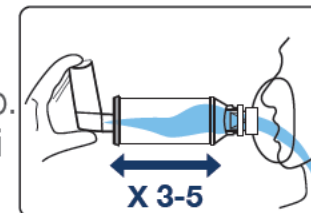


FASE 5:

(per soggetti non collaboranti)

Per i bambini in età prescolare

si deve usare una mascherina che aderisca bene al viso. Far eseguire 3-5 atti respiratori.



Inhaler technique in a pediatric emergency department: Impact of an education intervention among healthcare professionals. Jové-Blanco A, *Pediatr Pulmonol.* 2023;58(2):441-448.

- **Asthma exacerbations** are one of the main reasons for presentation to the Pediatric Emergency Department (PED), representing 5% of all consultations.
- **Correct inhaler technique (IT)** is a simple but effective method to improve **asthma control** in children.
- **WHAT** the majority of the healthcare providers involved in caring for patients with respiratory diseases have poor knowledge of IT

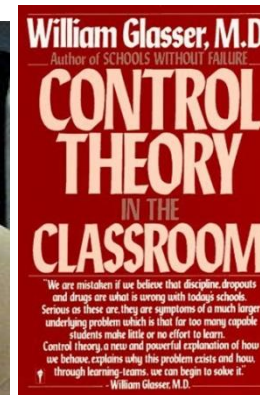
WHY ?

We learn...

- 10% of what we read
- 20% of what we hear
- 30% of what we see
- 50% of what we see and hear
- 70% of what we discuss with others
- 80% of what we experience personally
- 95% of what we teach to someone else

WHY ?

William Glasser, Control Theory in the Classroom, 1986. ISBN 0-06-095287-3



How do patients determine that their metered-dose inhaler is empty?

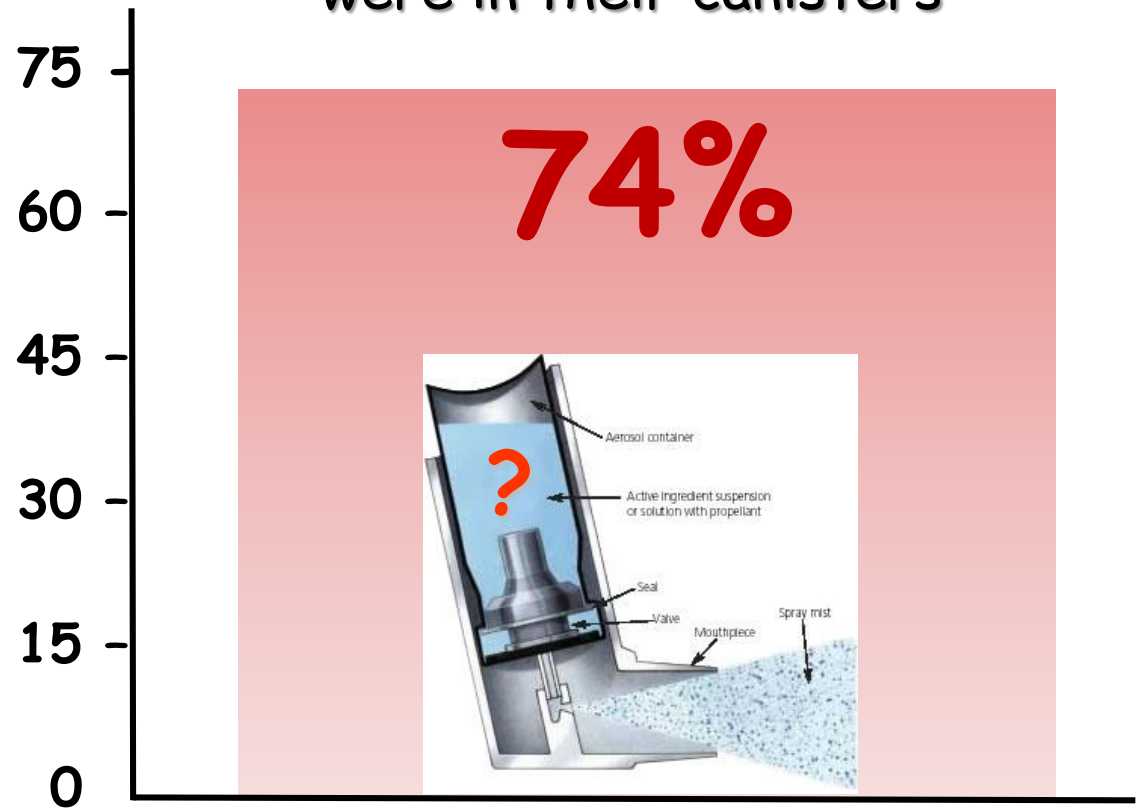
Rubin BK, Chest. 2004 Oct;126(4):1134-7.

% patients or parents who
did not know how many actuations
were in their canisters

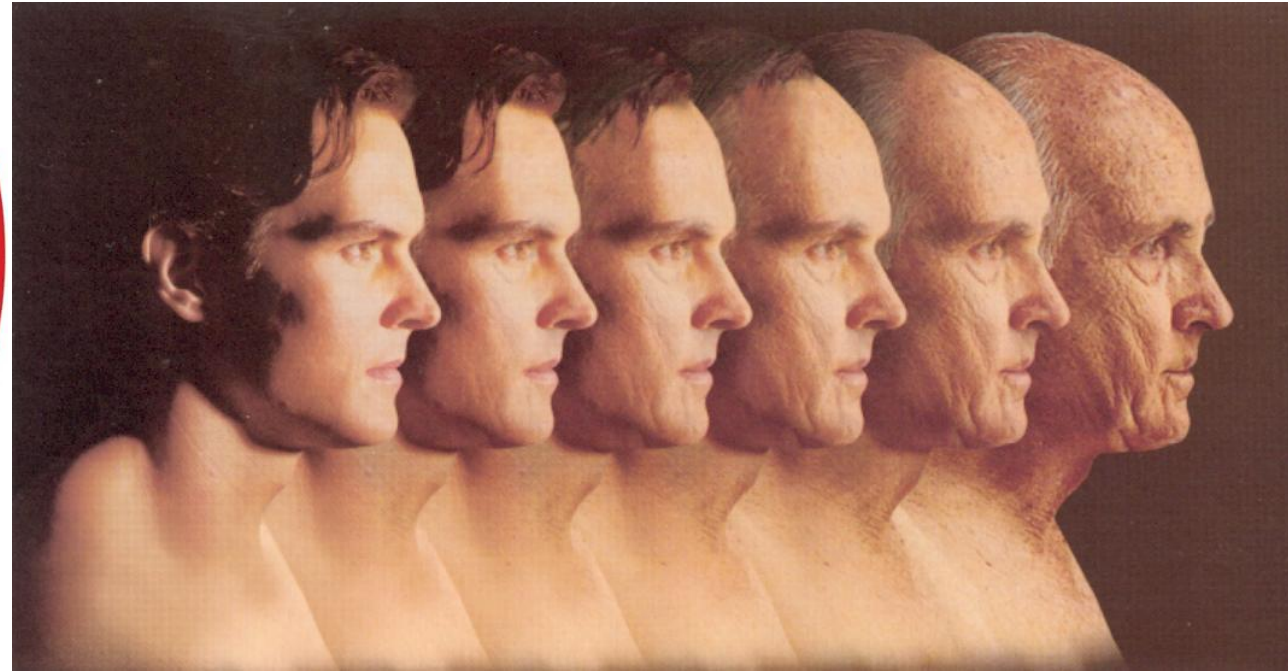
✓ 50 consecutive patients
attending the Children's
Hospital Asthma Center



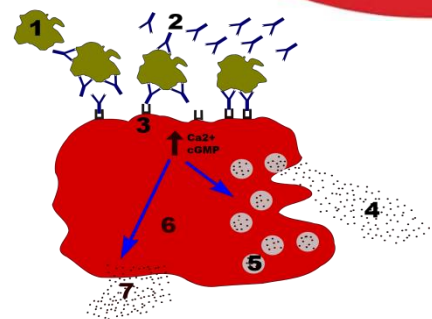
200 dosi



10° errore: dimenticare l'effetto dello Stress Ossidativo nella patogenesi delle malattie allergiche e invecchiamento

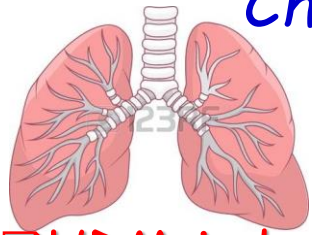


fatal in 100% of cases



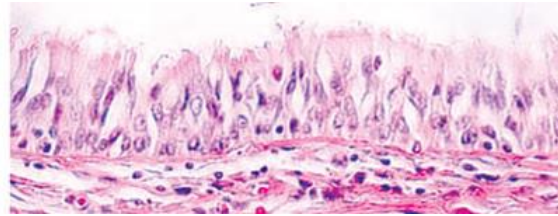
House dust mite-induced asthma causes oxidative damage and DNA double-strand breaks in the lungs.

Chan TK, J Allergy Clin Immunol. 2016;138(1):84-96.e1.



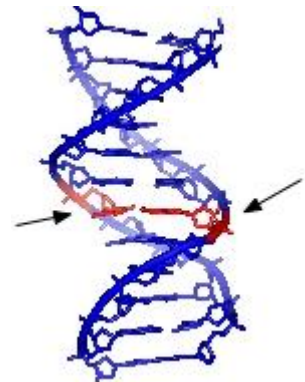
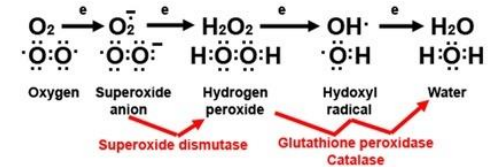
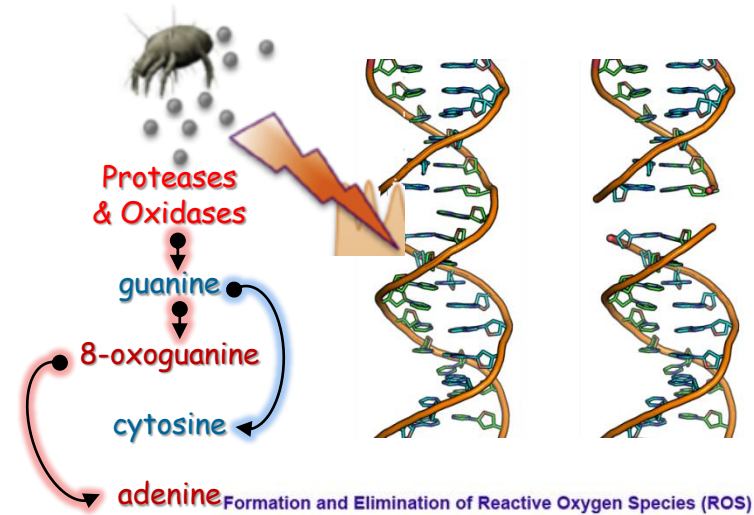
lung samples from asthmatic patients

□ **HDM-induced allergic asthma causes a significant increase in DNA double-strand break (DSBs)** in lung tissue and specifically in the bronchial epithelium.



□ Direct exposure of human bronchial epithelial cells to HDM leads to reactive oxygen species (ROS) production and increased DNA damage in cells.

□ **A defect in DNA DSB repair augments DNA damage,** proinflammatory cytokine production, and apoptosis bronchial epithelium.

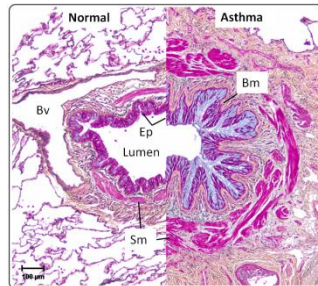


House dust mite-induced asthma causes oxidative damage and DNA double-strand breaks in the lungs.

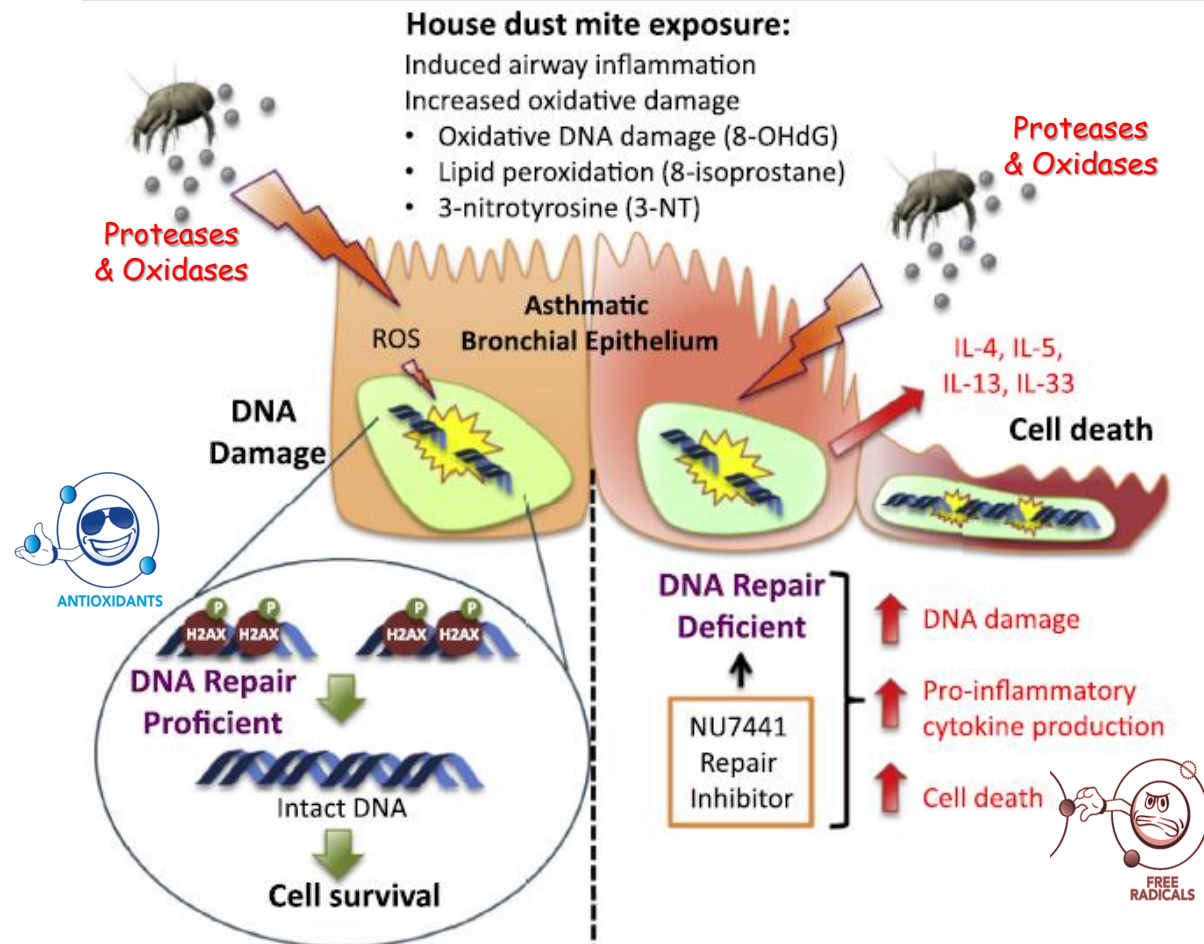
Chan TK, *J Allergy Clin Immunol*. 2016;138(1):84-96.e1.

✓ DNA damage and DNA damage responses induced by house dust mite in vivo (mice model) and in vitro (human bronchial epithelial cells).

✓ DNA double-strand breaks (DSBs), DNA repair proteins, and apoptosis in an HDM-induced allergic asthma model and in lung samples from asthmatic patients who died for asthma.



human bronchial epithelial cells exposed to HDM showed enhanced DNA damage



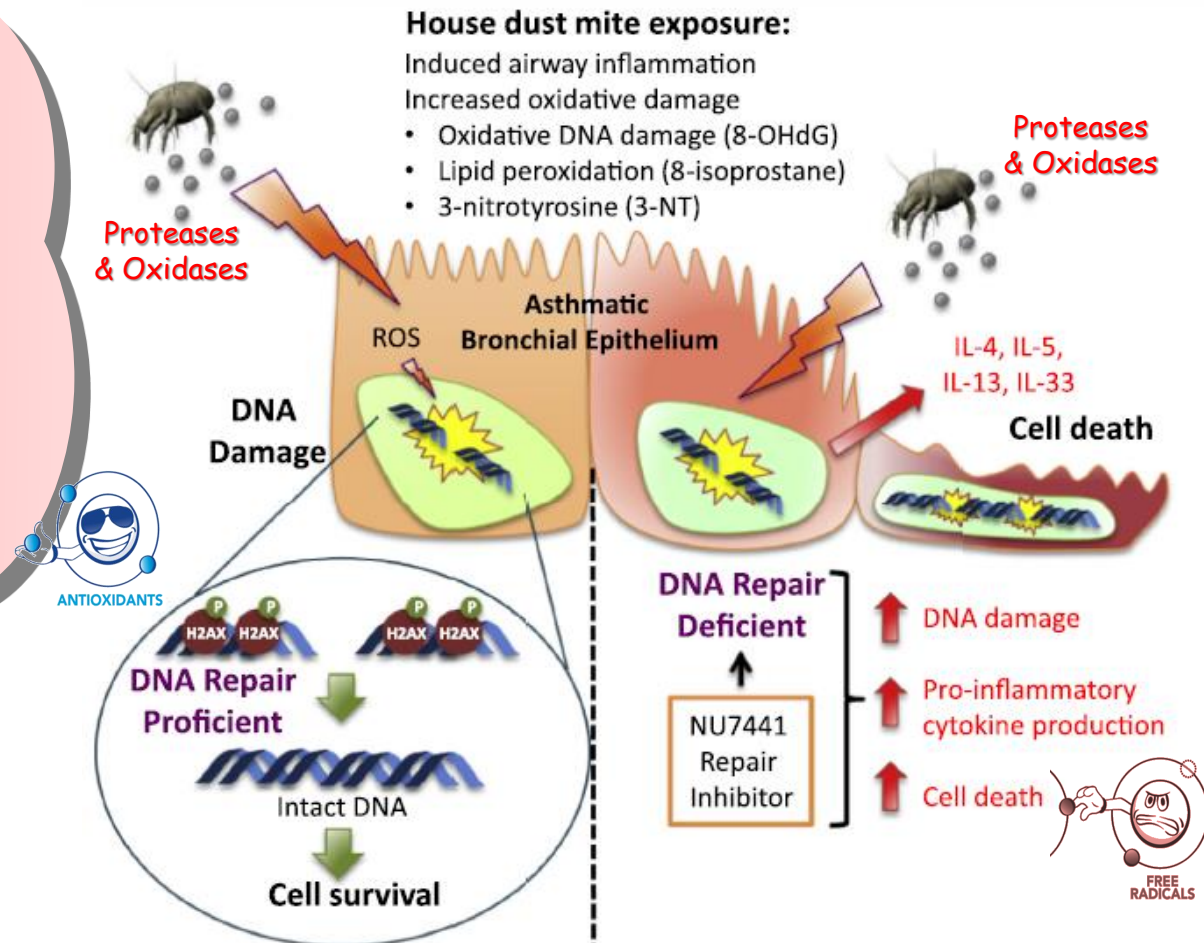
House dust mite-induced asthma causes oxidative damage and DNA double-strand breaks in the lungs.

Chan TK, *J Allergy Clin Immunol*. 2016;138(1):84-96.e1.

HDM exposure causes airway inflammation, oxidative damage, DNA damage, and cell death in the airway independently by the presence of mite sIgE.

Direct HDM exposure to bronchial epithelial cells in vitro induces DNA damage accompanied by increased ROS production.

human bronchial epithelial cells exposed to HDM showed enhanced DNA damage



Infant respiratory symptoms in relation to mite allergen exposure.

van Strien RT, Eur Respir J. 1996 May;9(5):926-31.

❖ **Der p I** in house dust was associated with the frequency of parental reports of **wheeze** and/or frequent **cough** in 3-15 month old infants.

❖ The relationship was most prominent when infants exposed to **> 2,000 ng·g⁻¹**



Proteases & Oxidases



✓ 104 Dutch infants,
aged 3-15 months,

✓ Der p I content
in dust extracts.

Infant respiratory symptoms in relation to mite allergen exposure.

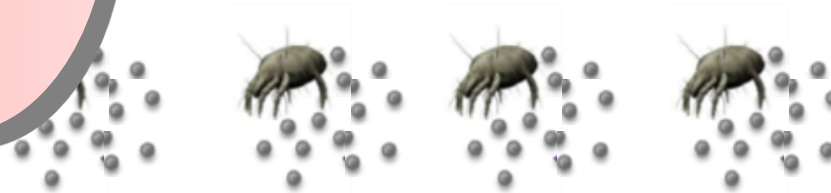
van Strien RT, Eur Respir J. 1996 May;9(5):926-31.

a (+) association between
airway responsiveness
to histamine and *Der p I*
concentrations in mattress
dust was demonstrated
in 45 one month old
infants.

O'Keefe PT, Association between *Der p I*
exposure and airway responsiveness
in early infancy.
Eur Respir J 1994;
7 (Suppl. 18): 29s (Abstract).

in house dust was associated with the
of parental reports of **wheeze** and/or
cough in 3-15 month old infants.

onship was most prominent
exposed to **> 2,000 ng·g⁻¹**



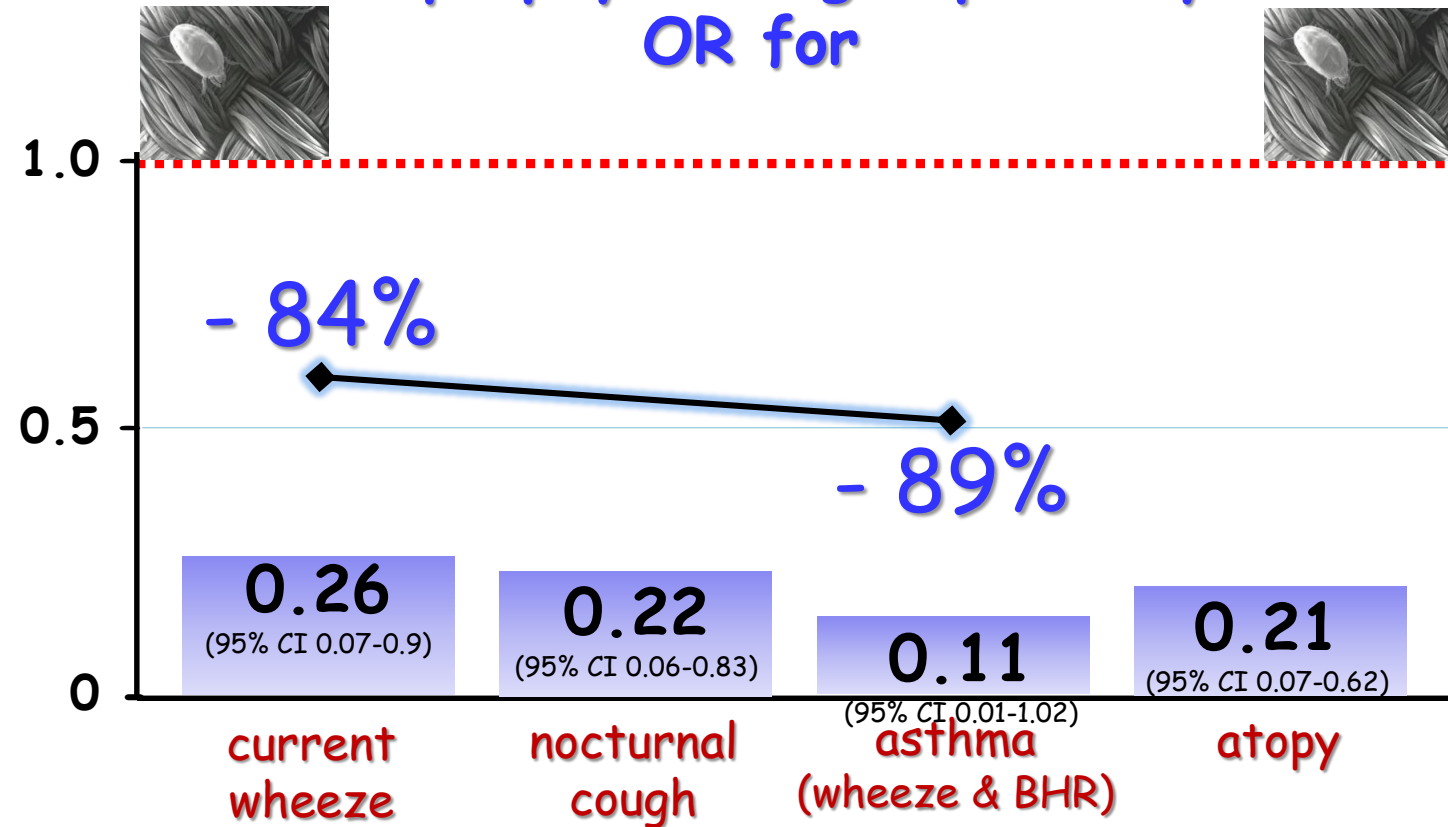
Proteases & Oxidases



Primary Prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study.

Arshad SH, Thorax. 2003 Jun;58(6):489-93.

in the prophylactic group at 8 years
OR for



✓ 120 infants at high risk
of developing atopy
randomised into
prophylactic (n=58)
and
control (n=62) groups.

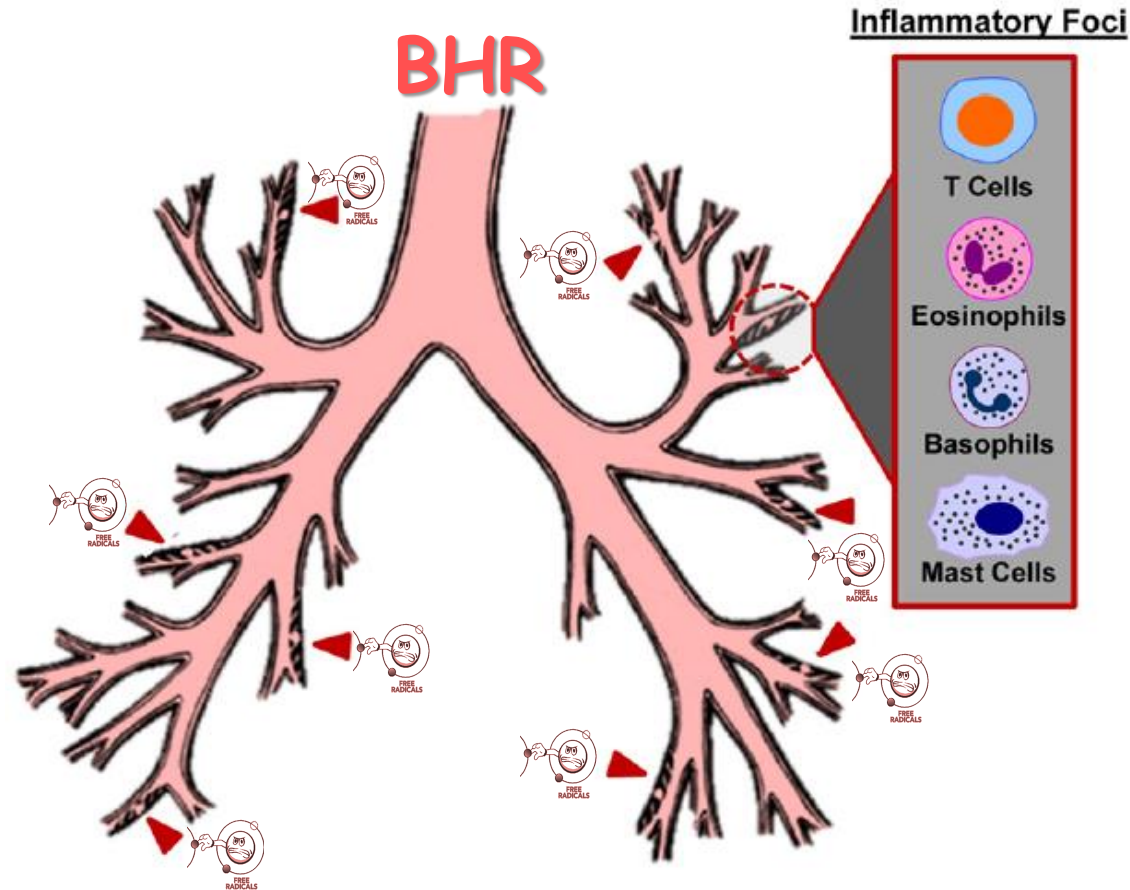
✓ Isle of Wight study

Contrast between natural exposure to airborne allergen (A) and bronchial provocation with nebulized extract (B).

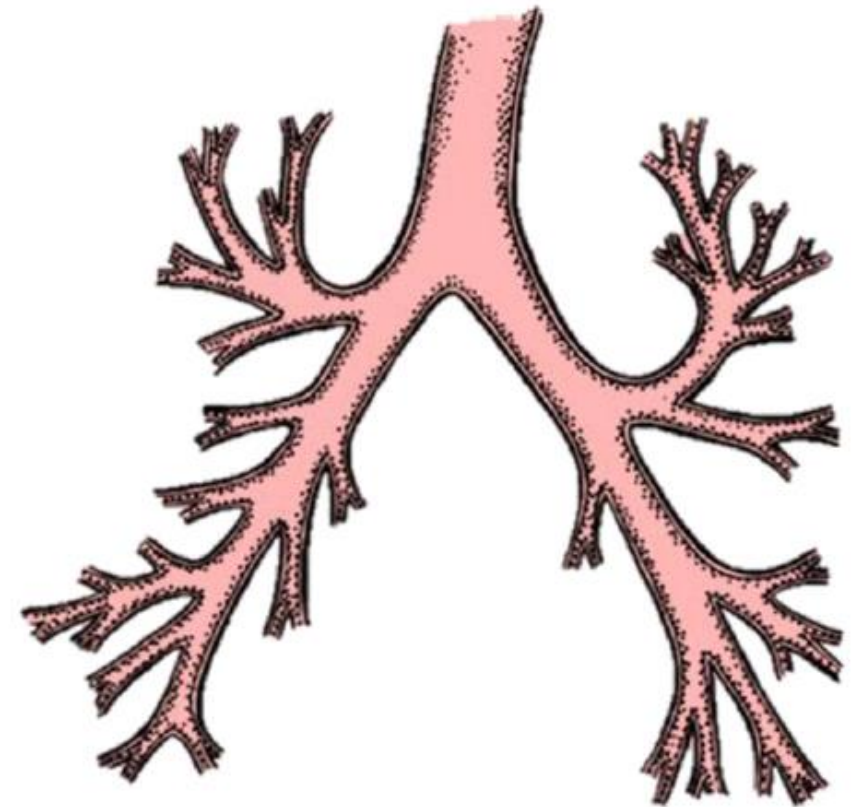
Platts-Mills TAE, *J Allergy Clin Immunol.* 2016 Jun;137(6):1662-1670.

A Natural exposure consist of a small number (10-200) of large particles per day

B Bronchial challenge with nebulized allergen extracts ($>10^7$ droplets in 2-5 min)



The concentration of allergen in the particles is sufficient to produce local inflammatory foci that can contribute to a prolonged increase in bronchial hyperreactivity.



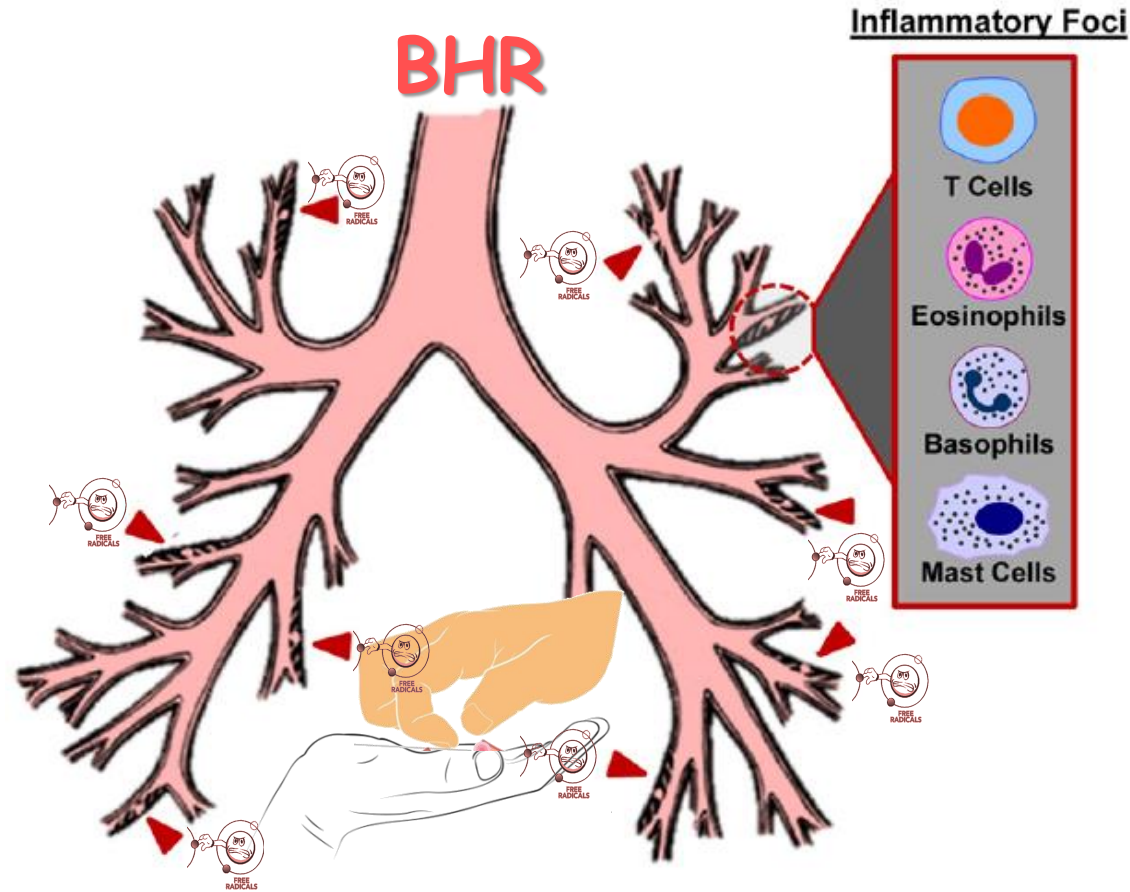
Challenge of an allergic patient can produce a fall in FEV1 and in some cases a transient increase in bronchial hyperreactivity

Contrast between natural exposure to airborne allergen (A) and bronchial provocation with nebulized extract (B).

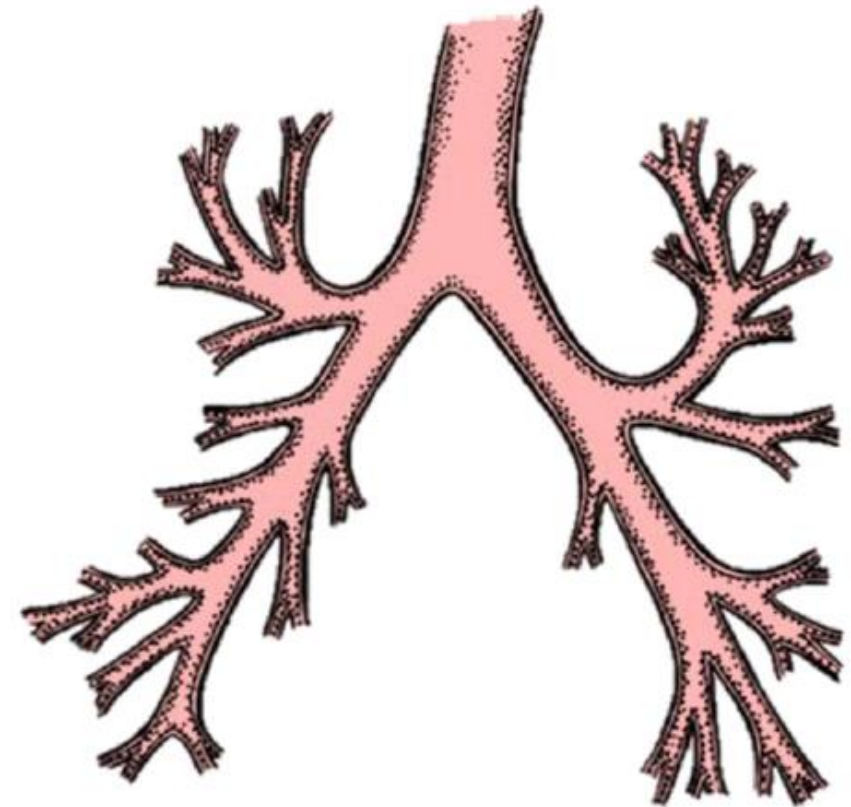
Platts-Mills TAE, *J Allergy Clin Immunol.* 2016 Jun;137(6):1662-1670.

A Natural exposure consist of a small number (10-200) of large particles per day

B Bronchial challenge with nebulized allergen extracts (>10⁷ droplets in 2-5 min)



The concentration of allergen in the particles is sufficient to produce local inflammatory foci that can contribute to a prolonged increase in bronchial hyperreactivity.



Challenge of an allergic patient can produce a fall in FEV1 and in some cases a transient increase in bronchial hyperreactivity

Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable

Murray CS, Am J Respir Crit Care Med. 2017;196:150-158

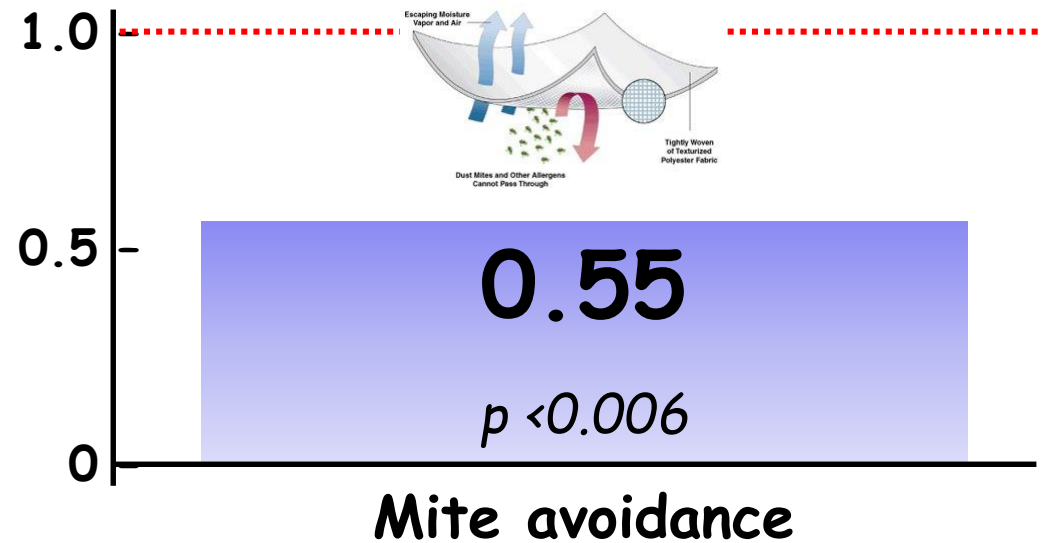
- ✓ Mite-sensitized children with asthma (ages 3-17 yr) after an emergency hospital attendance with an asthma exacerbation.



- ✓ Mite-impermeable (active group, n=146) or control (placebo group, n=138) bed encasings.

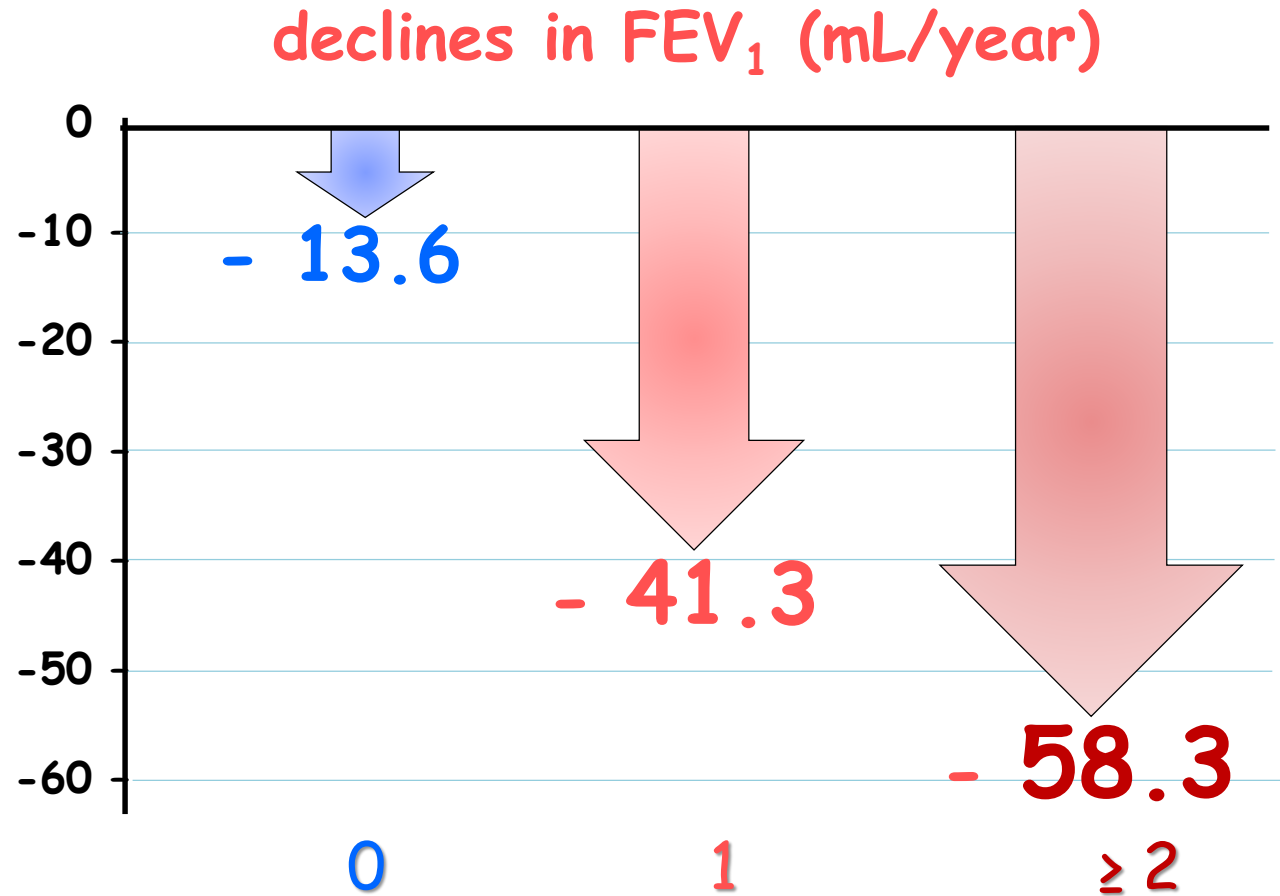
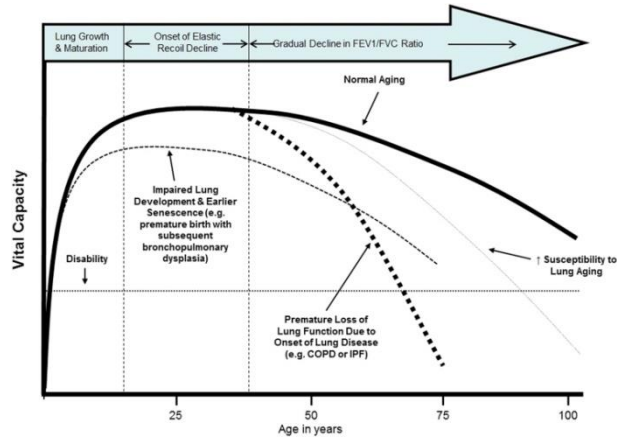


*HR for emergency
hospital attendance*



Progression of Irreversible Airflow Limitation in Asthma: Correlation with Severe Exacerbations.

Matsunaga K, J Allergy Clin Immunol Pract. 2015;3(5):759-64.e1.



✓ 140 nonsmoking patients with well-controlled asthma at baseline and followed for 3 yrs

✓ changes in FEV1 and BDR associated with the frequency of severe asthma exacerbations.

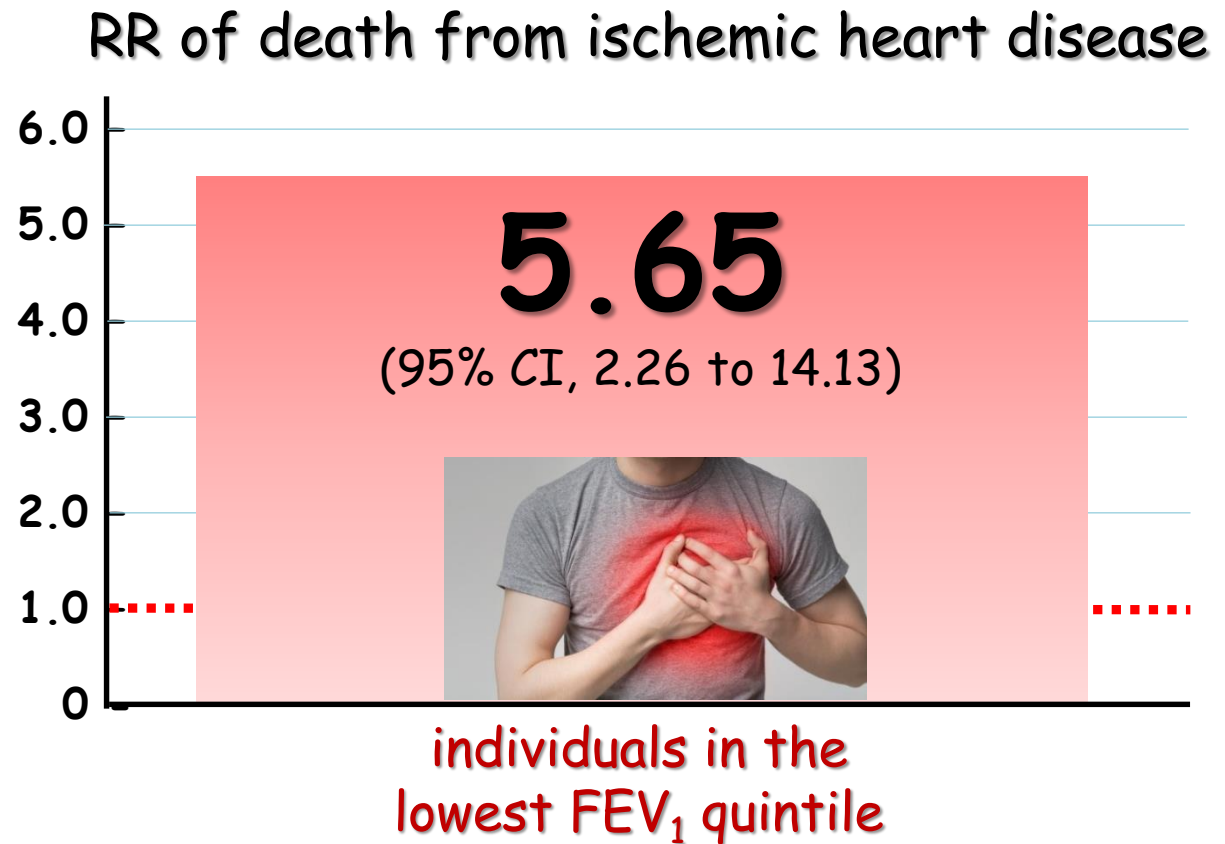
N° of exacerbations in the 3 years follow-up

The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature.

Sin DD, Chest. 2005 Jun;127(6):1952-9.

✓ 1,861 Participants of the 1st National Health and Nutrition Examination Survey Epidemiologic who were 40 to 60 years of age at baseline

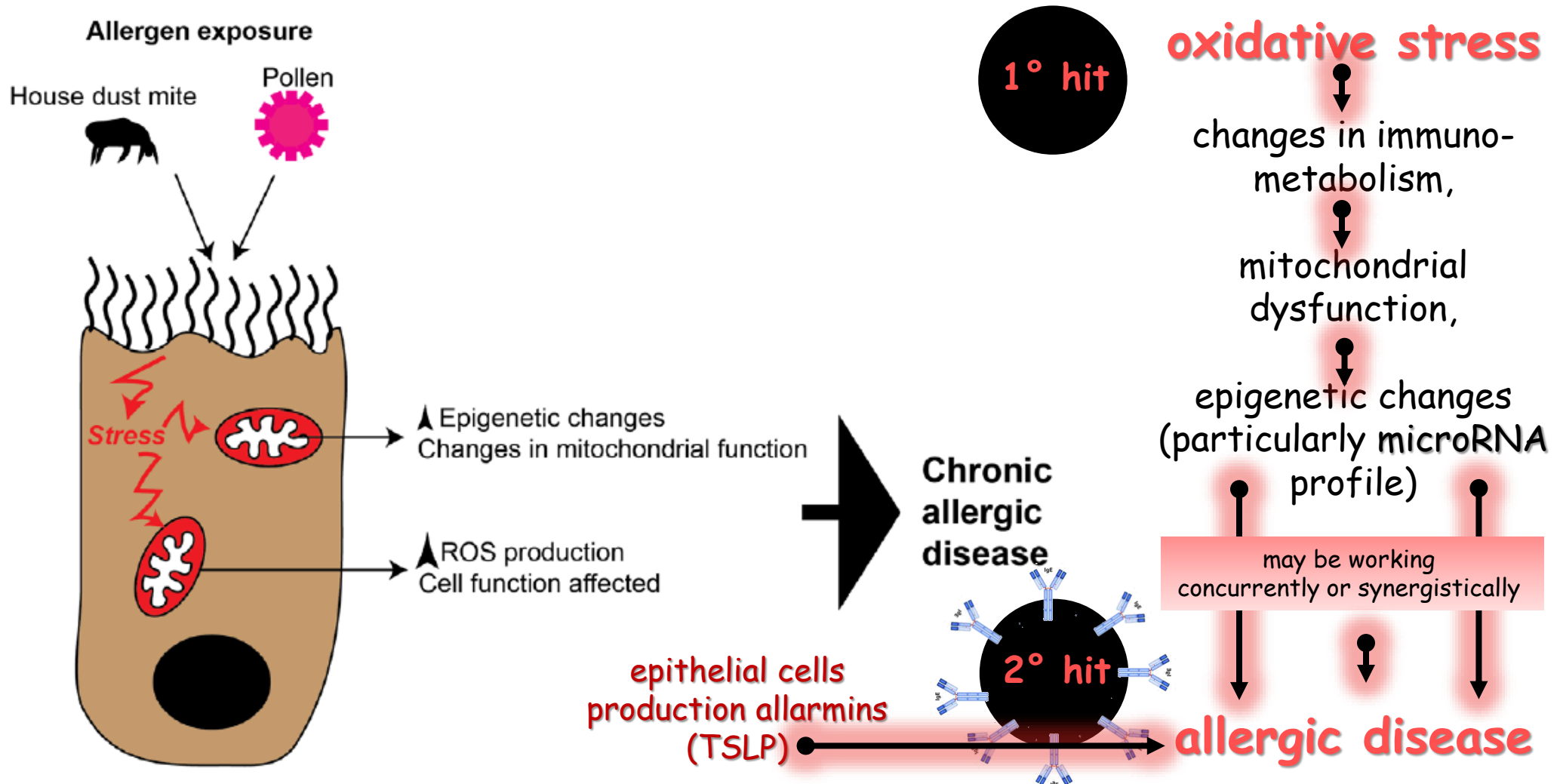
✓ risk of cardiovascular mortality across quintiles of FEV₁.



Chronic allergy signaling: is it all stressed-out mitochondria?

Hussain SA, Fac Rev. 2022 Dec 15;11:37.

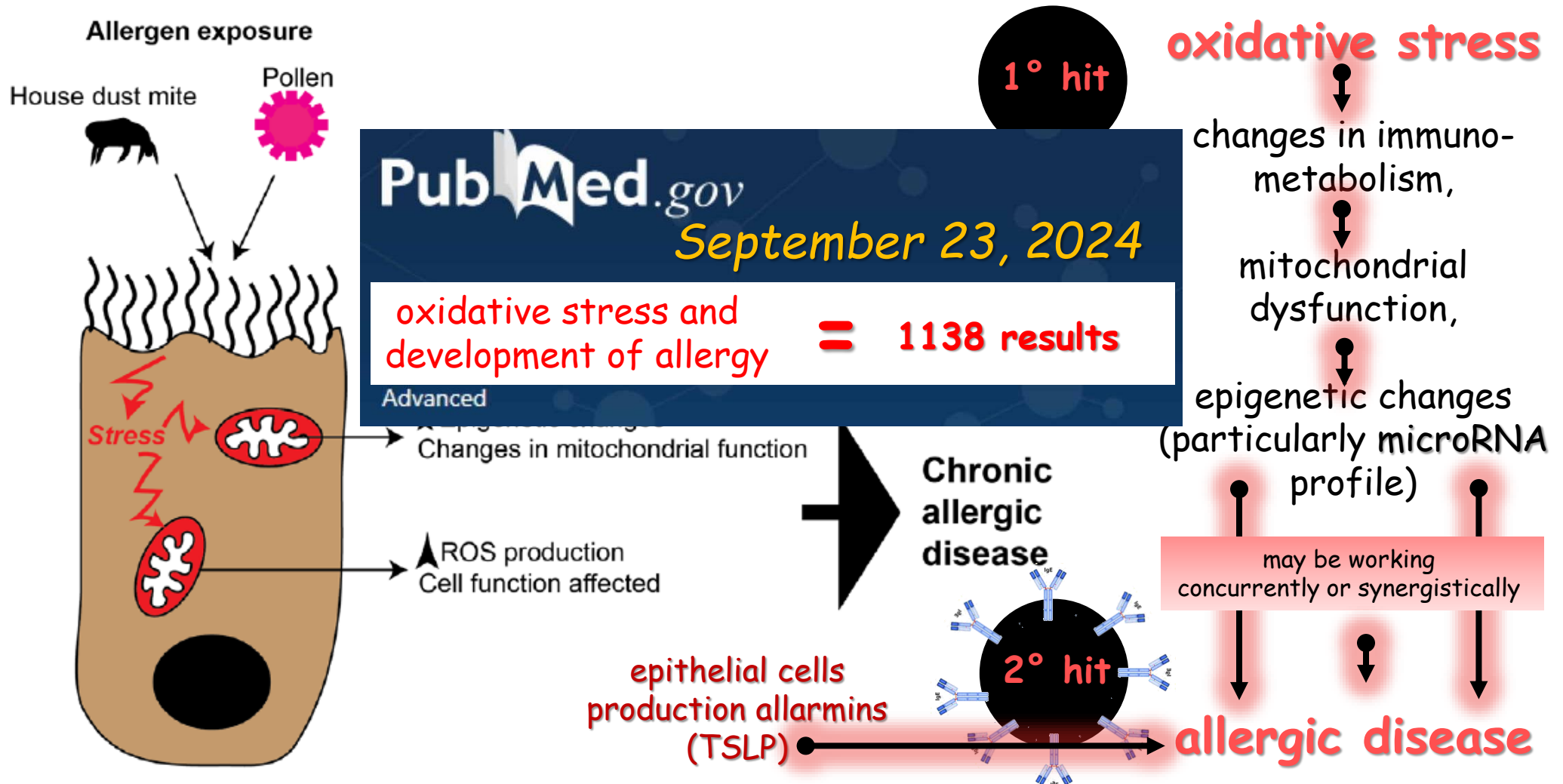
Division of Allergy and Immunology, The Ohio State University College of Medicine, Columbus, OH, USA



Chronic allergy signaling: is it all stressed-out mitochondria?

Hussain SA, Fac Rev. 2022 Dec 15;11:37.

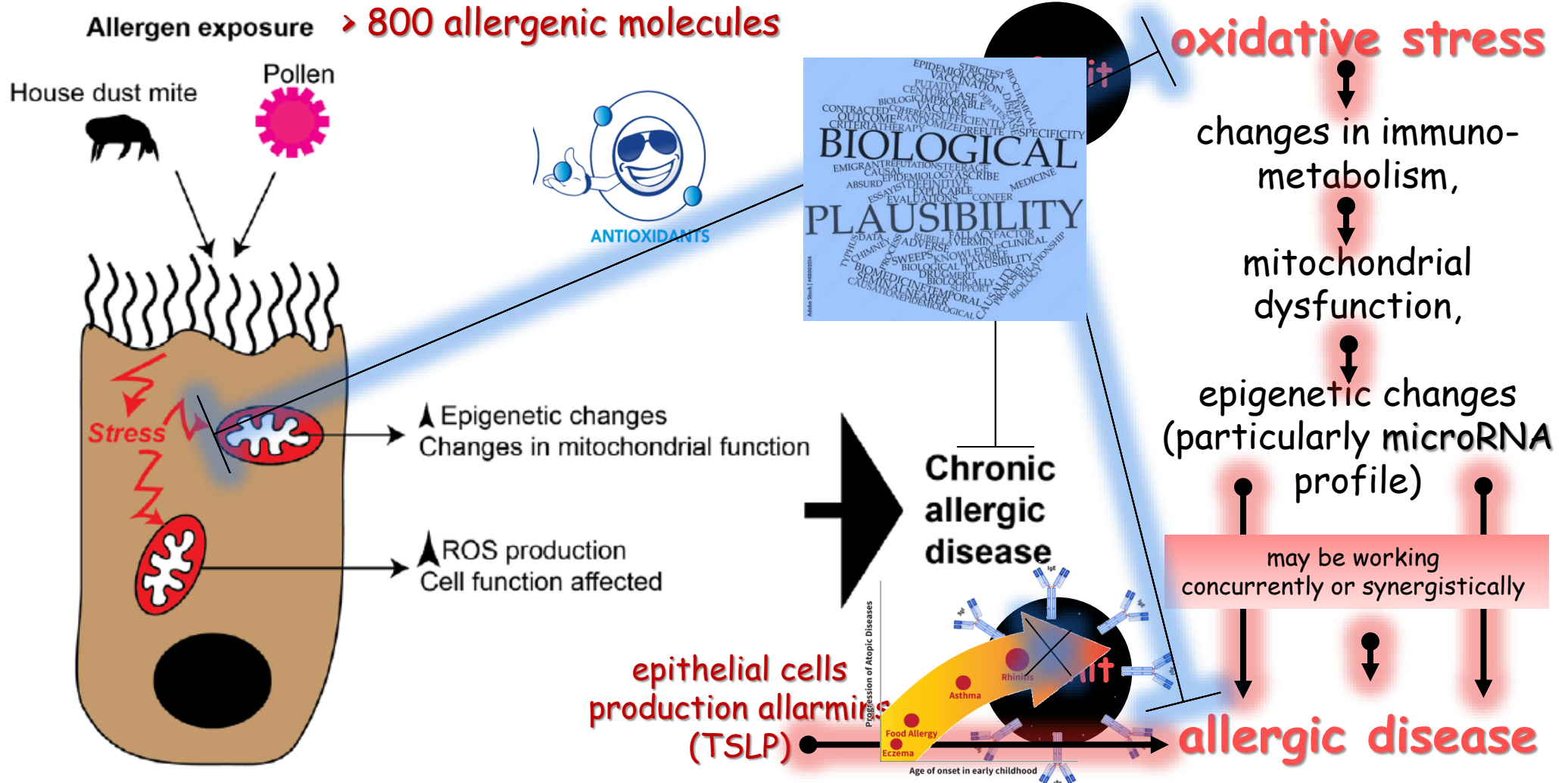
Division of Allergy and Immunology, The Ohio State University College of Medicine, Columbus, OH, USA



Chronic allergy signaling: is it all stressed-out mitochondria?

Hussain SA, Fac Rev. 2022 Dec 15;11:37.

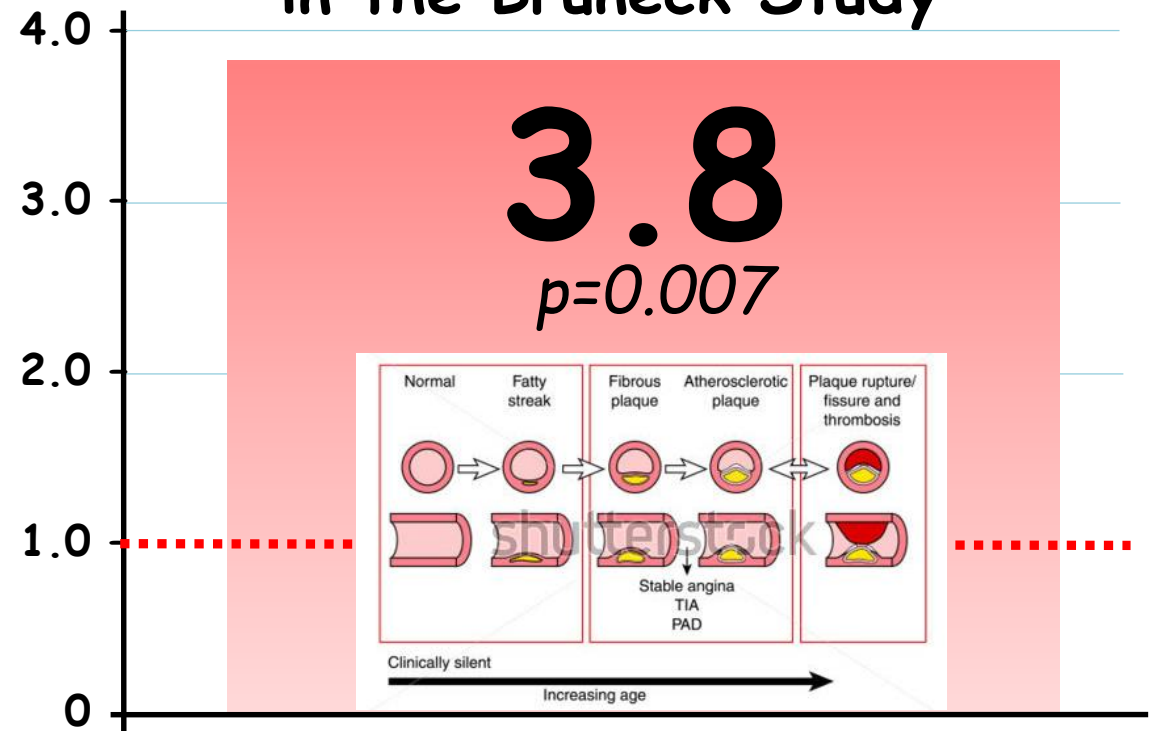
Division of Allergy and Immunology, The Ohio State University College of Medicine, Columbus, OH, USA



Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies.

Knoflach M, Arch Intern Med 2005;165:2521-6.

OR for atherosclerosis development and progression in the Bruneck Study



in subjects with allergic disorders

✓ The ARMY study is a cross-sectional evaluation of 141 men aged 17 or 18 years

✓ The Bruneck Study is a prospective population-based survey of 826 men and women aged 40 to 70 years;

Centenarian Rates and Life Expectancy Related to the Death Rates of Multiple Sclerosis, Asthma, and Rheumatoid Arthritis and the Incidence of Type 1 Diabetes in Children.

Lens-Pechakova L.S. Rejuvenation Res. 2016 Feb;19(1):53-8.

✓ 29 developed countries,



**OXIDATIVE STRESS
& Inflammation**



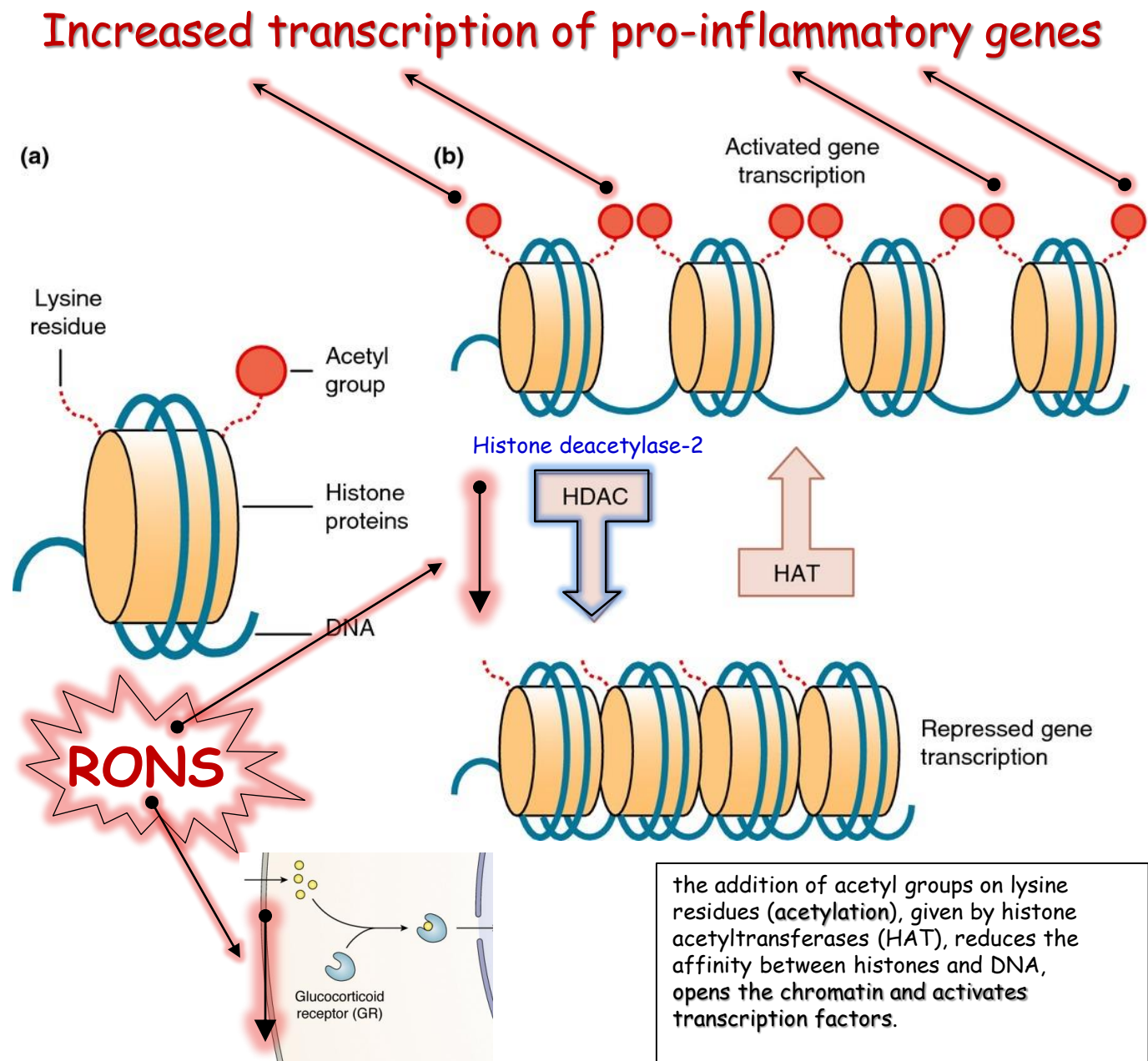
- ❖ multiple sclerosis,
- ❖ rheumatoid arthritis,
- ❖ asthma,
- ❖ type 1 diabete

Centenarian Rates



Reactive Oxygen Nitrogen Species (RONS) and Glucocorticoid receptor (GR) Signaling.

- The activation of pro-inflammatory signaling pathways (Tumor necrosis factor Receptor (TNFR), Toll-like Receptor, and Cytokine Receptors) leads to:
- increases in RONS production in mitochondria and cytosol.
- posttranslational modification such as acetylation and phosphorylation **reduce GR and HDAC2 activity**, in the nucleus leading to augmented pro-inflammatory responses.



the addition of acetyl groups on lysine residues (acetylation), given by histone acetyltransferases (HAT), reduces the affinity between histones and DNA, opens the chromatin and activates transcription factors.

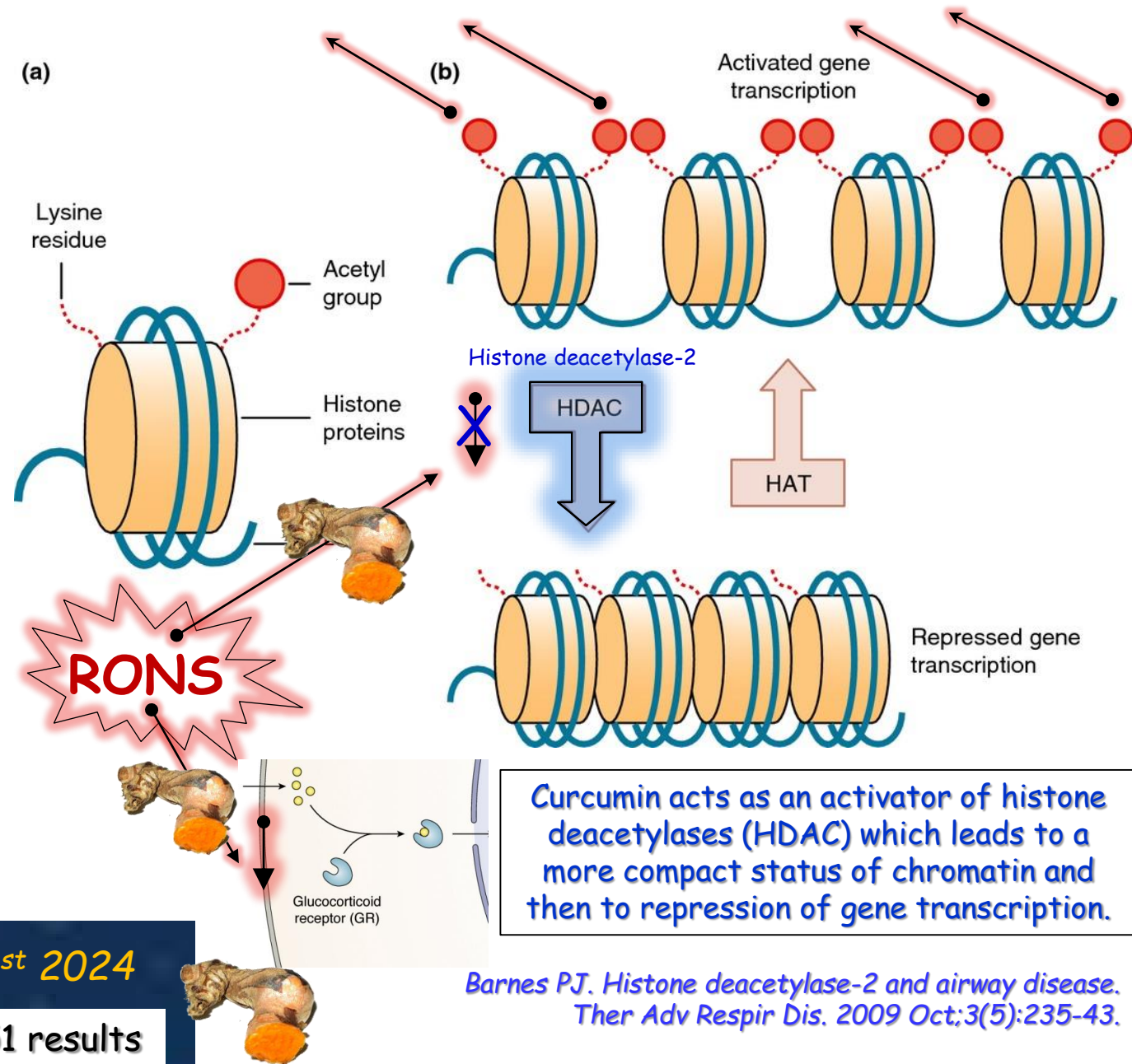
On the other hand, deacetylation induced by histone deacetylases (HDAC) leads to a more compact status of chromatin and then to repression of gene transcription.

Lewis BW, Oxidative Stress Promotes Corticosteroid Insensitivity. Antioxidants (Basel). 2021 Aug 24;10(9):1335.

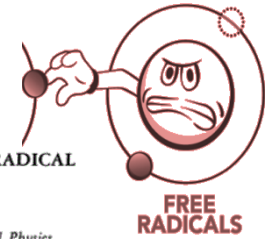
Reactive Oxygen Nitrogen Species (RONS) and Glucocorticoid receptor (GR) Signaling.

- The activation of pro-inflammatory signaling pathways (Tumor necrosis factor Receptor (TNFR), Toll-like Receptor, and Cytokine Receptors) leads to:
- increases in RONS production in mitochondria and cytosol.
- posttranslational modification such as acetylation and phosphorylation **reduce GR and HDAC2 activity**, in the nucleus leading to augmented pro-inflammatory responses.

Increased transcription of pro-inflammatory genes



Mitochondria Oxidative Stress and AGING



AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY

DENHAM HARMAN, M.D., Ph.D.

(From the Donner Laboratory of Biophysics and Medical Physics,
University of California, Berkeley)

The phenomenon of growth, decline and death—aging—has been the source of considerable speculation (1, 8, 10). This cycle seems to be a more or less direct function of the metabolic rate and this in turn depends on the species (animal or plant) on which are superimposed the factors of heredity and the effects of the stresses and strains of life—which alter the metabolic activity.

The universality of this phenomenon suggests that the reactions which cause it are basically the same in all living things. Viewing this process in the light of present day free radical and radiation chemistry and of radiobiology, it seems possible that one factor in aging may be related to deleterious side attacks of free radicals (which are normally produced in the course of cellular metabolism) on cell constituents.*

Irradiation of living things induces mutation, cancer, and aging (9). Inasmuch as these also arise spontaneously in nature, it is natural to inquire if the processes might not be similar. It is believed that one mechanism of irradiation effect is through liberation of OH and HO₂ radicals (12). There is evidence, although indirect, that these two highly active free radicals are produced normally in living systems. In the first place, free radicals are present in living cells; this was recently demonstrated in vivo by a paramagnetic resonance absorption method (3). Further, it was shown that the concentration of free radicals increased with increasing metabolic activity in conformity with the postulates set forth some years ago that free radicals were involved in biologic oxidation-reduction reactions (11, 13). Are some of these free radicals OH and/or HO₂, or radicals of a similar high order of reactivity, and where might they arise in the cell?

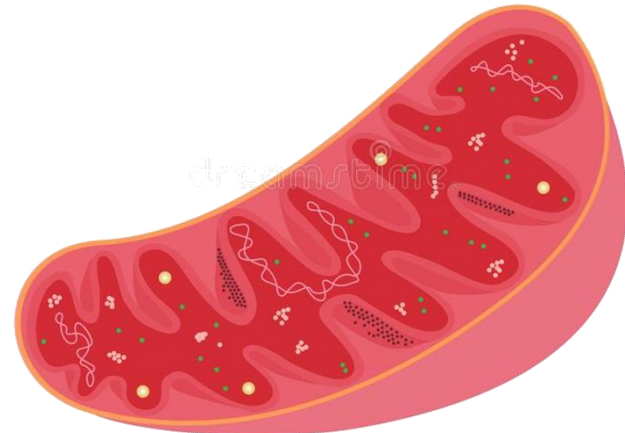
The most likely source of OH and HO₂ radicals, at least in the animal cell, would be the interaction of the respiratory enzymes involved

in the direct utilization of molecular oxygen, particularly those containing iron, and by the action of catalase on hydrogen peroxide. This follows from the fact that it has been known for many years that iron salts catalyze the air oxidation of organic compounds (5, 6, 14, 15); OH radicals are believed to be involved in these reactions (13). Iron salts also catalyze the decomposition of hydrogen peroxide to water and oxygen—a reaction that involves OH and HO₂ radicals (16). Further, recent studies in this laboratory on the inactivation of rat liver catalase suggest that the OH radical is involved. The catalase activity of the homogenates both in the presence and absence of hydrogen donors such as sodium bisulfite, sodium hypophosphite, pyrogallol, and mercaptans remains relatively constant under an atmosphere of nitrogen. However, in the presence of air, catalase activity rapidly decreases and the rate of decrease is accelerated in the presence of the hydrogen donors. In addition, methanol, ethanol, and sodium formate (compounds (2) which are oxidized by hydrogen peroxide in the presence of catalase) stabilize the enzyme in the presence of air. A free radical mechanism involving the OH radical has been implicated in the analogous degradation of hemoglobin and myoglobin (7).

Thus, although the evidence is indirect, there are good reasons for assuming that the changes produced by irradiation and those which arise spontaneously in the living cell have a common source—the OH and HO₂ radicals. These arise on the one hand through the dissociation of water and on the other largely by the interaction of the oxidative enzymes with oxygen and hydrogen peroxide. (It is not unlikely that other metal-containing enzymes, such as vitamin B₁₂, which contains cobalt, also contribute.)

The manner in which a highly reactive radical such as OH would exert its effect on a cell is obscure. However, it would be expected to react for the most part near the area where it

Submitted for publication March 23, 1956.
* This research was performed under the auspices of the Atomic Energy Commission.
Published on a grant from the Forest Park Foundation to the Journal of Gerontology.



❖ The free radical theory of aging was first expressed by Harman as early as 1954.

HARMAN D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956 Jul;11(3):298-300.

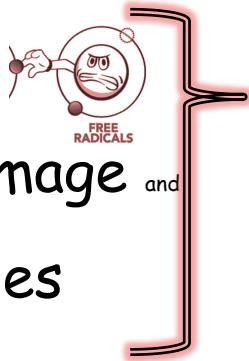
❖ Theory was then extended to include mitochondria.

Cadenas E, Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med. 2000 Aug;29(3-4):222-30.

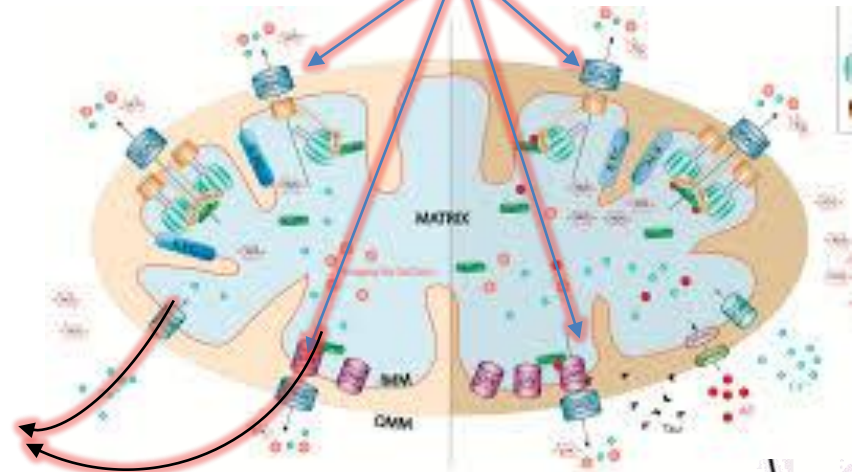
Steven S, Vascular Inflammation and Oxidative Stress: Major Triggers for Cardiovascular Disease. Oxid Med Cell Longev. 2019 Jun 23;2019:7092151.

Interplay of Oxidative Stress and Chronic Low Grade Inflammation

- ❖ protein oxidation,
- ❖ oxidative DNA damage
- ❖ oxidized nucleotides



increase mitochondrial permeability
(by opening of the mitochondrial permeability transition pore)

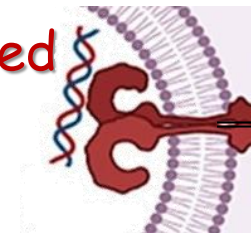


Wenzel P, Redox regulation of cardiovascular inflammation - Immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species. *Free Radic Biol Med.* 2017 Aug;109:48-60.

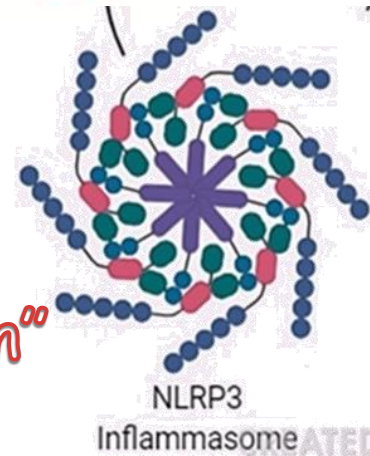
release of (oxidized) mtDNA



which represents a damage-associated molecular pattern (DAMP) recognized by Toll Like Receptors



"sterile inflammation"

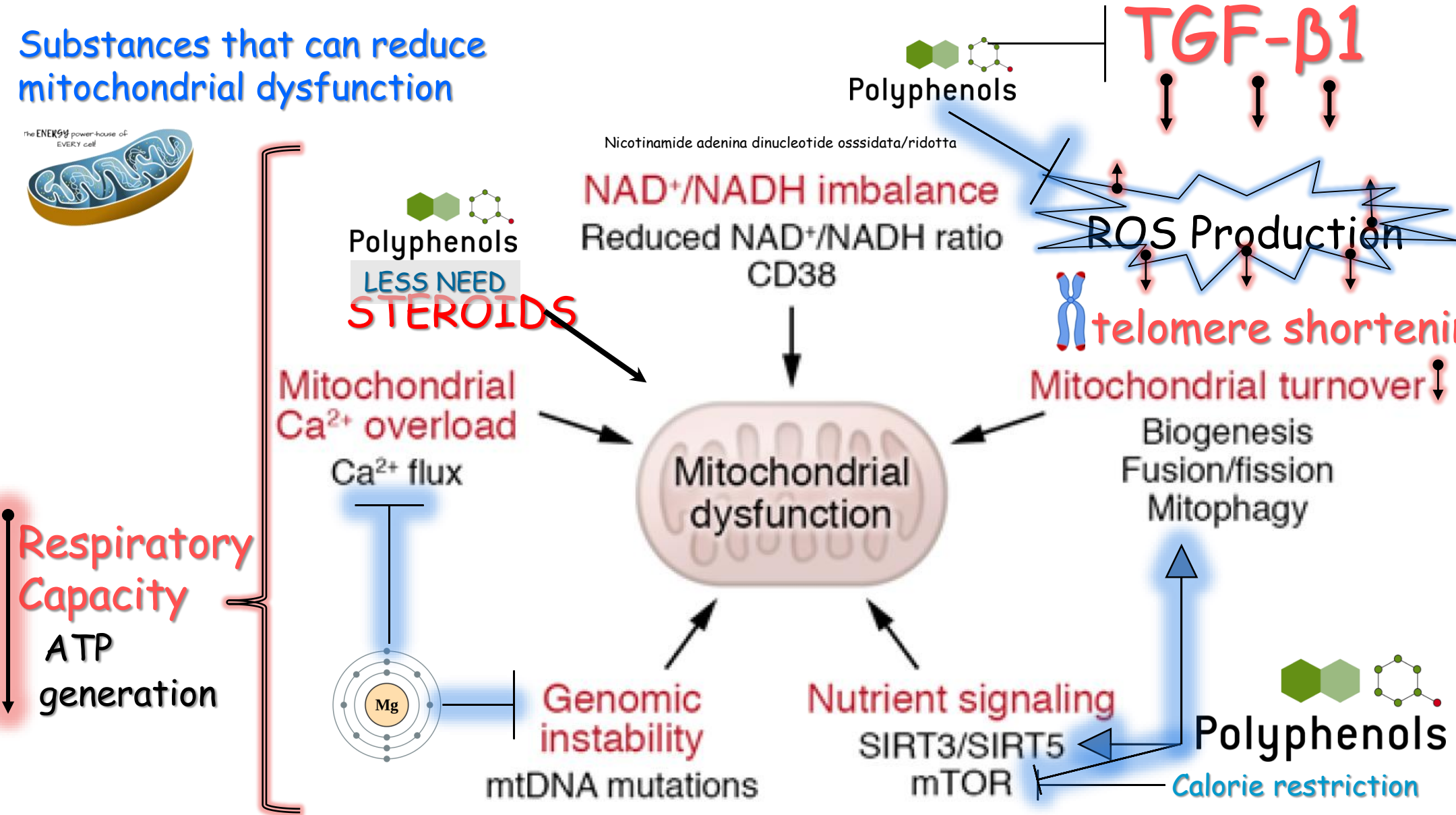
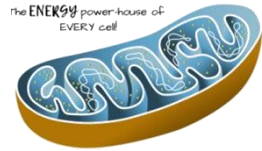


Pittman K, Damage-associated molecular patterns control neutrophil recruitment. *J Innate Immun.* 2013;5(4):315-23.

Mitochondrial dysfunction in cell senescence and aging.

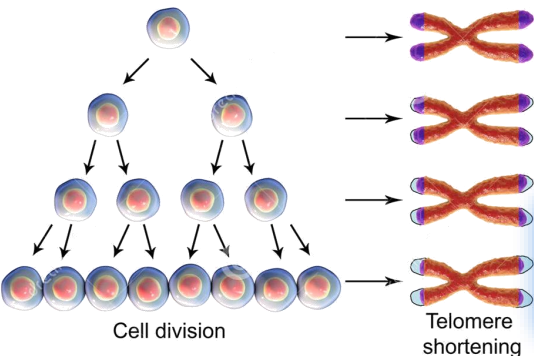
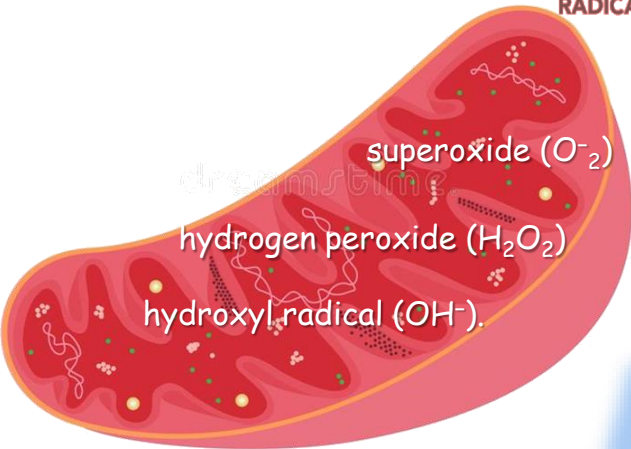
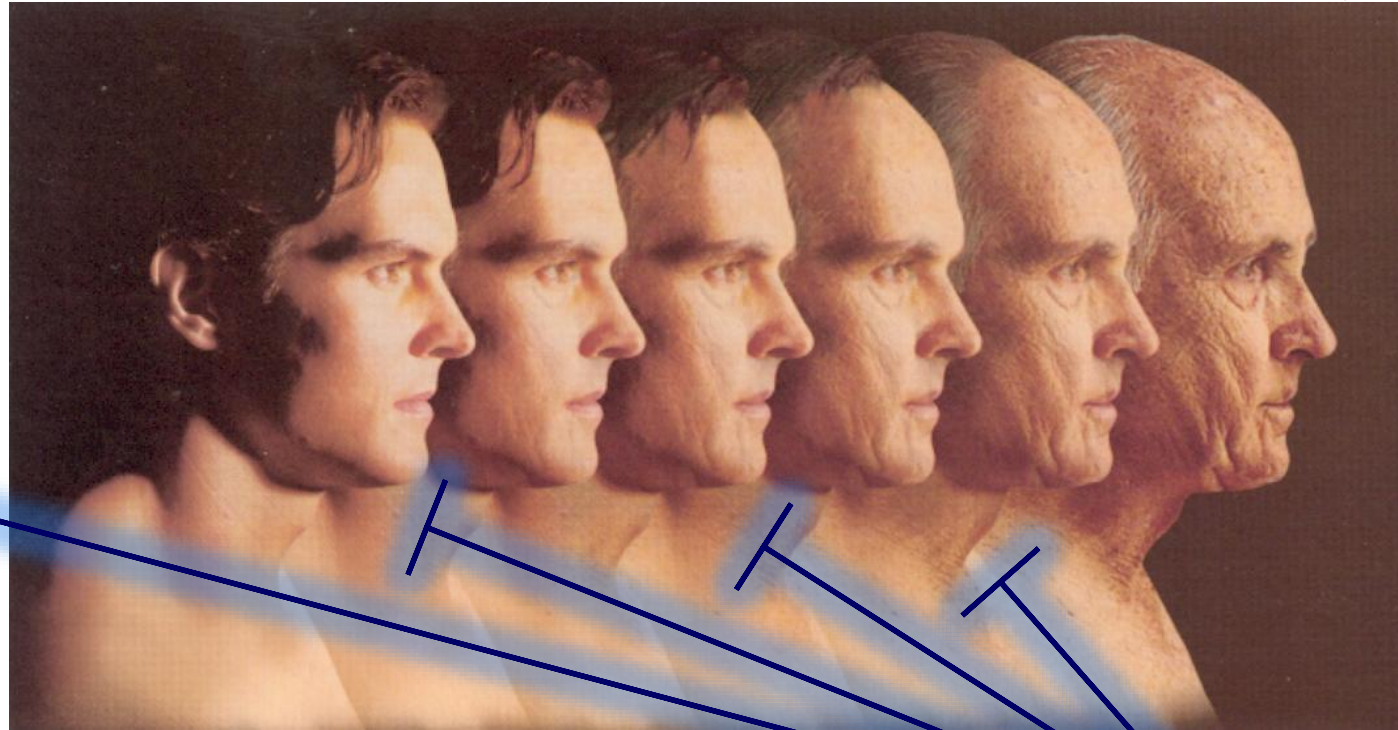
Miwa S, J Clin Invest. 2022 Jul 1;132(13):e158447.

Substances that can reduce mitochondrial dysfunction

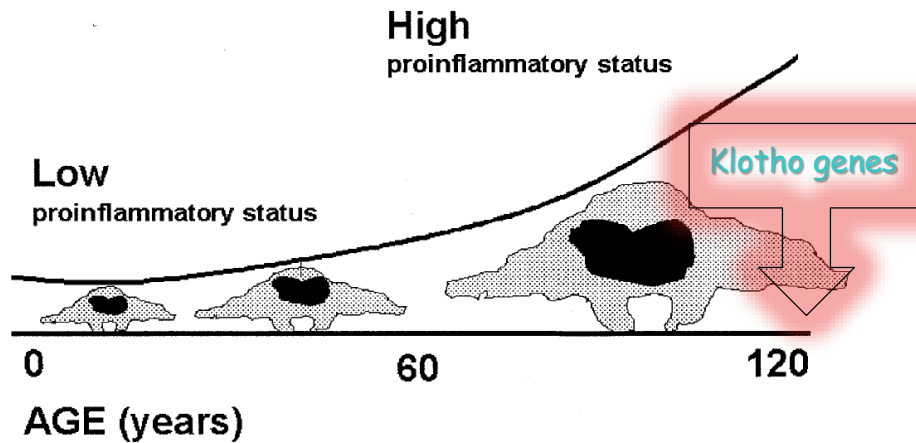


Mitochondrial free radical generation, oxidative stress, and aging.

Cadenas E, Free Radic Biol Med. 2000 Aug;29(3-4):222-30.

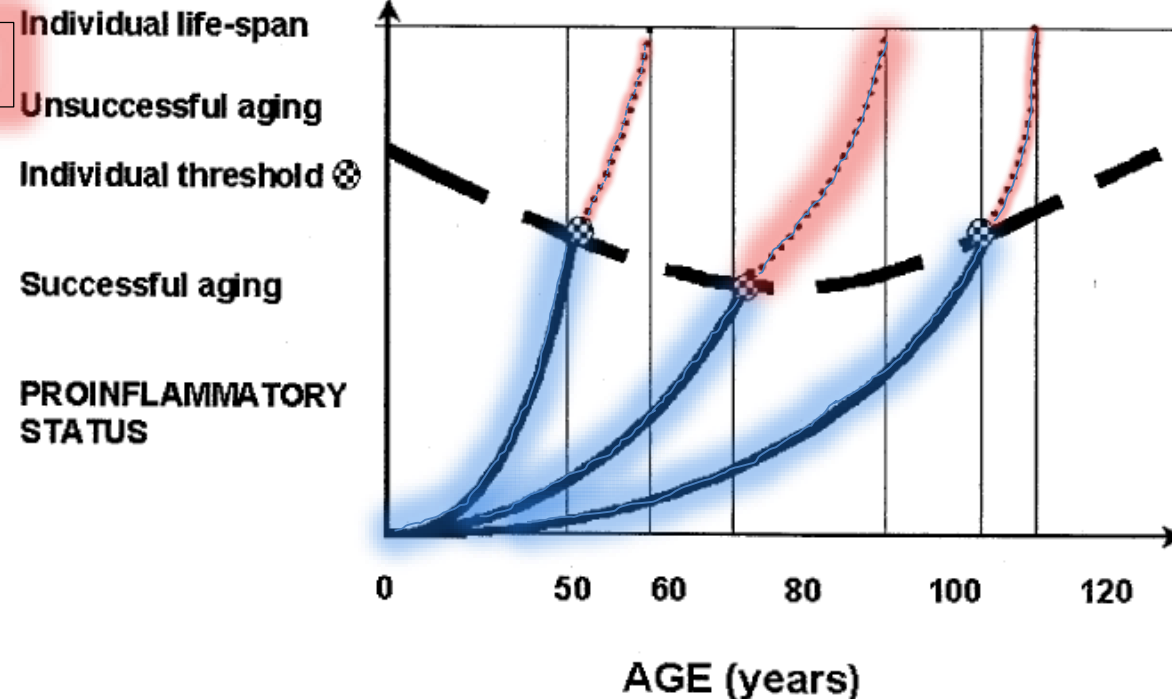


Inflamm-aging as a consequence of macroph-aging.



The **increase in proinflammatory status**, caused by chronic age-related stimulation of the macrophage, called "**macroph-aging**," is referred to as "**inflamm-aging**."

The individual thresholds of inflamm-aging.



An individual threshold of the capability to cope with stress is hypothesized. If inflamm-aging trespasses on this level, the transition between **successful** (continuous line) and **unsuccessful aging** (dotted line) will occur.

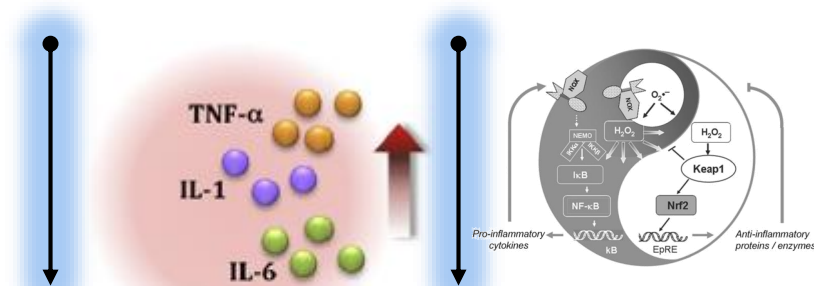
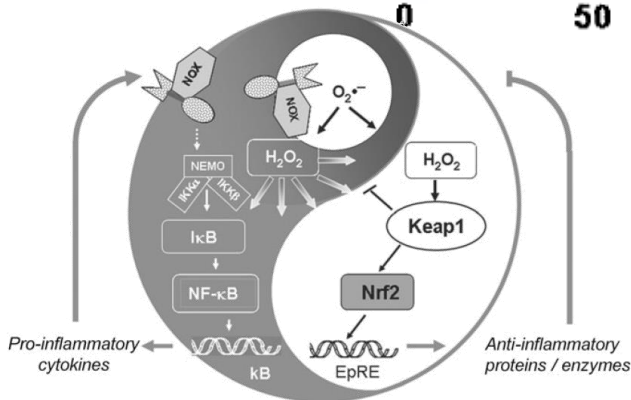
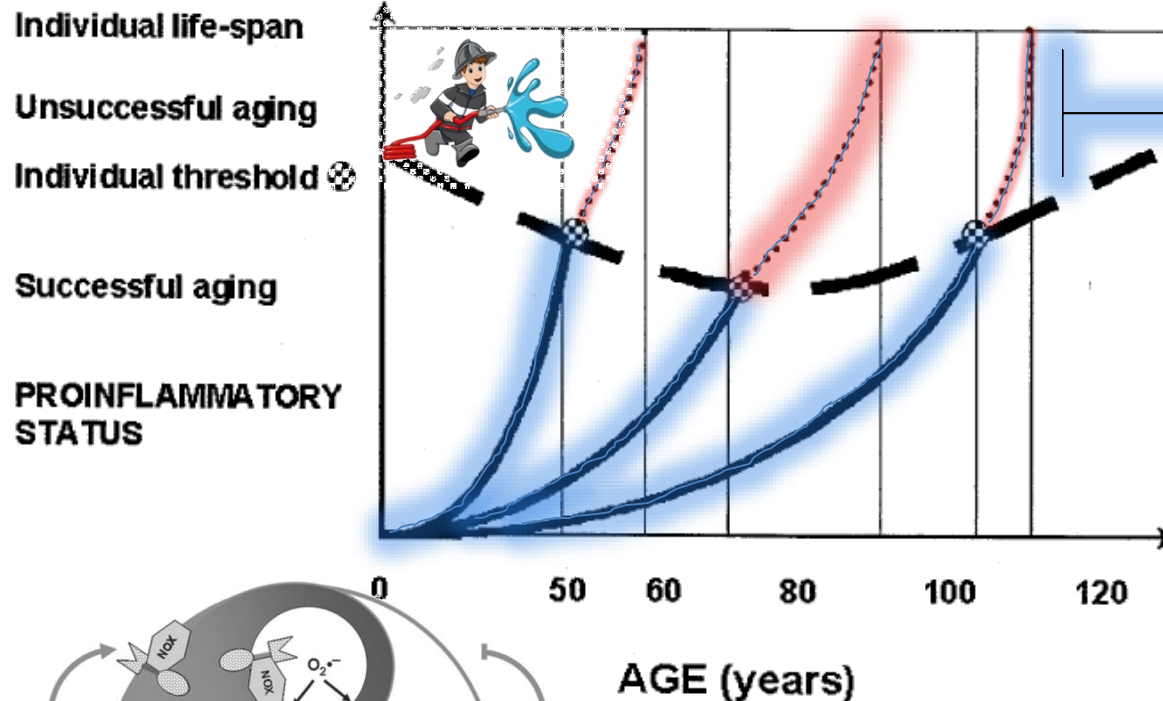
In accordance with epidemiologic data, the period of life during unsuccessful aging (disability) is maximal in the elderly (60-80 years) and minimal in young people and centenarians.

*Franceschi C, Inflamm-aging.
An evolutionary perspective
on immunosenescence.
Ann N Y Acad Sci.
2000 Jun;908:244-54.*



Inflamm-aging as a consequence of macroph-aging.

The individual thresholds of inflamm-aging.

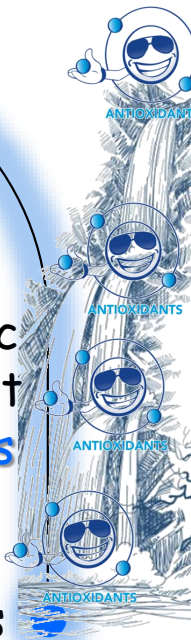


Inflammaging

Chronic low-grade inflammation (inflamm-aging) is a physiological response to the life-long antigenic stress and represents an efficient defense mechanism as long as it is under control by a cascade of anti-inflammatory molecules as shown in the case of centenarians

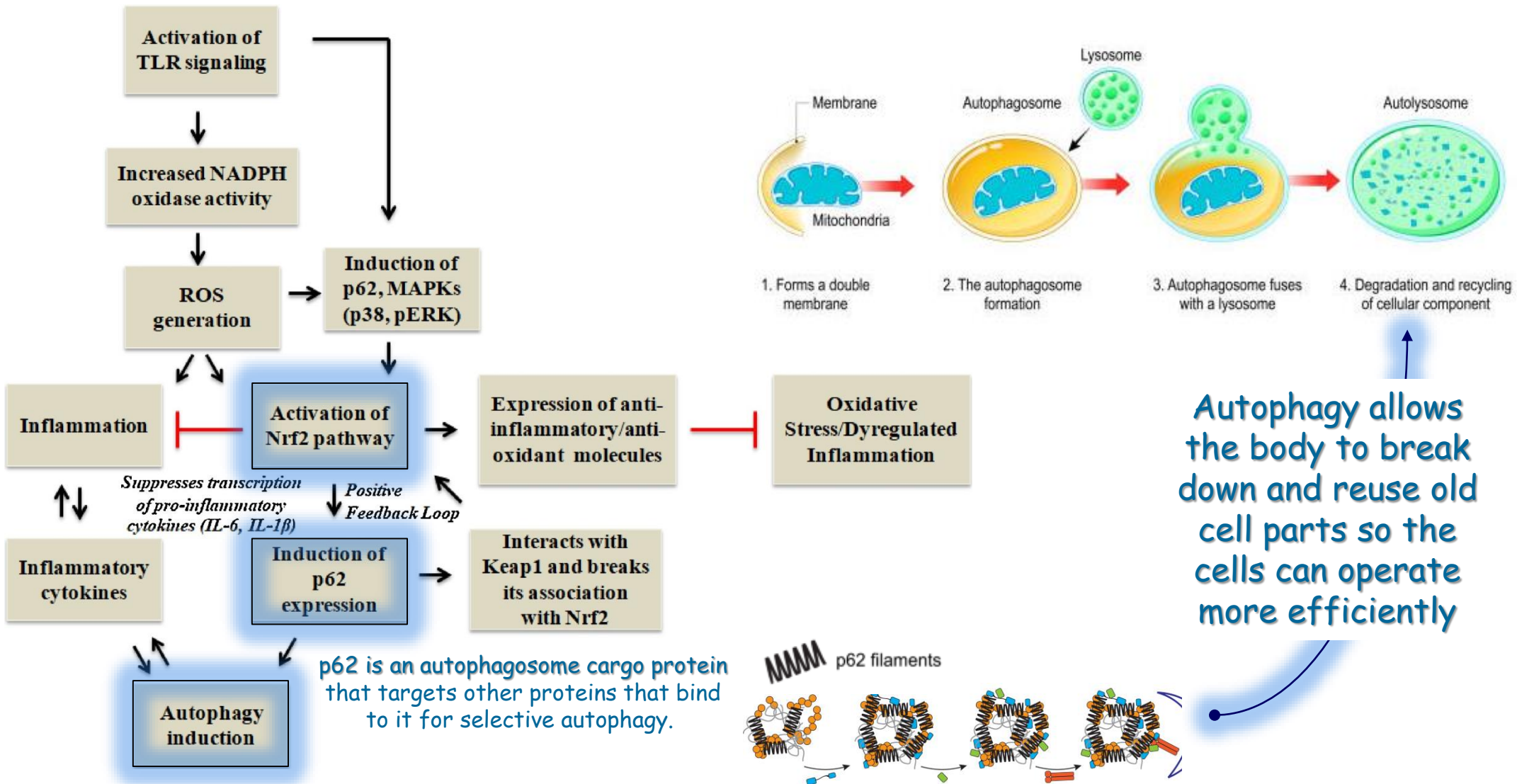
Fulop T, Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes?

Front Immunol. 2018 Jan 10;8:1960.



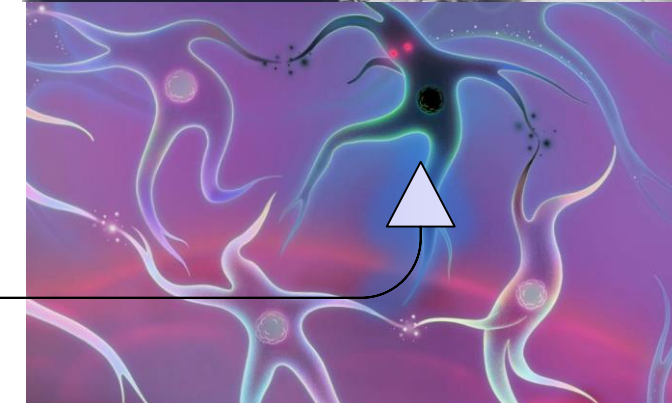
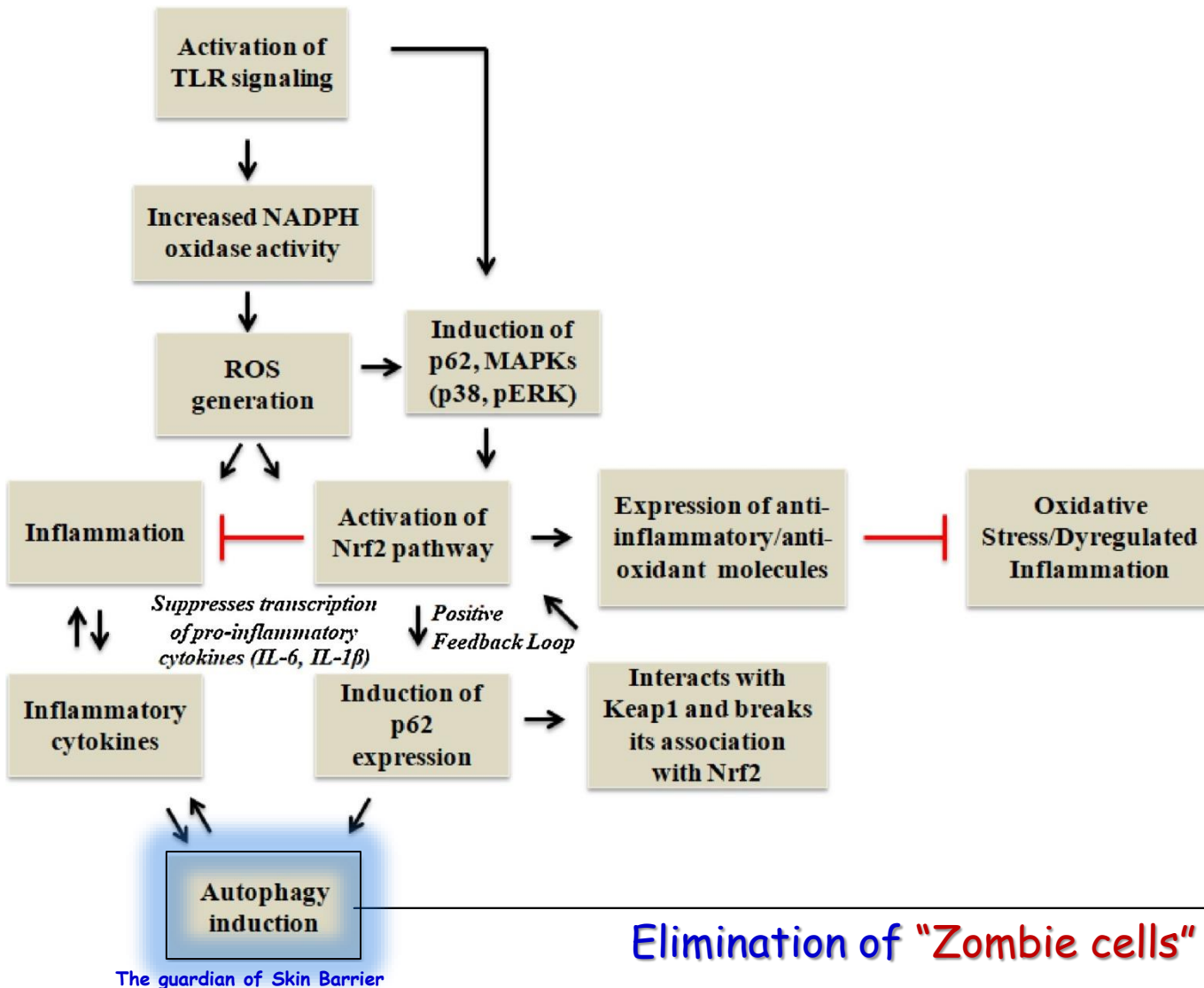
Crosstalk of toll-like receptors signaling and Nrf2 pathway for regulation of inflammation.

Mohan S, Biomed Pharmacother. 2018 Dec;108:1866-1878.



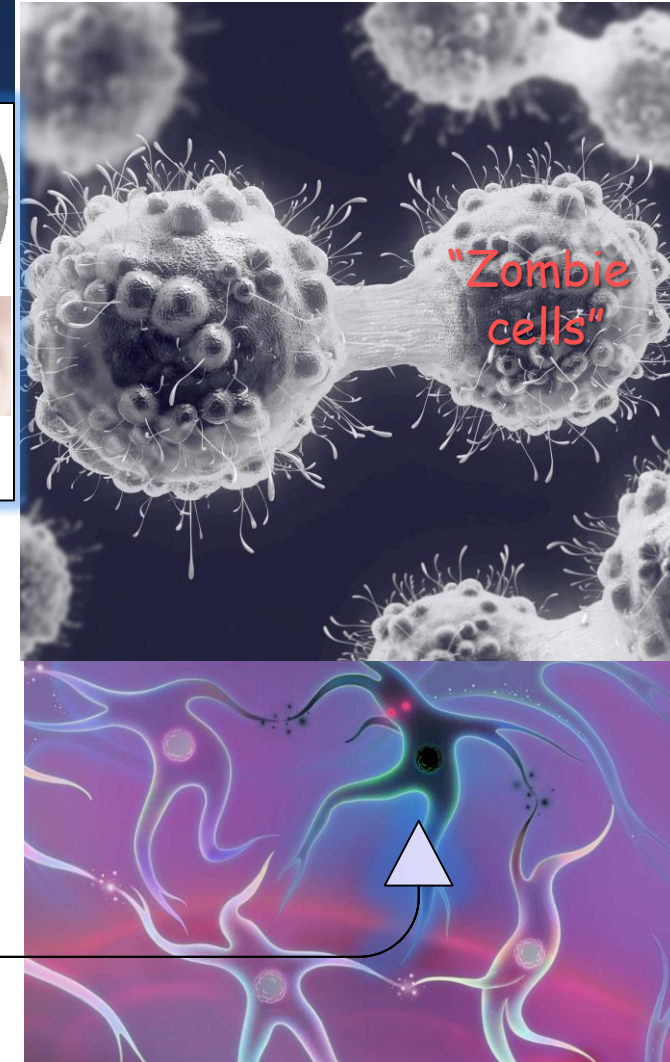
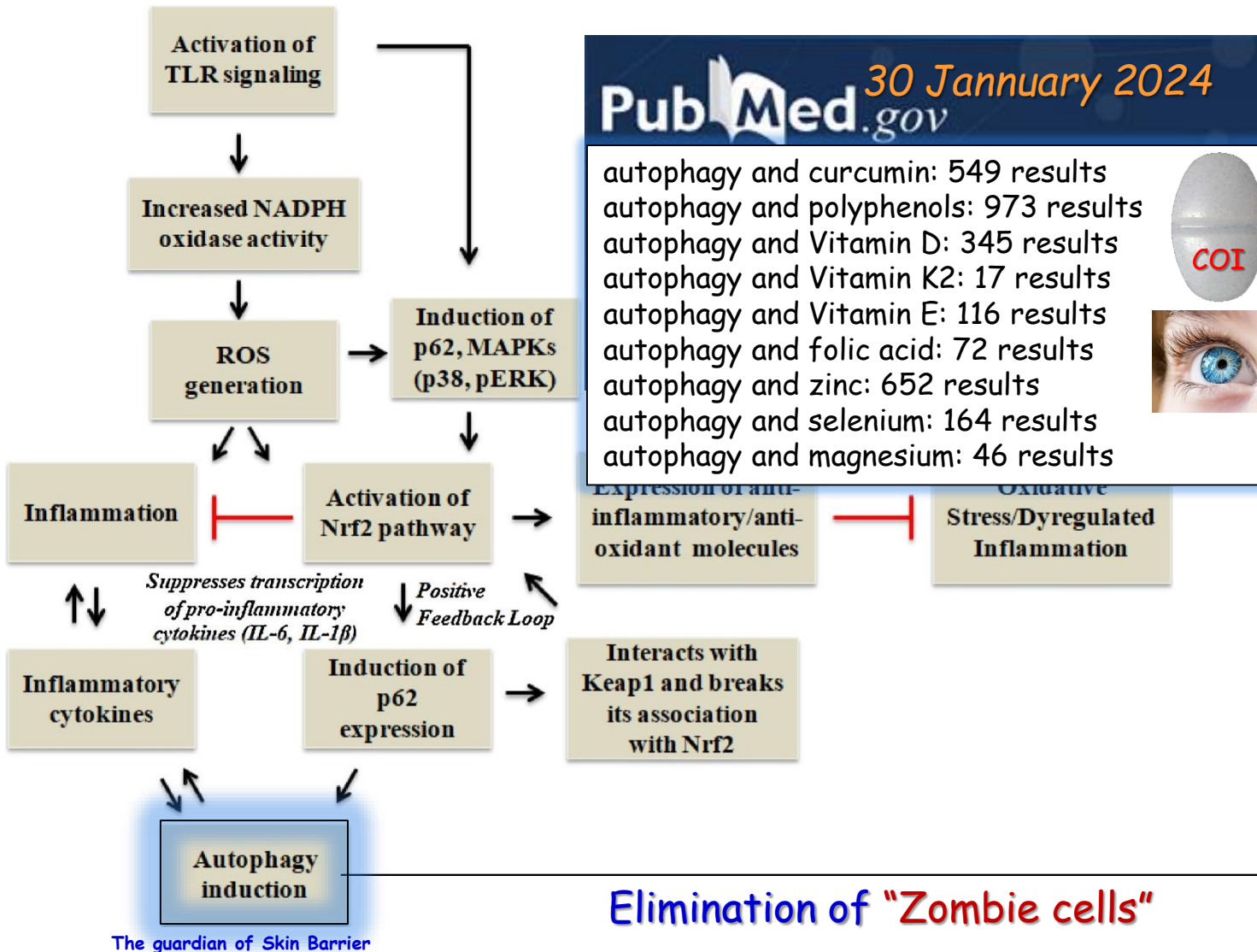
Crosstalk of toll-like receptors signaling and Nrf2 pathway for regulation of inflammation.

Mohan S, Biomed Pharmacother. 2018 Dec;108:1866-1878.



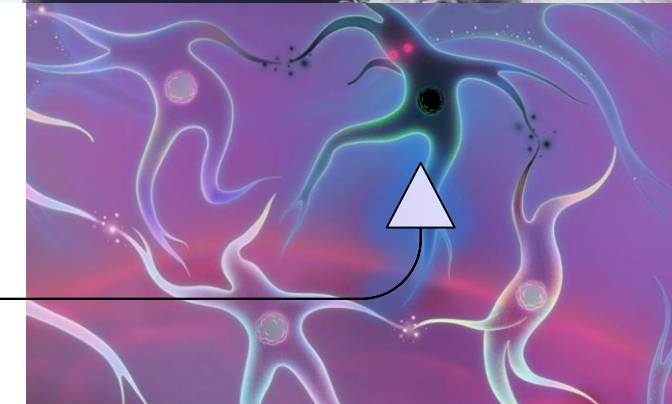
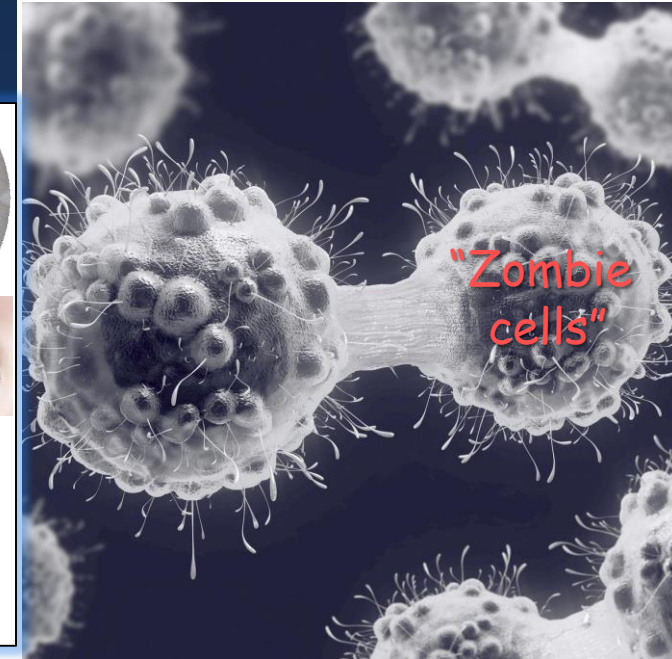
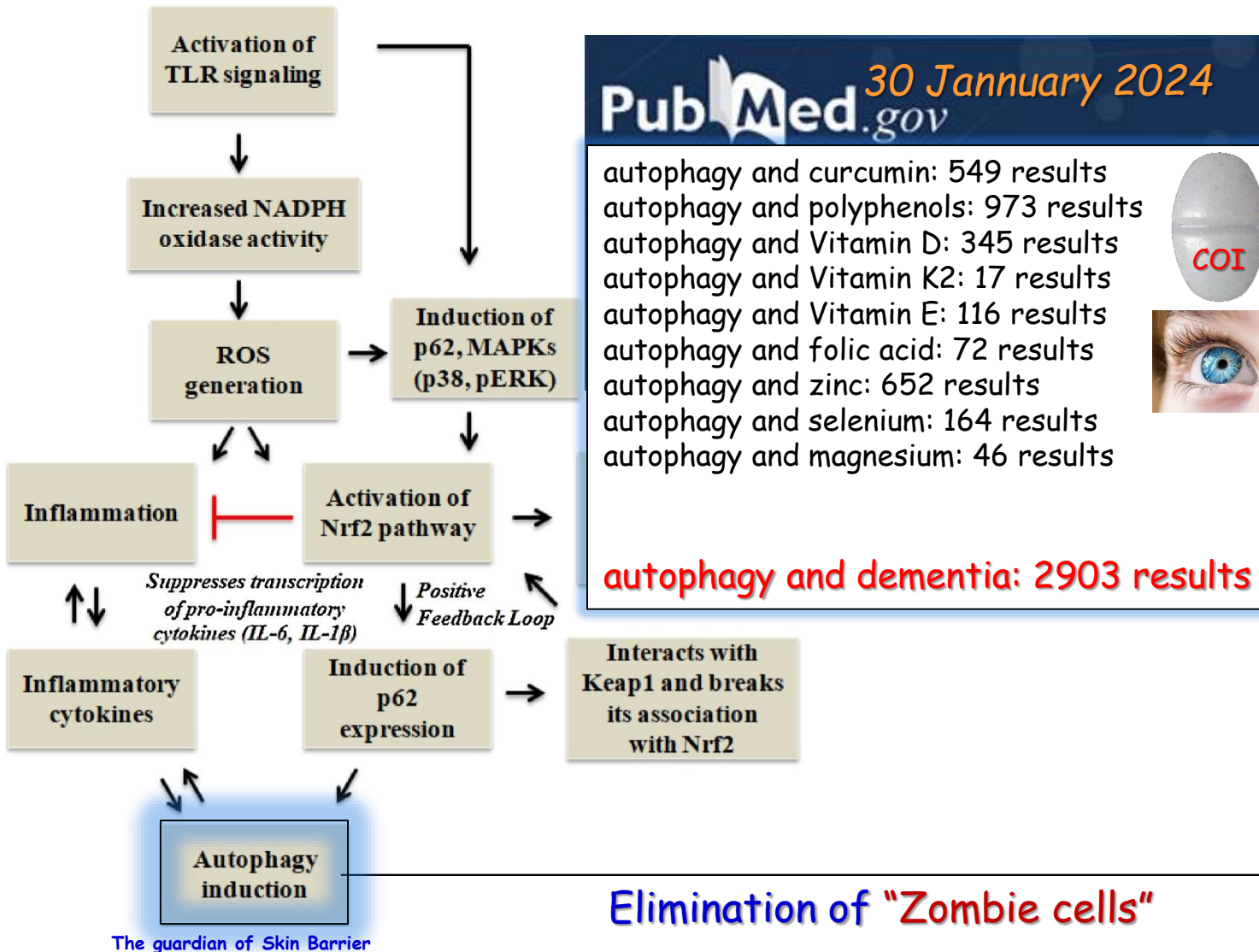
Crosstalk of toll-like receptors signaling and Nrf2 pathway for regulation of inflammation.

Mohan S, Biomed Pharmacother. 2018 Dec;108:1866-1878.

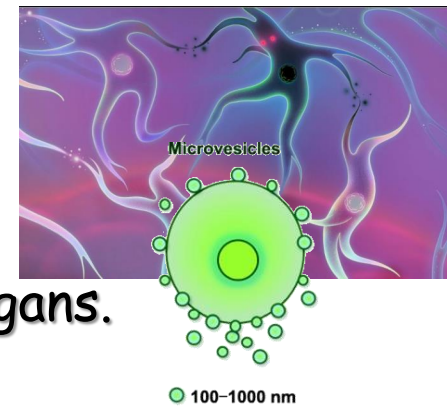


Crosstalk of toll-like receptors signaling and Nrf2 pathway for regulation of inflammation.

Mohan S, Biomed Pharmacother. 2018 Dec;108:1866-1878.



INFLAMM-AGING

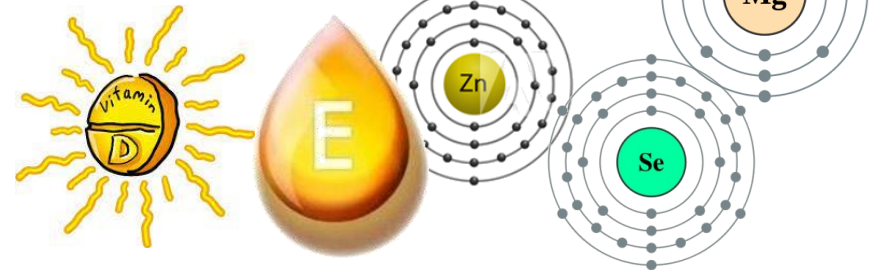


❖ **SASP** is responsible for spreading of senescence to neighbouring cells or systemically from organ to organ by circulating factors and *microvesicles* resulting in progressive damage of tissues and organs.

❖ The most prominent component of **SASP** is **IL-6**.

PubMed.gov *October 16, 2024*

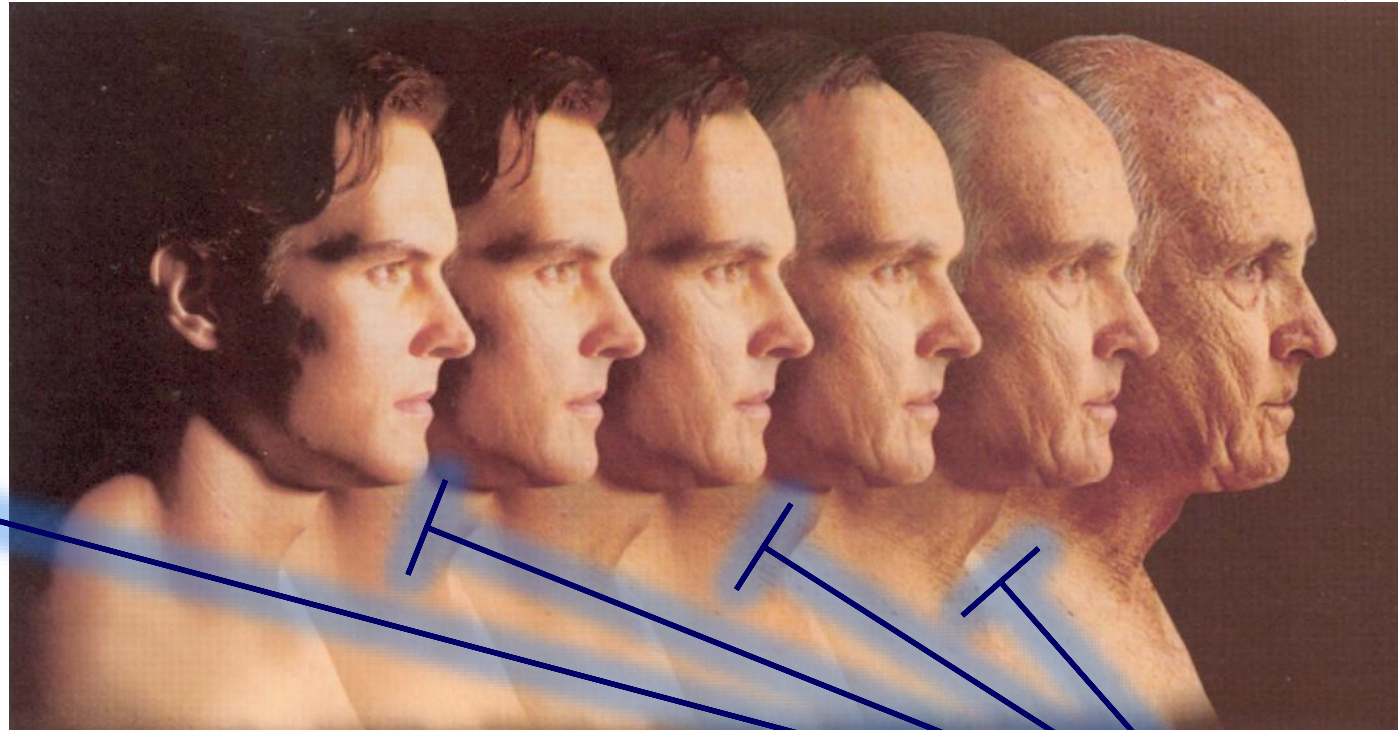
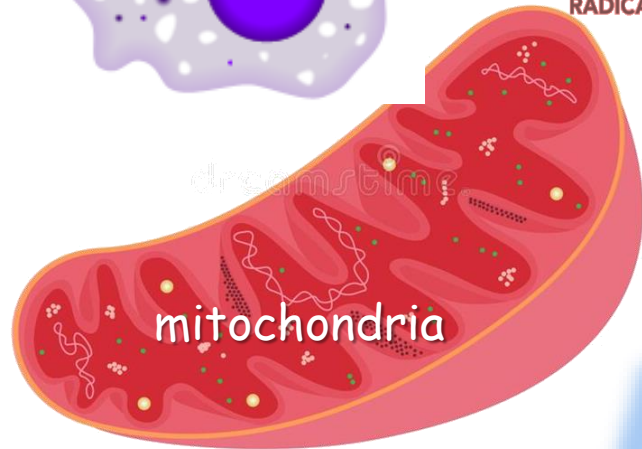
IL-6 inhibition and polyphenols: 903 results
IL-6 inhibition and curcumin: 467 results
IL-6 inhibition and vitamin D: 328 results
IL-6 inhibition and vitamin K2: 13 results
IL-6 inhibition and vitamin E: 105 results
IL-6 inhibition and folic acid: 44 results
IL-6 inhibition and magnesium: 85 results
IL-6 inhibition and selenium: 112 results
IL-6 inhibition and zinc: 297 results



Cardoso AL, Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev. 2018 Nov;47:214-277.

Mitochondrial free radical generation, oxidative stress, and aging.

Cadenas E, Free Radic Biol Med. 2000 Aug;29(3-4):222-30.

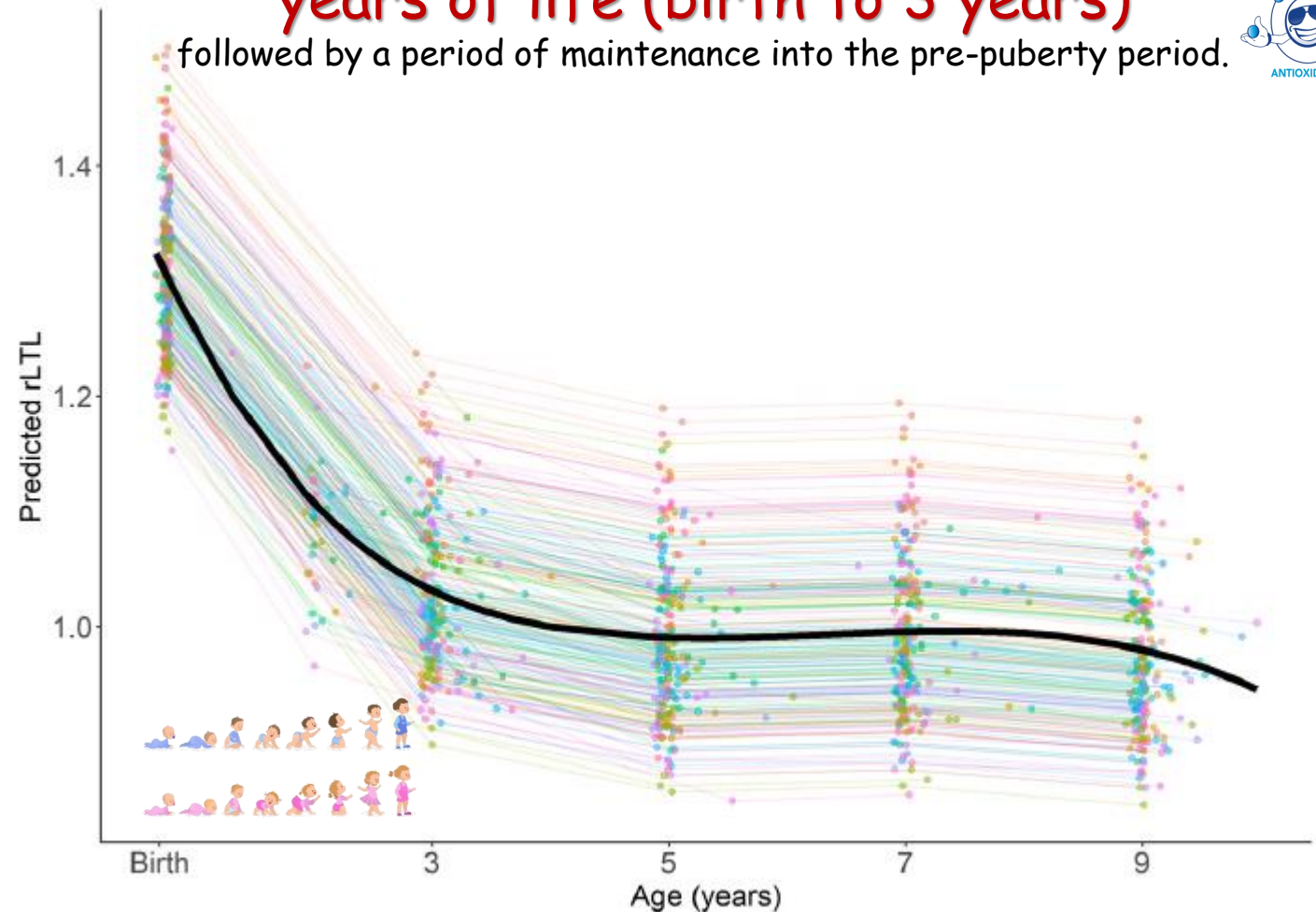


Telomere dynamics across the early life course: Findings from a longitudinal study in children.

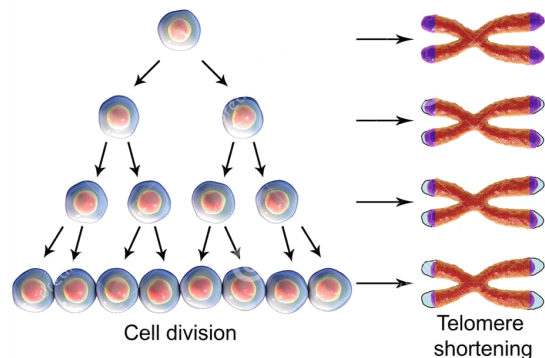
Cowell W, Psychoneuroendocrinology. 2021 Jul;129:105270.

**Telomere decrease most rapidly in the first
years of life (birth to 3 years)**

followed by a period of maintenance into the pre-puberty period.



- ✓ 224 children enrolled in a New York City-based birth cohort.
- ✓ monochrome multiplex quantitative polymerase chain reaction to measure relative TL in leukocytes isolated from cord blood and child blood collected at ages 3, 5, 7, and 9 years

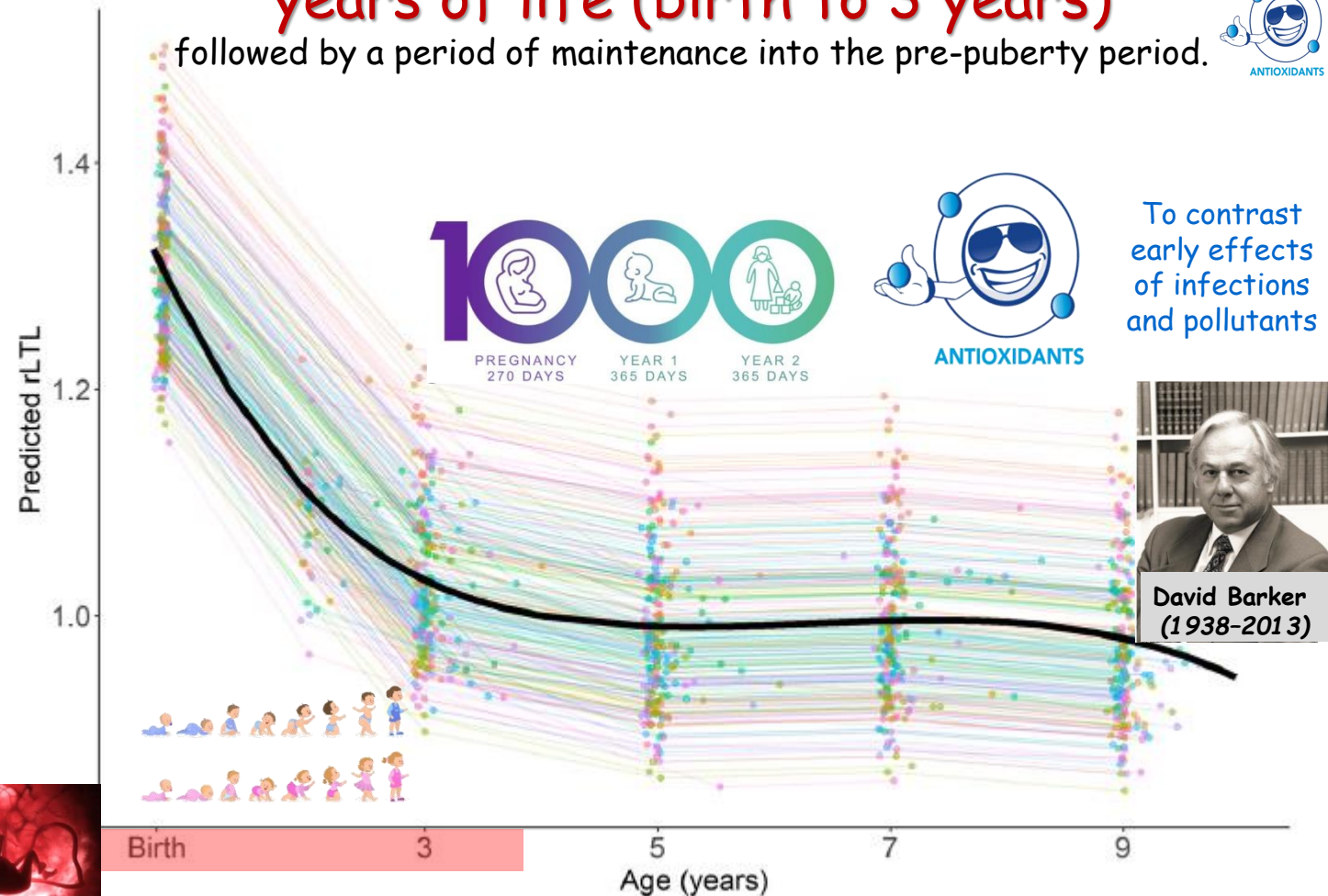


Telomere dynamics across the early life course: Findings from a longitudinal study in children.

Cowell W, Psychoneuroendocrinology. 2021 Jul;129:105270.

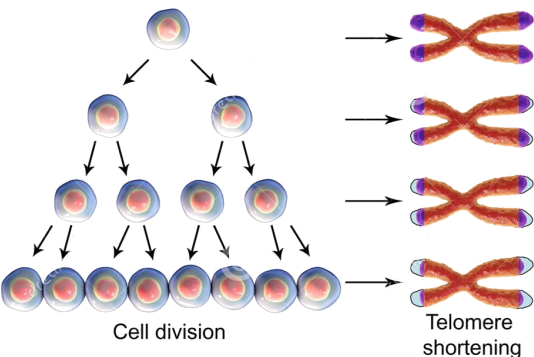
Telomere decrease most rapidly in the first years of life (birth to 3 years)

followed by a period of maintenance into the pre-puberty period.



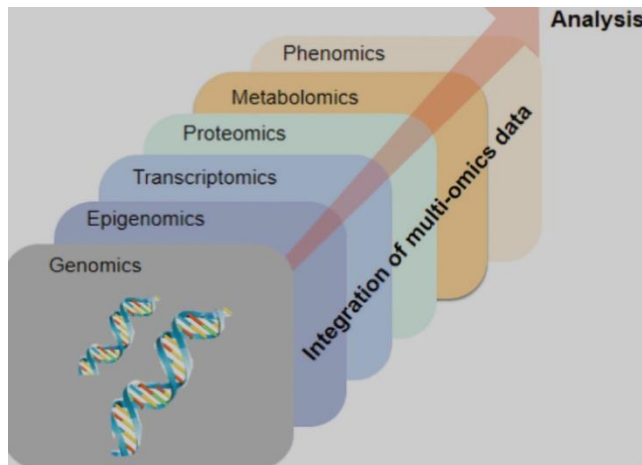
✓ 224 children enrolled in a New York City-based birth cohort.

✓ monochrome multiplex quantitative polymerase chain reaction to measure relative TL in leukocytes isolated from cord blood and child blood collected at ages 3, 5, 7, and 9 years

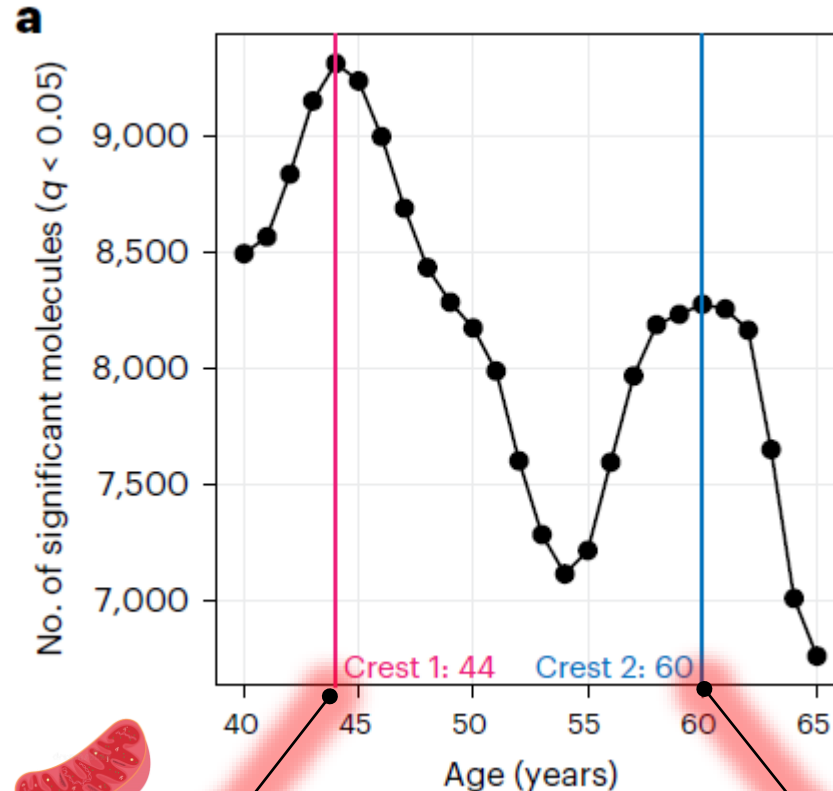


Nonlinear dynamics of multi-omics profiles during human aging. Shen X, Nat Aging. 2024 Aug 14..

markers of aging, are dysregulated at approximately 44 years and 60 years



✓ multi-omics profiling on a longitudinal human cohort of 108 participants, aged between 25 years and 75 years.



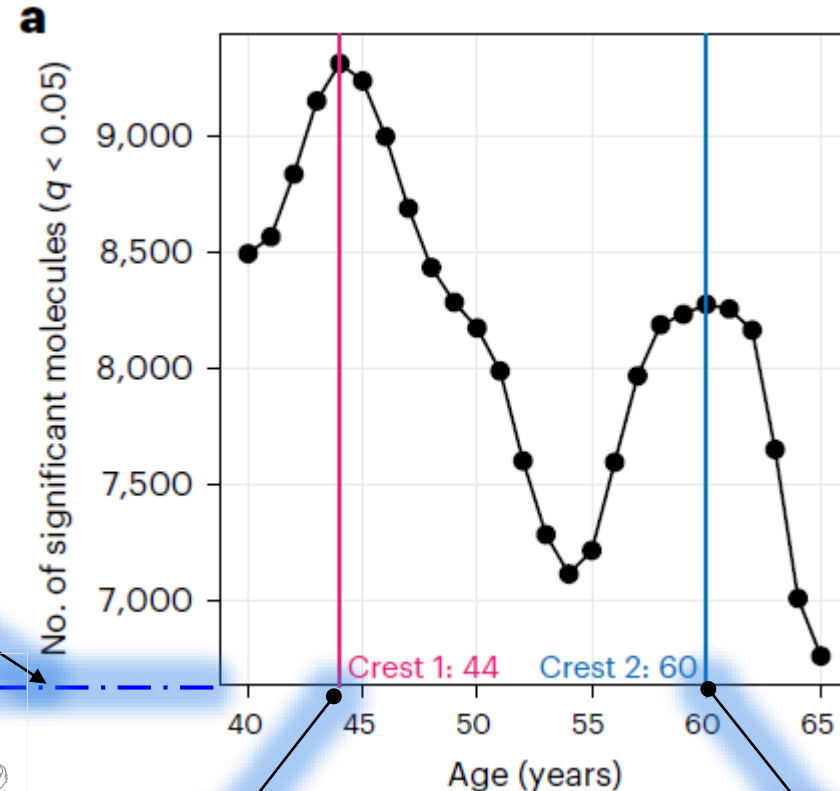
cardiovascular disease,
lipid and alcohol
metabolism

immune regulation
and
carbohydrate metabolism

Nonlinear dynamics of multi-omics profiles during human aging. Shen X, Nat Aging. 2024 Aug 14..

markers of aging, are dysregulated at approximately 44 years and 60 years

Prevention must start early!



cardiovascular disease,
lipid and alcohol
metabolism

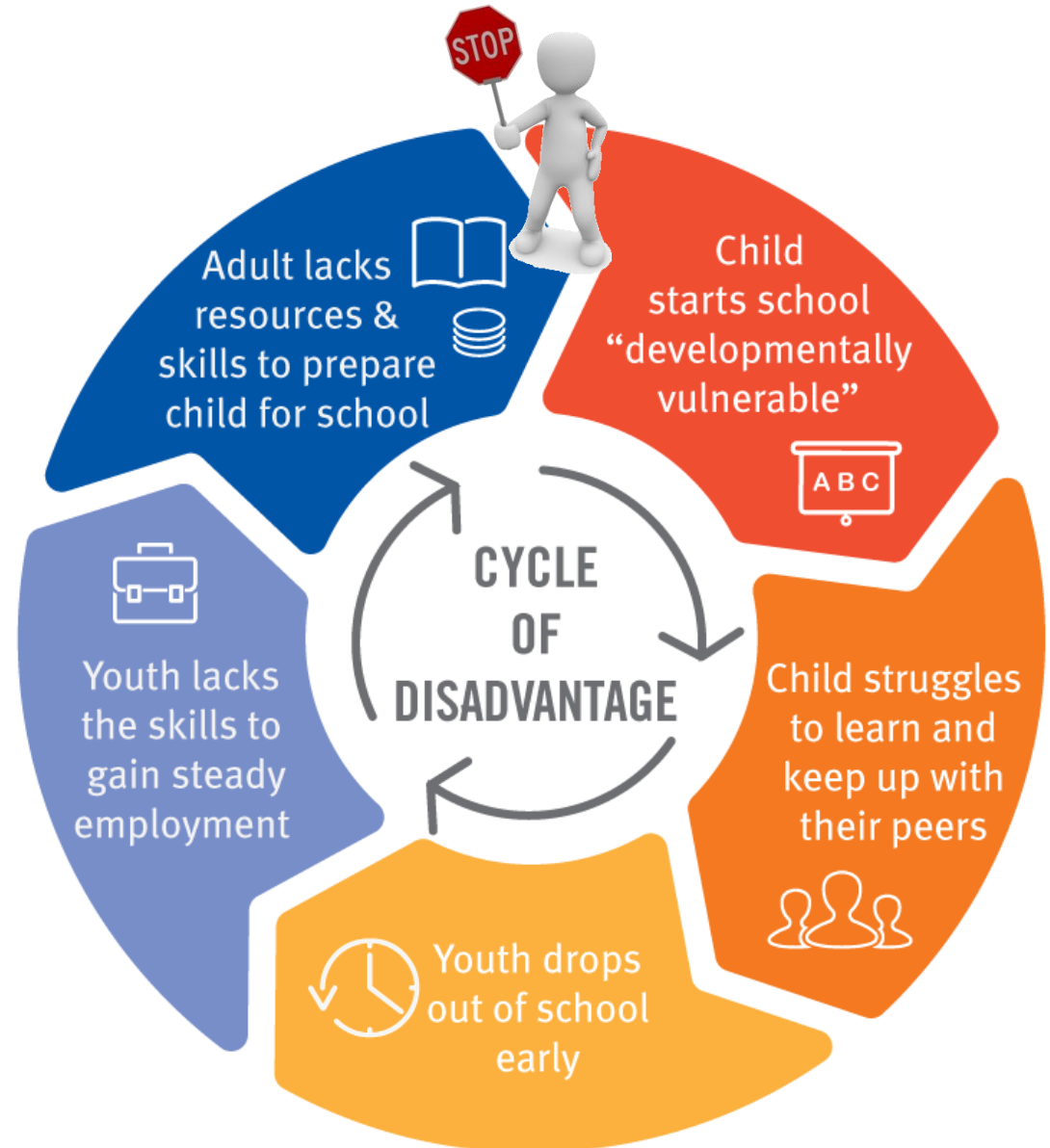
immune regulation
and
carbohydrate metabolism

Caring for Children by Supporting Parents

Shuster MA, NEJM 2017;376(5):410



"Indeed, physicians' greatest effect on the health of children may, at times, be the result not of what they do for children, but of what they do for parents".



Does oxidative stress shorten telomeres in vivo?

A meta-analysis.

Armstrong E, Ageing Res Rev. 2023 Mar;85:101854.

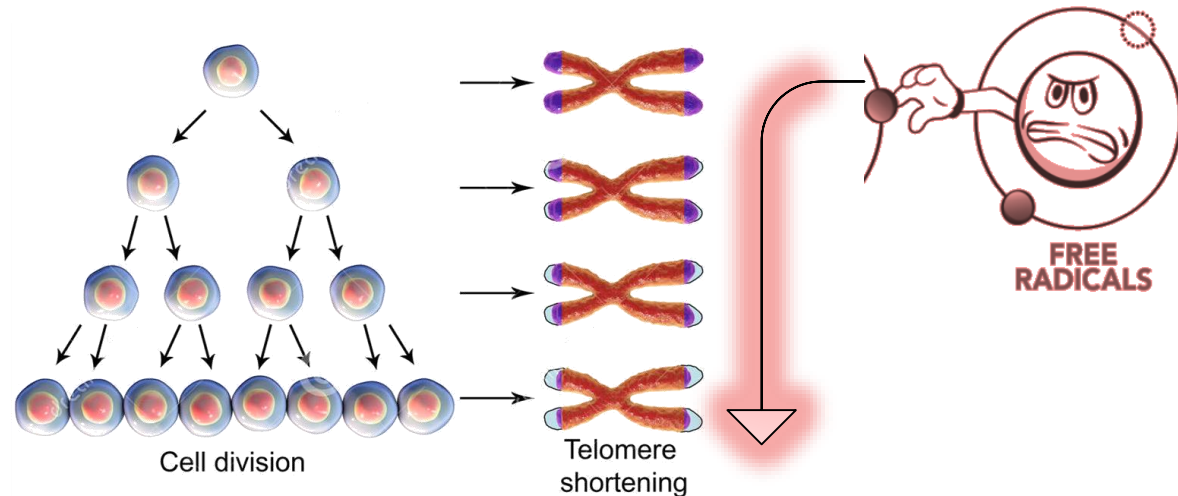
✓ meta-analysis



✓ association between oxidative stress and telomere dynamics in vivo,

✓ 37 studies, 4969 individuals, and 18,677 correlational measurements

There is a significant overall correlation ($r = 0.09$) between oxidative stress and accelerated telomere shortening.



von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci. 2002 Jul;27(7):339-44.

Does oxidative stress shorten telomeres in vivo?

A meta-analysis.

Armstrong E, Ageing Res Rev. 2023 Mar;85:101854.

contrasting oxidative stress
has a protective effect on telomere shortening

✓ meta-analysis

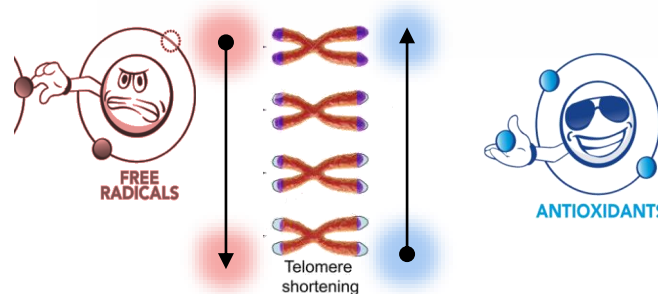
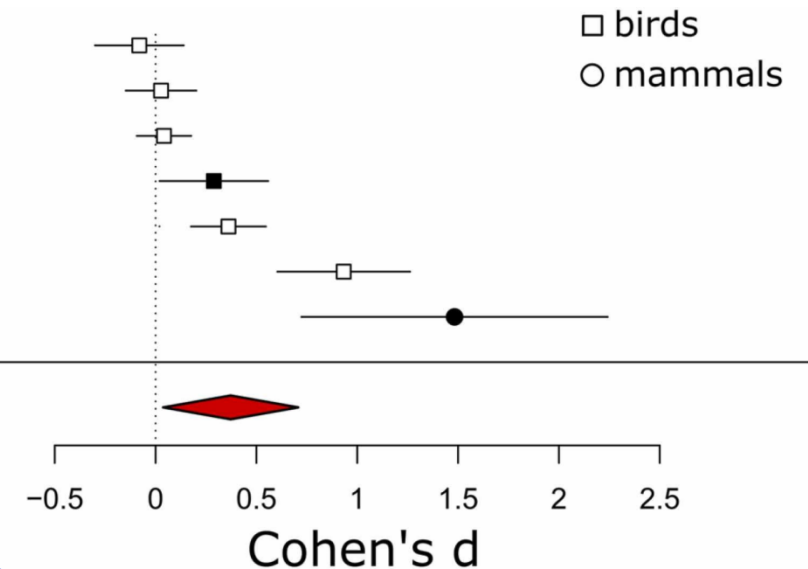


✓ association between
oxidative stress and
telomere dynamics in vivo,

✓ 37 studies, 4969 individuals,
and 18,677 correlational
measurements

Parolini 2017
Pérez-Rodríguez 2019
Kim 2015
Pineda-Pampliega 2020
Noguera 2015
Badás 2015
Cattan 2008

overall effect size



Mistakes to Avoid in the Management of Children's Respiratory Diseases to Plan Long Term Health



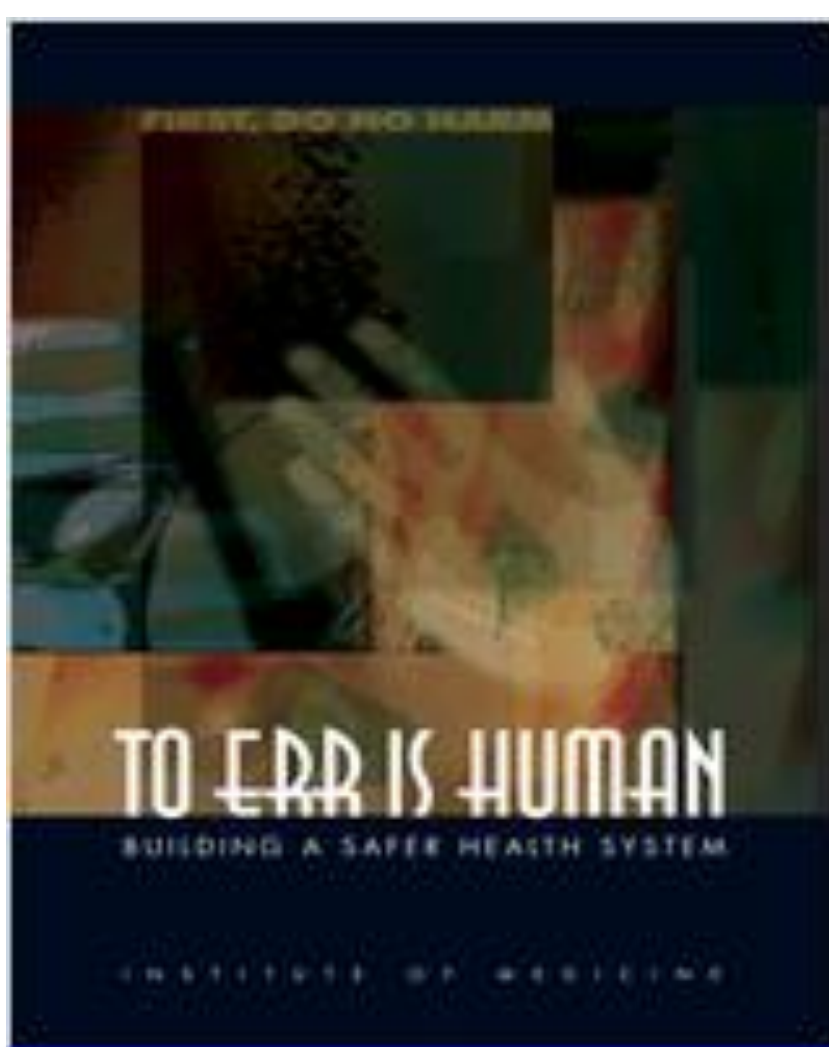
Attilio Boner
University of
Verona, Italy

attilio.boner@univr.it



335 6274799

- ✓ Introduction
- ✓ Why is avoiding mistakes important?
The long-term consequences of early respiratory diseases
- ✓ Early respiratory diseases: "a canary in the mine"
- ✓ 10 Mistakes to avoid
- ✓ Summary & Conclusions



**To Err is Human
Building a Safer Health System**

Institute of Medicine (US) Committee on Quality of Health Care in America; Editors: Linda T. Kohn, Janet M. Corrigan, and Molla S. Donaldson. Washington (DC): [National Academies Press \(US\)](#); 2000. ISBN-10: 0-309-06837-1

- In 1999, the Institute of Medicine released a landmark report, **"To Err is Human,"** which brought unprecedented public attention to bear on the safety of American health care.
- **To Err Is Human** breaks the silence that has surrounded medical errors and their consequence--but not by pointing fingers at caring health care professionals who make honest mistakes.
- **To Err Is Human** asserts that the problem is not bad people in health care--it is that good people are working in bad systems that need to be made safer.



Pathogenesis is Important

What

•

•

•

•

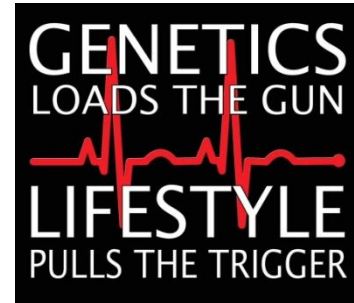
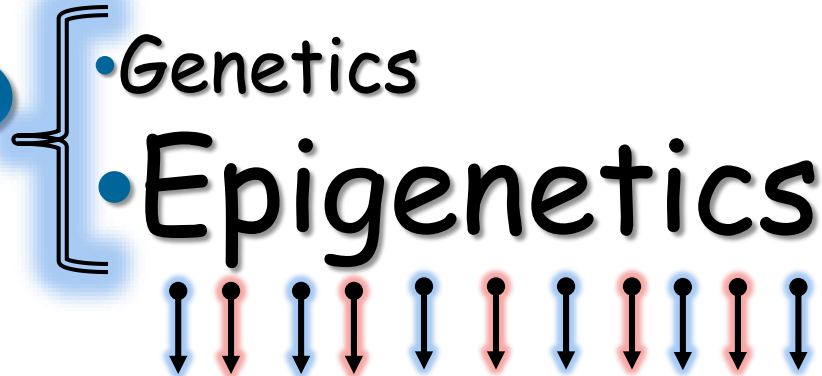
•

•

•

• $\geq 10,000$

Why ?



Few biological systems:

- chronic inflammation
- oxidative stress
- immune hypo/hyperactivity
- dysbiosis
- mental detoxification





The art of
teaching is the
art of assisting
discovery

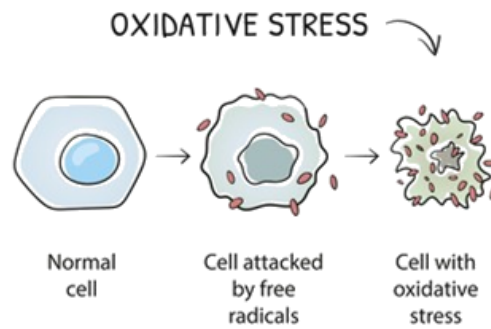
- ❖ Respect environment
- ❖ Optimal diet starting with breastfeeding
- ❖ Prevention strategies starting with vaccines
- ❖ Fever is not always bad
- ❖ Treat causes not effects
- ❖ Ask about the quality of cough
- ❖ Teach how to use the devices
- ❖ Be sure to have been understood "Ask me 3"

What is my main problem?

What do I need to do?

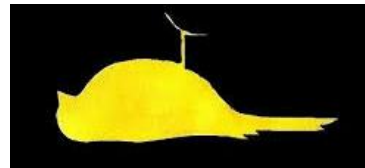
Why is it important for me to do this?

- ❖ *Steroids don't solve everything*
- ❖ *Oxidative stress is a neglected big problem*



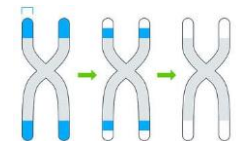
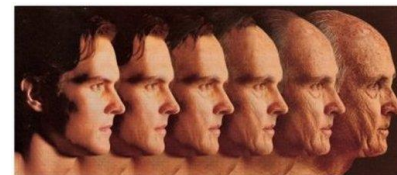
➤ OXIDATIVE STRESS and: RESULTS

- bronchiolitis → 66
- asthma → 2,440
- COPD → 2,769
- allergic rhinitis → 163
- atopic dermatitis → 293

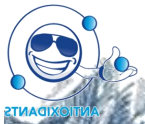


OUR DUTY

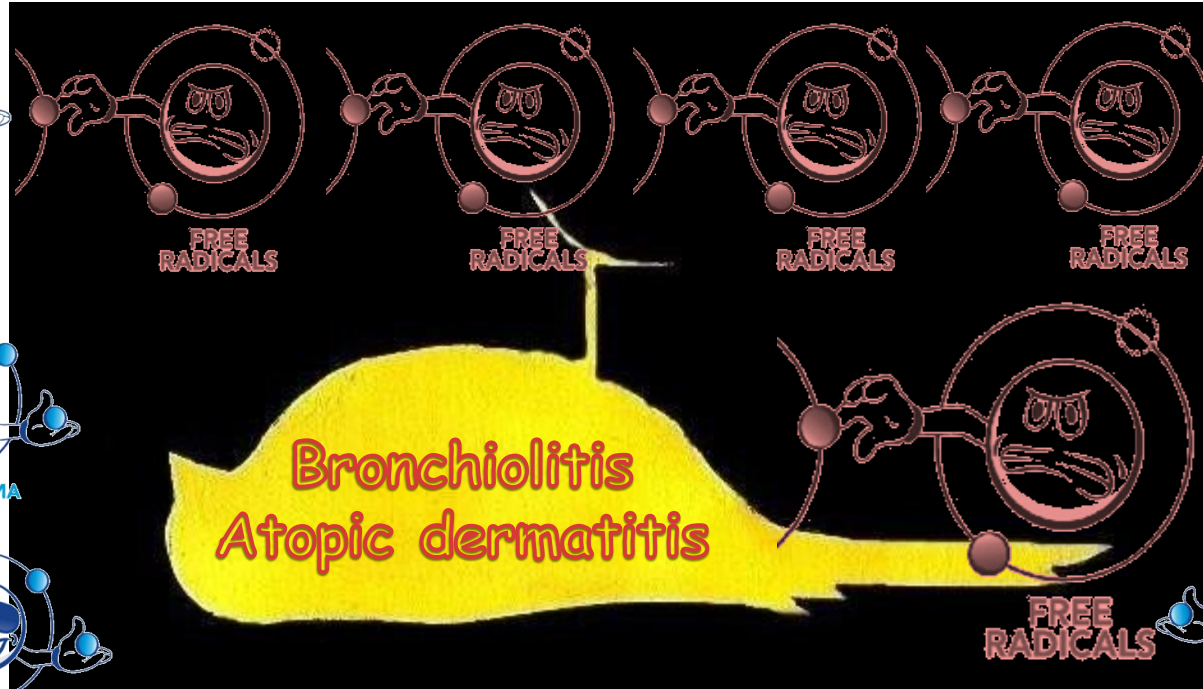
- Metabolic diseases → 38,383
- Cardiovascular diseases → 46,870
- Neurodegenerative diseases → 20,839
- Kidney diseases → 14,073



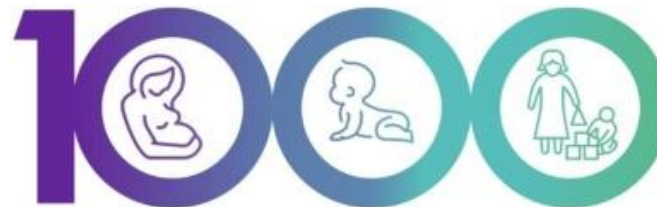
Take home message



ANTIOXIDANTS



ANTIOXIDANTS



PREGNANCY
270 DAYS

YEAR 1
365 DAYS

YEAR 2
365 DAYS



- antioxidant activity AND curcumin: 5,533 results
- antioxidant activity AND quercetin: 18,890 results
- antioxidant activity AND resveratrol: 13,294 results
- antioxidant activity AND magnesium: 4,811 results
- antioxidant activity AND selenium: 28,973 results
- antioxidant activity AND zinc: 14,185 results
- antioxidant activity AND vitamin D: 3,562 results
- antioxidant activity AND vitamin E: 40,633 results
- antioxidant activity AND Vitamin K2: 201 results
- antioxidant activity AND folic acid: 2,815 results





- antiinflammatory activity AND curcumin: 10,011 results
- antiinflammatory activity AND quercetin: 3,171 results
- antiinflammatory activity AND resveratrol: 2,226 results
- antiinflammatory activity AND magnesium: 755 results
- antiinflammatory activity AND selenium: 771 results
- antiinflammatory activity AND zinc: 1,744 results
- antiinflammatory activity AND vitamin D: 1,750 results
- antiinflammatory activity AND vitamin E: 1,233 results
- antiinflammatory activity AND Vitamin K2: 40 results
- antiinflammatory activity AND folic acid: 464 results



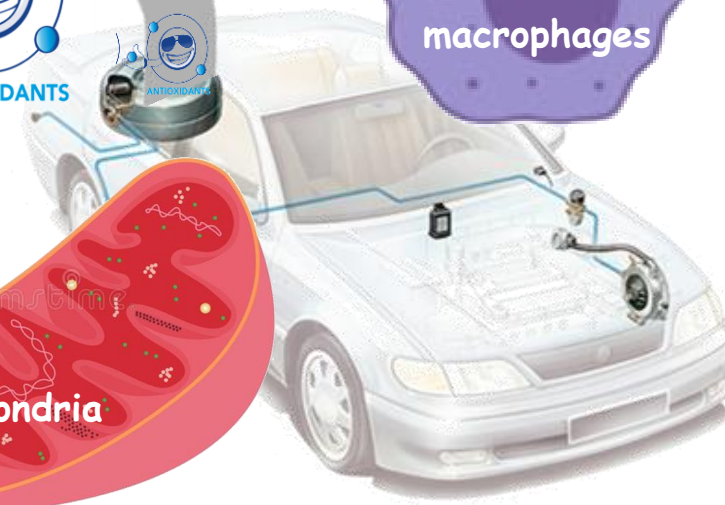


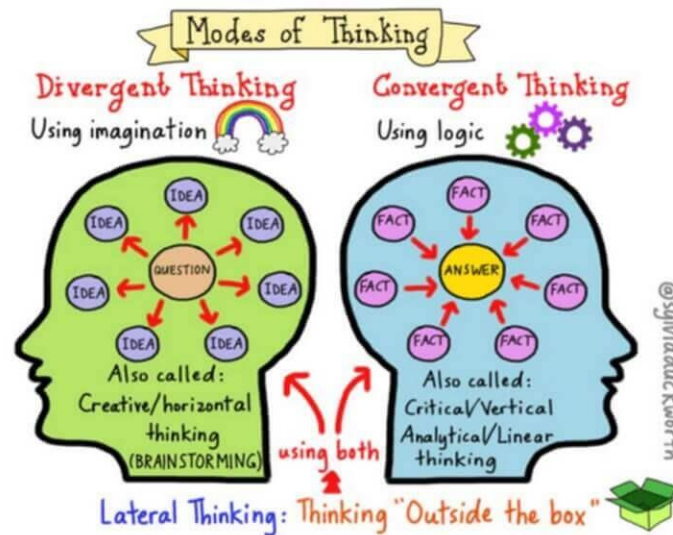
•antiviral activity AND curcumin:	474 results
•antiviral activity AND quercetin:	749 results
•antiviral activity AND resveratrol:	322 results
•antiviral activity AND magnesium:	452 results
•antiviral activity AND selenium:	341 results
•antiviral activity AND zinc:	1,404 results
•antiviral activity AND vitamin D:	602 results
•antiviral activity AND vitamin E:	310 results
•antiviral activity AND Vitamin K2:	9 results
•antiviral activity AND folic acid:	257 results





FOOD SOURCES:
Cheese
Margarine
Butter
Fortified Milk
Healthy Cereals
Fatty Fish





attilio.boner@univr.it



335 627 4799