

From 1996 to 2021: what has change in pediatric allergology in the last 25 years



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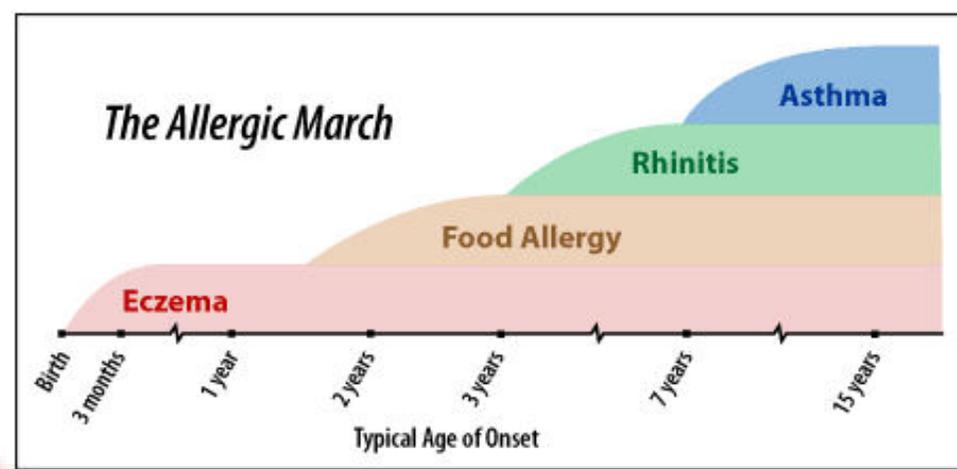
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- ✓ Atopic march
- ✓ Atopic Dermatitis
- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ Meta-analysis vs Biological Plausibility

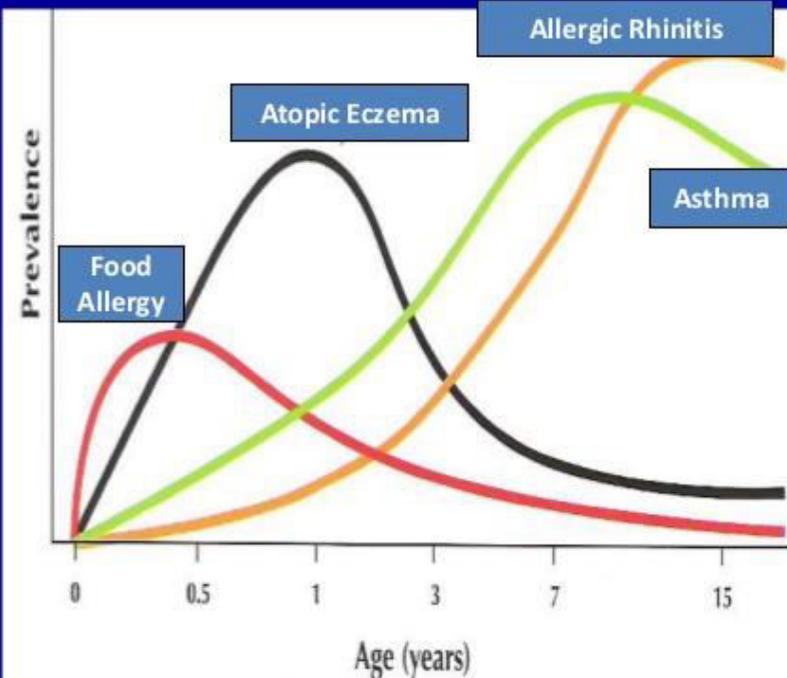


The atopic march

Google

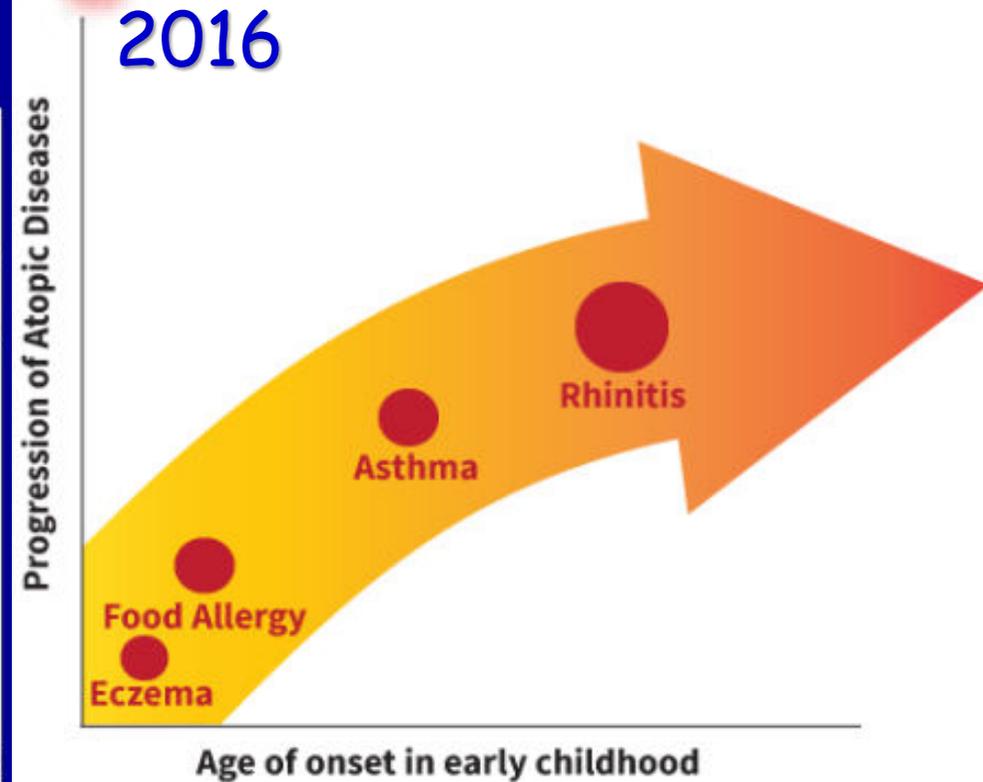


' The Atopic March '



1998 *Prevalence of various atopic diseases in relation to age (atopic march)*

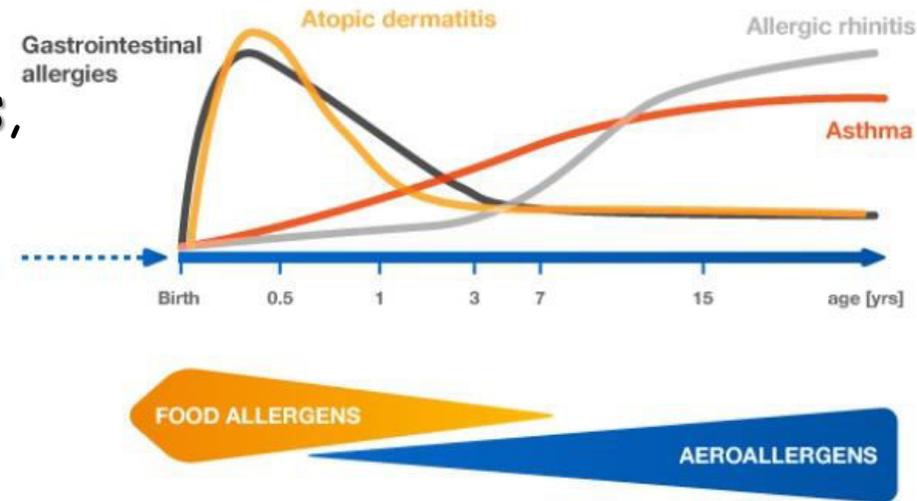
Adapted from Wahn, 1998



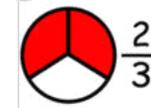
The Atopic March: Definition.

AD and IgE-Mediated FA: Early Members of the Atopic March

- The atopic march has been defined as the natural history of atopic manifestations, characterized by a typical sequence of atopic disease in childhood, generally with AD in infancy or early childhood predating the development of other allergic disorders later in childhood.



- It has been estimated that approximately one-third of patients with AD develop asthma and two-thirds develop allergic rhinitis.

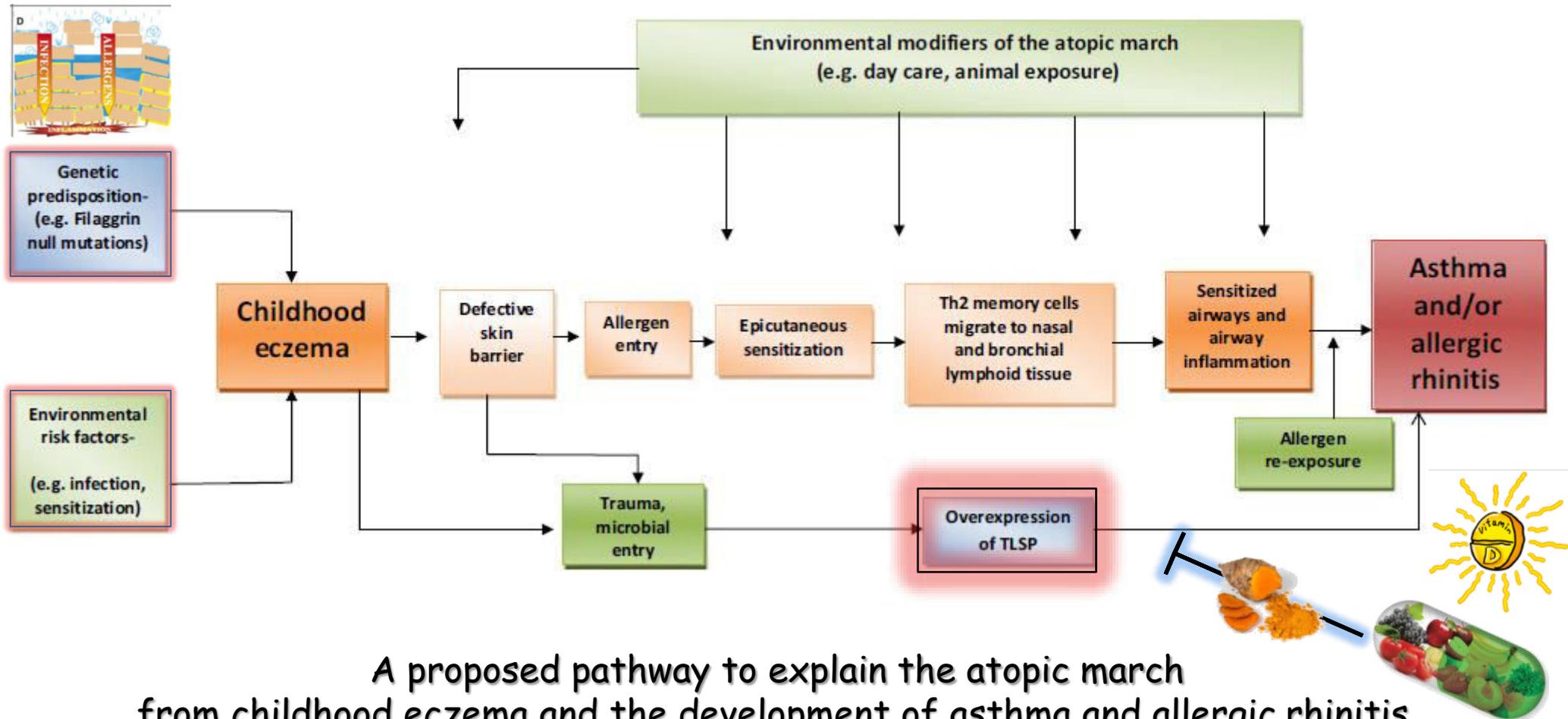


- van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol 2007;120:565-569.*
- Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am 2010;30:269-280.*

Dharmage SC, Allergy. 2014 Jan;69(1):17-27.

Atopic dermatitis and the atopic march revisited.

Dharmage SC, Allergy. 2014 Jan;69(1):17-27.



A proposed pathway to explain the atopic march from childhood eczema and the development of asthma and allergic rhinitis. The hypotheses on plausible biological mechanisms for the atopic march focus on defective skin barrier function and overexpression of inflammatory mediators released by the skin affected by AD (including thymic stromal lymphopoietin)

Thymic stromal lymphopoietin and anti-oxidants in PubMed

• **Air Pollution** During Pregnancy and Cord Blood Immune System Biomarkers. *Ashley-Martin J, J Occup Environ Med. 2016 Oct;58(10):979-986.*



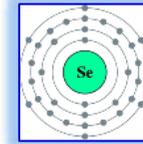
• **Diesel exhaust** particle-exposed human bronchial epithelial cells induce dendritic cell maturation and polarization via thymic stromal lymphopoietin. *Bleck B, J Clin Immunol. 2008 Mar;28(2):147-56.*



• **Cigarette smoke** extract induces thymic stromal lymphopoietin expression, leading to T(H)2-type immune responses and airway inflammation. *Nakamura Y. J Allergy Clin Immunol. 2008 Dec;122(6):1208-14.*



➤ The suppression of thymic stromal lymphopoietin expression by **selenium**. *Moon PD, Amino Acids. 2012 Aug;43(2):999-1004.*



➤ **Epigallocatechin-3-O-gallate** inhibits the production of thymic stromal lymphopoietin by the blockade of caspase-1/NF- κ B pathway in mast cells. *Moon PD, Amino Acids. 2012 Jun;42(6):2513-9.*



➤ Down-regulation of thymic stromal lymphopoietin by **curcumin**. *Moon PD, Pharmacol Rep. 2013;65(2):525-31.*



➤ **Resveratrol** ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis-like lesions through effects on the epithelium. *Caglayan Sozmen S, PeerJ. 2016 Mar 31;4:e1889*



➤ **1,25-dihydroxyvitamin D3** pretreatment inhibits house dust mite-induced thymic stromal lymphopoietin release by human airway epithelial cells. *Zhou L, Nan Fang Yi Ke Da Xue Xue Bao. 2014 Apr;34(4):492-6.*



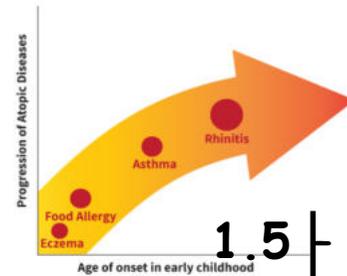
Celiac disease in children with atopic dermatitis.

Ress K, *Pediatr Dermatol*. 2014;31(4):483-8.

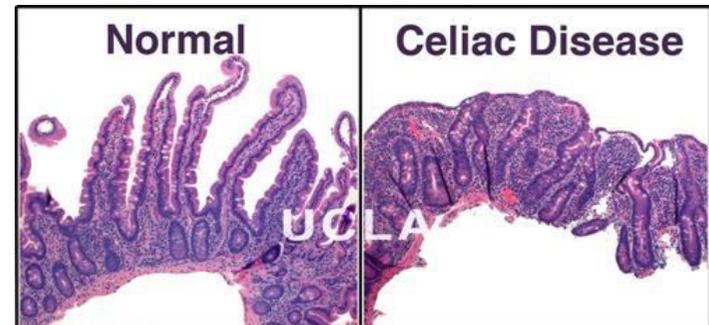
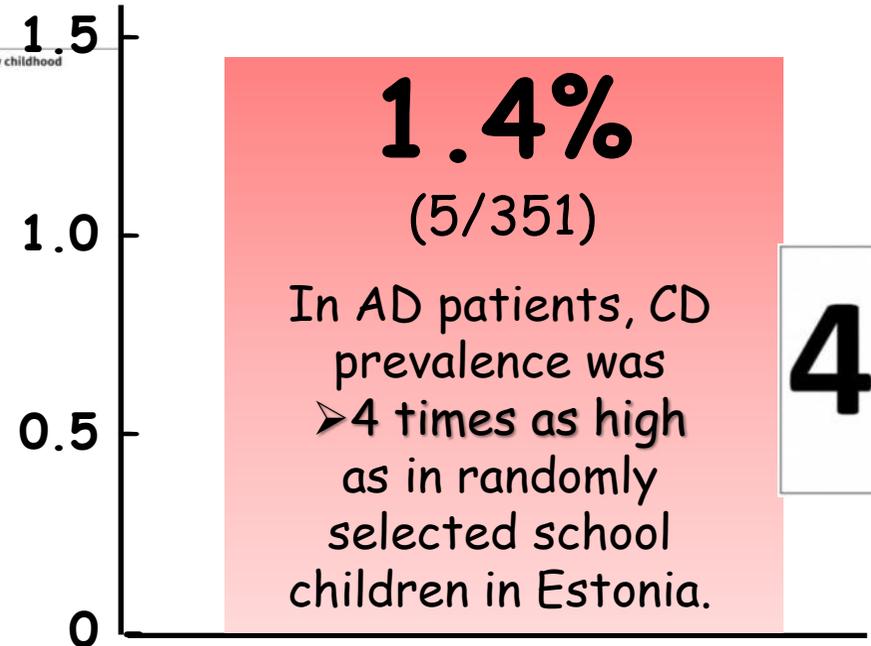
✓ 351 consecutive Estonian children with active atopic dermatitis (AD), (mean age 5.8 yrs)

✓ total serum IgA, IgA- and IgG-type autoantibodies to tissue transglutaminase (IgA-anti-TG2, IgG-anti-TG2) and to deamidated gliadin peptides (IgA-anti-DGP, IgG-anti-DGP).

✓ diagnosis of CD confirmed by small intestine biopsy

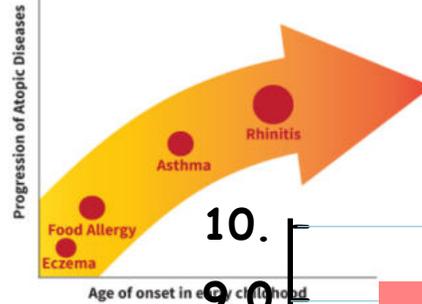


% children with AD and biopsy confirmed CD



Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March.

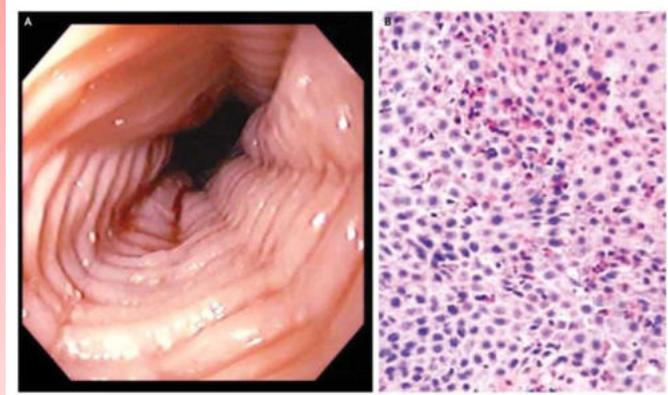
Hill DA, *J Allergy Clin Immunol Pract.* 2018 Sep - Oct;6(5):1528-1533.



HR of EoE diagnosis within age 10 yrs

10.
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

9.1



IgE mediated food allergy

- ✓ a primary care birth cohort of 130,435 children,
- ✓ natural histories of:
 - atopic dermatitis (AD),
 - IgE-mediated food allergy (IgE-FA),
 - asthma,
 - eosinophilic esophagitis (EoE), and
 - allergic rhinitis (AR) in individual patients

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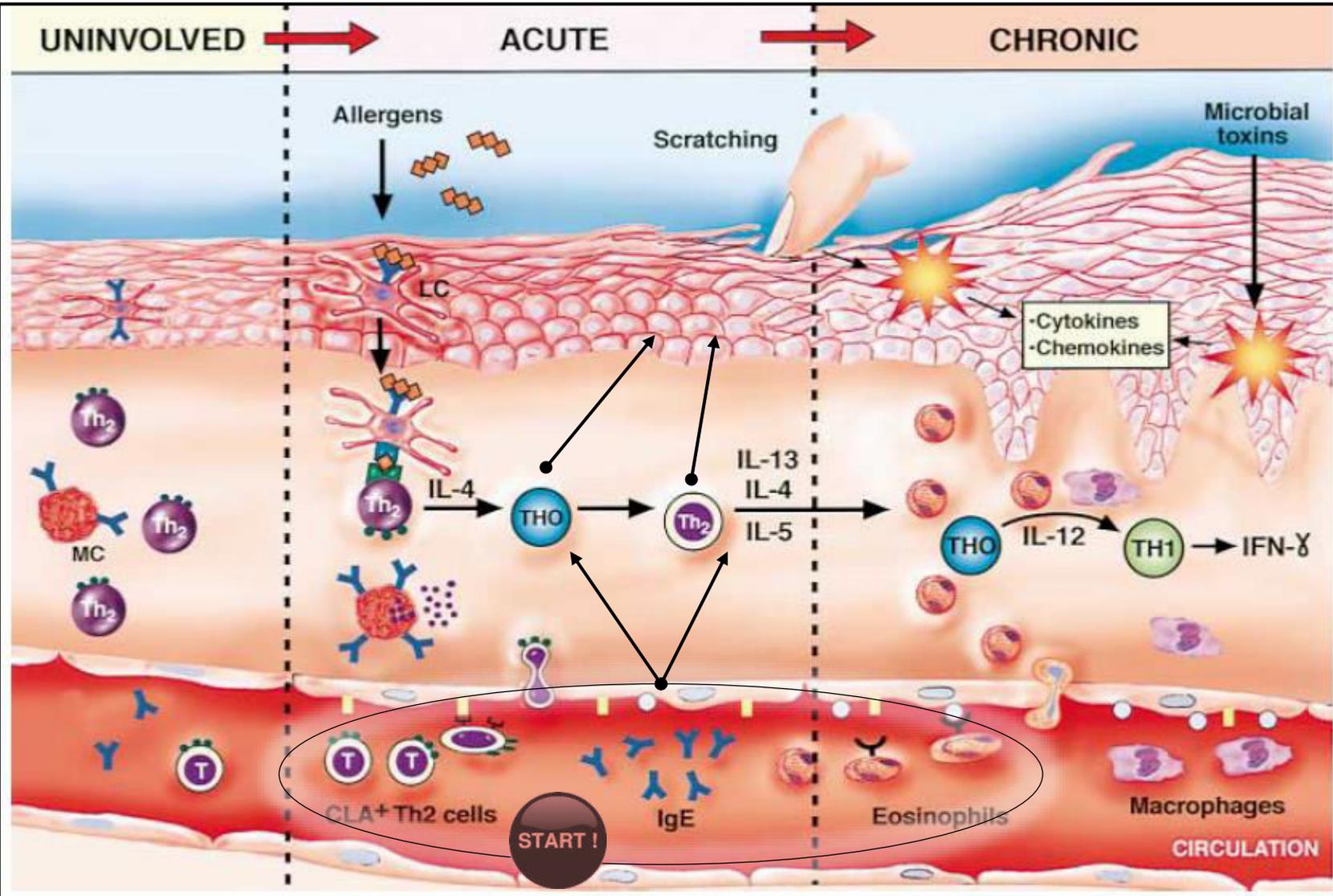
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- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ Meta-analysis vs Biological Plausibility



Atopic dermatitis: new **insights** and opportunities for therapeutic intervention.

Leung DY, *J Allergy Clin Immunol.* 2000 May; 105(5):860-76

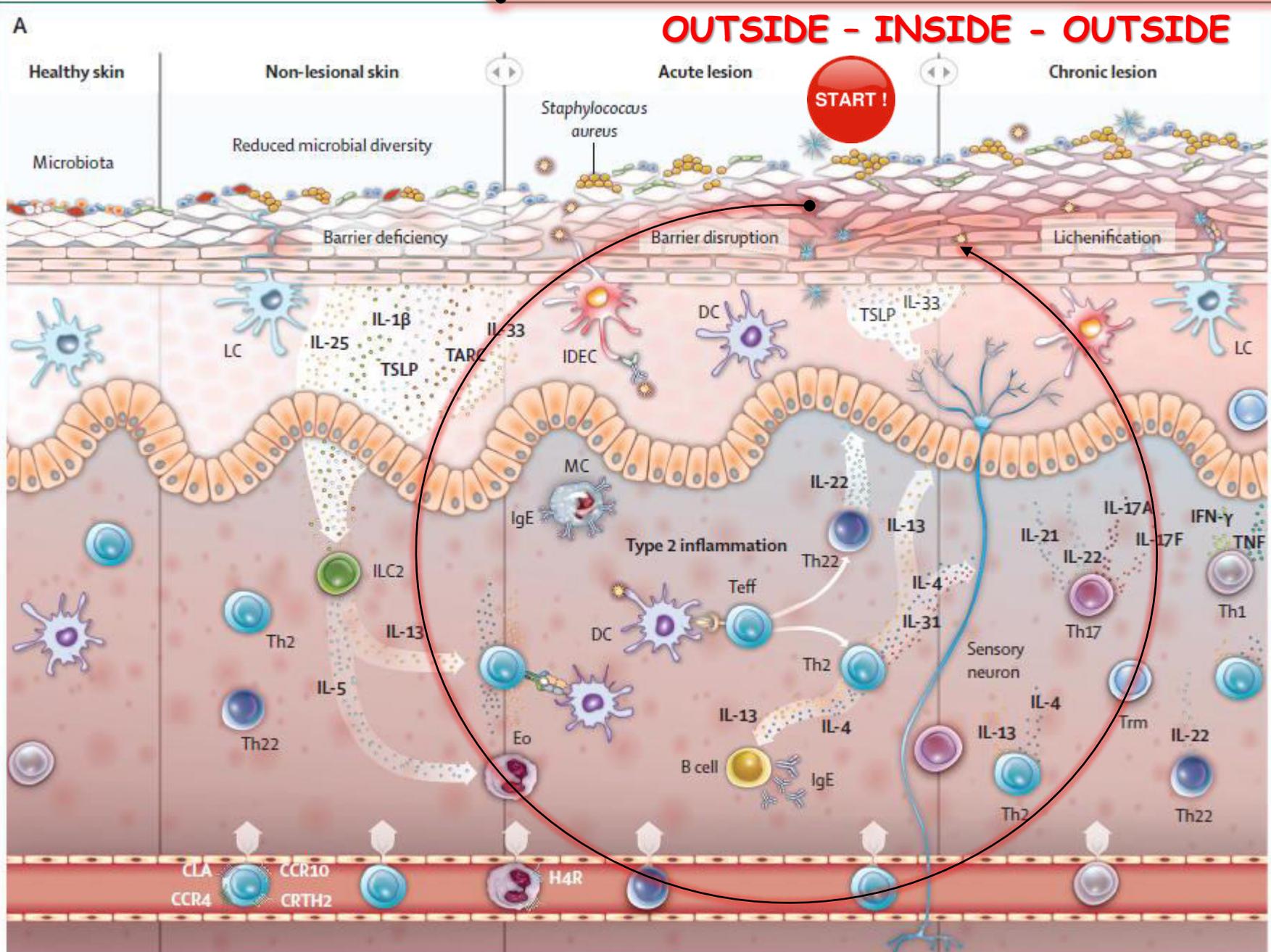


Immunologic pathways involved in the progression of AD.

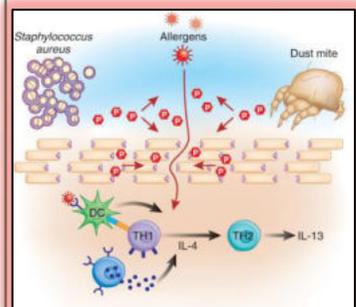
These patients have a **systemic T helper type 2 (TH2) response** with **elevated IgE** and **eosinophilia** with low-level TH2 cytokine expression in uninvolved skin.

The acute skin lesions are associated with marked infiltration of TH2 cells.

However, with the infiltration of eosinophils and macrophages in chronic AD, there is a rise in IL-12 expression and a switch to T helper type 1 (TH1) cellular responses.



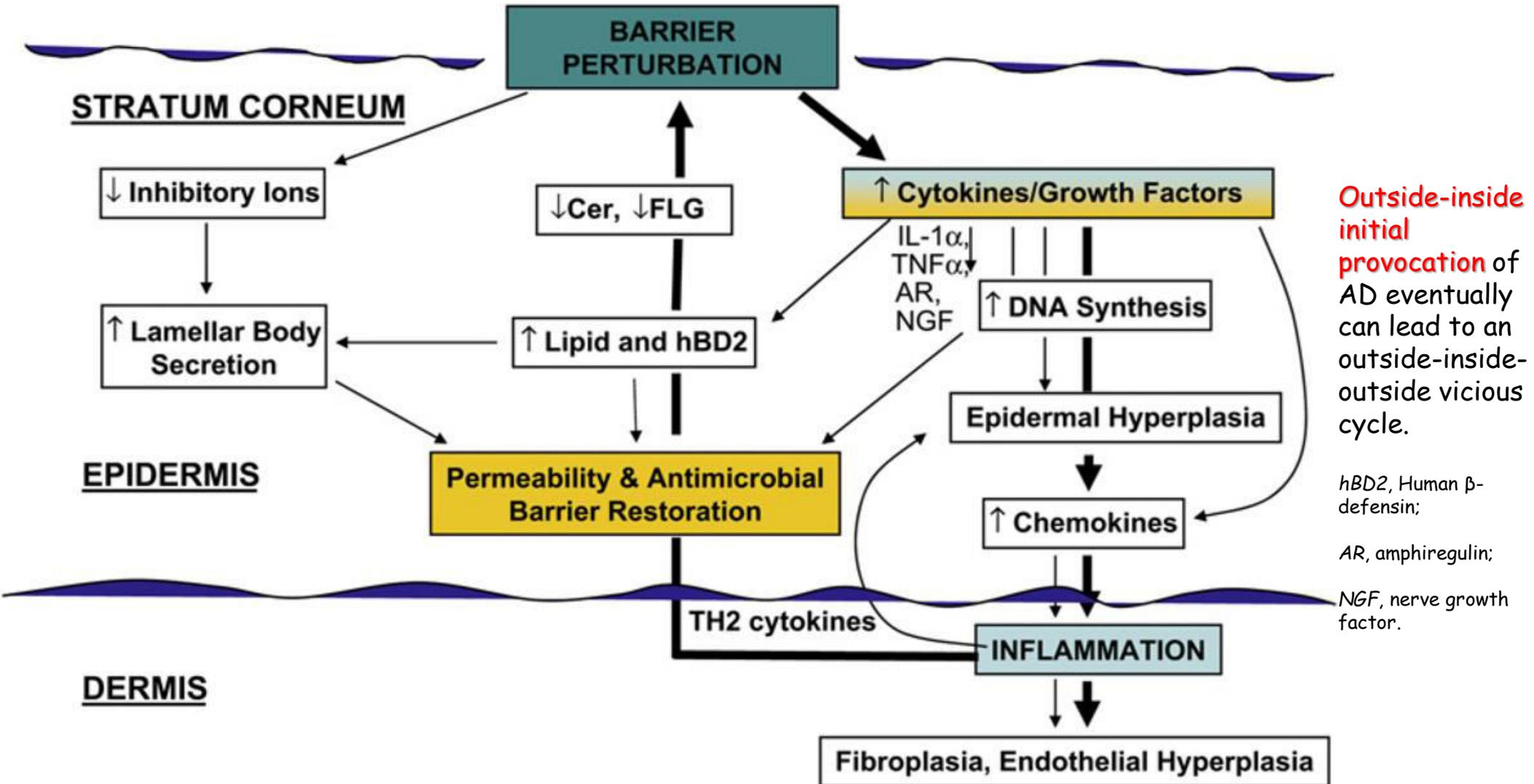
A). **Clinically unaffected skin** has an epidermal barrier dysfunction with a reduced diversity of the surface microbiome. In lesional skin, Langerhans cells, inflammatory epidermal dendritic cells bearing specific IgE bound to the high affinity receptor for IgE, and dermal dendritic cells take up allergens and antigens. The type-2 cytokines IL-4, IL-13, and IL-31 directly activate sensory nerves, which promotes pruritus.

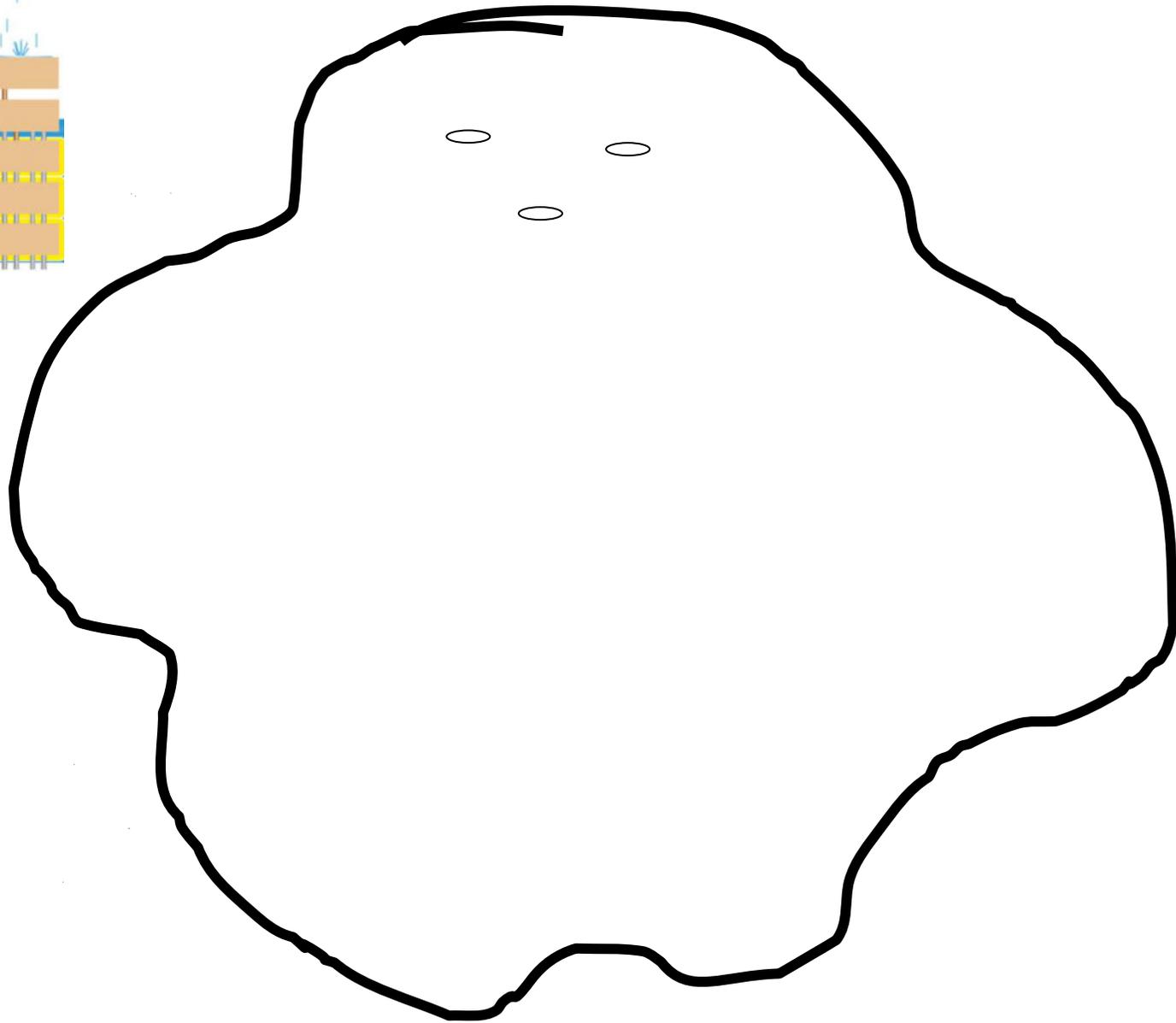
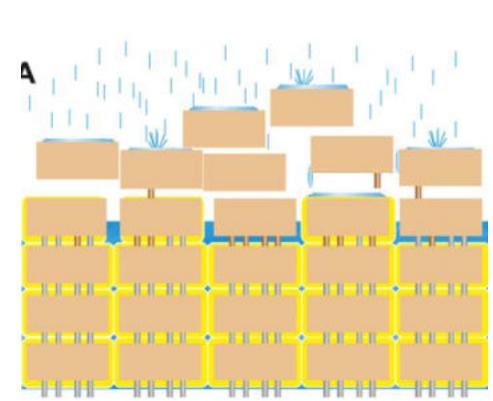


Basis for the barrier abnormality in atopic dermatitis:

outside-inside-outside pathogenic mechanisms.

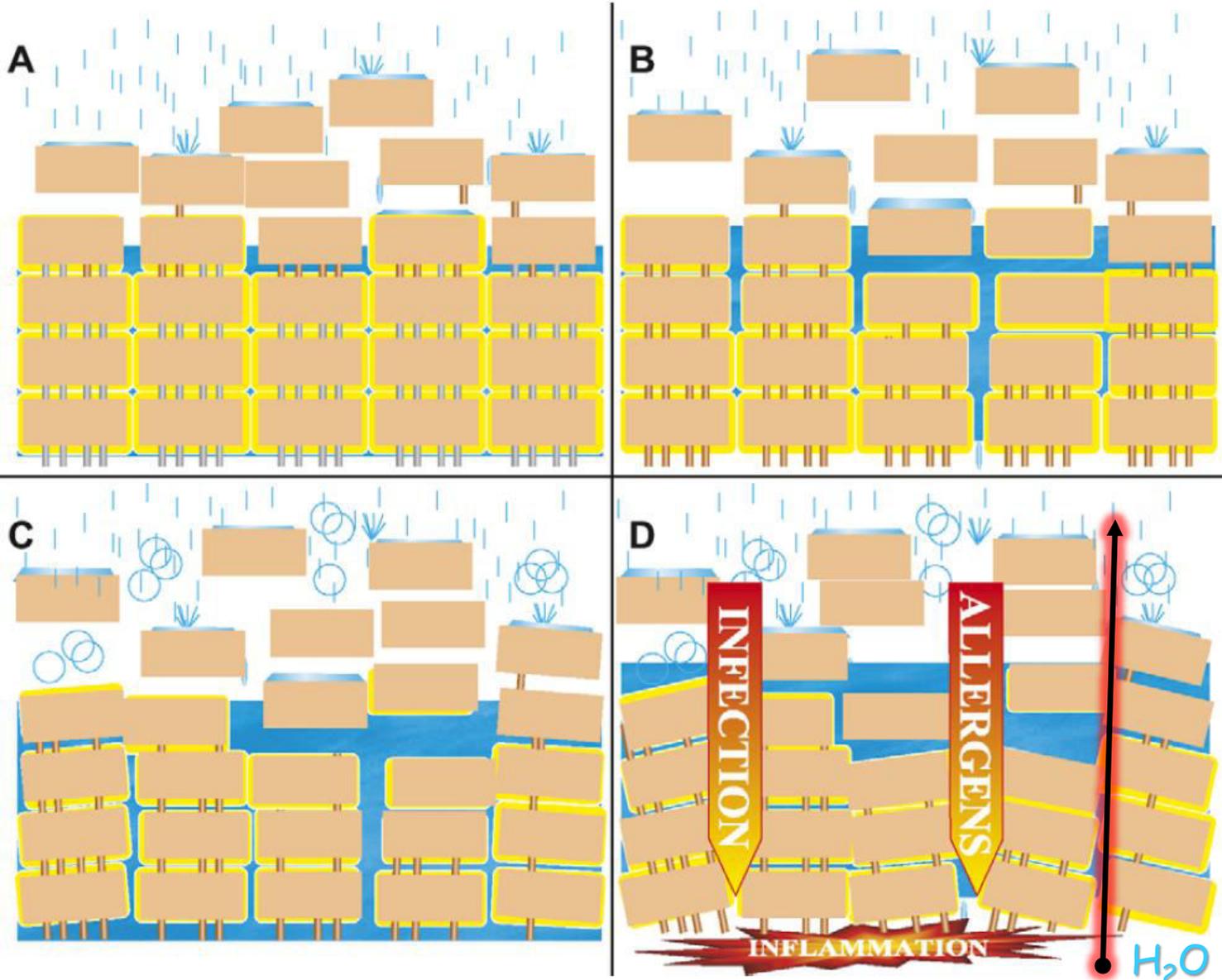
Elias PM, J Allergy Clin Immunol. 2008 Jun; 121(6):1337-43.





Courtesy of Prof Carlo Gelmetti

Role of Epidermal Barrier Dysfunction in Atopic Dermatitis Pathogenesis. *Cork MJ, J Allergy Clin Immunol. 2006;118:3-21*



The brick wall analogy of the stratum corneum of the epidermal barrier.

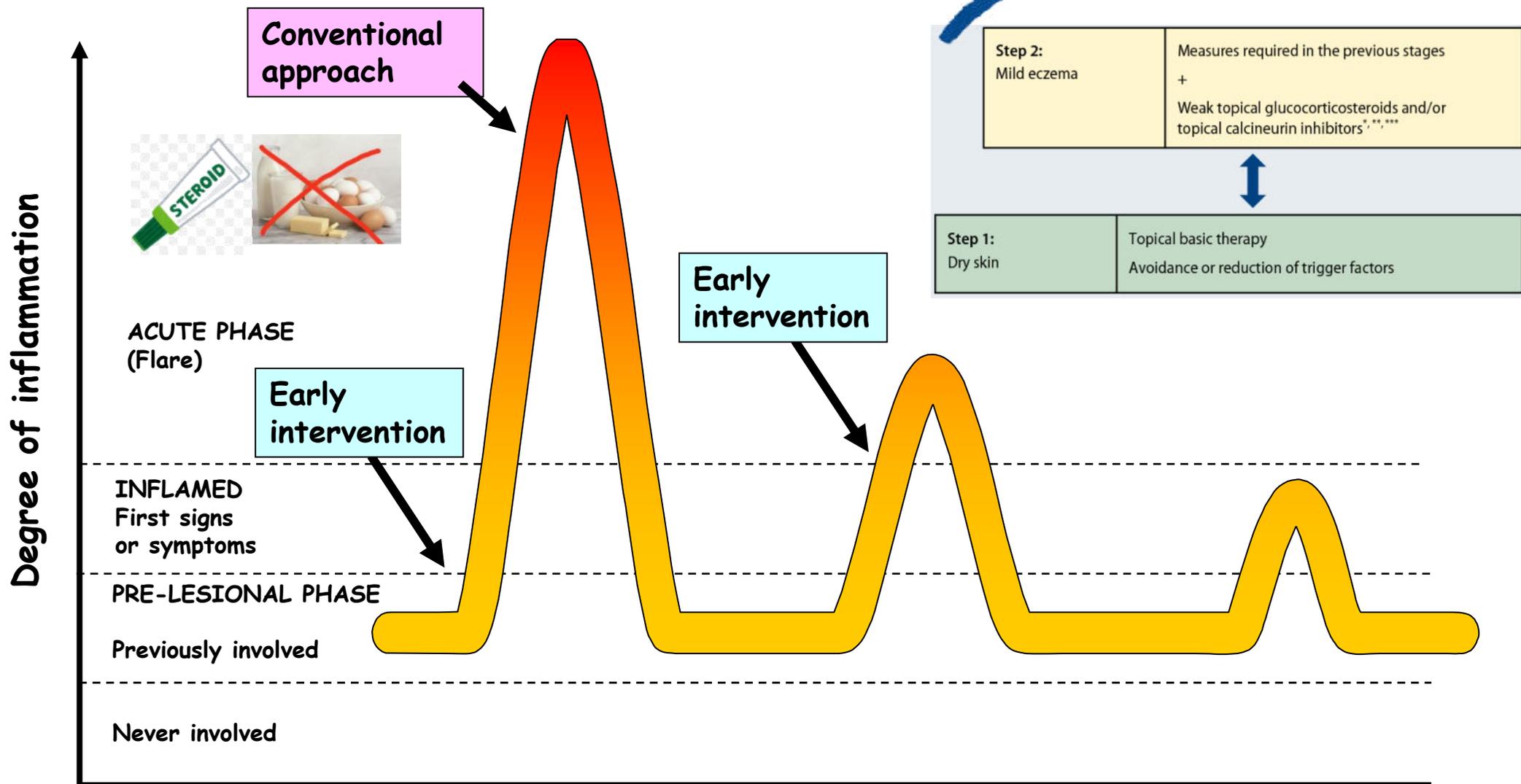
In healthy skin the corneodesmosomes (iron rods) are intact throughout the stratum corneum.

At the surface, the corneodesmosomes start to break down as part of the normal desquamation process, analogous to iron rods rusting (A).

FROM symptomatic treatment TO gaining long-term control - treat at very first signs or symptoms

1995 - 2000

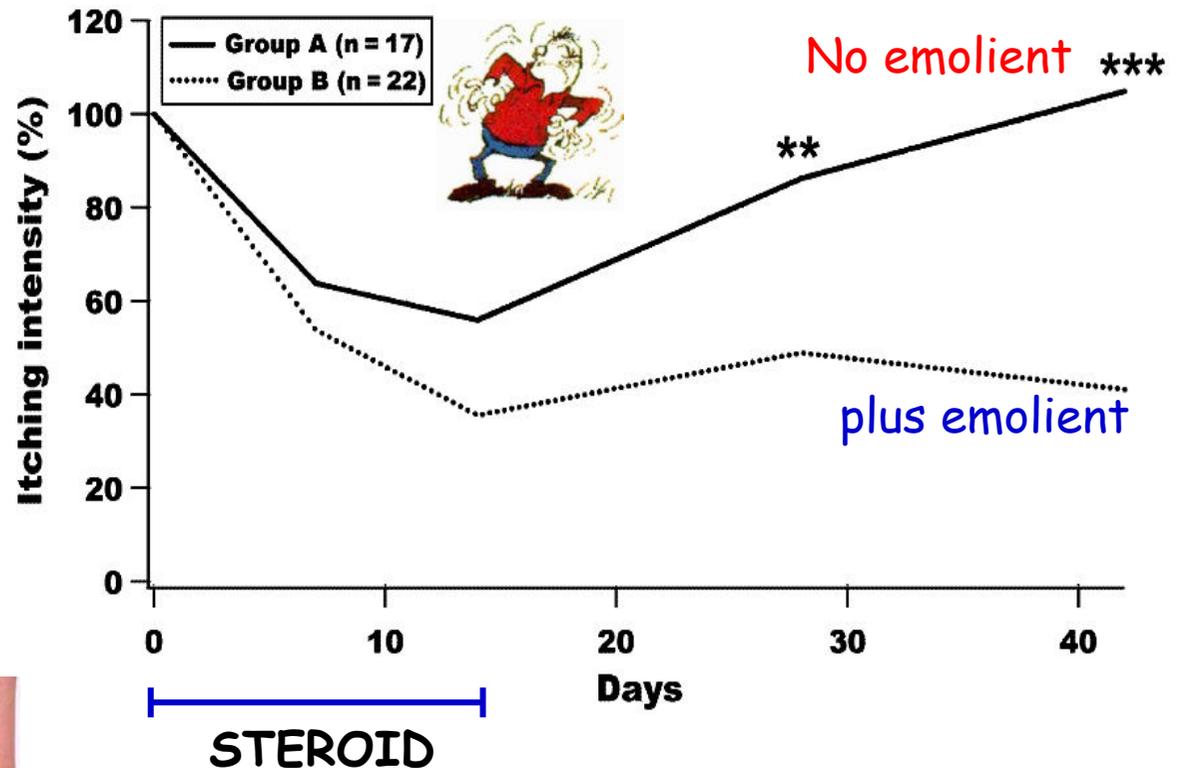
2005 - 2021



Emollients Improve Treatment Results with Topical Corticosteroids in Childhood Atopic Dermatitis: a Randomized Comparative Study

Szczepanowska *Ped All Immunol* 2008;19:614

- ✓ 52 ch with AD (2-12 yrs).
- ✓ 26 ch received a steroid cream for 2 weeks (+4 weeks follow-up with no treatment) (Group A).
- ✓ 26 ch received steroid cream for 2 weeks + emollients for 6 weeks (Group B).

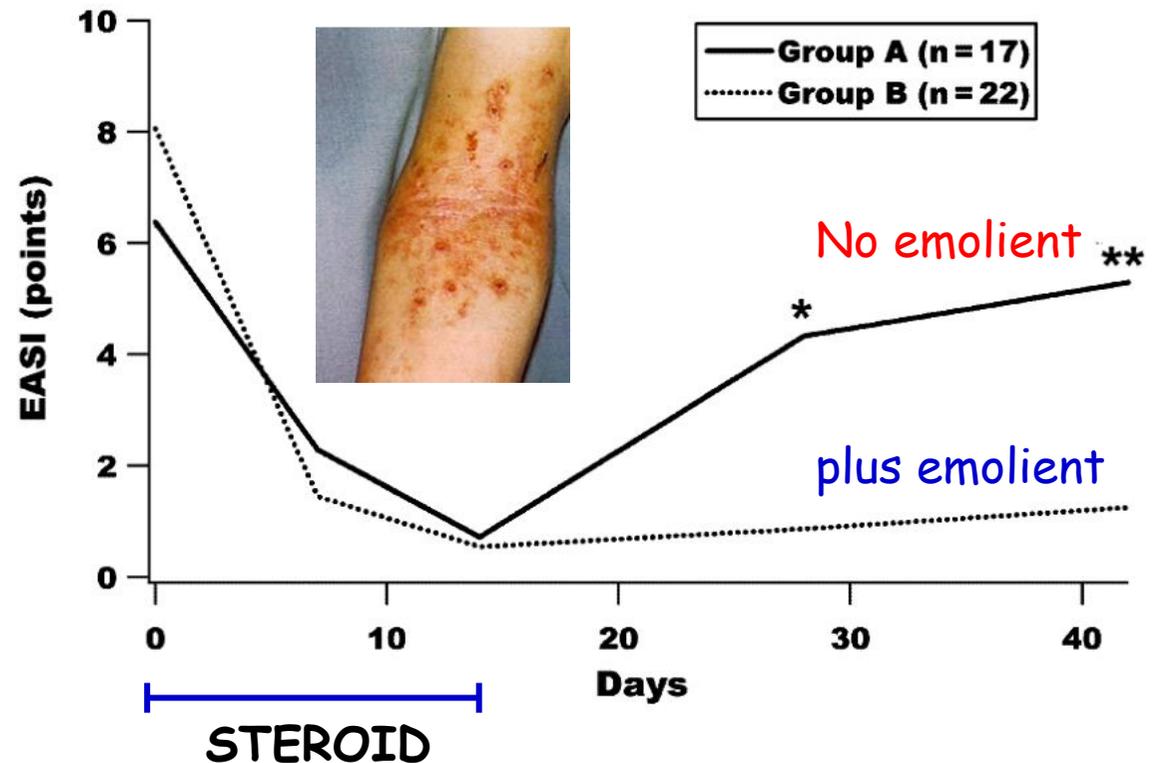


* p=0.004 ** p=0.01 ***p<0.001

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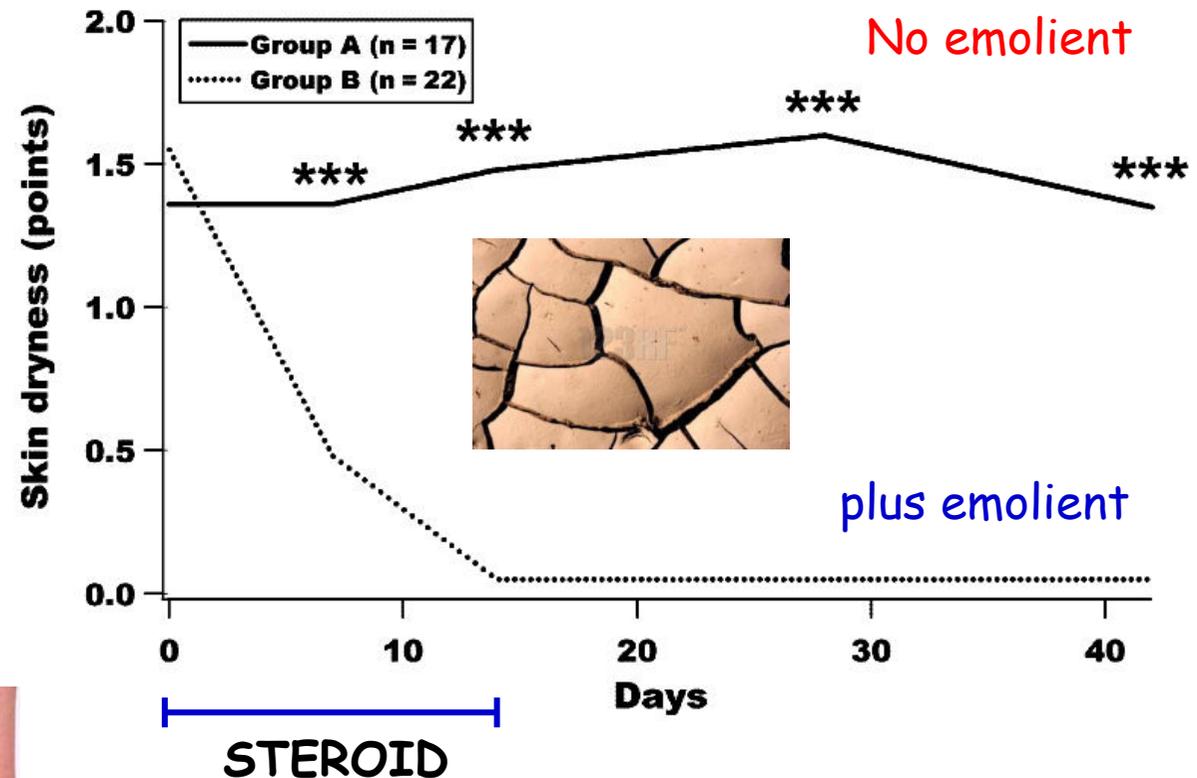


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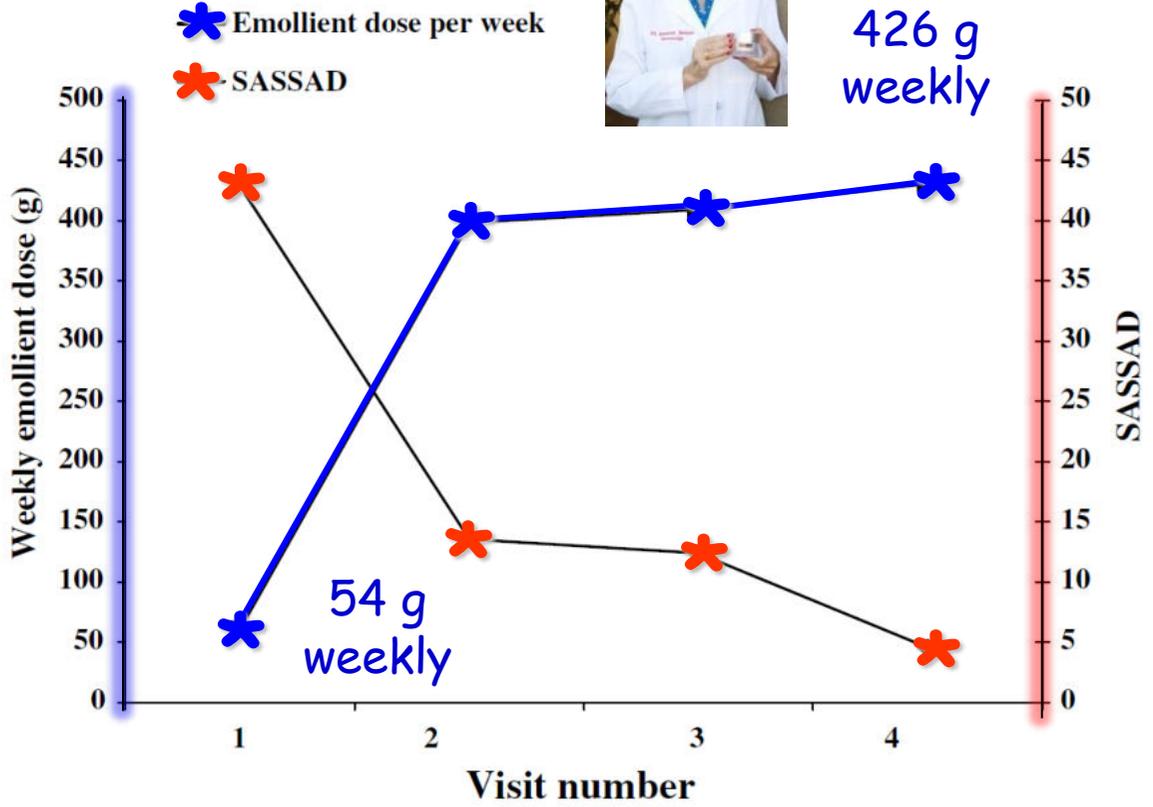
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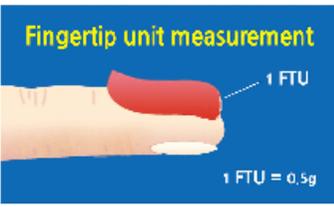
Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse *MJCork, Br J Dermatol 2003;149:582-9.*

The mean quantity (g) of emollient cream / ointment being used per week reported at each clinic visit plotted against the mean investigator's assessment of severity of the eczema using the **six area, six sign atopic dermatitis severity score (SASSAD)** at each visit.

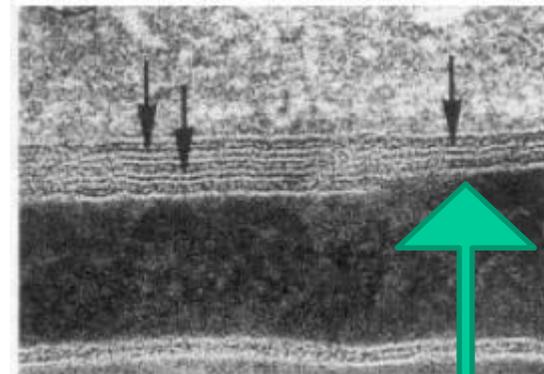
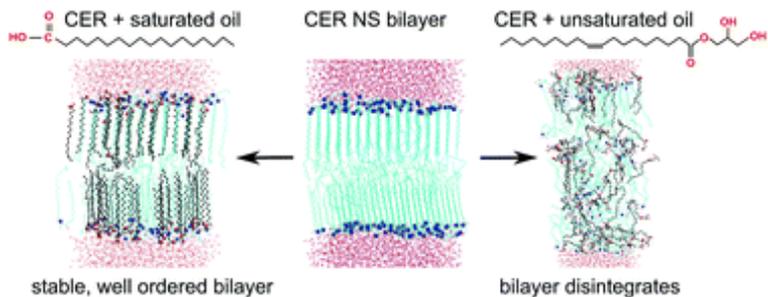


The fingertip unit method*
 FTU = Fingertip unit (adult)
 1 FTU = 0.5 g of cream or ointment.
 Measurement based on 5mm nozzle.

FACE & NECK	ARM & HAND	LEG & FOOT	TRUNK (Front)	TRUNK (Back)	Age Group		
1	1	1 1/2	1	1 1/2	3-6 months		
1 1/2	1 1/2	2	2	3	1-2 years		
1 1/2	2	3	3	3 1/2	3-5 years		
2	2 1/2	4 1/2	3 1/2	5	6-10 years		
FACE & NECK	ONE ARM	ONE HAND	ONE LEG	ONE FOOT	TRUNK (Front)	TRUNK (Back)	Adult
3 1/2	3	1	6	2	7	7	



Physiologic Lipid-Based Therapy of Atopic Dermatitis



- The 3 key physiologic lipids: ceramides, cholesterol, and free fatty acids are present in an approximately equimolar ratio in normal SC.

(long chain - more than 20 carbons - saturated fatty acids)

Man MQ, J Invest Dermatol, 1996;106:1096-1101

Man MQ, Arch Dermatol, 1995;131:809-816.

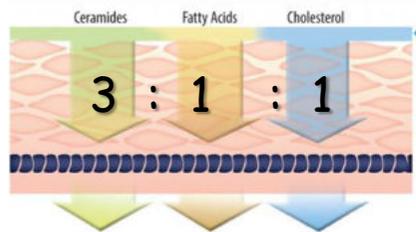
- Applications of incomplete, 1- or 2-component mixtures of these lipids delay barrier recovery by disrupting this molar ratio,

Man MQ, J Invest Dermatol, 1996;106:1096-1101

- Whereas, conversely, applications of the 3 lipids in equimolar proportions allow normal recovery.

Elias PM, Ann Allergy Asthma Immunol. 2018;121:653-656.

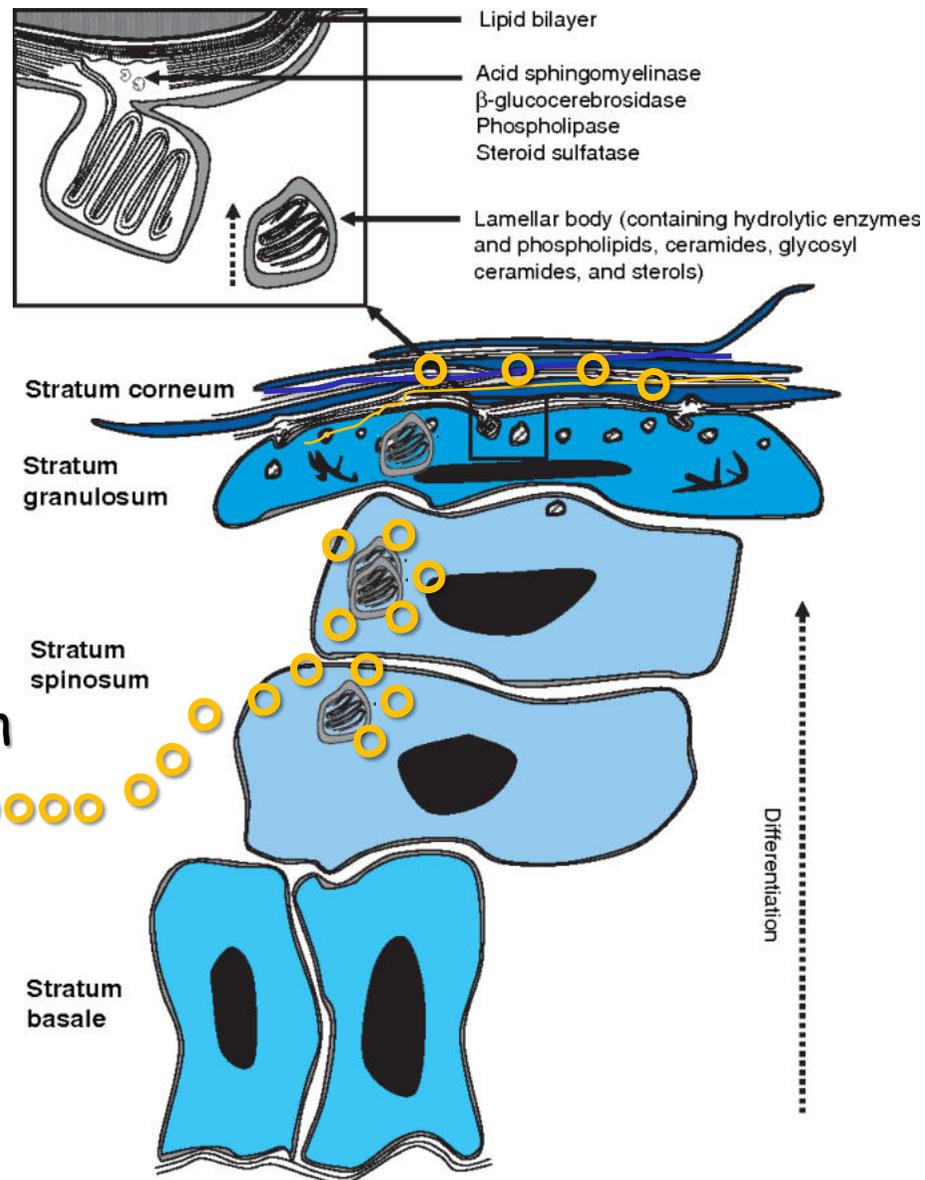
Physiologic Lipid-Based Therapy of Atopic Dermatitis



Subsequently, it was demonstrated that increasing the molar ratio of any of the 3 key lipids up to a 3:1:1 ratio accelerated barrier recovery in normal skin.

Man MQ, J Invest Dermatol, 1996;106:1096-1101

The absorbed lipids join synthesized lipids, immediately before their secretion into the extracellular spaces.

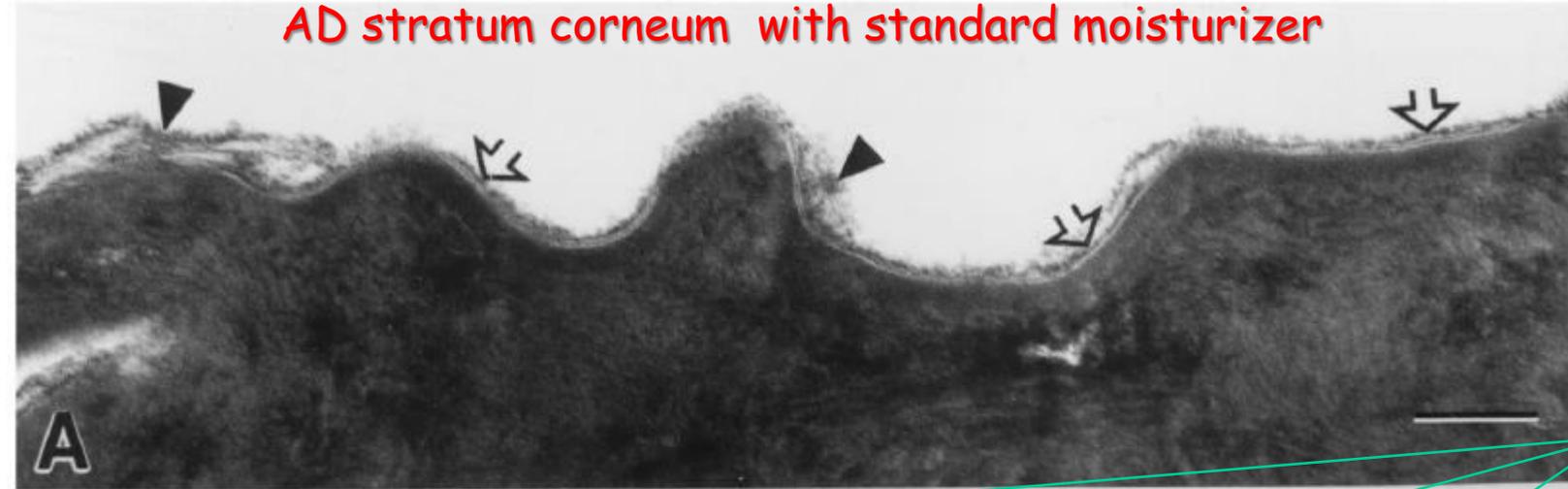


Elias PM, Ann Allergy Asthma Immunol. 2018;121:653-656.

Ceramide dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity.

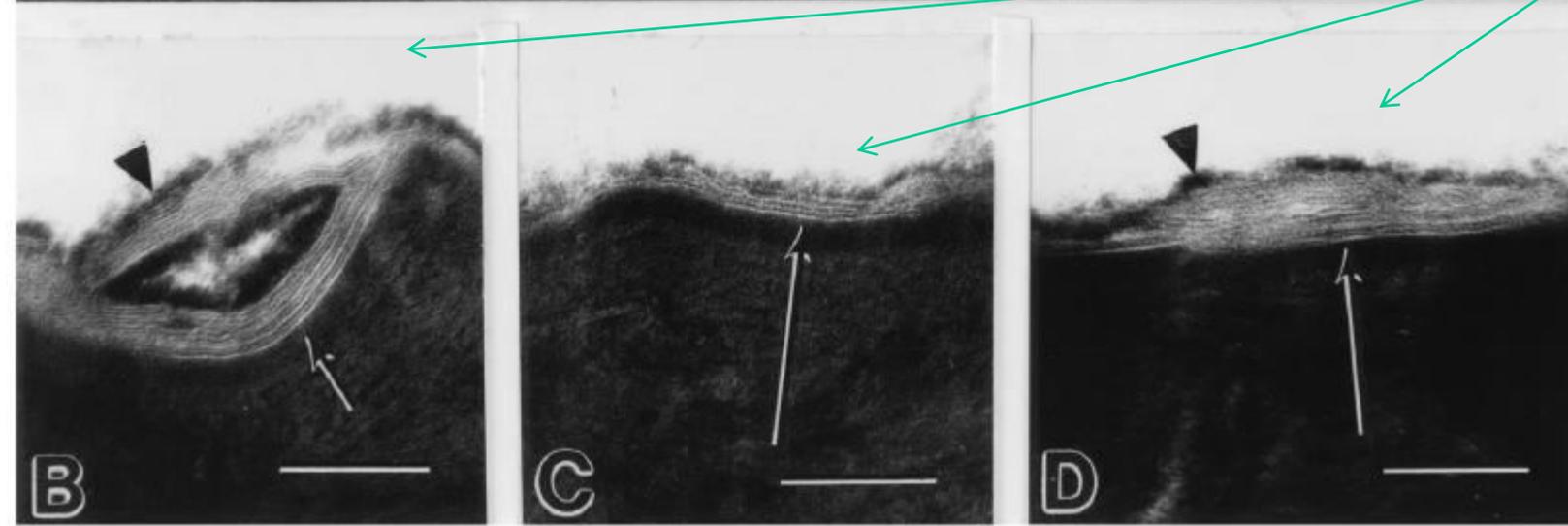
Chamlin SL, . *J Am Acad Dermatol* 2002;47:198-208.

AD stratum corneum with standard moisturizer



Improved barrier function correlates with appearance of membrane bilayer structures in stratum corneum (SC).

After application of the ceramide-dominant preparation for 6 weeks, extracellular lamellar bilayers appear in foci throughout SC (B-D, arrows). Bars 0.01 μ m.



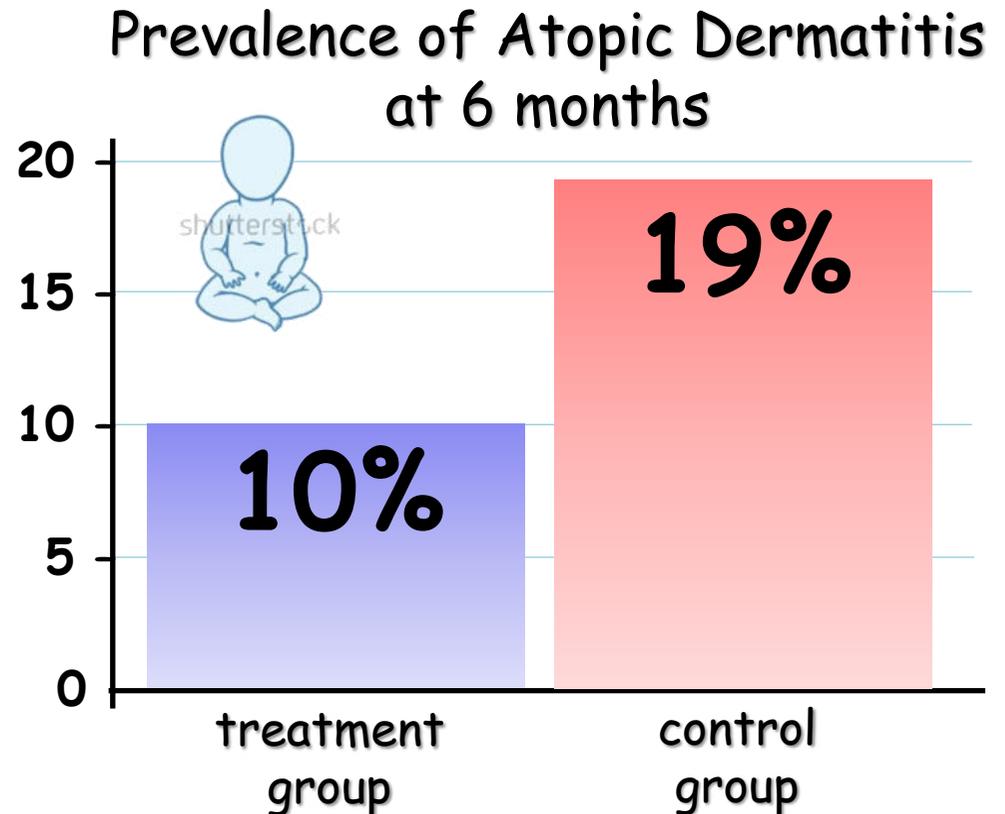
A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study.

Lowe AJ, Br J Dermatol. 2018 Jan;178(1):e19-e21.

✓ twice-daily application of a ceramide-dominant emollient (EpiCeram™) for the first 6 months of life in 80 infants

✓ parents of infants in the intervention group were shown how to apply approximately 6 g of EpiCeram to the full skin surface of their child twice per day.

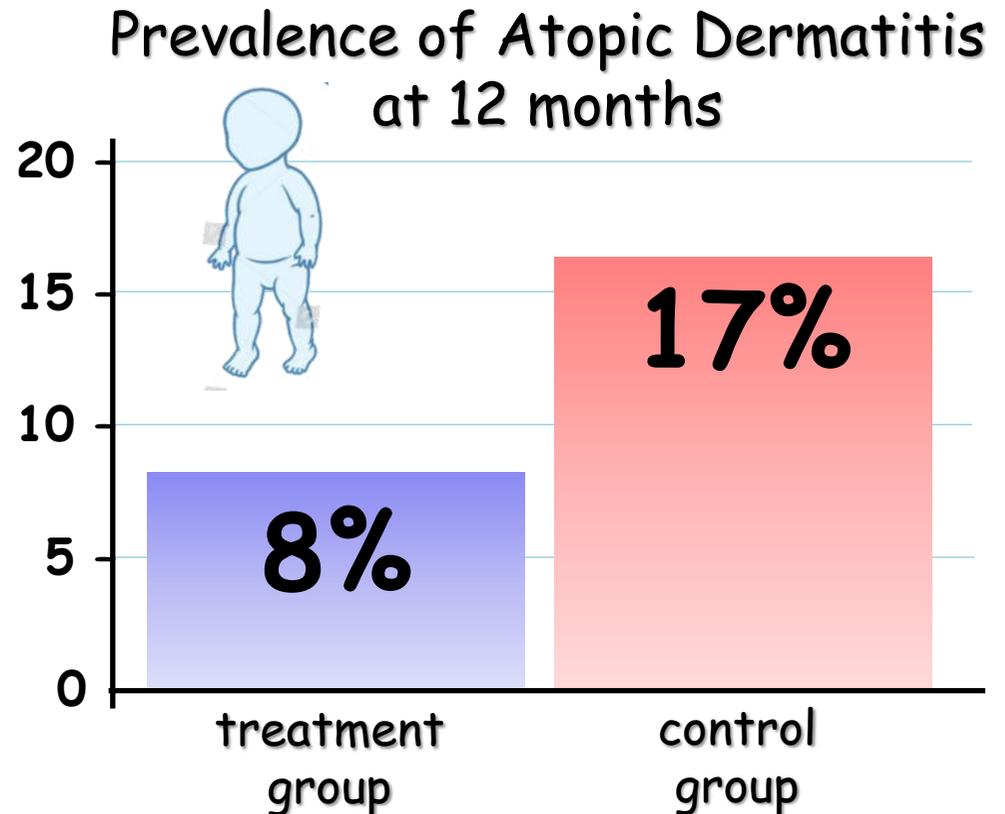
✓ Treatment was to commence within the first 3 weeks.



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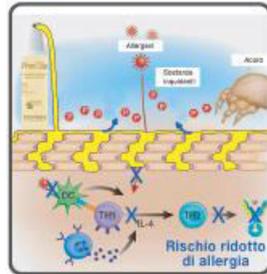


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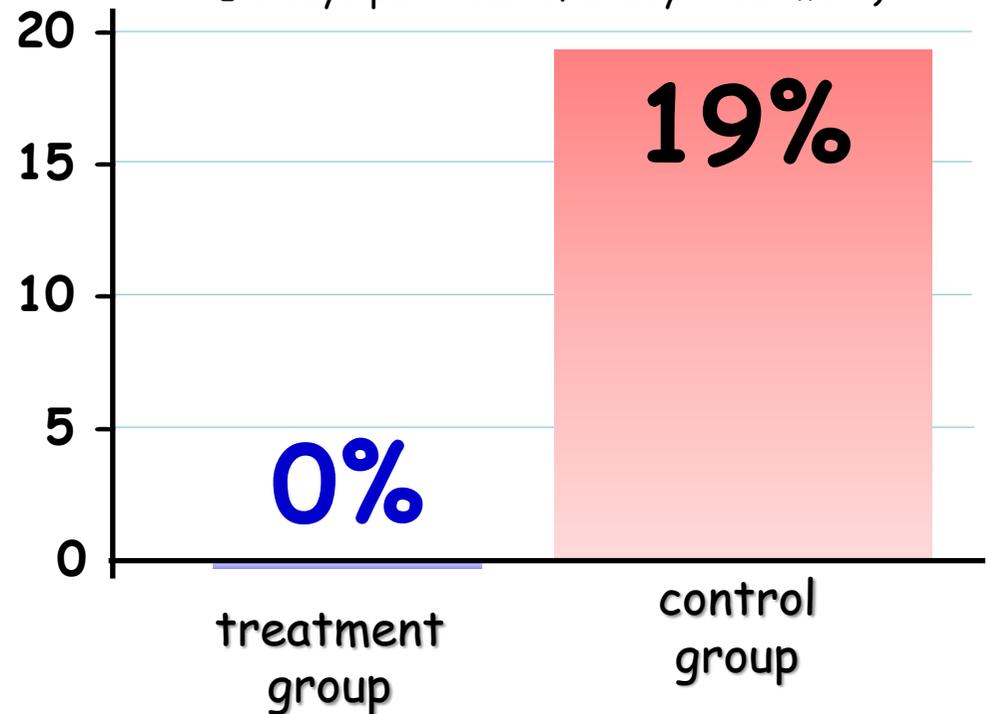
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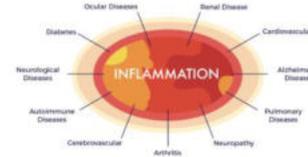
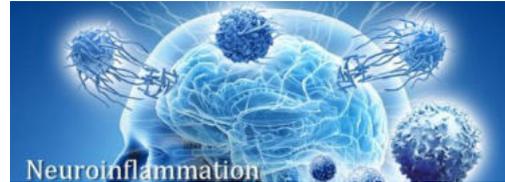
✓ Treatment was to commence within the first 3 weeks.

Prevalence of food sensitization at 12 months in the per protocol analyses (only including infants who received ≥ 5 days per week of study treatment)



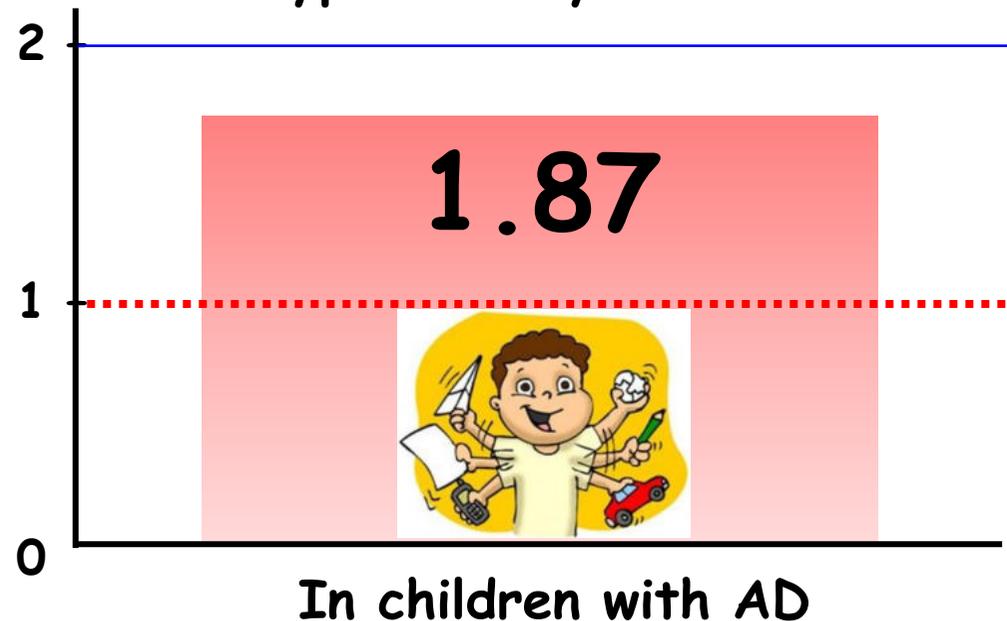
Mental health comorbidity in patients with atopic dermatitis

Yaghmaie P, JACI 2013;131:428-33



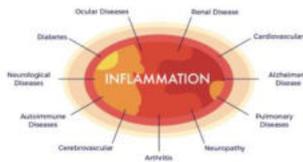
- ✓ 92642 noninstitutionalized children aged 0 to 17 years.
- ✓ Lifetime prevalence of provider-diagnosed **mental health conditions** for those with and without a history of AD.

OR of having attention deficit hyperactivity disorder

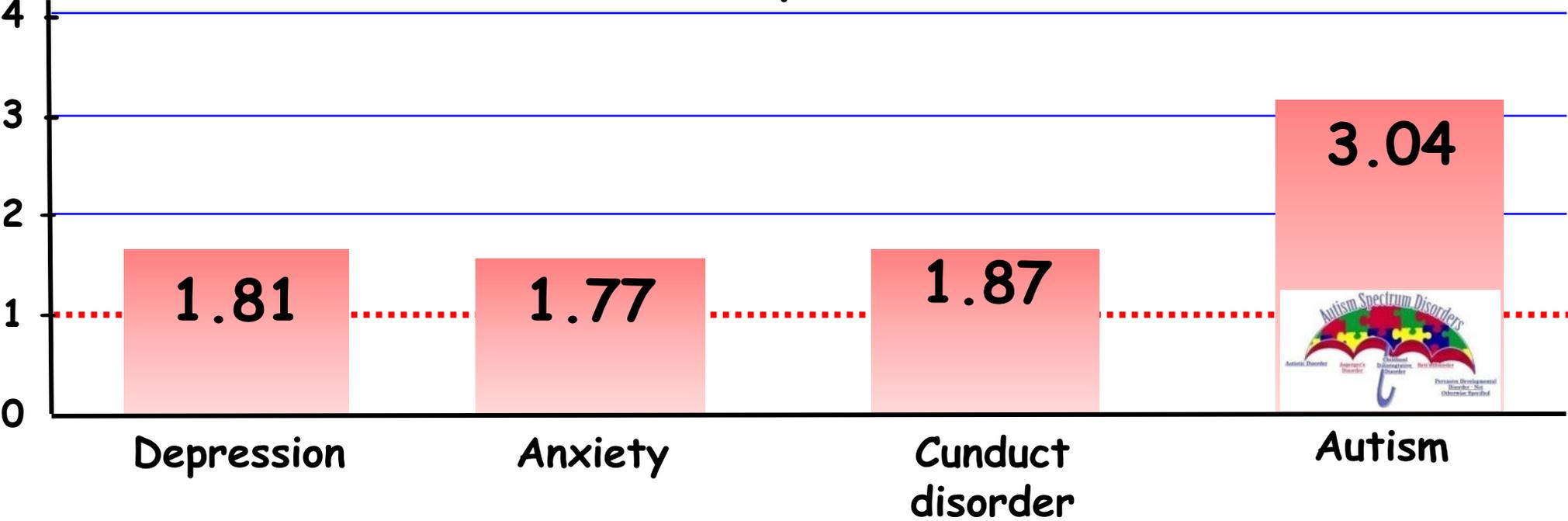


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In children with Atopic Dermatitis OR for



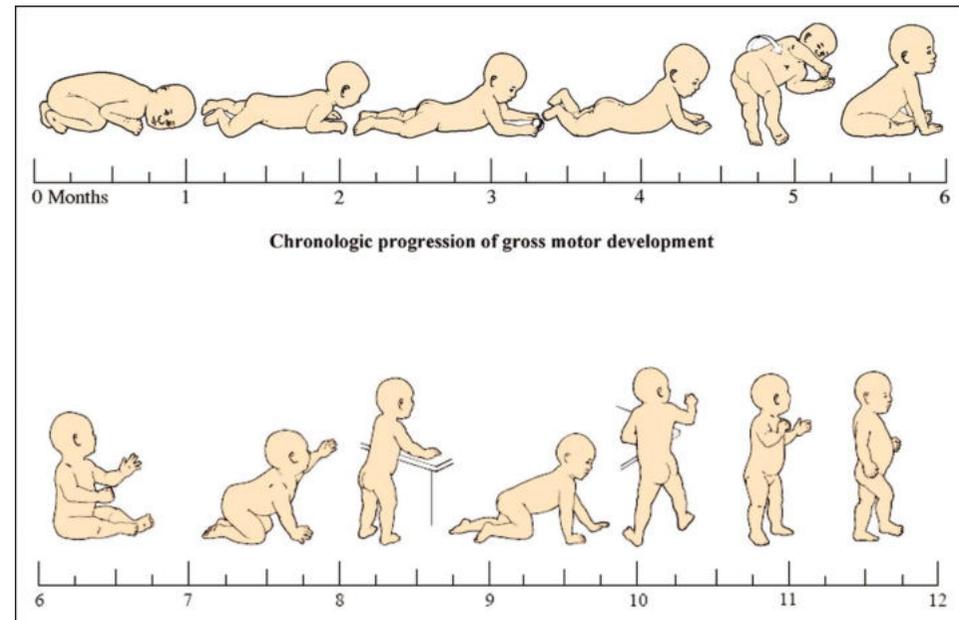
Allergic disease in the first year of life is associated with differences

in subsequent neurodevelopment and behaviour.

Meldrum SJ, Prescott SL. Early Hum Dev. 2012 Jul;88(7):567-73.

- ✓ 324 infants with a maternal history of allergic disease
- ✓ at 12 months of age allergen sensitisation, eczema, IgE-mediated and food allergy,
- ✓ at 18 neurodevelopmental outcomes by:
 - the Bayley Scales of Infant Toddler Development III Edition,
 - the Achenbach Child Behaviour Checklist and
 - the Macarthur Scales of Infant Toddler Development.

Children with **any diagnosed allergic disease at 12 months** had evidence of:
reduced motor scores ($p=0.016$),



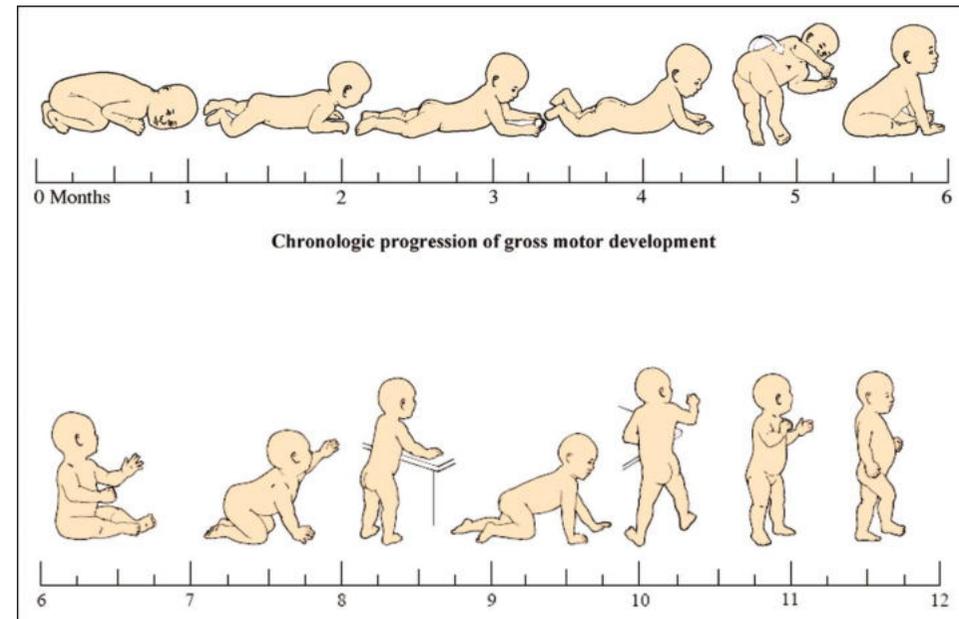
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this was most apparent for diagnosis of eczema ($p=0.007$).

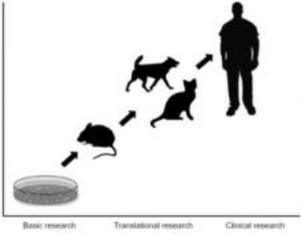
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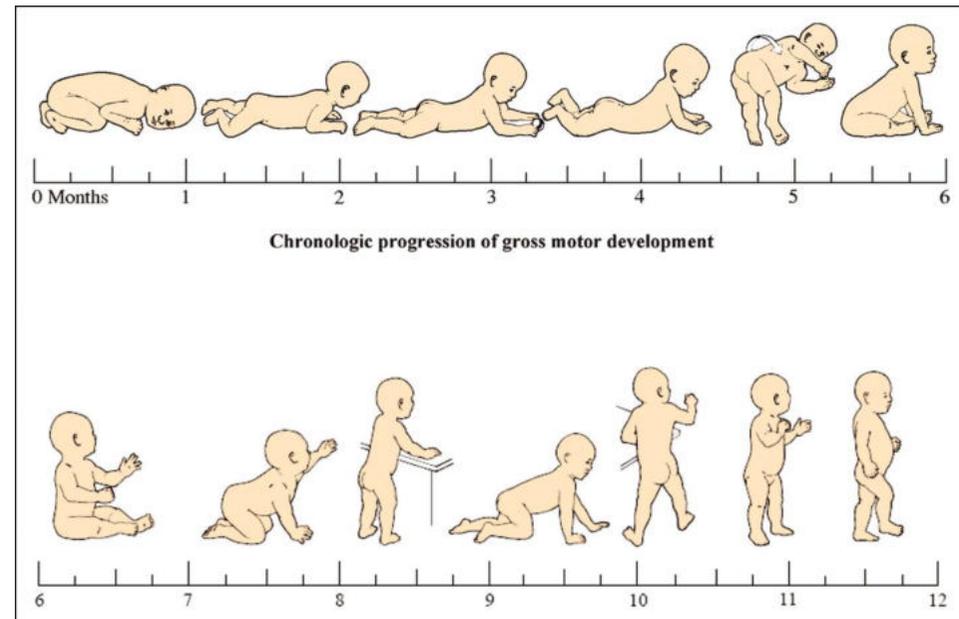
Meldrum SJ, Prescott SL. *Early Hum Dev.* 2012 Jul;88(7):567-73.



The importance of immune activation in neurological outcomes are further demonstrated in animal models where blocking effects of cytokines (such as **TNF α** or **IL-1**) reduces neurological injury during inflammatory events



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Allergic disease in the first year of life is associated with differences

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October 10, 2021

PubMed.gov

551 results

TNF- α inhibition and curcumin

Advanced

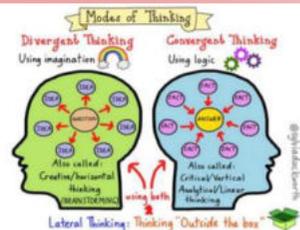
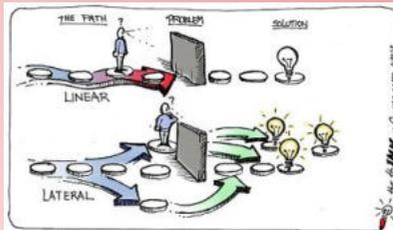


PubMed.gov

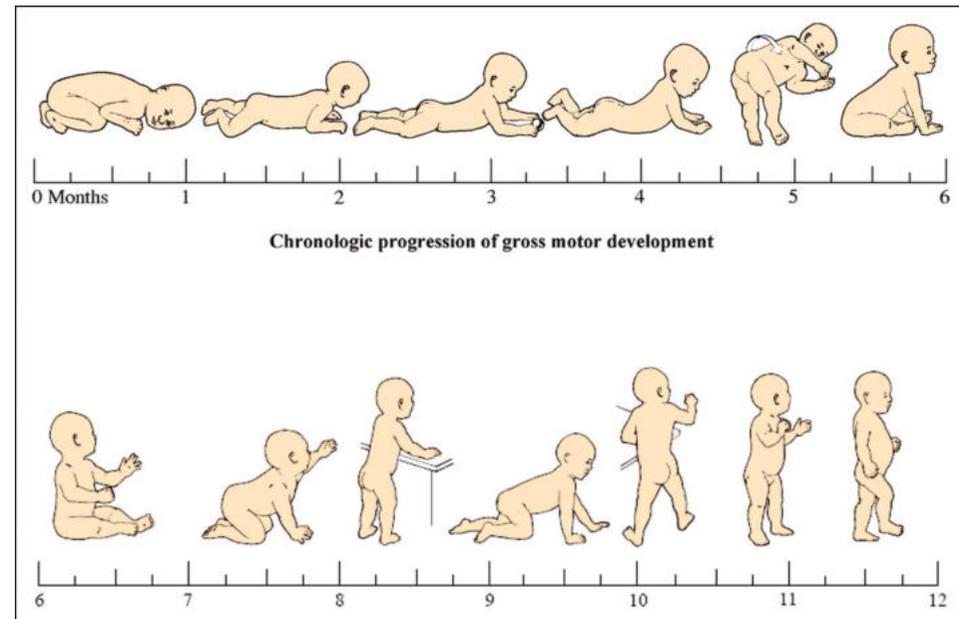
465 results

TNF- α inhibition and resveratrol

Advanced



Children with **any diagnosed allergic disease at 12 months** had evidence of: **reduced motor scores** ($p=0.016$),



Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour.

Meldrum SJ, Prescott SL. *Early Hum Dev.* 2012 Jul;88(7):567-73.

October 10, 2021

PubMed.gov 302 results

IL-1 inhibition and curcumin

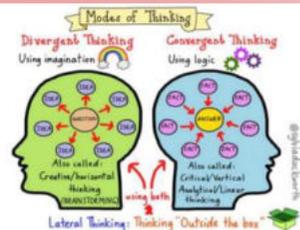
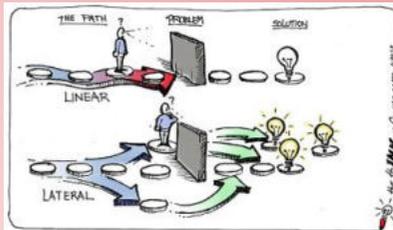
Advanced



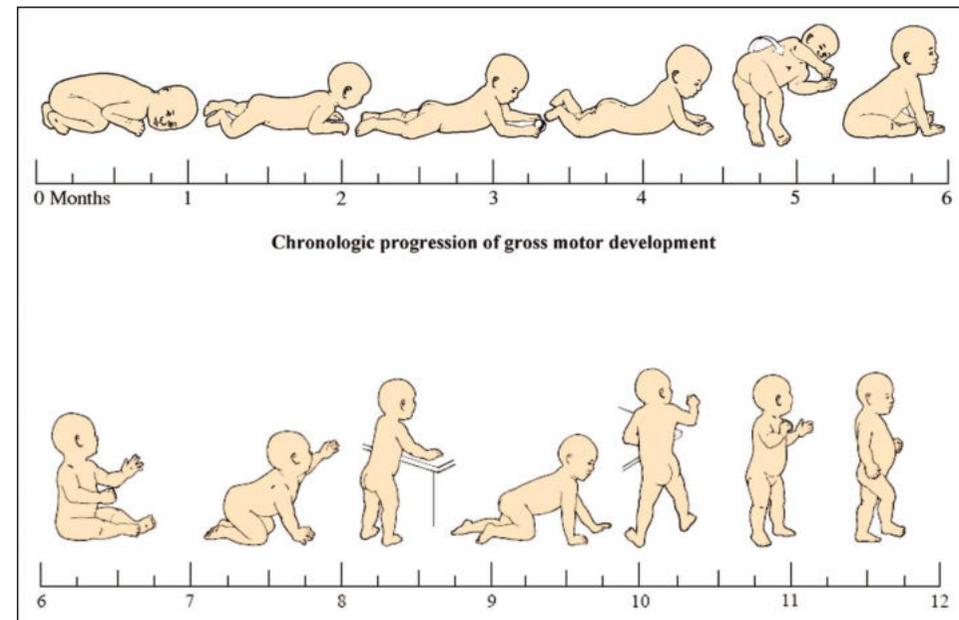
PubMed.gov 248 results

IL-1 inhibition and resveratrol

Advanced



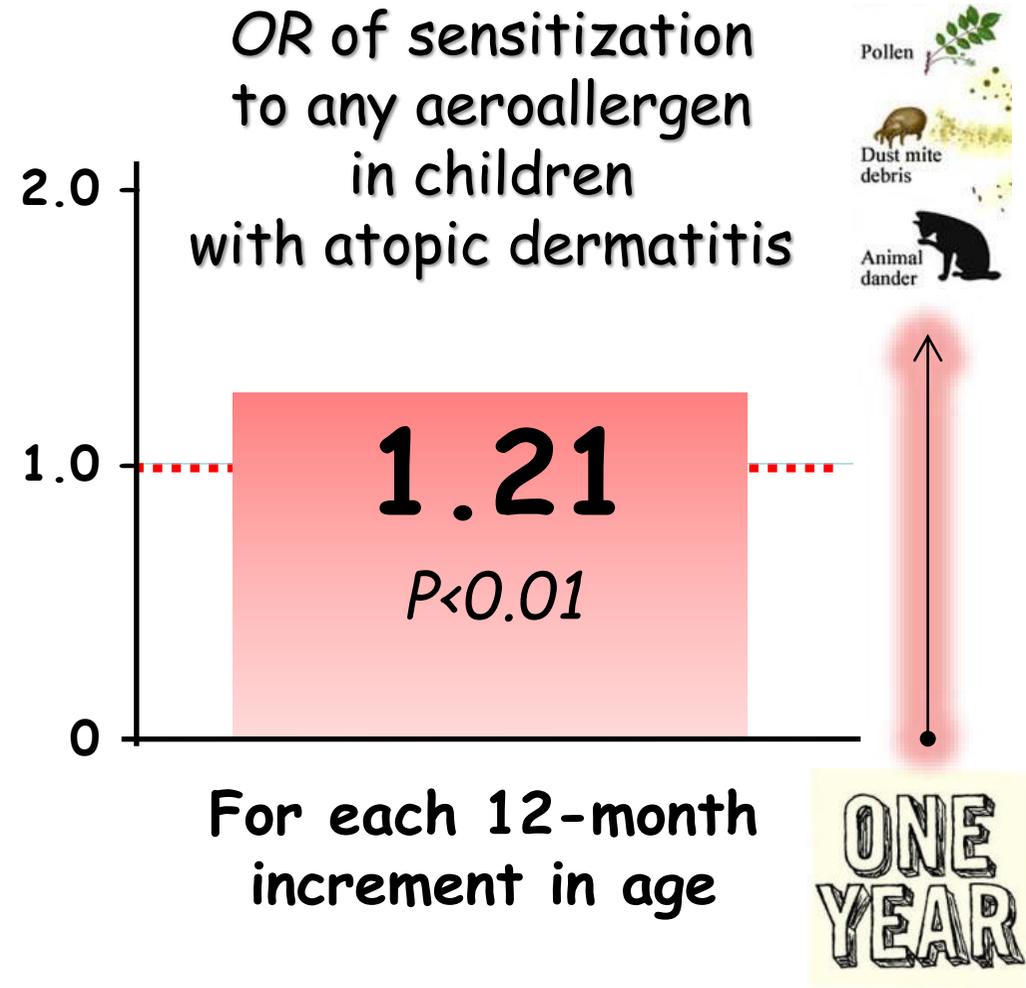
Children with **any diagnosed allergic disease at 12 months** had evidence of: **reduced motor scores** ($p=0.016$),



Sensitization to food and inhalant allergens in relation to age and wheeze among children with atopic dermatitis

Wisniewski JA, Clin Exp Allergy. 2013 Oct;43(10):1160-70.

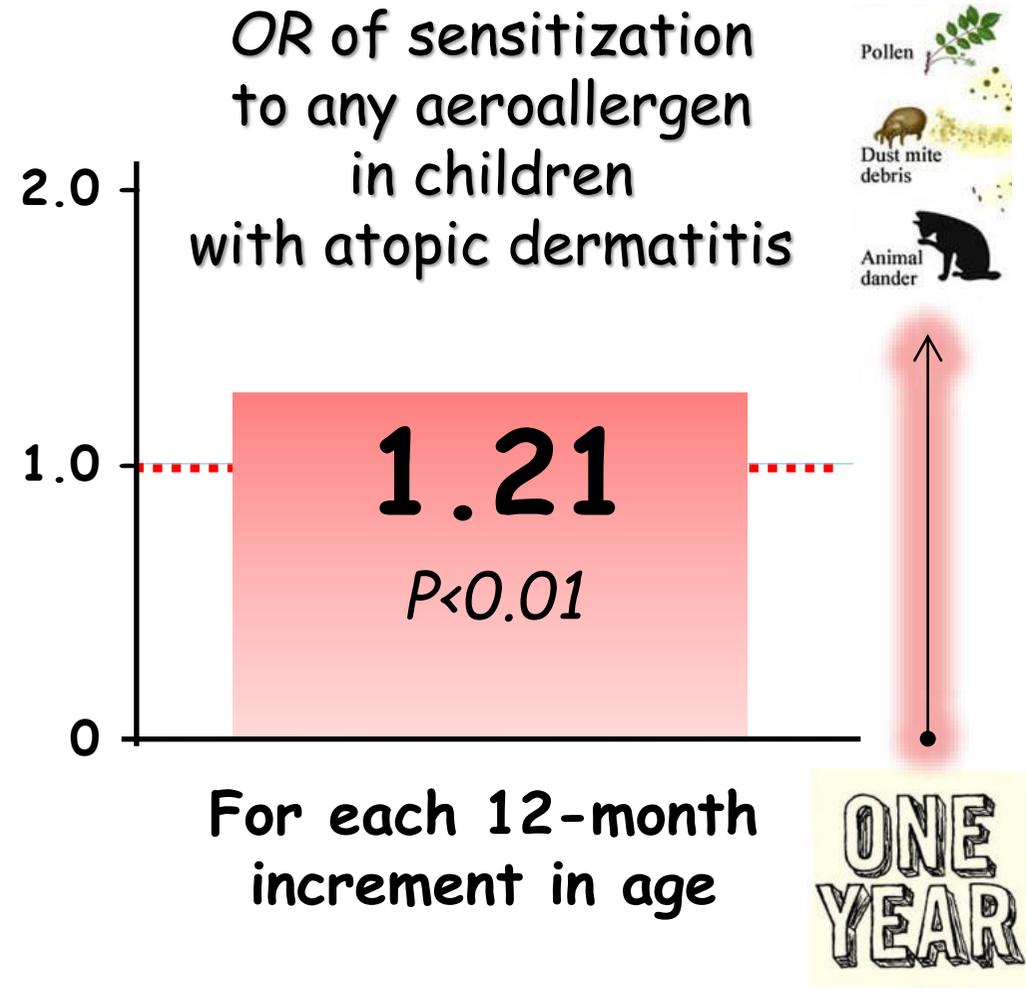
- ✓ IgE antibodies to food and inhalant allergens
- ✓ children with active atopic dermatitis (AD) (5 mo.-15 yrs, n = 66), with and without history of wheeze



Sensitization to food and inhalant allergens in relation to age and wheeze among children with atopic dermatitis

Wisniewski JA, Clin Exp Allergy. 2013 Oct;43(10):1160-70.

✓ With the largest effect observed for dust mite (OR = 1.56, $P < 0.001$)



Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years.

Nickel R. J *Allergy Clin Immunol.* 1997 May;99(5):613-7.

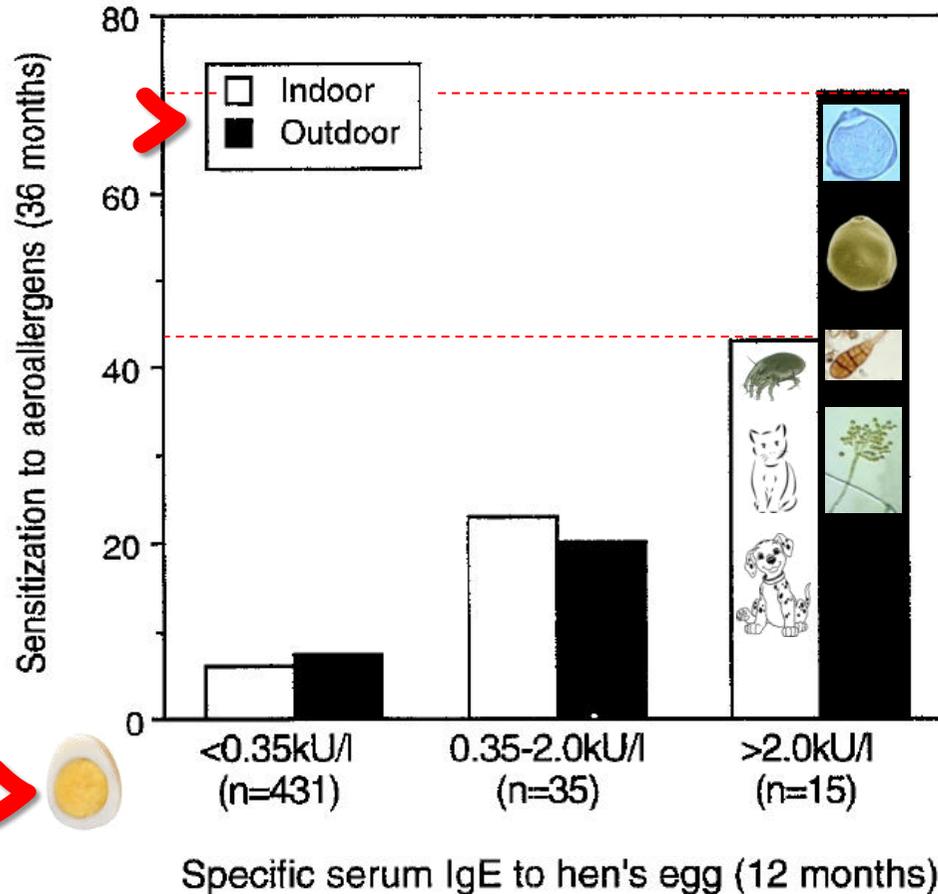


Ulrich Wahn



✓ 1314 children in 5 German cities followed up from birth (1990) to the age of 3 years.

✓ Total serum IgE and sIgE antibodies to common food and inhalant allergens from cord blood and at follow-up visits at the ages of 1, 2, and 3 years



Prevalence of sIgE to at least one indoor and/or outdoor allergens at age 36 months according to different concentrations of hen's egg-sIgE at age 12 months.



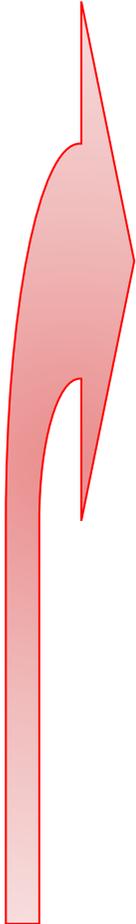
Long-lasting sensitization to food during the first two years precedes allergic airway disease.

The MAS Study Group, Germany.

Kulig M, Pediatr Allergy Immunol. 1998 May;9(2):61-7.



Ulrich Wahn



Children persistently sensitized to food (persistently sensitized for > 1 year) had:

persistently

- 1) a **3.4** fold higher risk of developing allergic rhinitis and
- 2) a **5.5** fold higher risk of developing asthma

than infants who were only transiently food sensitized.

Transiently

✓ A birth cohort of 508 children

✓ sIgE to food and inhalant allergens at 1 and 2 years of age

✓ occurrence of subsequent allergic airway diseases until 5 years of age

Long-lasting sensitization to food during the first two years precedes allergic airway disease.

The MAS Study Group, Germany.

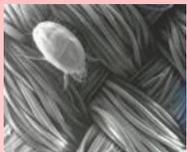
Kulig M. Pediatrics Allergy Immunol. 1998 May;9(2):61-7.



Ulrich Wahn



Persistently food-sensitized children especially in atopic families have to be regarded as a high-risk group and should be considered for preventive measures against respiratory atopy.



Children persistently sensitized to food (persistently sensitized for > 1 year) had:

persistently

- 1) a **3.4** fold higher risk of developing allergic rhinitis and
- 2) a **5.5** fold higher risk of developing asthma

than infants who were only transiently food sensitized.

Transiently

Early life risk factors for adult asthma: a birth cohort study of subjects at risk.

Rhodes HL. Holgate ST. *J Allergy Clin Immunol.* 2001 Nov;108:720-5.

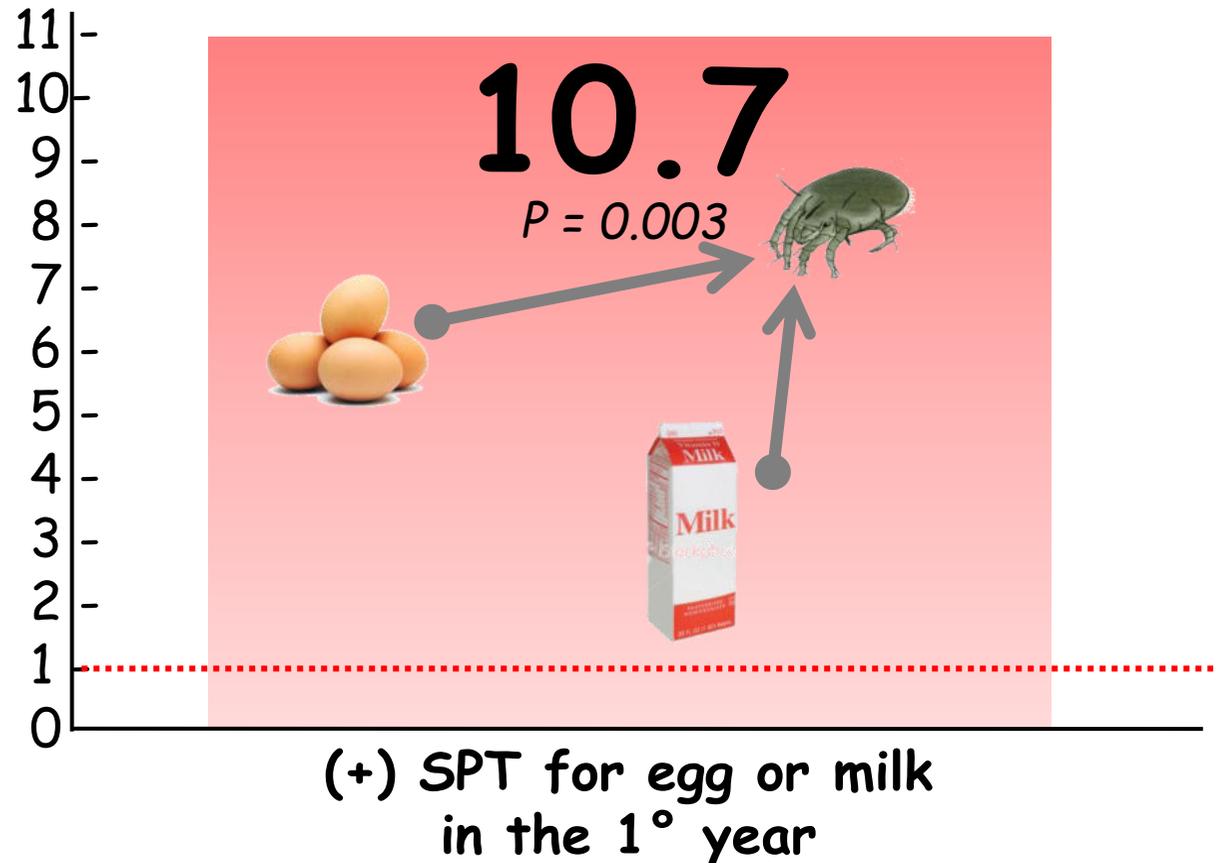


- ✓ Cohort study of 100 babies of atopic parents

- ✓ Followed
 - at 5 yrs,
 - at 11 yrs,
 - at 22 yrs



OR for adult asthma

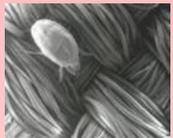


Early life risk factors for adult asthma: a birth cohort study of subjects at risk.

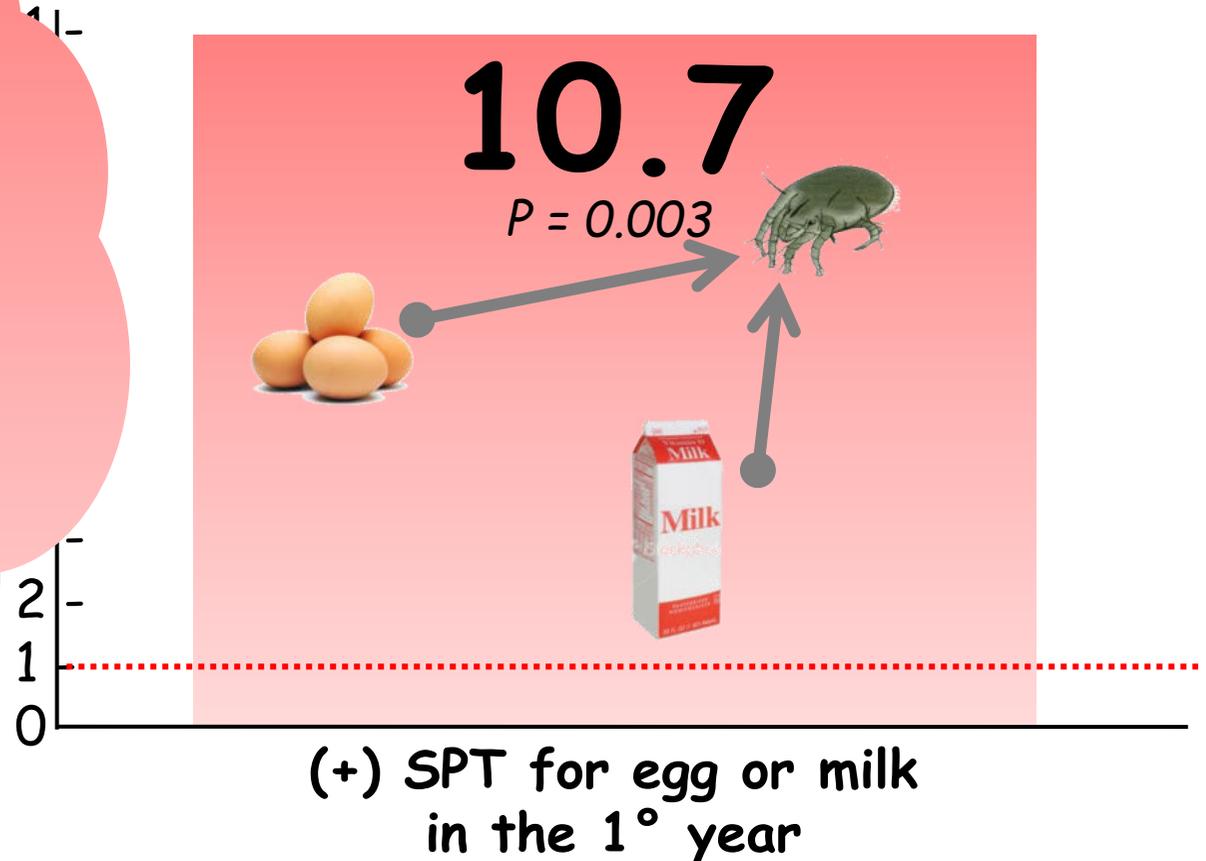
Rhodes HL. Holgate ST. *J Allergy Clin Immunol.* 2001 Nov;108:720-5.



✓ Mite allergen avoidance measures and optimal skin care should be started early in these subjects



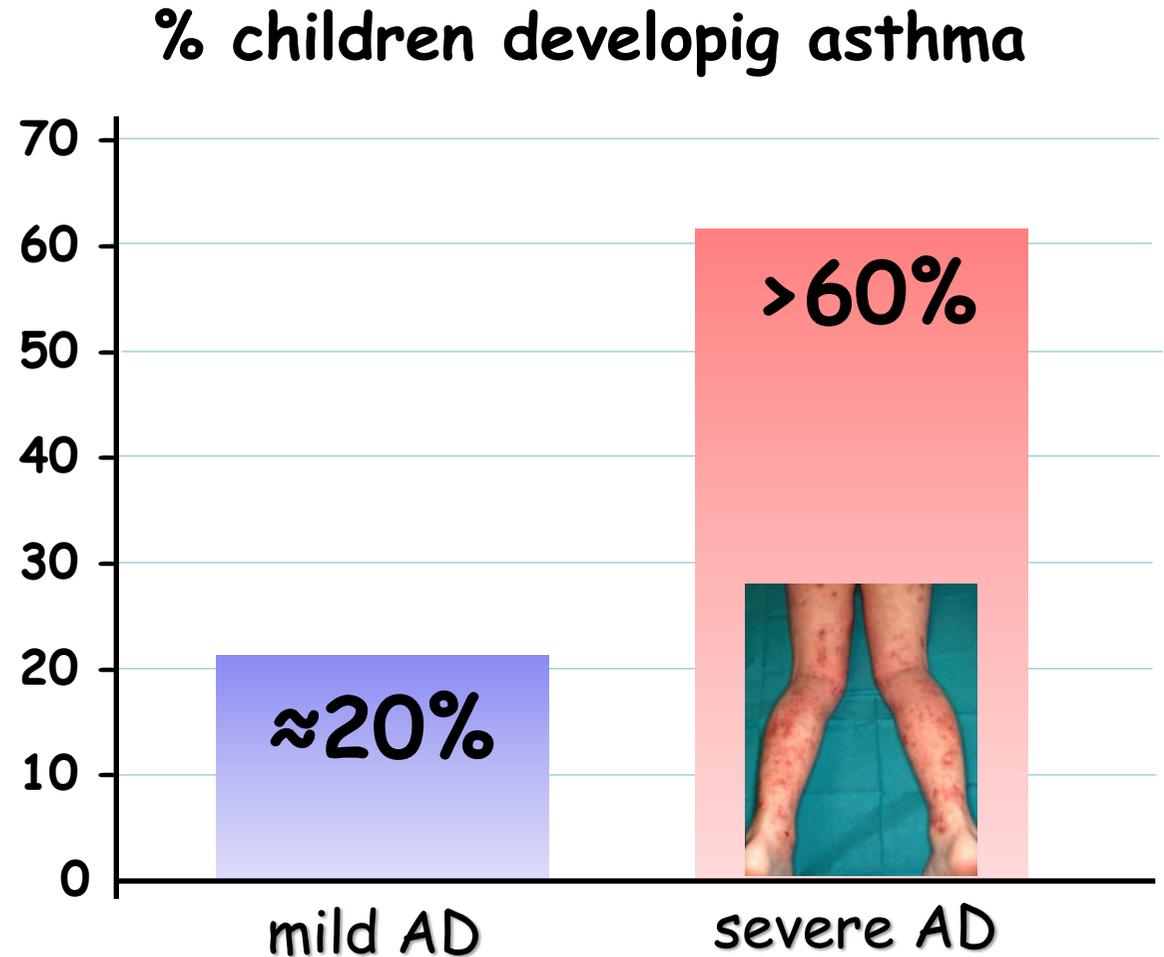
OR for adult asthma



Severity of Atopic Dermatitis and Asthma Development

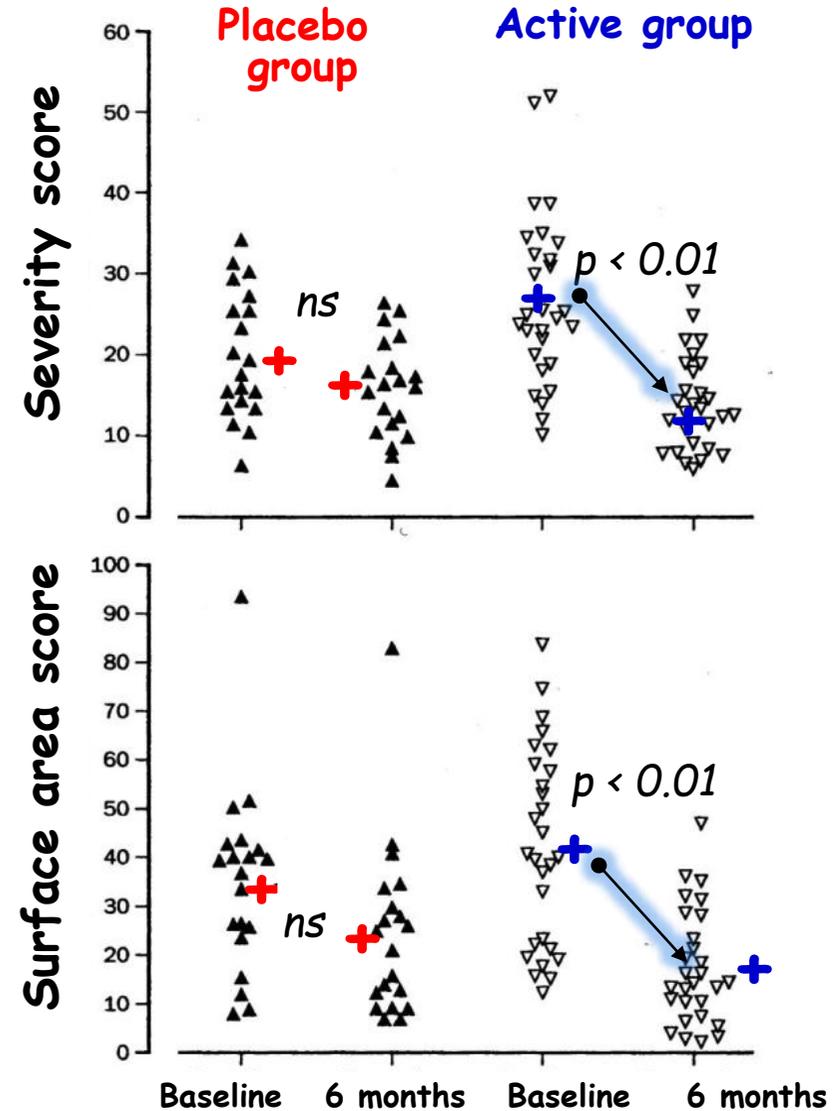
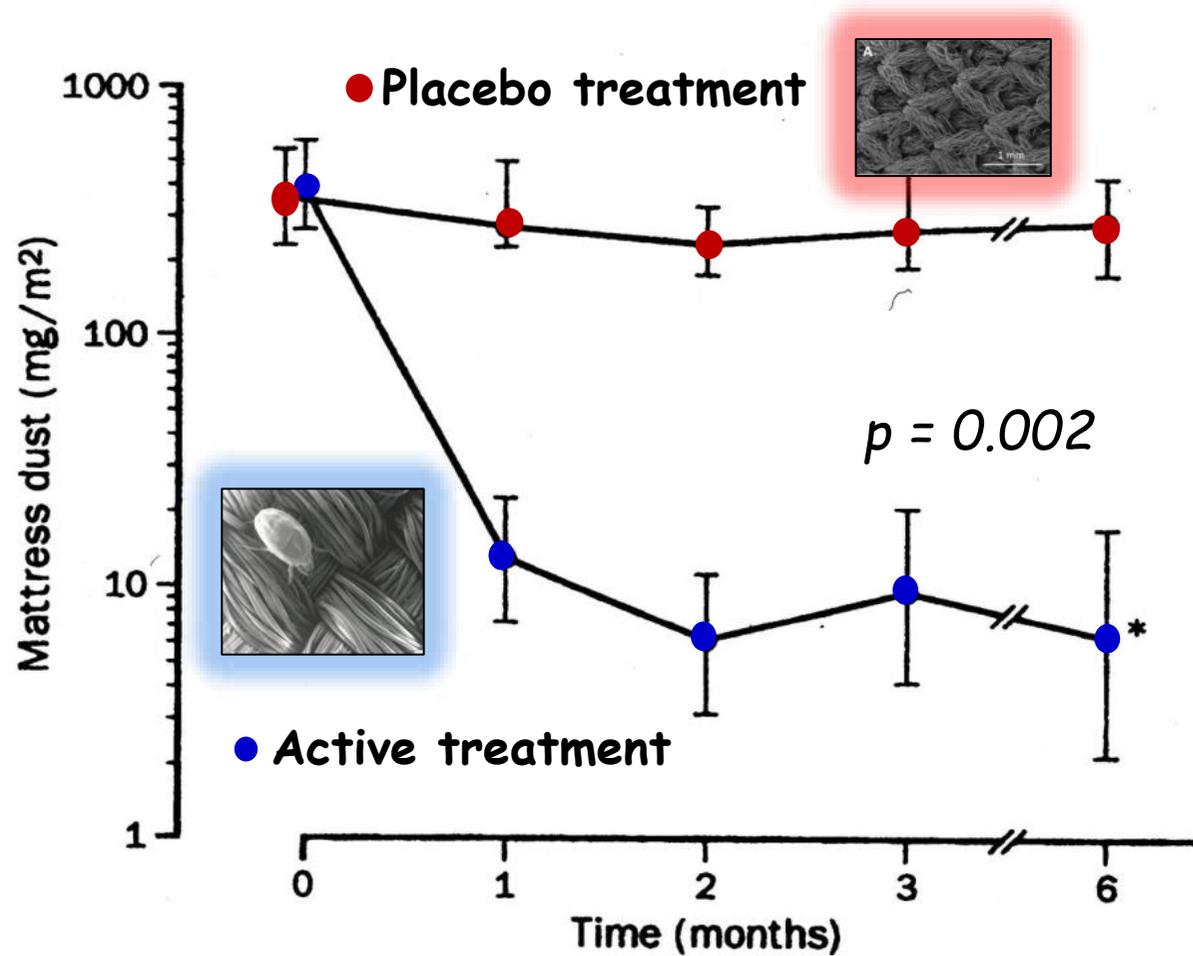
➤ *Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis: a prospective follow-up to 7 years of age. Allergy. 2000;55:240-245.*

➤ *Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62:758-766.*



Activity of atopic dermatitis can be greatly reduced by effective HDM avoidance

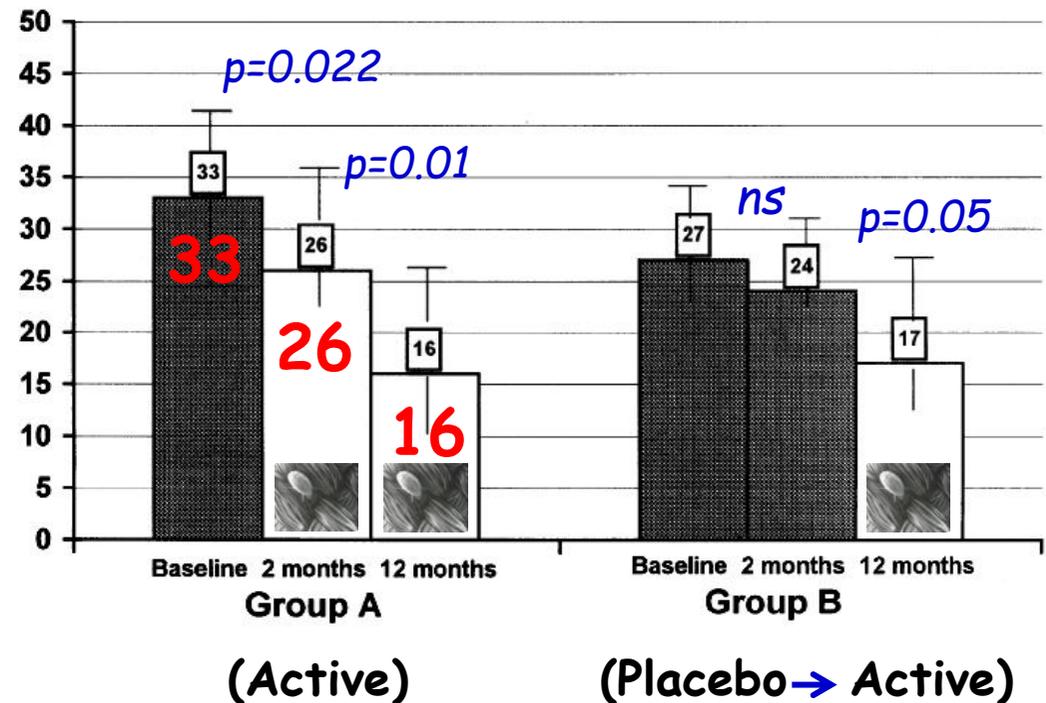
Tan BB, Lancet 1996;347:15-8.



Effect of house dust mite avoidance measures in children with atopic dermatitis. Ricci G, Br J Dermatol 2000;143:379

- ✓ 41 children (mean age 3-9 years) with AD.
- ✓ Severity Scoring of AD (SCORAD) index.
- ✓ A placebo-controlled trial of 2 months duration, mite allergen avoidance measures (encasing mattresses and pillows) recommended to group A patients, but not to group B.
- ✓ In the second part of the study, environmental avoidance measures were recommended to initial control group B patients also.
- ✓ Follow-up: 1 yr.

Effect of house dust mite (HDM) avoidance on SCORAD



Effectiveness of occlusive bedding in the treatment of atopic dermatitis--a placebo-controlled trial of 12 months' duration. Holm L, Allergy. 2001 Feb;56(2):152-8.

- Eczema severity decreased significantly in both HDM sensitive and non sensitive patients ($p < 0.001$)
- sCD30 levels were significantly reduced in both groups ($p < 0.001$)
- Patients not sensitized to HDM allergens benefited from the bedcovers as much as sensitized patients



A result which could be due to a reduction in beds of:

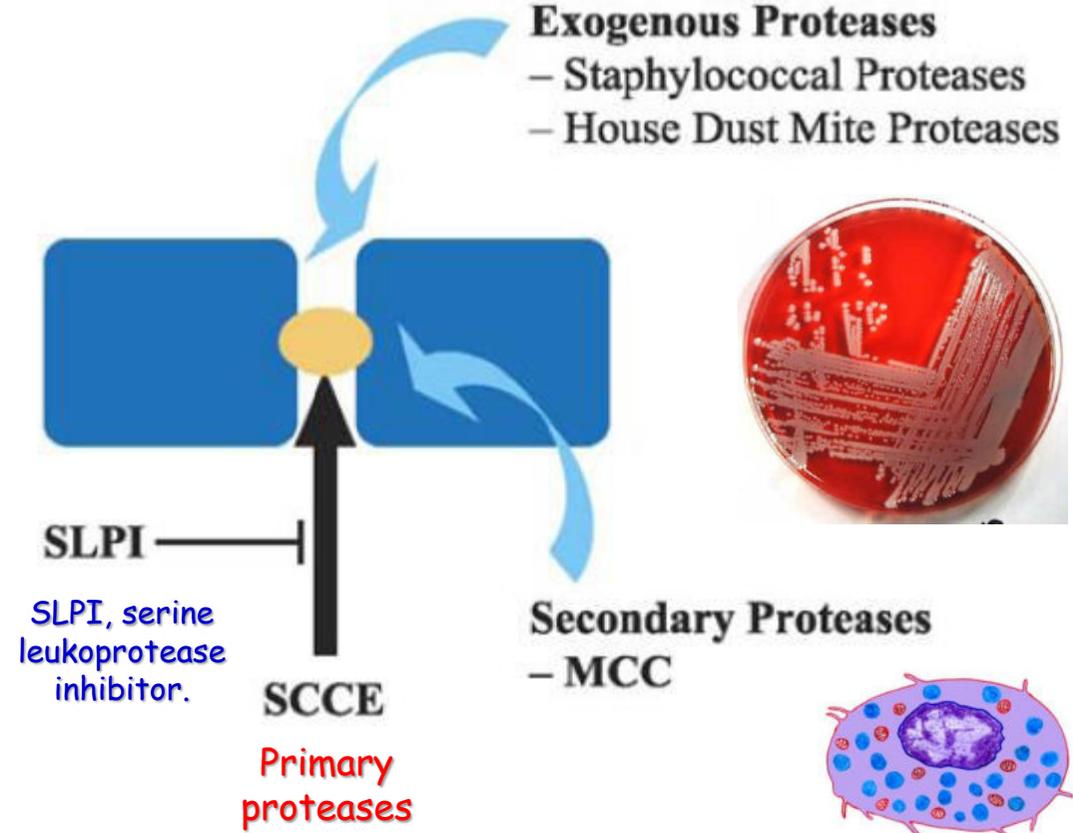
- other important allergens
- supertantigens
- irritants and enzymes



"bedcovers should be part of routine treatment for AD"

Role of Epidermal Barrier Dysfunction in Atopic Dermatitis Pathogenesis. *Cork MJ, J Allergy Clin Immunol. 2006;118:3-21*

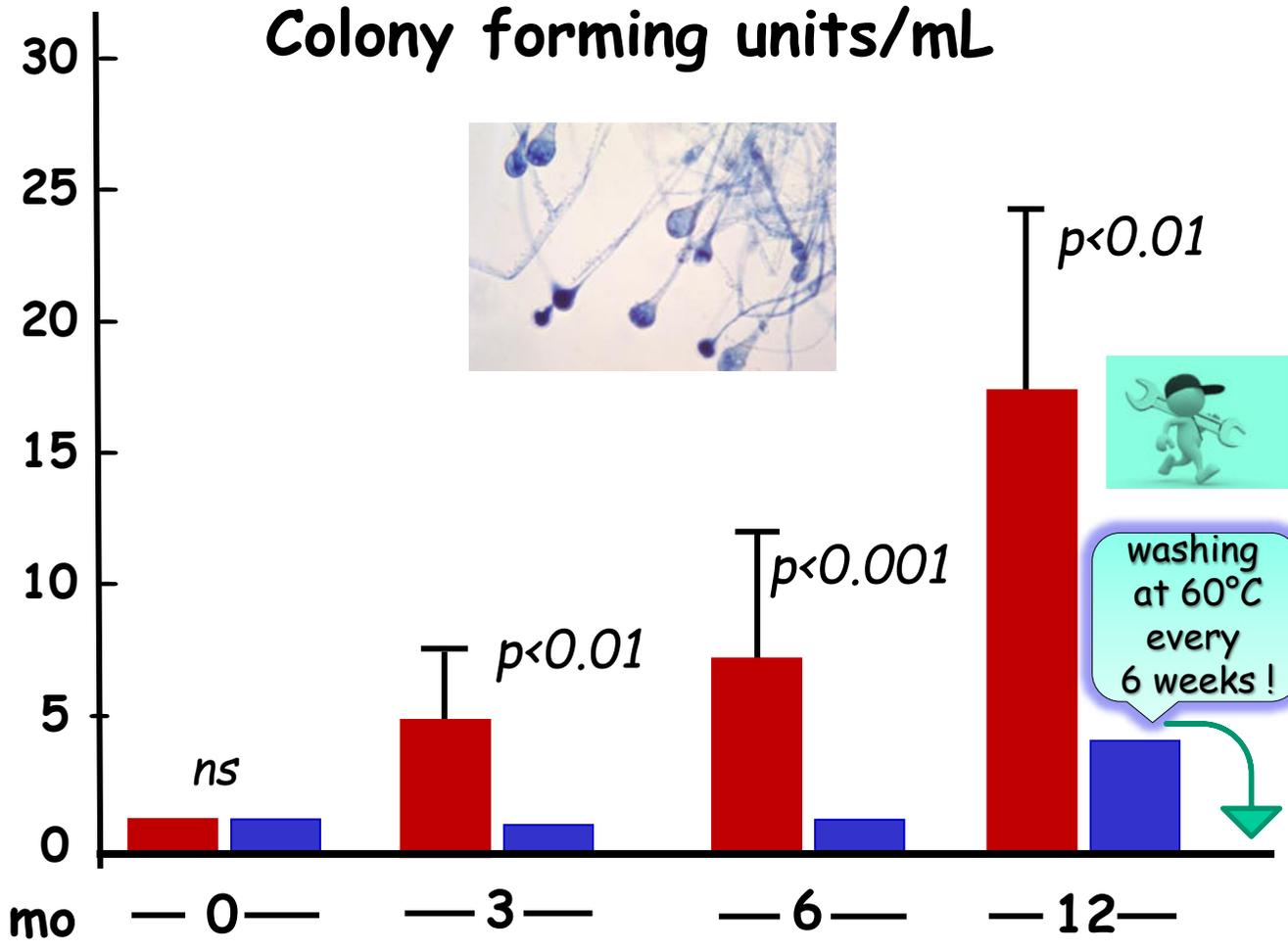
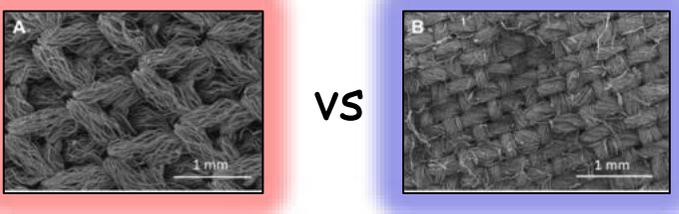
- Corneodesmosomes are not only broken down by endogenous proteases.
- Once a flare of AD has been triggered, cells within the inflammatory infiltrate produce secondary proteases, which can also break down the skin barrier eg, mast cell chymase (MCC).



- The stratum corneum is also exposed to many exogenous proteases from the environment, such as *Staphylococcus aureus* and house dust mites.

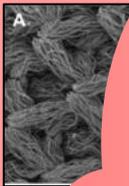
Filamentous Fungi and Yeasts on Mattresses Covered with Different Encasings. *Pitten Eur. J. Dermatol. 2001;11: 534*

- ✓ 35 cotton encase ■
- 35 synthetic encase ■
impermeable to particles > 3 μg
- ✓ All new foam mattresses
- ✓ Sampling time 3-6-12 mo



Filamentous Fungi and Yeasts on Mattresses Covered with Different Encasings. *Pitten Eur. J. Dermatol. 2001;11: 534*

✓ 35 cotton



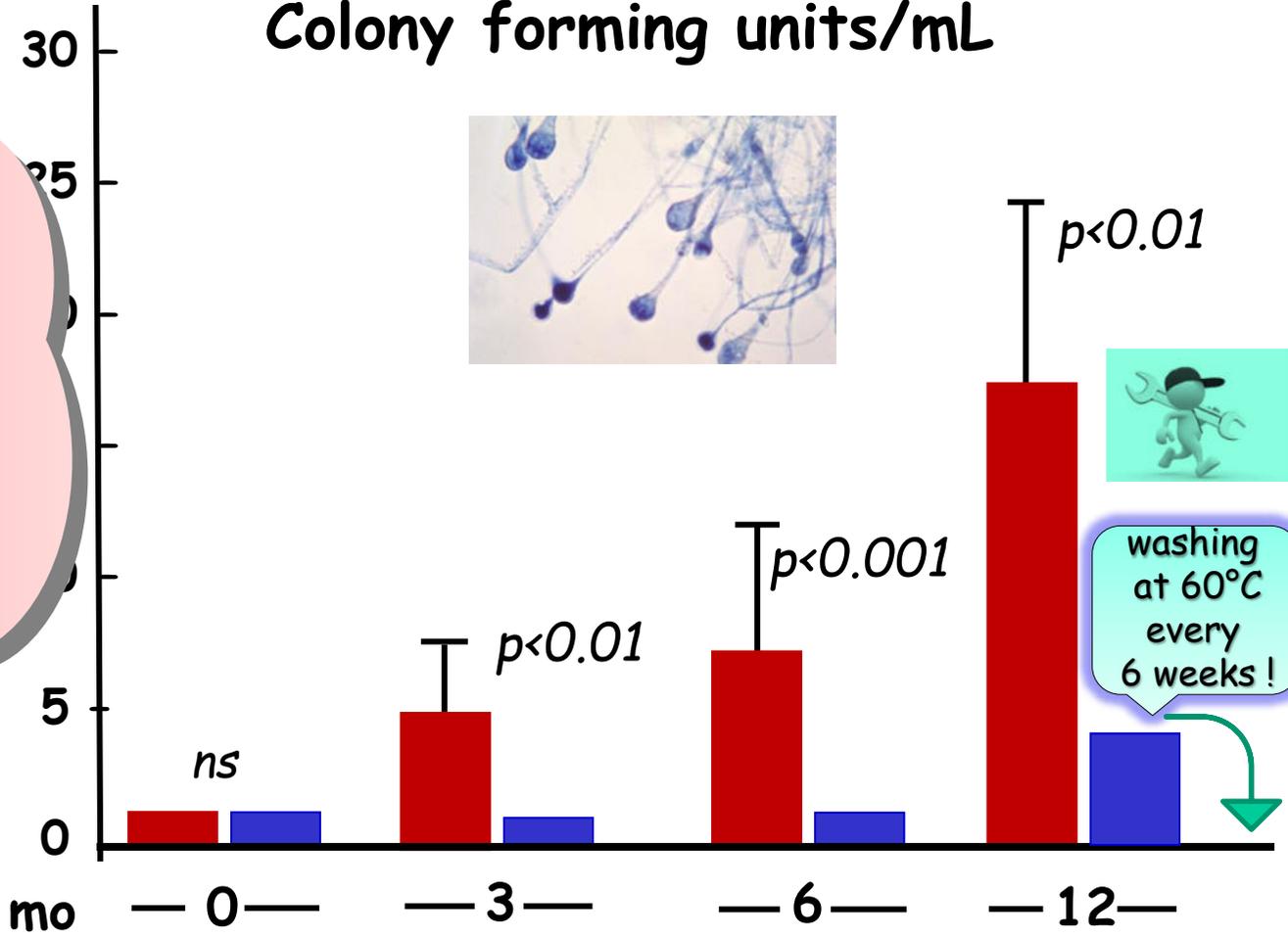
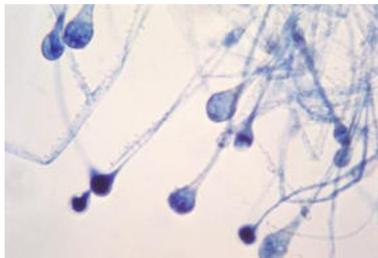
35

✓

✓ San

Mattresses covered by cotton encasing are more rapidly colonized by fungi than mattresses with synthetic encasing

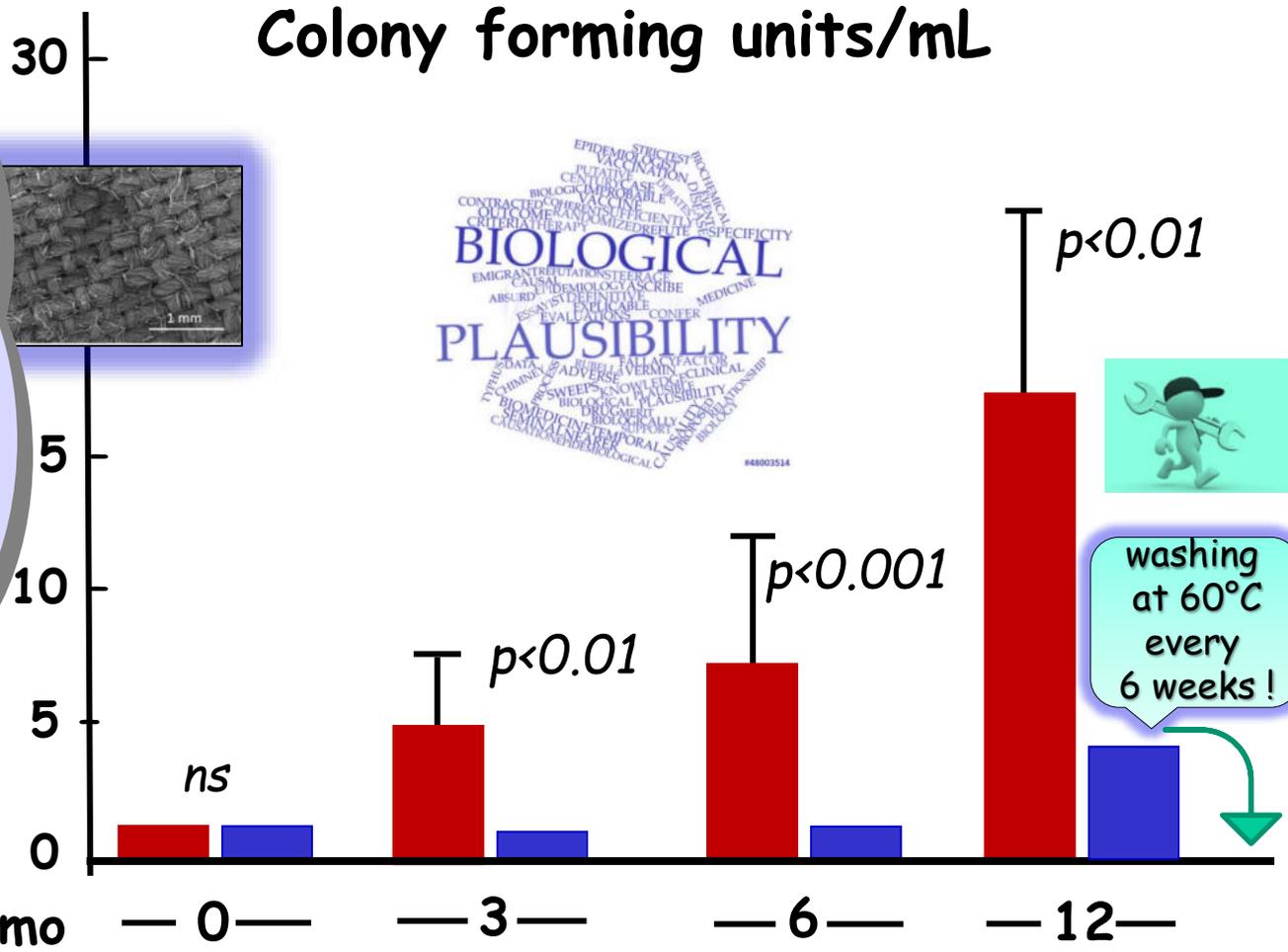
Colony forming units/mL



washing at 60°C every 6 weeks!

Filamentous Fungi and Yeasts on Mattresses Covered with Different Encasings. *Pitten Eur. J. Dermatol. 2001;11: 534*

Application of synthetic encasing is recommended as a part of an allergen avoidance strategy for patients sensitized to fungal allergens

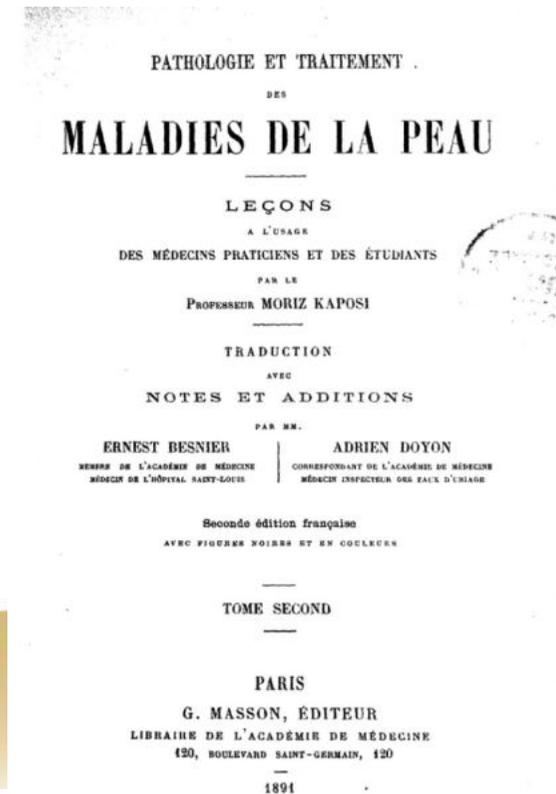



Does bathing frequency matter in pediatric atopic dermatitis?

The debate about the clinical role of bathing frequency in atopic dermatitis (AD) has been ongoing for more than 100 years.

*Hebra F. Traité des maladies de la peau.
Paris: Masson; 1872:567e572.*

*Besnier E. Traitement de l'eczéma et du psoriasis
Paris: Rueff; 1897:66e83.*



Cardona ID, Ann Allergy Asthma Immunol. 2016;117(1):9-13.

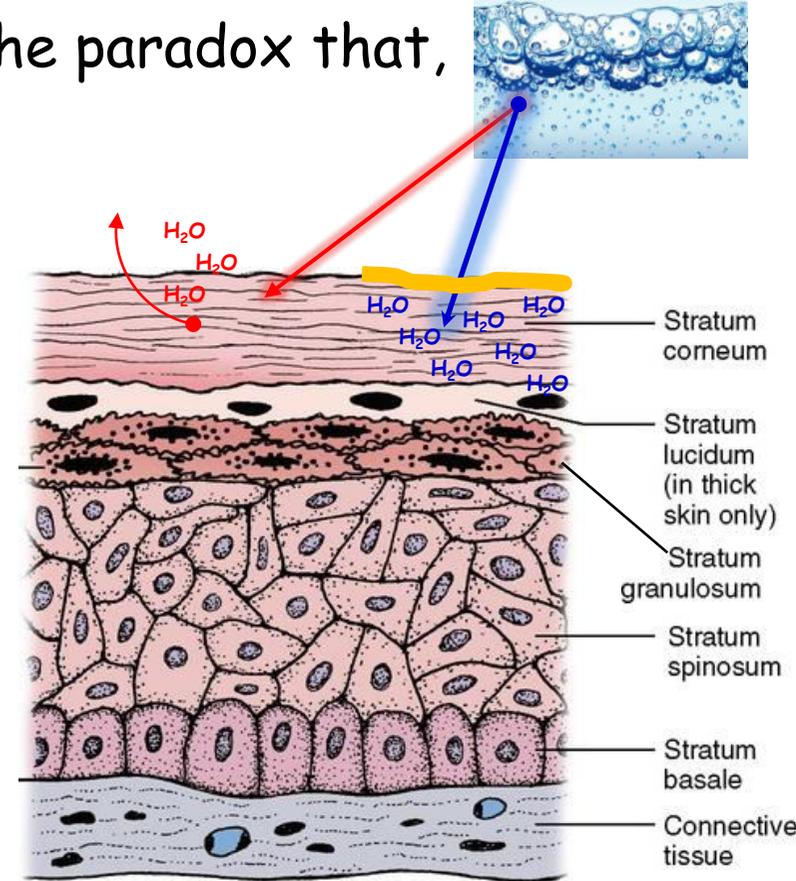
Rationale Behind Infrequent (bathing less than once a day) vs Frequent Bathing (bathing at least once a day)

Confusion about bathing frequency stems from the paradox that, for skin, water can be:

bad { bathing followed by **evaporation** causes stratum corneum contracture and fissures, thereby drying out the skin and impairing the epidermal barrier.

and

good { bathing followed by the application of a moisturizer within 3 minutes, could hydrate the skin and keep the epidermal barrier soft and flexible ("soak and smear" technique)



Rationale Behind Infrequent (bathing less than once a day) vs Frequent Bathing (bathing at least once a day)

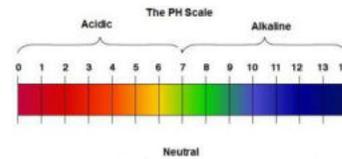
rationale behind infrequent bathing:



- Detergents can contribute to skin barrier breakdown by increasing stratum corneum pH.

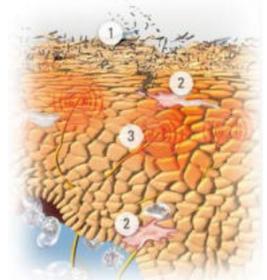
Burkhart CG. Int J Dermatol. 2008;47:1216e1217.

Cork MJ, J Allergy Clin Immunol. 2006;118:3e21.



- Routine bathing without application of an emollient can exacerbate xerosis.

Chiang C, Pediatr Dermatol. 2009;26:273e278.



- High water temperature and physical irritation from excess towel drying or scrubbing of the skin.

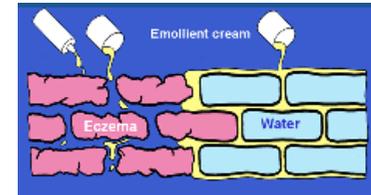
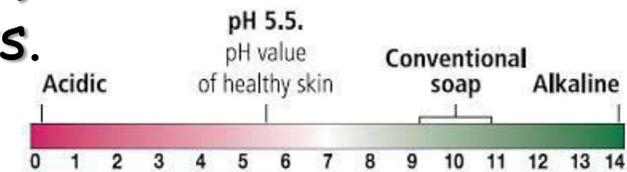
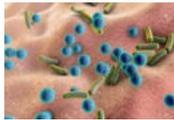
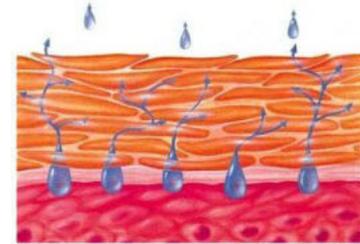


Rationale Behind Infrequent (bathing less than once a day) vs Frequent Bathing (bathing at least once a day)

rationale behind frequent bathing:



- the presence of xerosis mandates rehydration of the skin with daily baths,
- gentle bathing help to eliminate crusts and mechanically decontaminate the skin of bacteria.
- limited use of pH-balanced (5.5) skin cleansers, and cationic or nonionic surfactants.
- gentle patting dry with the immediate application of an emollient after the bath (to "seal" in the added moisture).



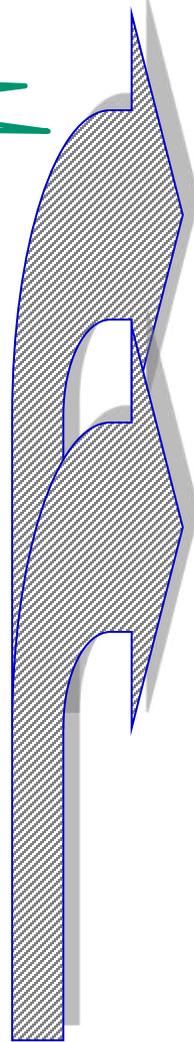
Soak and smear: A standard technique revisited.

Gutman AB, Arch Dermatol 2005;141:1556-1559

1° report of the bathing technique

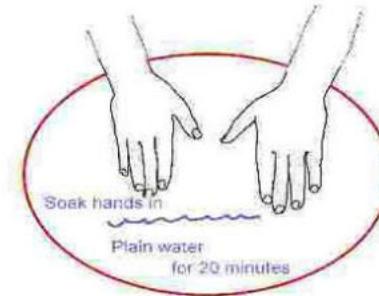
✓ 28 patients referred to a tertiary care center for refractory chronic pruritic eruptions.

✓ Intervention with a plain water 20-minute soak followed by smearing of mid-strength to high-strength corticosteroid ointment

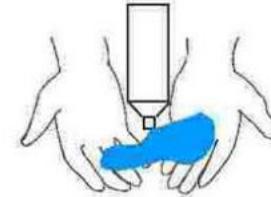


Soak and smear HANDS

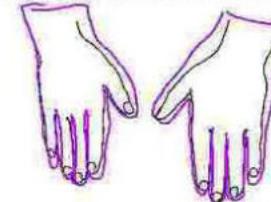
1. Soak in warm plain water for 20 minutes.



2. When the skin is still WET apply a thick layer of _____ ointment



3. Wear plastic gloves for 1-2 hours or overnight.

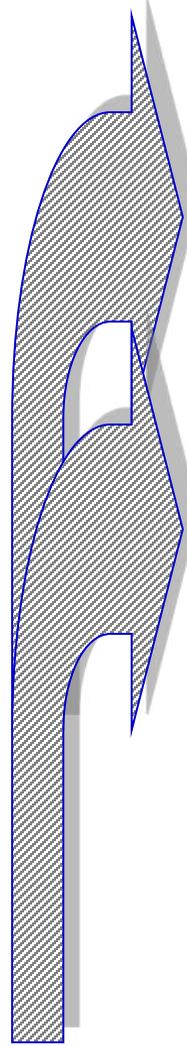


4. Apply moisturizers regularly at other times. Use a soap substitute to wash.

Soak and smear: A standard technique revisited.

Gutman AB, Arch Dermatol 2005;141:1556-1559

- ✓ 28 patients referred to a tertiary care center for refractory chronic pruritic eruptions.
- ✓ Intervention with a plain water 20-minute soak followed by smearing of mid-strength to high-strength corticosteroid ointment



- 1) This method led to clearing or dramatic improvement.
- 2) Hydration for 20 minutes before bedtime followed by ointment application to wet skin and alteration of cleansing habits is an effective method for caring for several common skin conditions.

Soak and smear: A standard technique revisited.

Gutman AB, Arch Dermatol 2005;141:1556-1559



A patient with psoriatic hand involvement before treatment (A and B). The patient was using clobetasol ointment at night with vinyl glove occlusion and frequent moisturization and cream in the morning.

Same patient four weeks after treatment. **The only change to the patient's regimen was to add a 20-minute plain water soak before the nighttime ointment application.**



Bathing in Atopic Dermatitis

The Diaper Area Analogy: Explaining Why the Wet Method Works

"Atopic dermatitis likes dry skin, but not moist and hydrated skin. Look at the area covered by your baby's diaper.

Feel how soft and supple it is? And notice that eczema does not occur in this area.

By bathing your baby every day and immediately applying the medications and then the moisturizer, we are trying to create the same sort of environment (a moist one) as in the diaper area on the rest of your baby's skin."

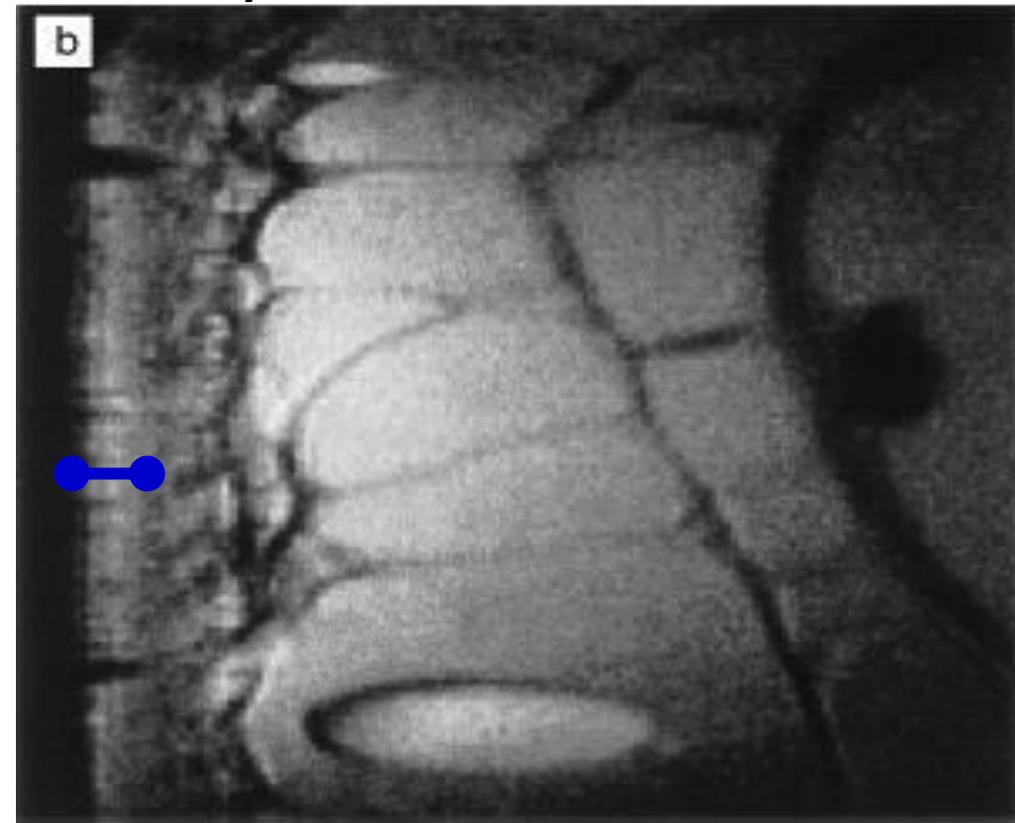
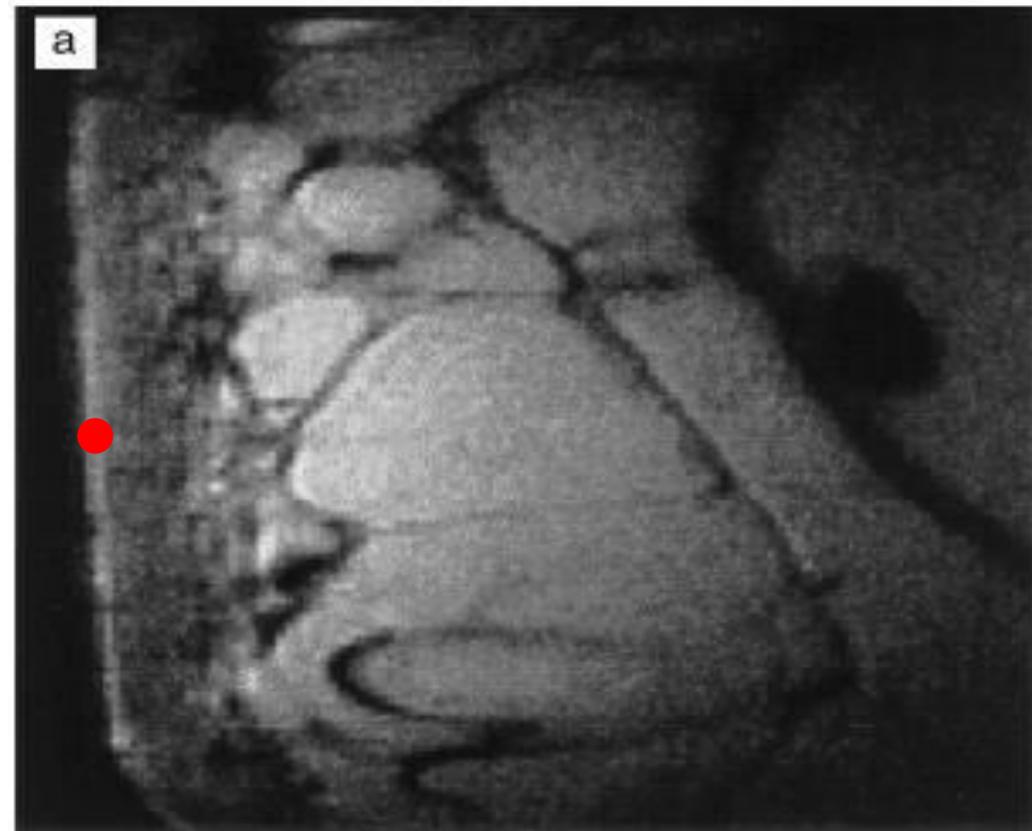


In vivo quantitative analysis of the effect of hydration (immersion and Vaseline treatment) in skin layers using high-resolution MRI and magnetisation transfer contrast

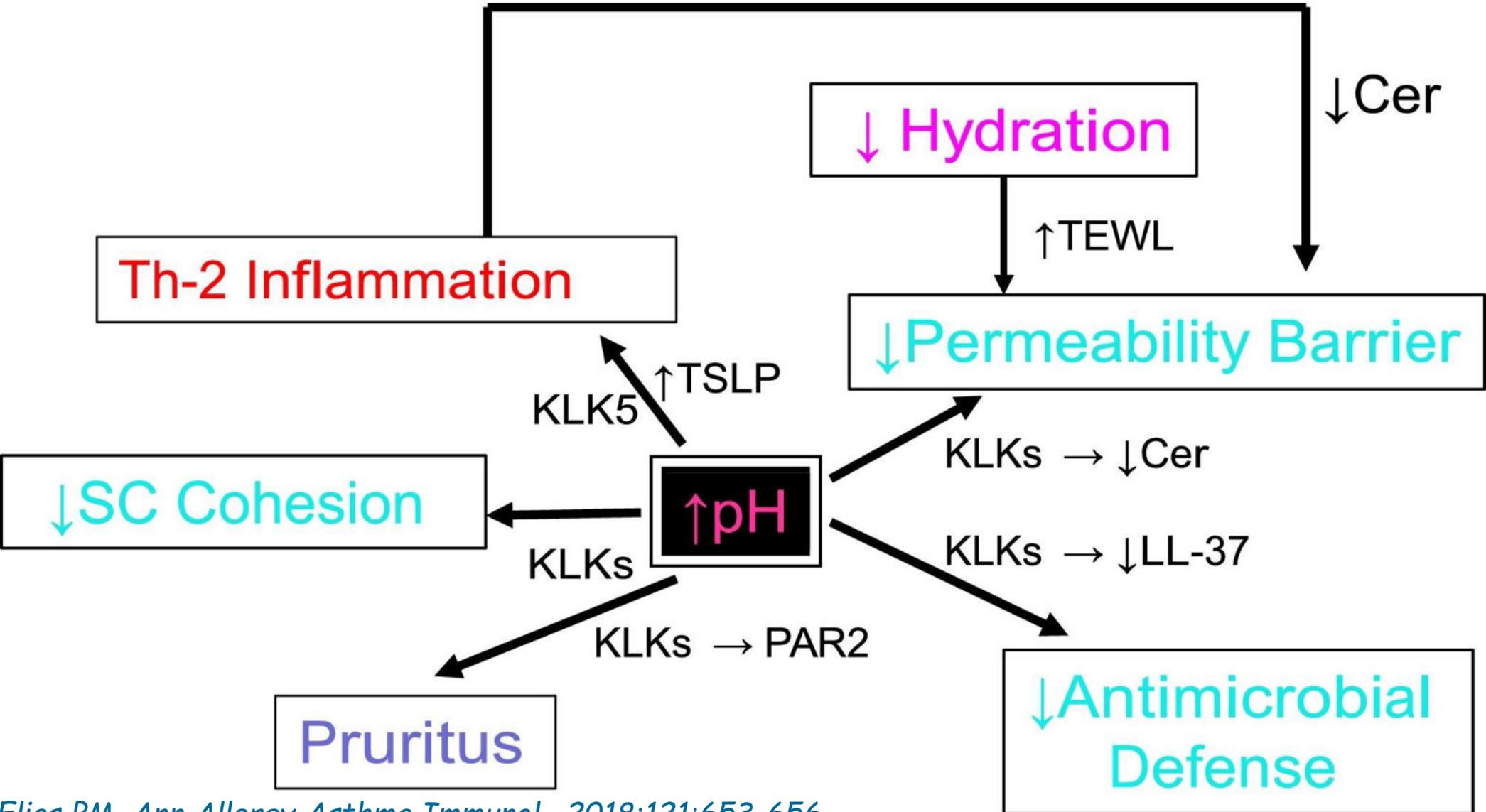
Mirrashed Skin Research and Technology 2004; 10: 14

Forearm pad skin images of
normal condition

hydrated condition



Central role of an increased pH in the pathogenesis of atopic dermatitis: the importance of the "acid mantle"



Elias PM, Ann Allergy Asthma Immunol. 2018;121:653-656.

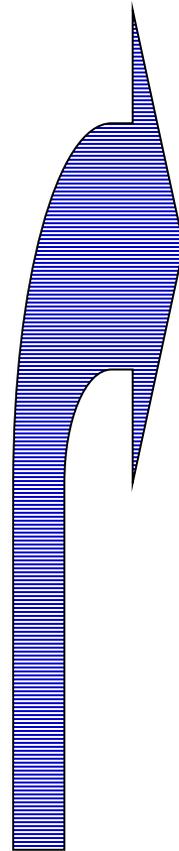
Bathing in a magnesium-rich Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin.

Proksch Int J Dermatol 2005;44:151



✓ Patients with atopic dry skin submerged one forearm for 15 min in a bain solution containing 5% DeadSea salt solution vs tap water.

✓ At time 0, 1 and 6 weeks later TEWL was evaluated.



- 1) Skin hydration was enhanced in the forearm treated with Sea salt solution.
- 2) TEWL was significantly reduced.
- 3) Skin roughness and redness were significantly reduced.

CLINICAL SCENARIO

A 12-year-old boy affected by severe AD since infancy, with no other atopic manifestation, was admitted to our department for a severe acute flare of eczema. Before this episode, the boy arrived at the emergency department four times in the past 5 years due to severe exacerbations, despite reporting the regular use of topical emollients, topical calcineurin inhibitors and proactive treatment with topical corticosteroids as well therapy in the case of superinfections.

Scoring Atopic Dermatitis (SCORAD) value of 78 of 103 (severe diseases if the SCORAD score is > 50).

Before each topical treatment, we decided to bathe the boy in a tub for 15-20 minutes by using a dose of plain water sufficient to cover the entire body surface, with the addition of 60 g of a new salt solution that contained $MgCl$, $MgSO_4$, $NaCl$, urea, and allantoin.

Comberinati P, Pearls and pitfalls of bathing in atopic dermatitis. Allergy Asthma Proc. 2019 May 1;40(3):204-206.



Figure 1. (a and b) Severity of atopic dermatitis at baseline.



Figure 2. (a and b) Changes in severity of atopic dermatitis at 3 days after admission to hospital.



Figure 3. (a and b) Changes in severity of atopic dermatitis 10 days after discharge and use of a daily soak-and-smear technique.

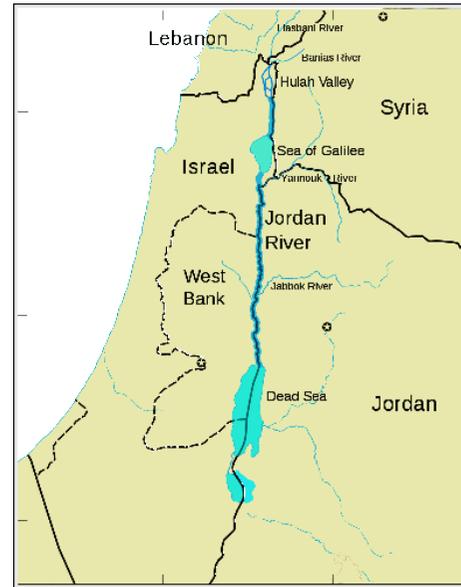
Pearls and pitfalls of bathing in atopic dermatitis.

Comberiat P, Allergy Asthma Proc. 2019 May 1;40(3):204-206.

Balneotherapy has been used for centuries.



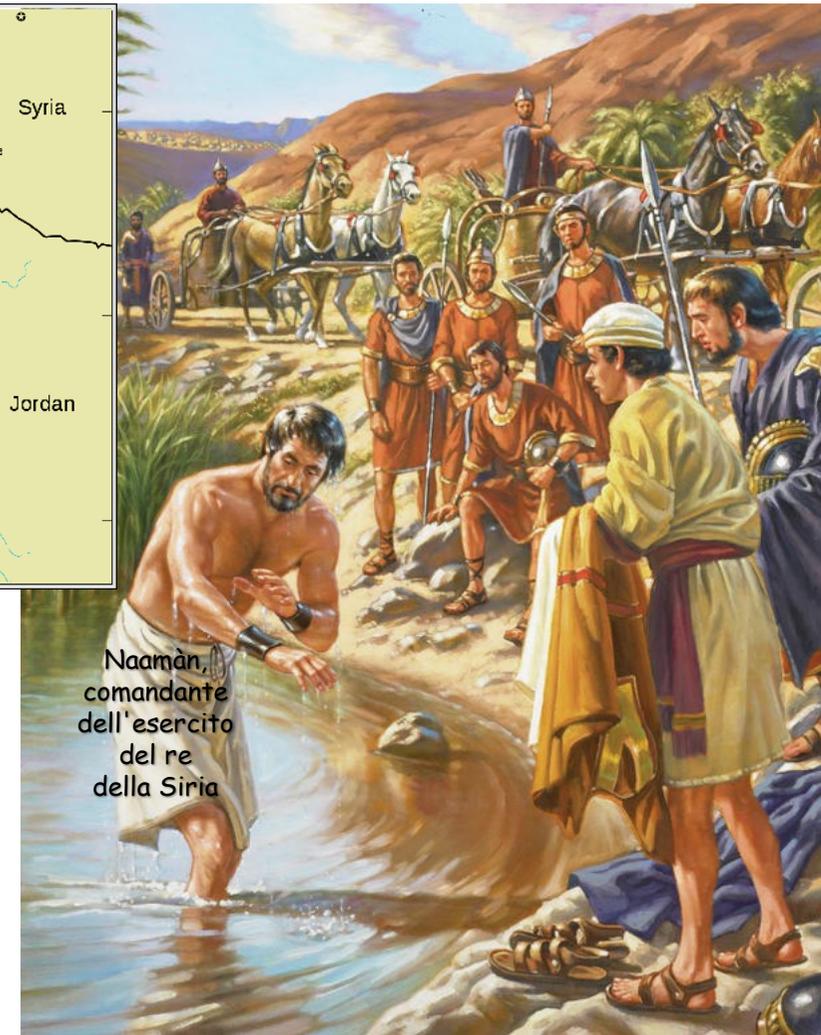
- In the Old Testament (reference: 2 Kings 5), in which Naaman, besieged with leprosy, was instructed by the prophet Eliseo to bathe 7 times specifically in the waters of the river Jordan to be cured.



- Like most of our parents of patients who do not adhere to bathing for the power of hydration of the skin, Naaman resisted, thinking that similar bathing in the rivers of Syria would do the same.

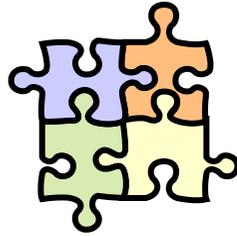
- His servants convinced him to listen and comply, and he was cured.

➤ So, the question might entail this:



is there a difference in salt contents amid the rivers?

Bathing in a complementary salt solution



MgCl salt

↑ Skin barrier
↑ Skin hydration
↓ Inflammation

Proksch, IntJ Derm. 2005; 44: 151

Allantoin

↑ Hydration
↑ Skin barrier
↑ Repair

Thornfeldt, Derm Surg. 2005; 31: 873

Urea A

one of the natural moisturizing factor (NMF) components in the stratum corneum

↑ Skin hydration

Loden, Acta Derm Ven. 2002; 82: 45

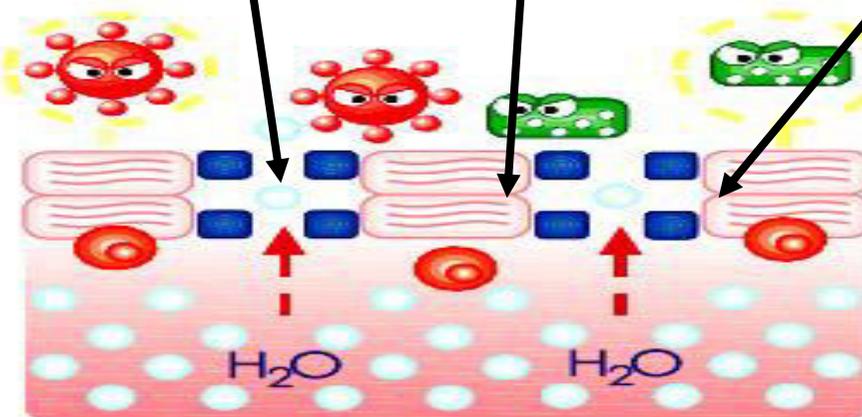
NaCl salt

↑ Urea's effects

Hagstromer, Skin Pha Ap Skin Phy. 2001; 14: 27

↓ S.aureus attachment

Akiyama J Dermat Sci 1998; 16: 216



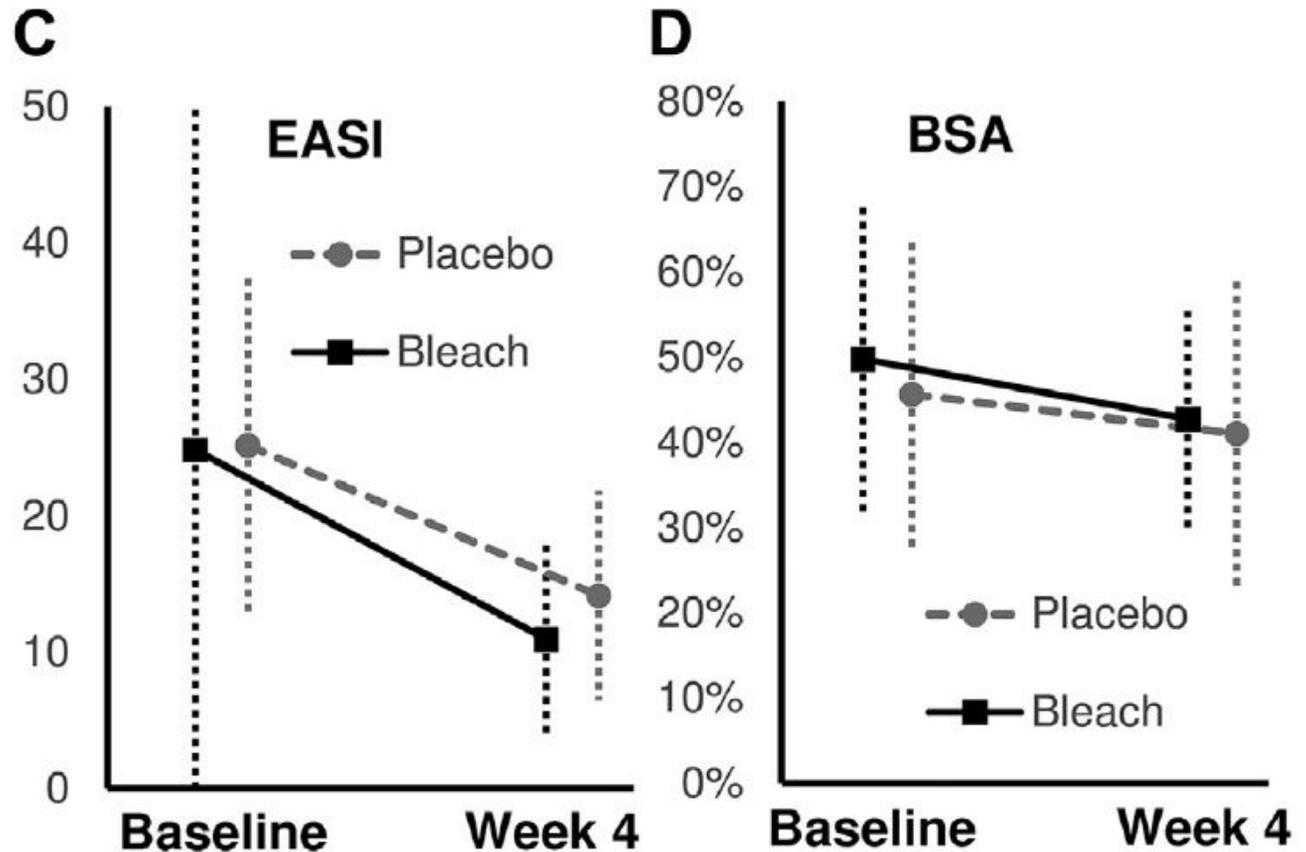
Efficacy of bleach baths in reducing severity of atopic dermatitis: A systematic review and meta-analysis

R Chopra, *Ann Allergy Asthma Immunol* 2017;119:435-440

Eczema Area and **Severity Index** (EASI) and body **Surface Area** (BSA) of bleach baths (solid lines) and water baths (dashed lines) are presented for 3 combined studies (pooled mean SD).



✓ 5 studies



Efficacy of bleach baths in reducing severity of atopic dermatitis: A systematic review and meta-analysis

R Chopra, *Ann Allergy Asthma Immunol* 2017;119:435-440



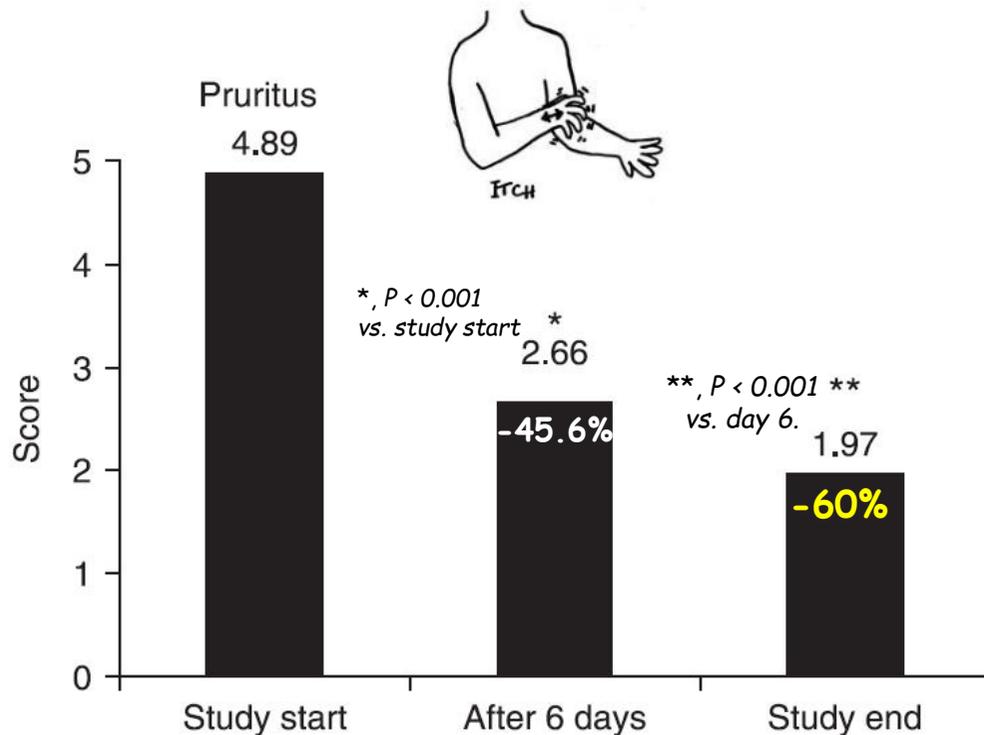
- There were no differences of *S aureus* density in patients treated with bleach vs water baths.
- Together, the results suggest that much of the efficacy of bleach baths at decreasing AD severity is attributable to water baths and less to bleach per se.
- Water baths alone can hydrate and sooth the skin and wash away scale and serum crust.
- Application of emollients and/or topical anti-inflammatories after the bath (referred to as prehydration, "soak and seal," or "soak and smear") can seal moisture in the stratum corneum, increase permeability, and enhance drug absorption.

Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study).

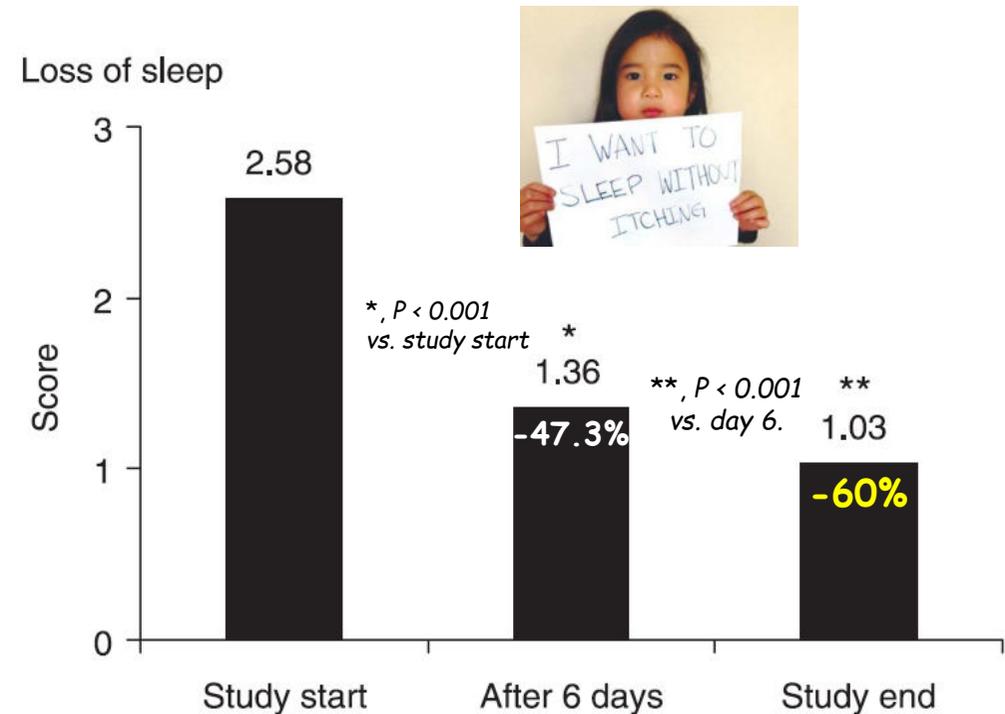
Eberlein B, J Eur Acad Dermatol Venereol. 2008 Jan;22(1):73-82.

on a visual analogue scale after 6 days,
pruritus was 45.6% lower
vs baseline value.

At study end, pruritus had diminished by 60%.

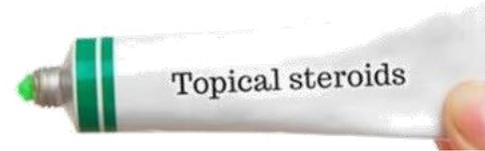


on a visual analogue scale after 6 days,
loss of sleep was 47.3% lower
and 60% lower at study end
vs baseline value



Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study).

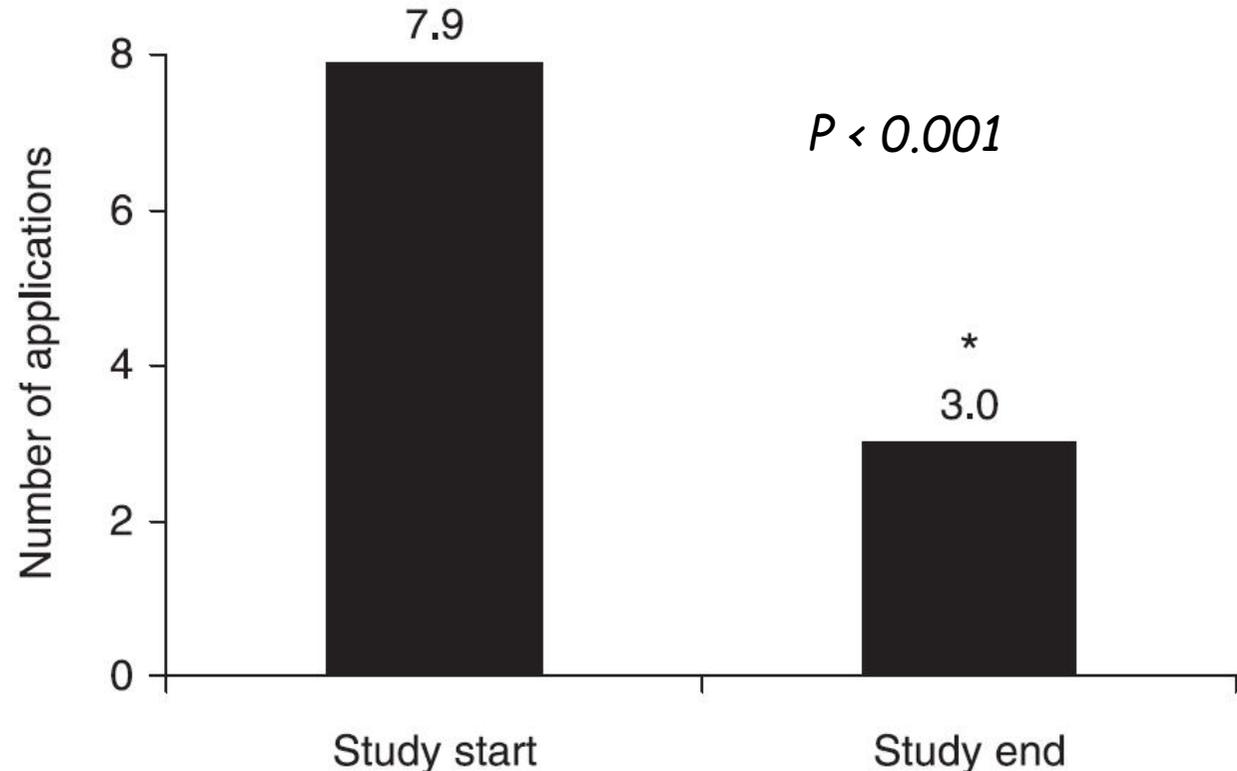
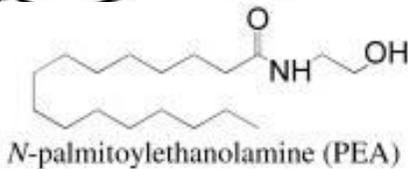
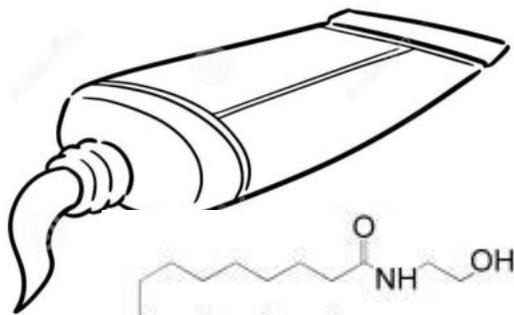
Eberlein B, *J Eur Acad Dermatol Venereol.* 2008 Jan;22(1):73-82.



Weekly application rate of topical corticosteroids

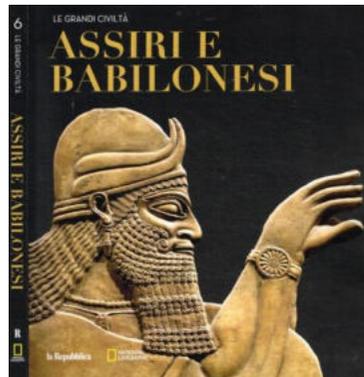
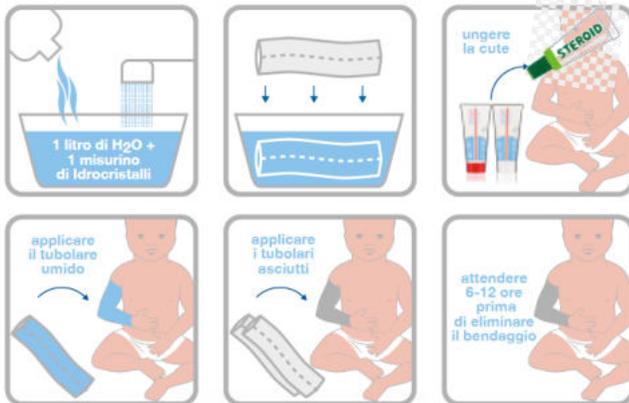
✓ 2456 patients with AD

✓ 4-6 weeks treatment with betaine, palmitoylethanolamine (0.3%) cream

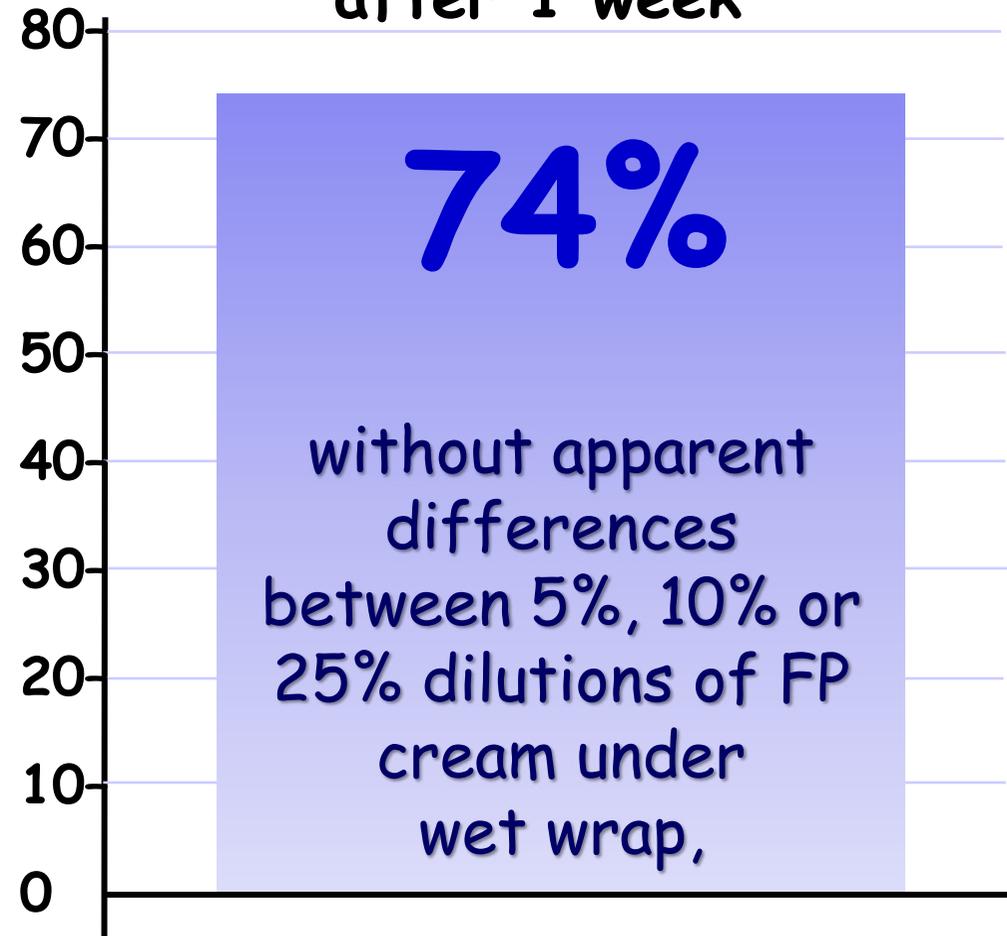


Efficacy and safety of wet-wrap dressings in children with severe atopic dermatitis: influence of corticosteroid dilution. *Wolkerstorfer A, Br J Dermatol 2000;143:999-1004.*

- ✓ 18 children treated with a 50% dilution of fluticasone propionate (FP) 0.05% cream for 2 weeks.
- ✓ 5 children a side-to-side comparison was conducted with 10%, 25% and 50% dilutions of FP cream under wet wrap.
- ✓ 8 children was treated with 0%, 5%, 10% or 25% emollient dilutions of FP cream applied on the whole body under wet wrap.



% average improvement after 1 week



Topical anti-inflammatory therapy and wet wraps

- Patients with **acute, oozing and erosive lesions**, and children in particular, sometimes **do not tolerate standard topical application**, and may first be treated with **'wet wraps'** until the oozing stops.



- They are highly effective in acute eczema and improve tolerance.

- The use of wetwrap dressings with diluted corticosteroids for up to 14 days (usual is up to 3 days) is a safe crisis intervention treatment of severe and/or refractory AE

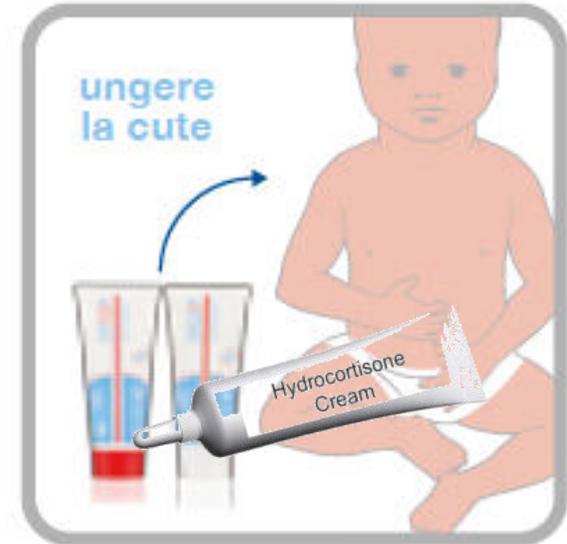
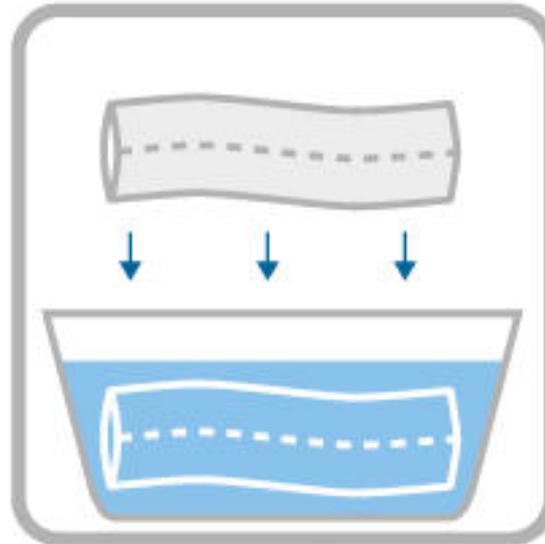


Guidelines for treatment of atopic eczema (atopic dermatitis) Part I

J. Ring, JEADV 2012, 26, 1045-1060



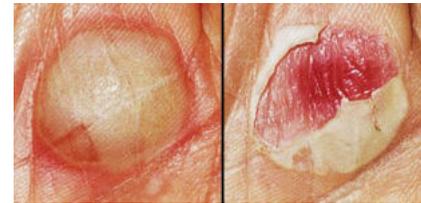
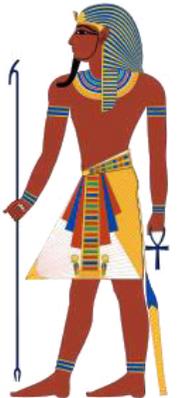
How to do do the wet wraps



Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature

Oranje AP, JEADV 2006,20:1277

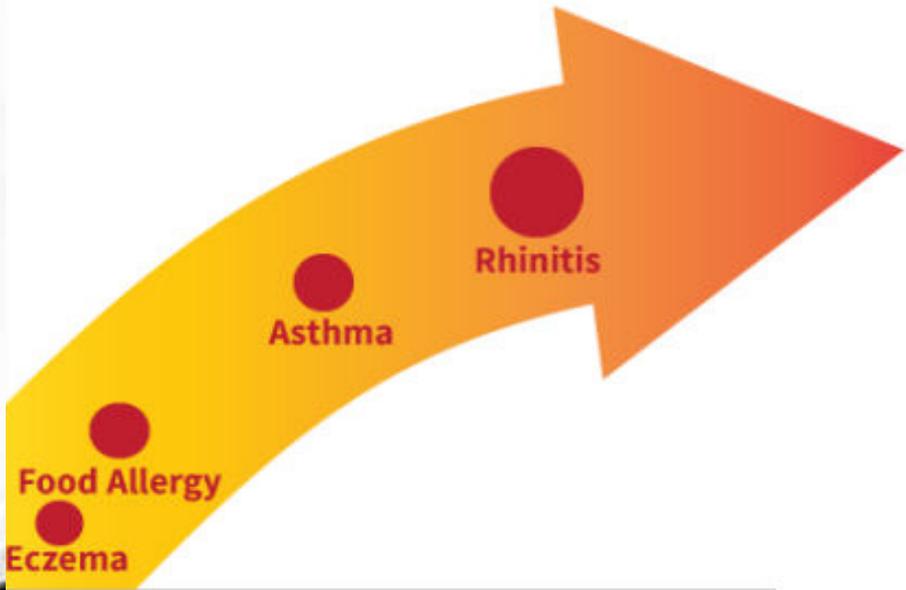
✓ THE ANCIENT **BABYLONIANS AND EGYPTIANS** OBSERVED THAT COVERED MOIST WOUNDS HEAL MORE RAPIDLY THAN OPEN DRY WOUNDS, but it took until 1958 for Odland to first describe that a blister healed faster when left unbroken.



✓ Since then many studies have demonstrated the beneficial effect of a moist environment on wound healing.

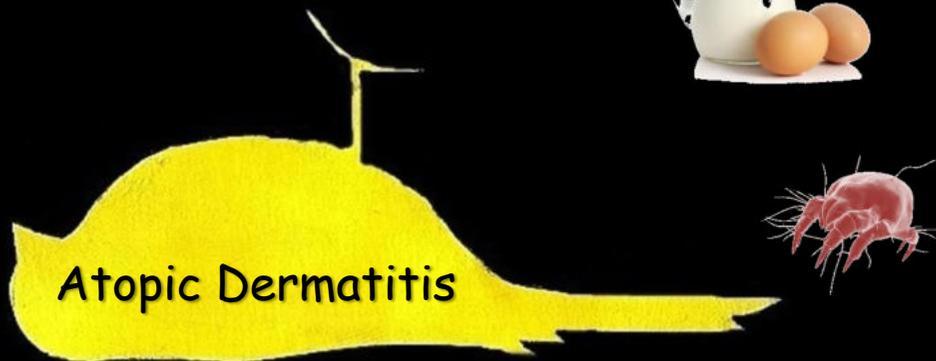
✓ Wet dressings support the rehydration of the skin and afford cooling of the skin through evaporation. This gradual cooling has an anti-inflammatory effect and reduces itching.

✓ The hydration and occlusion provided by the wet wraps also increases the absorption of topical medications.



Canary In A Coal Mine

dark, irreverent comedy



Age of onset in early childhood

**AD is predictive
of subsequent
sensitization to
food & environmental
allergens
and development of
respiratory
allergic diseases**

From 1996 to 2021: what has change in pediatric allergology in the last 25 years



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335 6274799

- ✓ Atopic march
- ✓ Atopic Dermatitis
- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ Meta-analysis vs Biological Plausibility



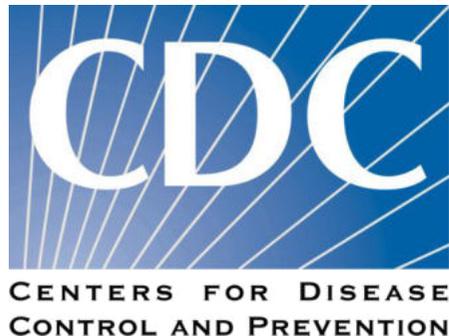
•Trends in allergic conditions among children: United States, 1997-2011

K.D. Jackson, NCHS Data Brief 2013;121:1-8

•The prevalence, severity, and distribution of childhood **food allergy** in the United States

R.S. Gupta, Pediatrics, 2011;128:e9-e17

The US Centers for
Disease Control
and Prevention
has reported:



• **≈ 50%** increase in the **PREVALENCE**
of food allergies in children
from 1997 to 2011,

• with estimates of up to 6 million
American children with food allergies

• at an economic cost of approximately
\$25 billion per year

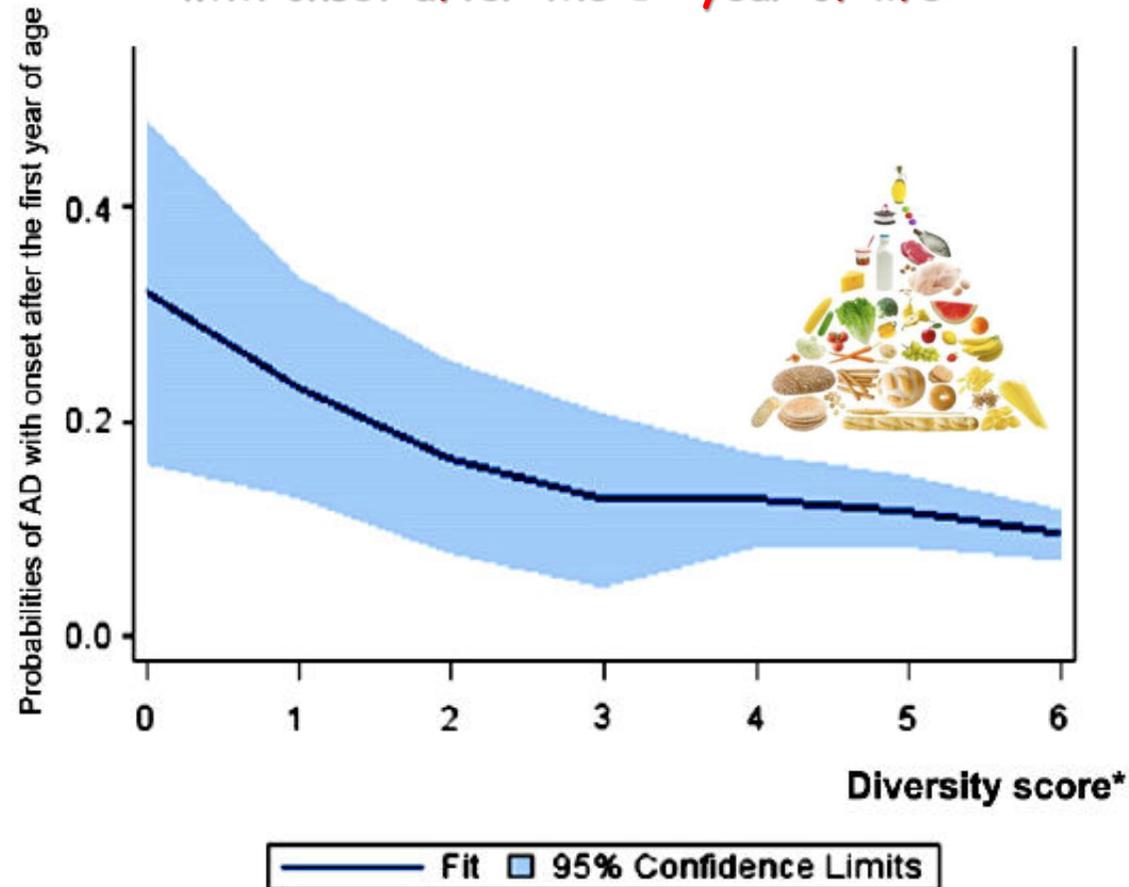


Development of atopic dermatitis according to age of onset and association with early-life exposures

Roduit C. *J Allergy Clin Immunol*. 2012 Jul;130(1):130-6.e5.

- ✓ Introduction to complementary food in the 1st year of life.
- ✓ Development of atopic dermatitis, taking into account the reverse causality.
- ✓ 1041 children birth cohort.
- ✓ Feeding practices reported by parents in monthly diaries between the 3rd and 12th months of life.

Association between increasing numbers of different major food items (n = 6) introduced in the 1st year of life and **atopic dermatitis with onset after the 1st year of life**.

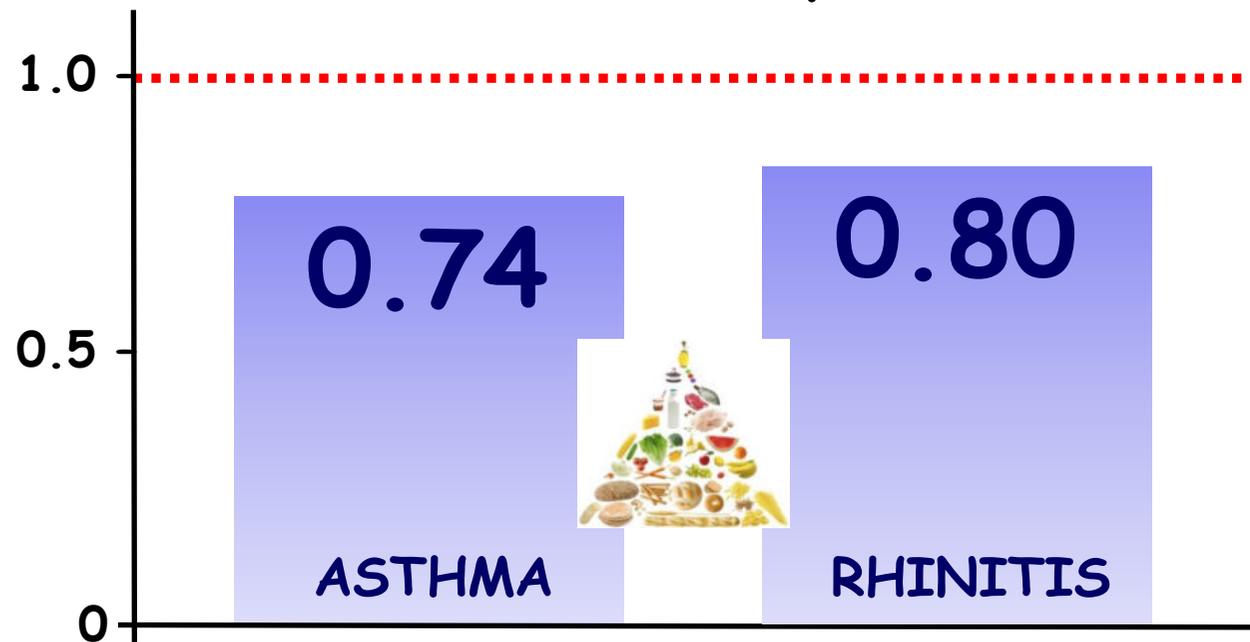


Increased food diversity in the first year of life is inversely associated with allergic diseases.

Roduit C, *J Allergy Clin Immunol*. 2014 Apr;133(4):1056-64.

- ✓ 856 children in a birth cohort study
- ✓ Feeding practices were reported by parents in monthly diaries during the 1st year of life
- ✓ Questionnaires from birth up to 6 years of life

by age 6 years
OR for Development of



Each additional food item introduced in the 1st year of life

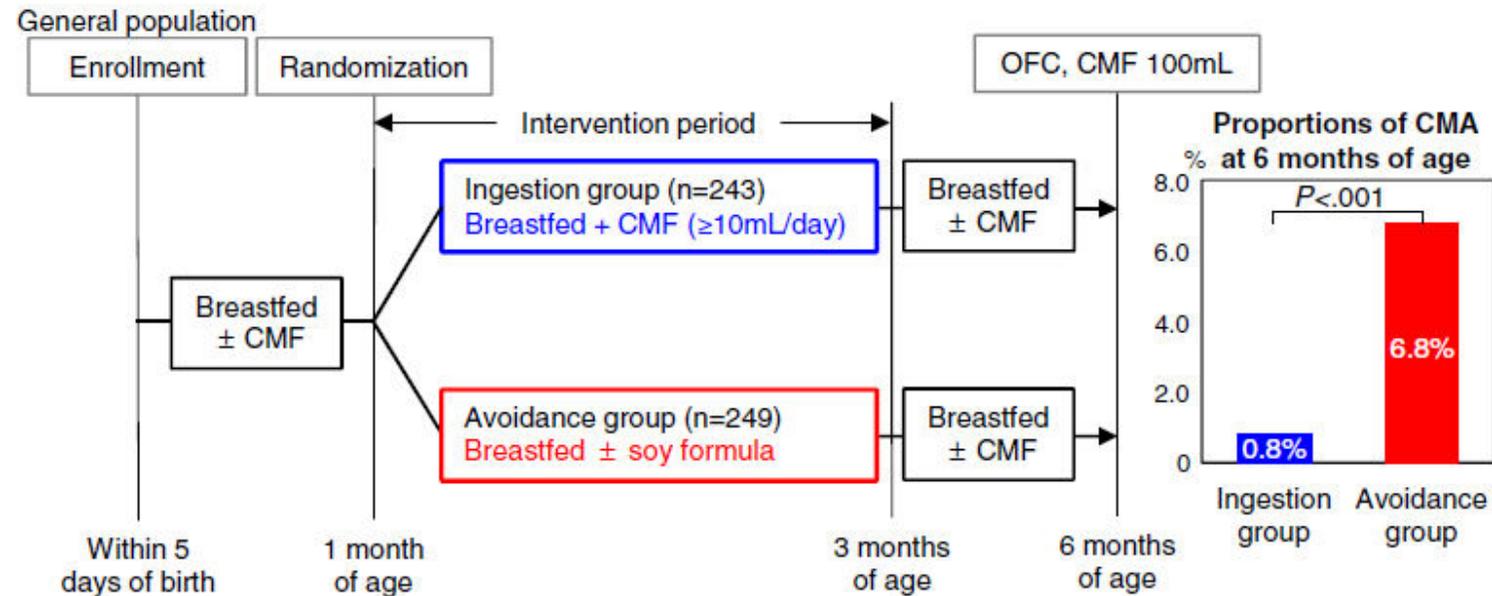
Randomized trial of early infant formula introduction to prevent cow's milk allergy.

Sakihara T, *J Allergy Clin Immunol*. 2021 Jan;147(1):224-232.e8.



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Overview of the SPADE study



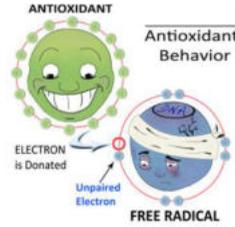
SPADE: Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy
CMF: Cow's milk formula
OFC: Oral food challenge
CMA: Cow's milk allergy



Participants were randomly allocated to ingest at least 10 mL of CMF daily (ingestion group) or avoid CMF (avoidance group) between 1 and 2 months of age. In the avoidance group breast-feeding was supplemented with soy formula as needed. Oral food challenge was performed at 6 months of age to assess CMA development. Continuous breast-feeding was recommended for both groups until 6 months of age.

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

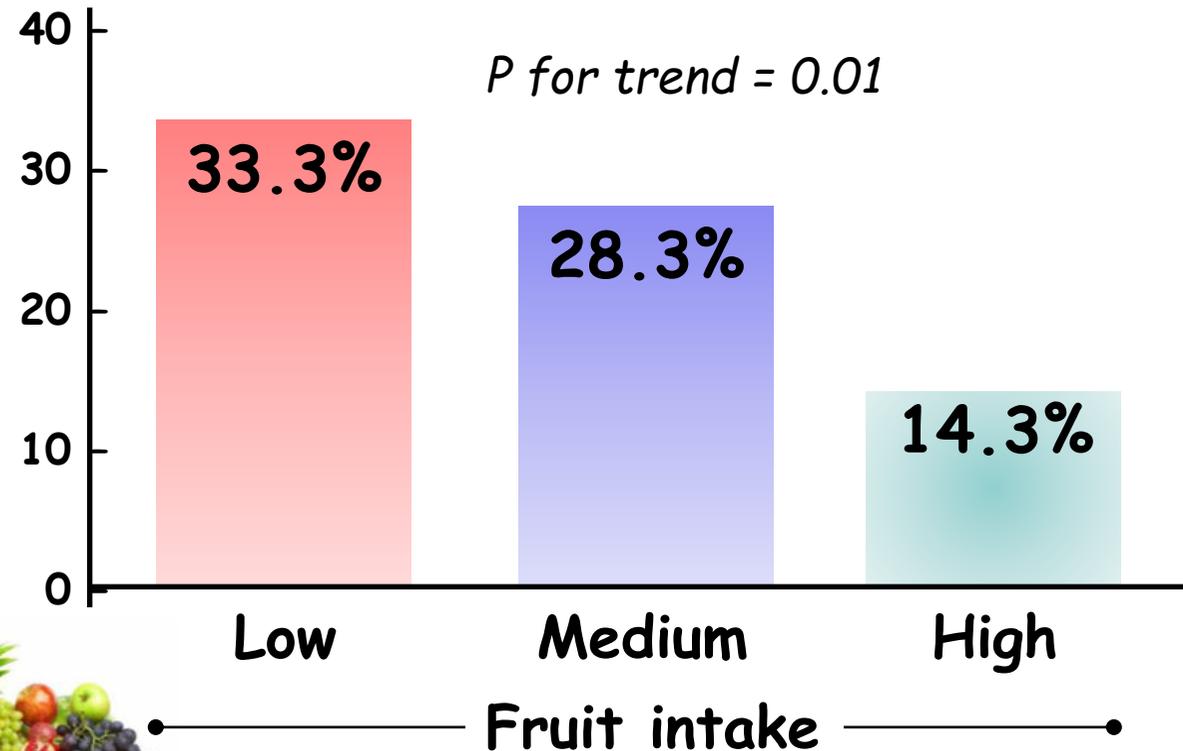
- ✓ 2359 children from the Swedish birth cohort BAMSE
- ✓ Dietary total antioxidant capacity (TAC) at age 8 years estimated by combining information on the child's diet the past 12 months from a food frequency questionnaire with a database of common foods analysed with the oxygen radical absorbance capacity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

Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren

T Kusunoki, PAI 2017;28:793-800

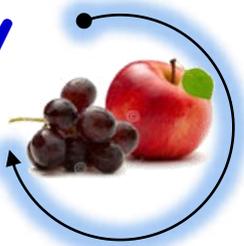
- ✓ A prospective cohort study on primary schools in Japan.
- ✓ Questionnaires regarding allergic symptoms and diet distributed to the parents of all 759 7-year-old schoolchildren for 4 consecutive years, from 2011 to 2014.
- ✓ sIgE to inhalant allergens at 10 years of age.

% children with any allergic symptoms at age 10



Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren

T Kusunoki, PAI 2017;28:793-800



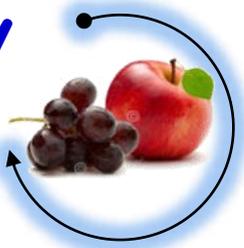
Fruit intake and % allergic symptoms in schoolchildren that existed at the start of the study and disappeared by the end of the study -4 yrs- follow-up (recovered symptoms)

Symptom	Fruit intake	Prevalence of recovered symptom (%)	Multivariate <i>OR</i> ^a (95% CI)	<i>P</i> for trend
Asthma (n = 60)	Low	3/8 (37.5)	Ref.	.02
	Medium	31/51 (60.8)	5.57 (0.96-32.17)	
	High	1/1 (100.0)	16.5 (0.38-718.50)	
Eczema (n = 95)	Low	5/10 (50.0)	Ref.	.21
	Medium	32/76 (42.1)	1.18 (0.26-5.28)	
	High	6/9 (66.7)	4.09 (0.49-34.09)	
Rhinitis (n = 142)	Low	5/16 (31.3)	Ref.	.18
	Medium	35/112 (31.3)	1.10 (0.34-3.60)	
	High	7/14 (50.0)	3.16 (0.63-15.72)	
Any (n = 219)	Low	12/27 (44.4)	Ref.	.17
	Medium	84/172 (48.8)	1.37 (0.57-3.29)	
	High	12/20 (60.0)	2.46 (0.69-8.71)	

^a Sex, season of birth, low birthweight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors.

Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren

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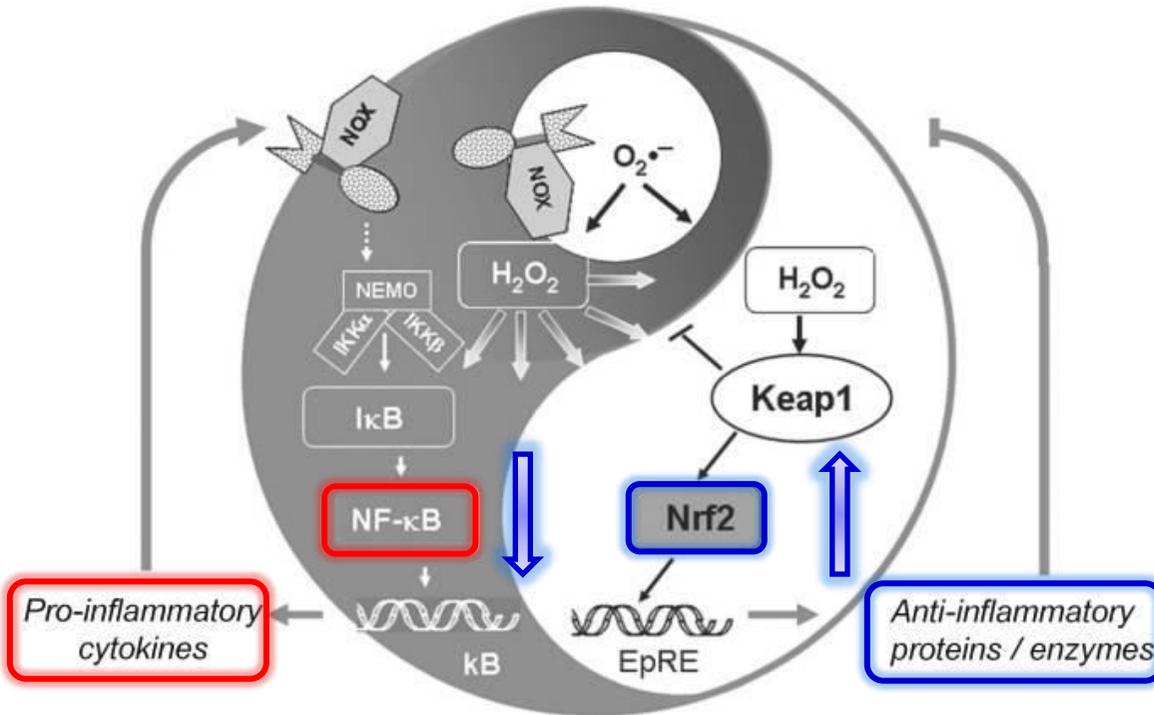
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higher intake of fruit can help decrease respiratory allergic symptoms in school aged children.

^a Sex, season of birth, low birthweight, birth order, parent's allergies, breastfeeding, and experience of food avoidance were included as confounding factors.

Fruits and vegetables in general health

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



NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells

Nrf2 = Nuclear factor (erythroid-derived 2)-like 2



curcumin



soy



quercetin



sulforaphane



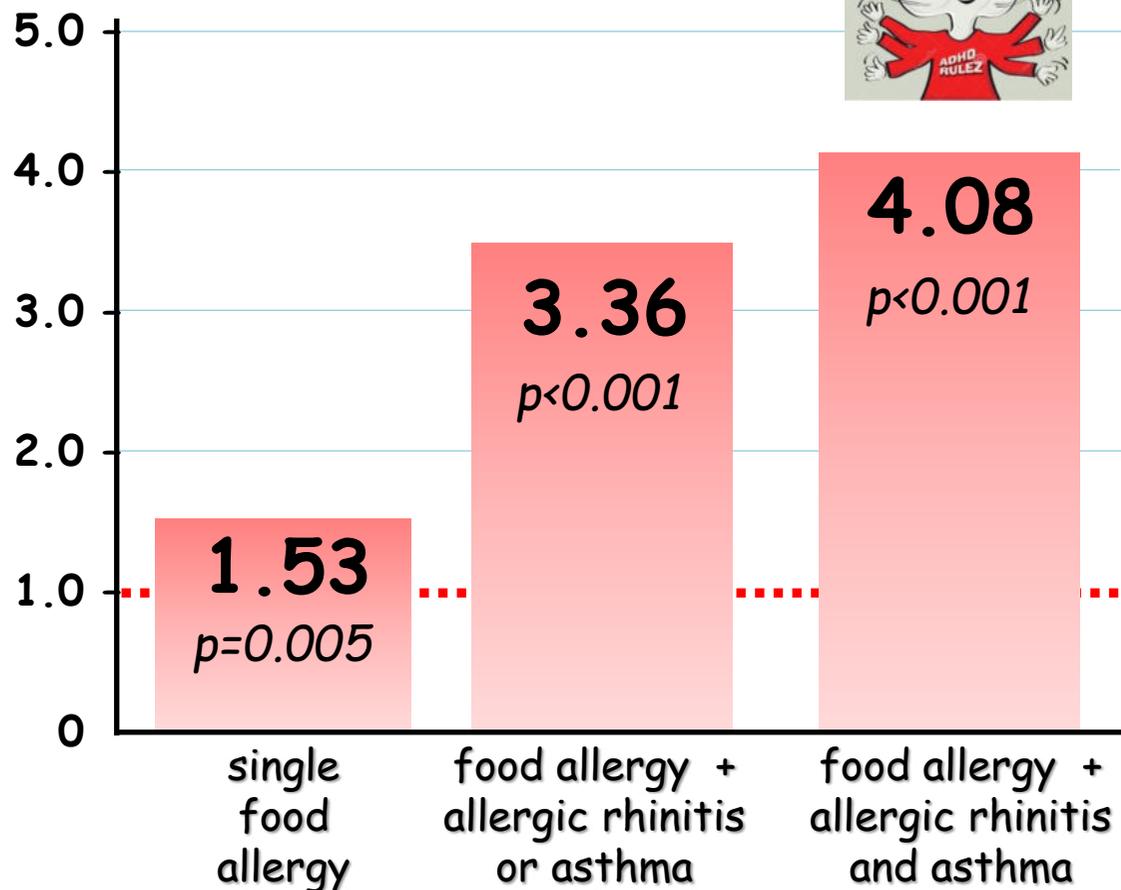
resveratrol



Early food allergy and respiratory allergy symptoms and attention-deficit/hyperactivity disorder in Chinese children: A cross-sectional study.

Jiang X, *Pediatr Allergy Immunol.* 2018 Jun;29(4):402-409.

OR of ADHD



✓ cross-sectional study in school-age children (n=22 018) from 9 cities across China between November and December 2005.

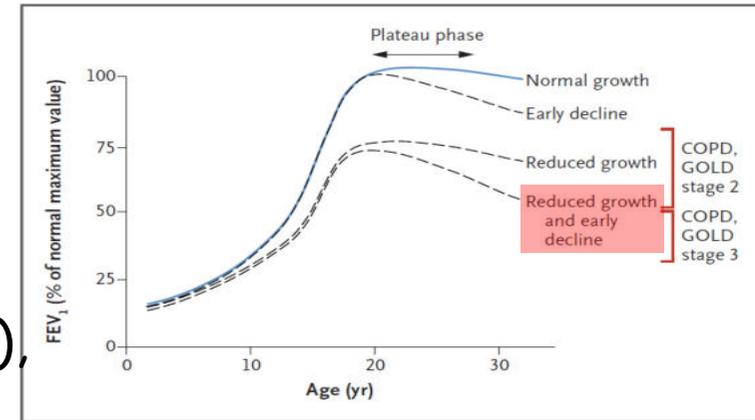
✓ A family and social environmental questionnaire including the diagnosis history of ADHD and allergic diseases (food allergy, allergic rhinitis, and bronchial asthma), as well as general information, completed by parents.

Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma

McGeachie MJ, *N Engl J Med* 2016;374:1842-52

□ Participants with reduced growth and an early decline, as compared with those who had normal growth, had:

- lower FEV₁ lung function at enrollment (OR, 0.85),
- a lower bronchodilator response (OR, 0.91), and
- increased airway hyperresponsiveness (OR, 0.66);
- were more likely to be male (OR, 3.07);
- were younger at enrollment (OR, 0.62 per year); and
- had a lower level of parental education (OR, 0.43 for at least a college degree vs. a lower level; $P = 0.01$),
- a greater number of positive skin tests at enrollment (OR for ≥ 3 positive tests vs. < 3 , 2.42; $P = 0.03$).



↑
Primary &
Secondary
Prevention !

Food protein-induced enterocolitis of infancy: differential diagnosis and management.

Powell GK. Compr Ther. 1986;12:28-37.

- FPIES was rarely recognized during the following 20 years, but it has been attracting a steadily increasing attention in the past decade.
- First international consensus guidelines were published in 2017.

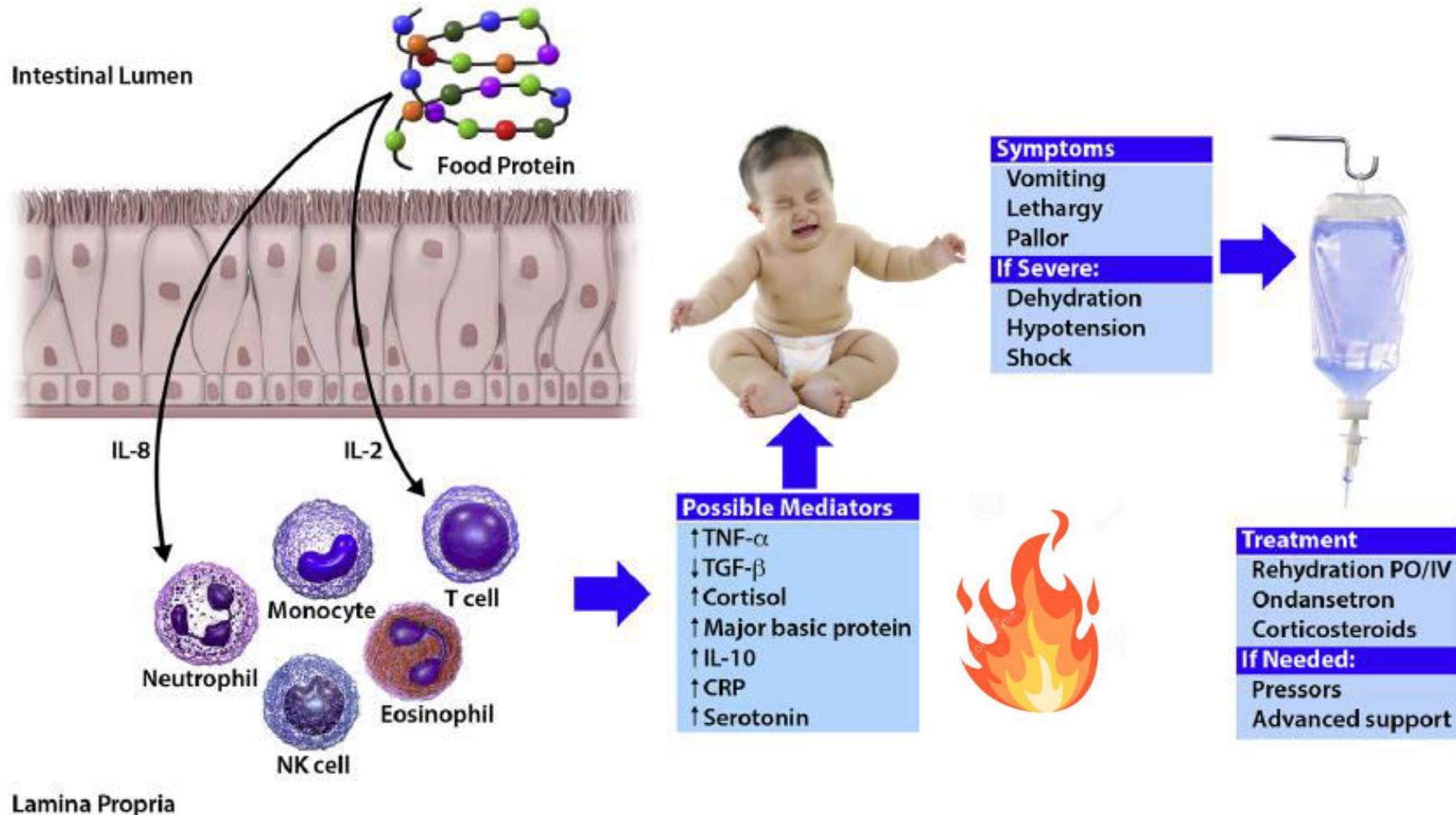
- prevalence up to **0.7% in infants in the 1st year of life.**
- **Cow Milk** is the most common reported FPIES trigger, whereas among solids, rice, oat and shellfish are predominant.
- **Acute FPIES** typically starts within the first 6 months with **profuse, repetitive vomiting, lethargy and pallor**, occurring 1 to 4 hours (usually 2 hours) after food ingestion progressing to dehydration and hypovolemic shock in 15% of cases.
- **Chronic FPIES** manifests with intermittent emesis, watery diarrhea, and poor growth

International consensus
guidelines for the
diagnosis and
management of food
protein-induced
enterocolitis syndrome.

*Nowak-Wegrzyn A,
J Allergy Clin Immunol.
2017;139(1111-26):e4.*

Management of acute food protein-induced enterocolitis syndrome emergencies at home and in a medical facility.

Leonard SA, Miceli Sopo S, *Ann Allergy Asthma Immunol.* 2021 May;126:482-488.



Food ingestion activates cells of the innate and adaptive immune systems including T cells, neutrophils, natural killer cells, monocytes, and eosinophils. C-reactive protein is particularly involved in severe events suggesting an important role of inflammation in more severe forms of FPIES

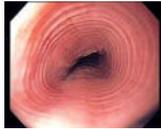
Eosinophilic gastroenteritis with esophageal involvement

Dobbins JW. *Gastroenterology*. 1977;72:1312-1316.

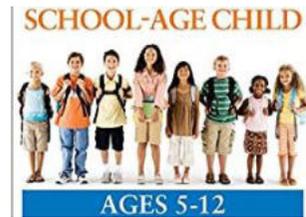
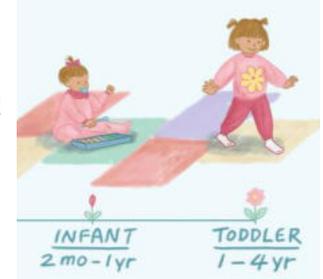
Although it was first described in 1977, **it was only in the mid 1990s** that EE became more recognized by gastroenterologists and pathologists.

Eosinophilic Esophagitis in Children.

Ruffner MA,
*Curr Allergy
Asthma Rep*. 2017
Aug;17(8):54.



- *Infants and toddlers* are more likely to present with failure to thrive and feeding difficulties,
- *School-age children* present with complaints of reflux symptoms not relieved by proton pump inhibitor including abdominal pain, and heartburn.
- *Preteens, adolescents, and adults* can present with dysphagia which may or may not respond to therapy,
- *Older patients* are also more likely to present with food impactions.

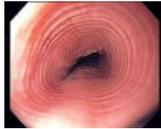


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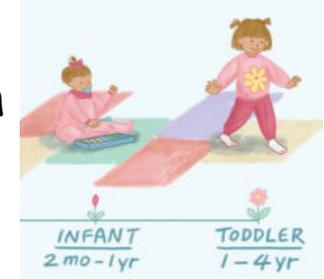


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➤ **Prevalence in children**
ranges
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Soon IS, *J Pediatr Gastroenterol*
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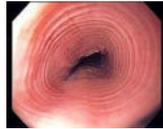


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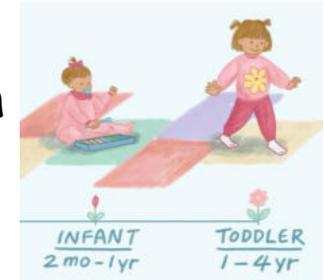
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Soon IS, *J Pediatr Gastroenterol
Nutr*. 2013 Jul;57(1):72-80.

- 26-50% have concomitant asthma,
- 30-90% have associated allergic rhinitis,
- 19-55% have atopic dermatitis,
- Up to 70% have food allergy



**Non-IgE- or Mixed IgE/Non-IgE Mediated
Gastrointestinal Food Allergies in the First Years of Life:
Old and New Tools for Diagnosis.**

Calvani M, *Nutrients*. 2021 Jan 14;13(1):226.

From 1996 to 2021: what has change in pediatric allergology in the last 25 years



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335 6274799

- ✓ Atopic march
- ✓ Atopic Dermatitis
- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ Meta-analysis vs Biological Plausibility



ASTHMA EPIDEMIOLOGY



- Asthma affects approximately **300 million people globally**, and represents the most common noncommunicable disease.

- It carries a disproportionately high impact on children, and nearly 6 billion dollars are spent annually due to pediatric asthma alone.



Gur M, Hakim F, Bentur L. Better understanding of childhood asthma, towards primary prevention - are we there yet? Consideration of pertinent literature. F1000Res 2017; 6:2152.

- Its impact is growing exponentially - it has been suggested that there may be **an additional 100 million people suffering from asthma by 2025**.



Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-478.

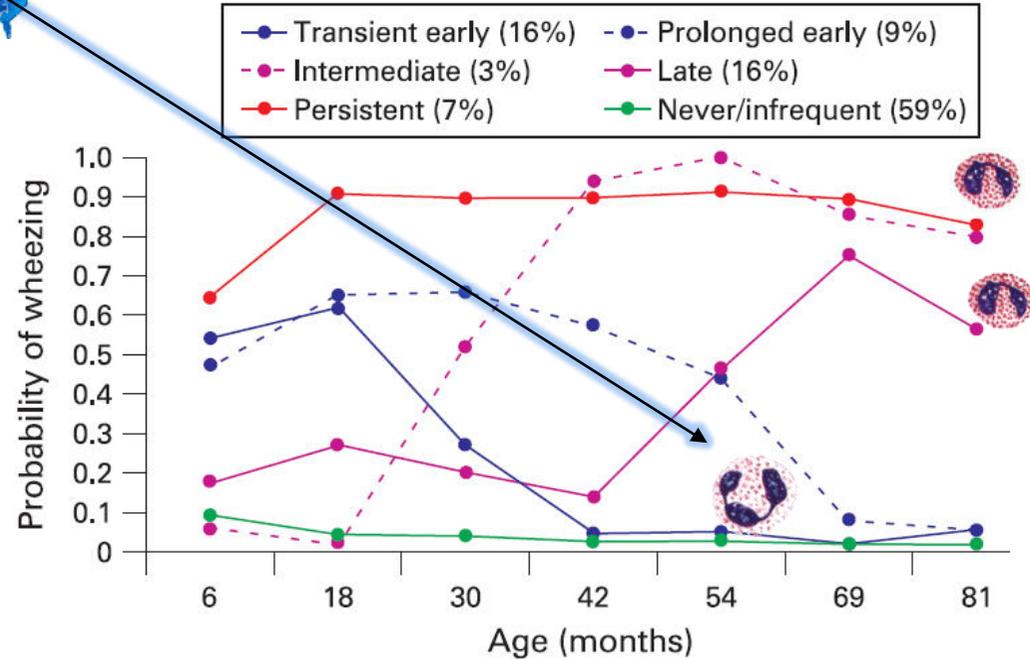
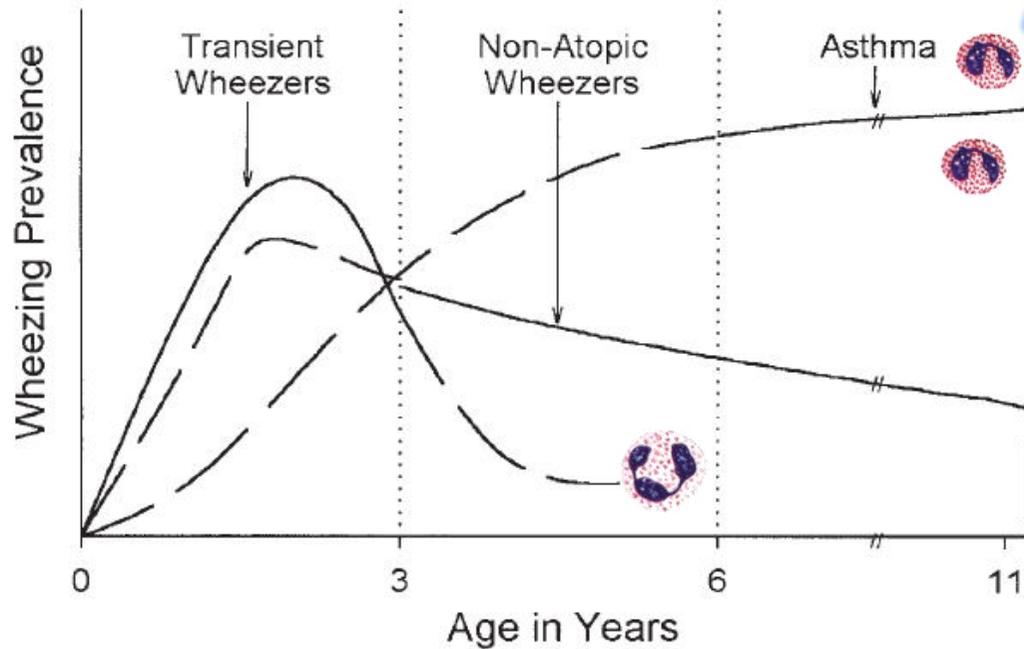
Different wheezing phenotypes in different birth cohorts

Tucson Children's Respiratory Study
N Engl J Med 1995; 332:133-138.

- 1246 unselected newborns assessed the presence of wheezing symptoms during the first 6 years of life

Avon Longitudinal Study of Parents and Children. Thorax 2008; 63:974-980.

- 6265 children in a longitudinal birth cohort (the ALSPAC study)



Phenotypes of wheezing and asthma in preschool children.

Kwong CG, Bacharier LB. Curr Opin Allergy Clin Immunol. 2019;19(2):148-153.

A clinical index to define risk of asthma in young children with recurrent wheezing.

Castro-Rodriguez JA, *AJCCM* 2000;162:1403-06.



A CLINICAL INDEX TO DEFINE ASTHMA RISK*

Major Criteria

1. Parental MD asthma[†]
2. MD eczema[‡]

Minor Criteria

1. MD allergic rhinitis[§]
2. Wheezing apart from colds
3. Eosinophilia ($\geq 4\%$)

* **Loose index** for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. **Stringent index** for the predication of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.

[†] History of a physician diagnosis of asthma.

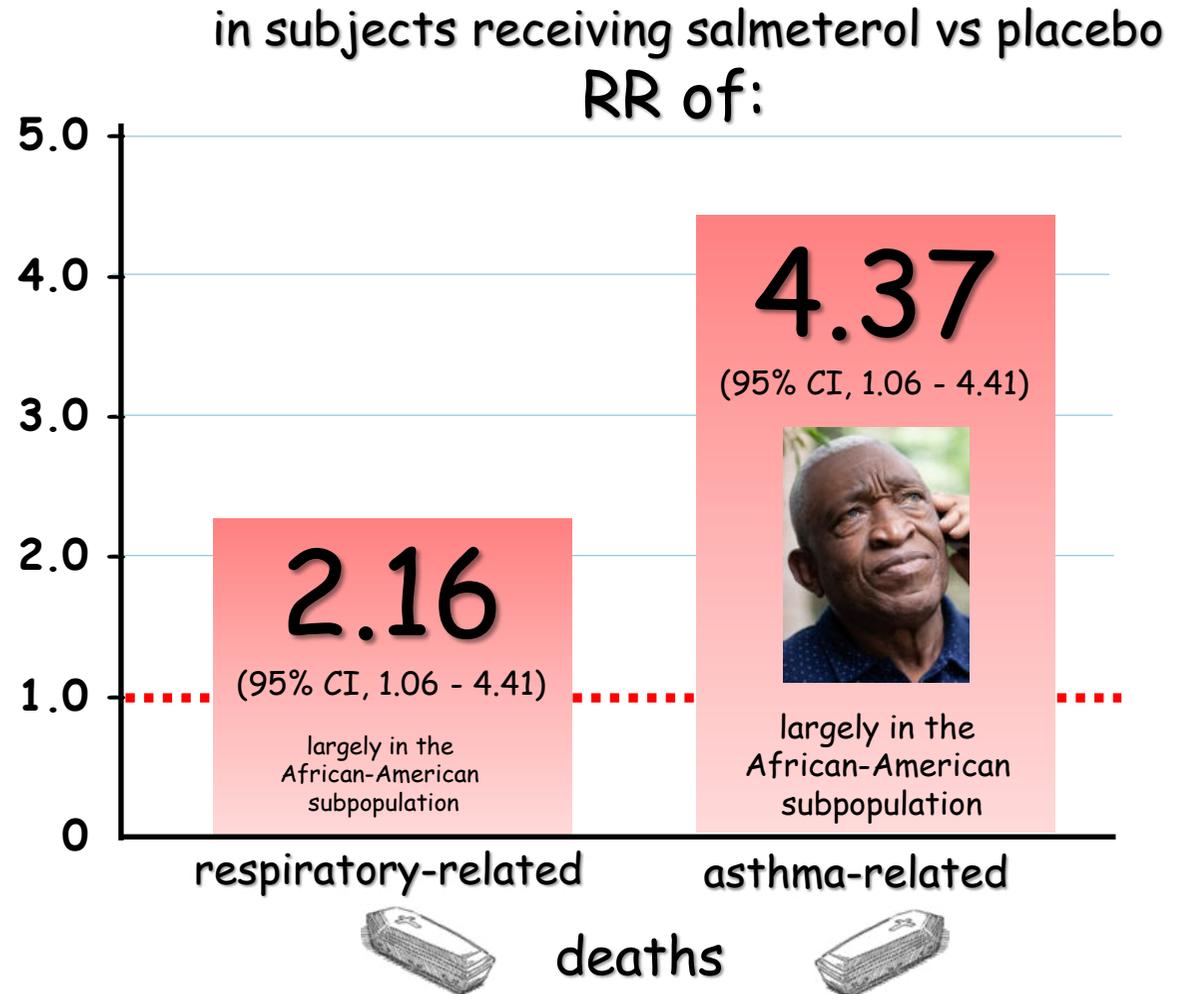
[‡] Physician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

[§] Physician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.

Nelson HS, Chest. 2006 Jan;129(1):15-26.

- ✓ A 28-week, randomized, double-blind, placebo-controlled, observational study
- ✓ 26,355 subjects (>12 years old) with asthma
- ✓ Salmeterol, 42 µg bid and placebo bid via MDI in adjunct to current therapy.



FDA RECOMMENDATIONS ABOUT USE OF A LABA

www.fda.gov/cder/drug/advisory/LABA.htm

November 18, 2005



1. LABAs should not be the first medicine used to treat asthma. LABAs should be added to the asthma treatment plan only if other medicines do not control asthma.
2. Do not use your LABA to treat wheezing that is getting worse.
3. LABAs do not relieve sudden wheezing. Always have a **short acting bronchodilator** medicine with you to treat sudden wheezing.



FDA RECOMMENDATIONS ABOUT USE OF A LABA

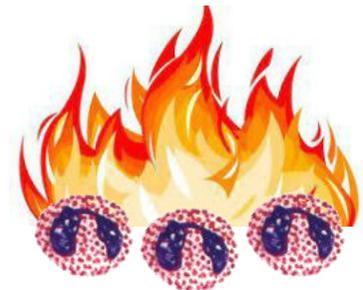
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2. Do not use your LABA to treat wheezing that is getting worse.
3. LABAs do not relieve sudden wheezing. Always have a **short acting bronchodilator** medicine with you to treat sudden wheezing.

The problem is not the speed of action onset

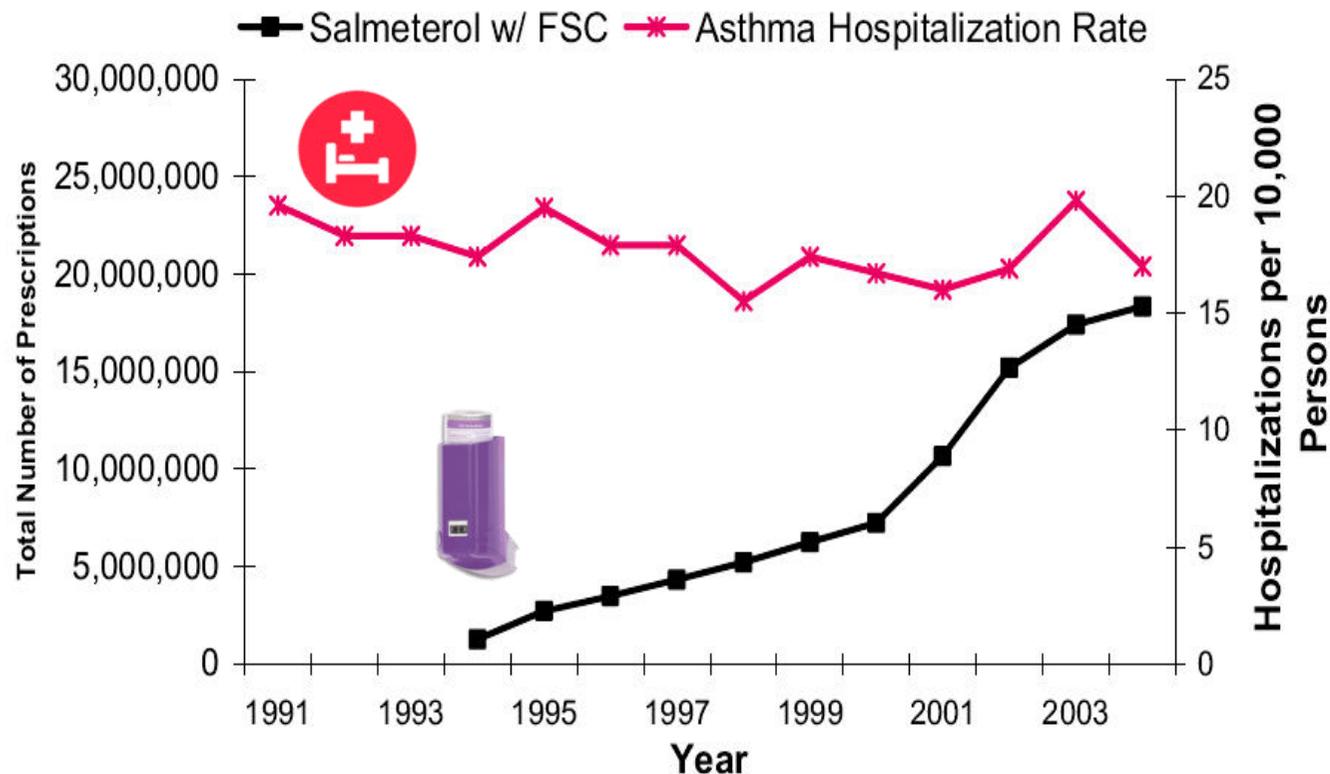


Ecologic analysis of asthma-related events and dispensing of inhaled corticosteroid- and salmeterol-containing products.

DiSantostefano RL, Ann Allergy Asthma Immunol. 2008;100(6):558-65.

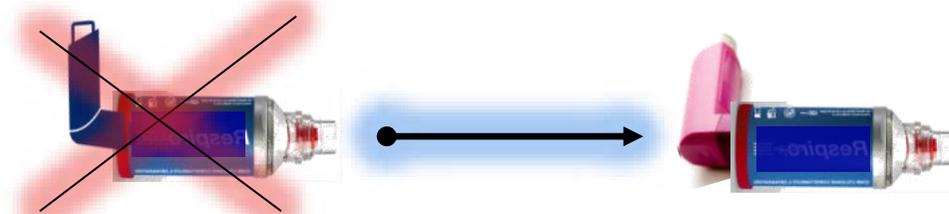
Age-adjusted asthma-related hospitalization relative to dispensing of fluticasone propionate/salmeterol (FSC)-containing medications.

- ✓ Annual age-adjusted rates of asthma-related hospitalization and asthma-related mortality graphed alongside annual number of prescriptions dispensed of salmeterol & ICS from 1991 to 2004.



What's new in GINA 2021? for mild asthma therapy

➤ **GINA no longer recommends treatment with SABA alone.**



❖ There is strong evidence that use of **SABA alone**, although providing short-term relief of asthma symptoms, **does not protect patients from severe exacerbations**, and that **regular or frequent use** of SABAs increases the risk of exacerbations and, of even greater concern, **death**.



This is based on results of the recent publication of two GINA-initiated studies:

- *O'Byrne PM, Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018; 378: 1865-1876.*
- *Bateman ED, As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018; 378: 1877-1887.*



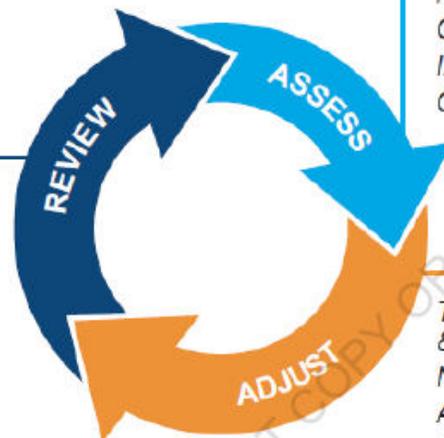
What's new in GINA 2021?

Children 6-11 years

Personalized asthma management:

Assess, Adjust, Review

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:

Adjust treatment up and down for individual child's needs

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

<p>STEP 1</p> <p>Low dose ICS taken whenever SABA taken</p>	<p>STEP 2</p> <p>Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)</p>	<p>STEP 3</p> <p>Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART) *</p>	<p>STEP 4</p> <p>Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice</p>	<p>STEP 5</p> <p>Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE</p>
<p>Consider daily low dose ICS</p>	<p>Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken</p>	<p>Low dose ICS + LTRA</p>	<p>Add tiotropium or add LTRA</p>	<p>Add-on anti-IL5, or add-on low dose OCS, but consider side-effects</p>

RELIEVER

As-needed short-acting beta2-agonist (or ICS-formoterol reliever for MART as above)

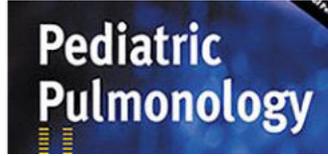
*MART = maintenance and reliever therapy with ICS-formoterol

*Very low dose: BUD-FORM 100/6 mcg

†Low dose: BUD-FORM 200/6 mcg (metered doses).

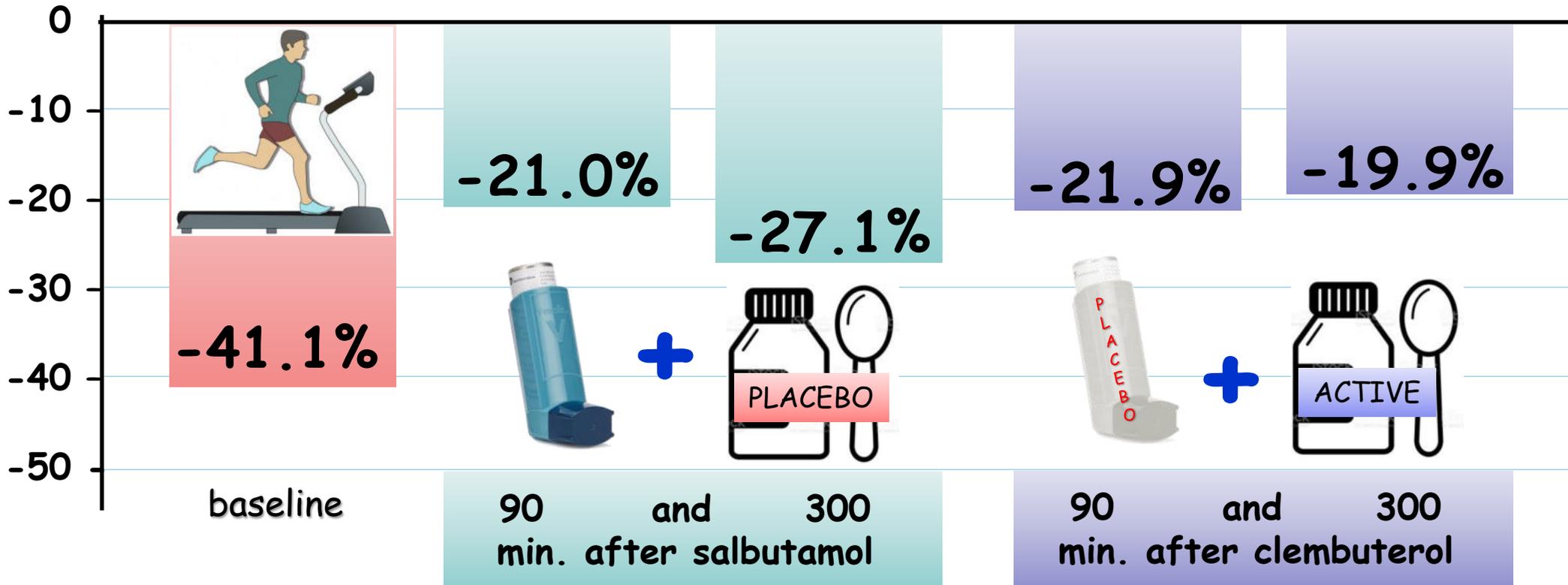
Comparison of the protective effect and duration of action of orally administered clenbuterol and salbutamol on exercise-induced asthma in children.

Boner AL, *Pediatr Pulmonol.* 1988;4(4):197-200.



GINA 2021
no longer
recommends
treatment
with SABA
alone.

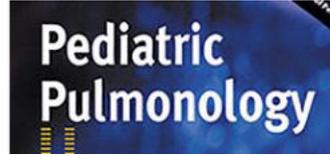
preliminary screening exercise test the mean fall of FEV1 was 41.1%, but it was 21.0% and 27.1% after S and 21.9% and 19.9% after C administered 90 and 300 min prior to the test, respectively.



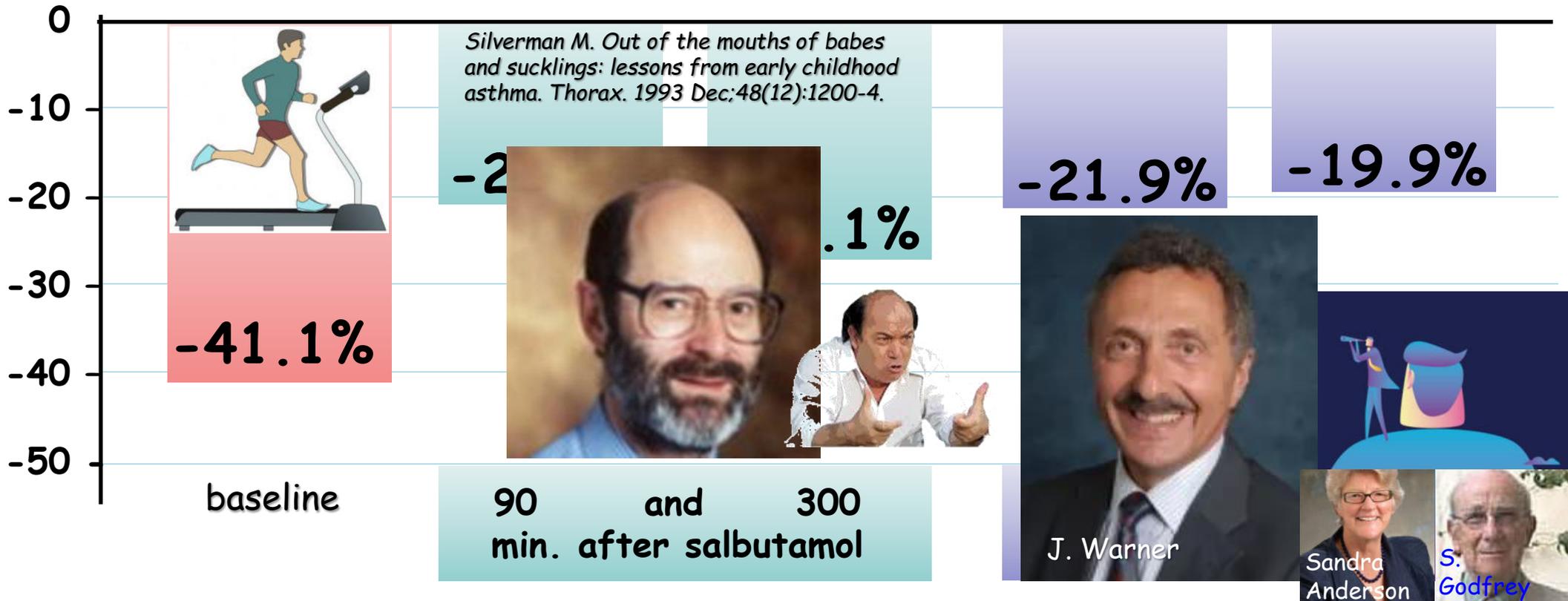
Comparison of the protective effect and duration of action of orally administered clenbuterol and salbutamol on exercise-induced asthma in children.

GINA 2021
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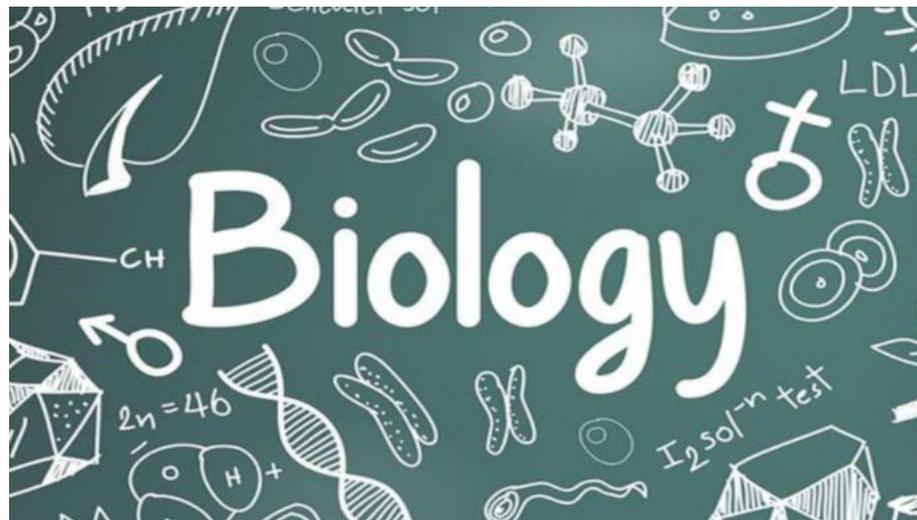
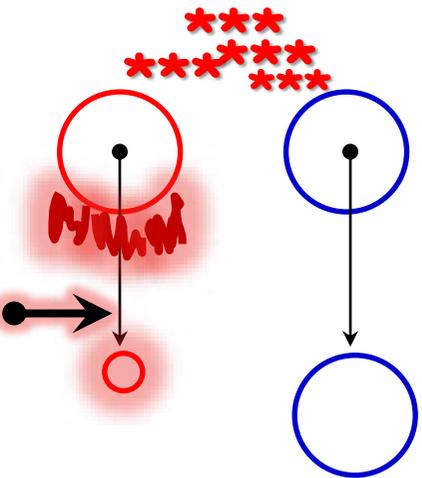
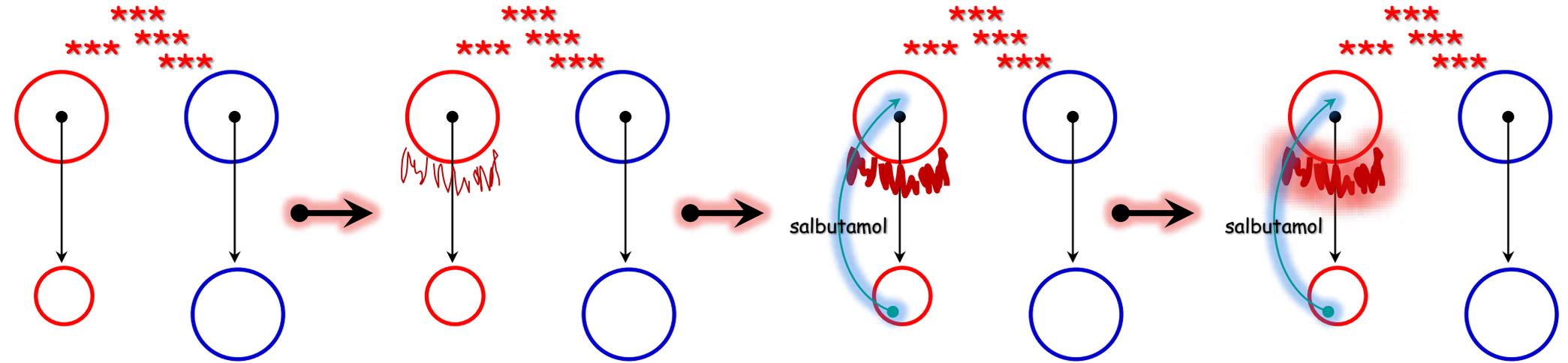
Boner AL, *Pediatr Pulmonol.* 1988;4(4):197-200.



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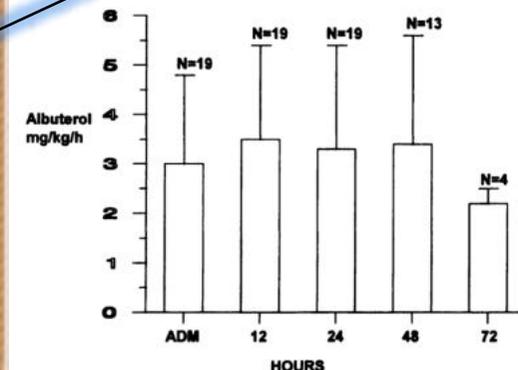
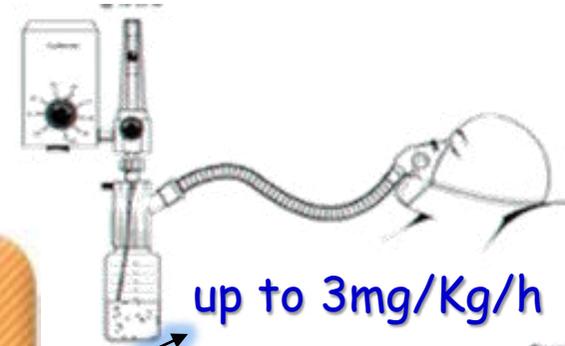
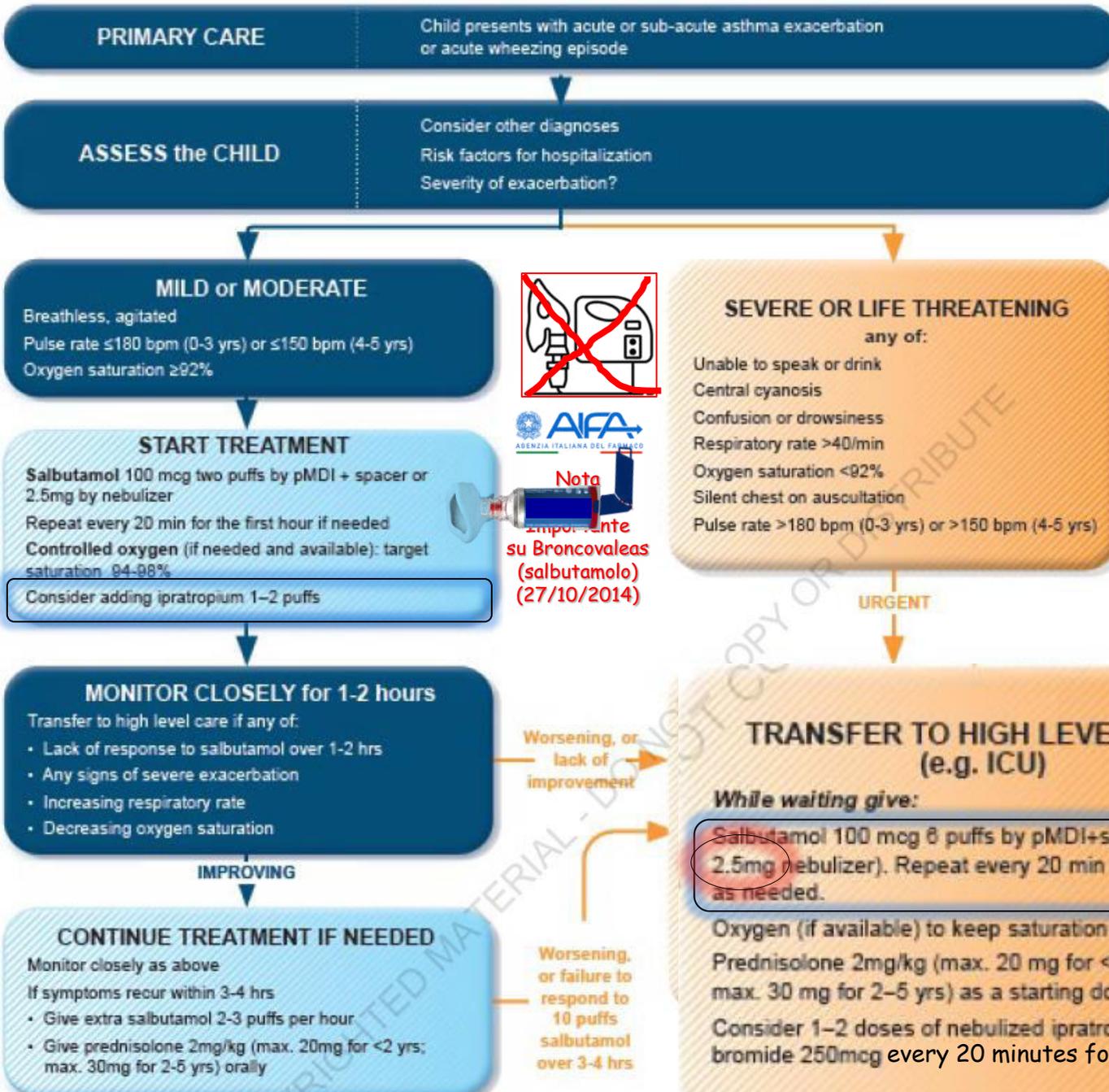


GINA 2021: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended



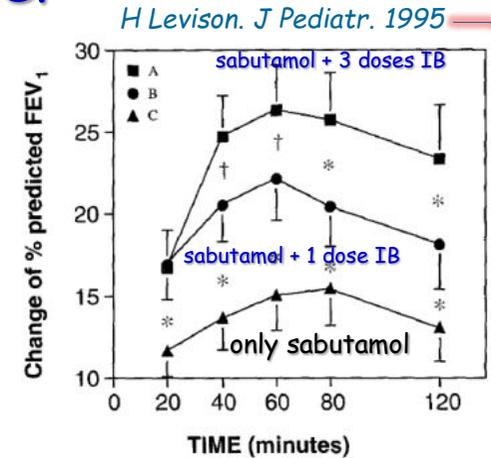
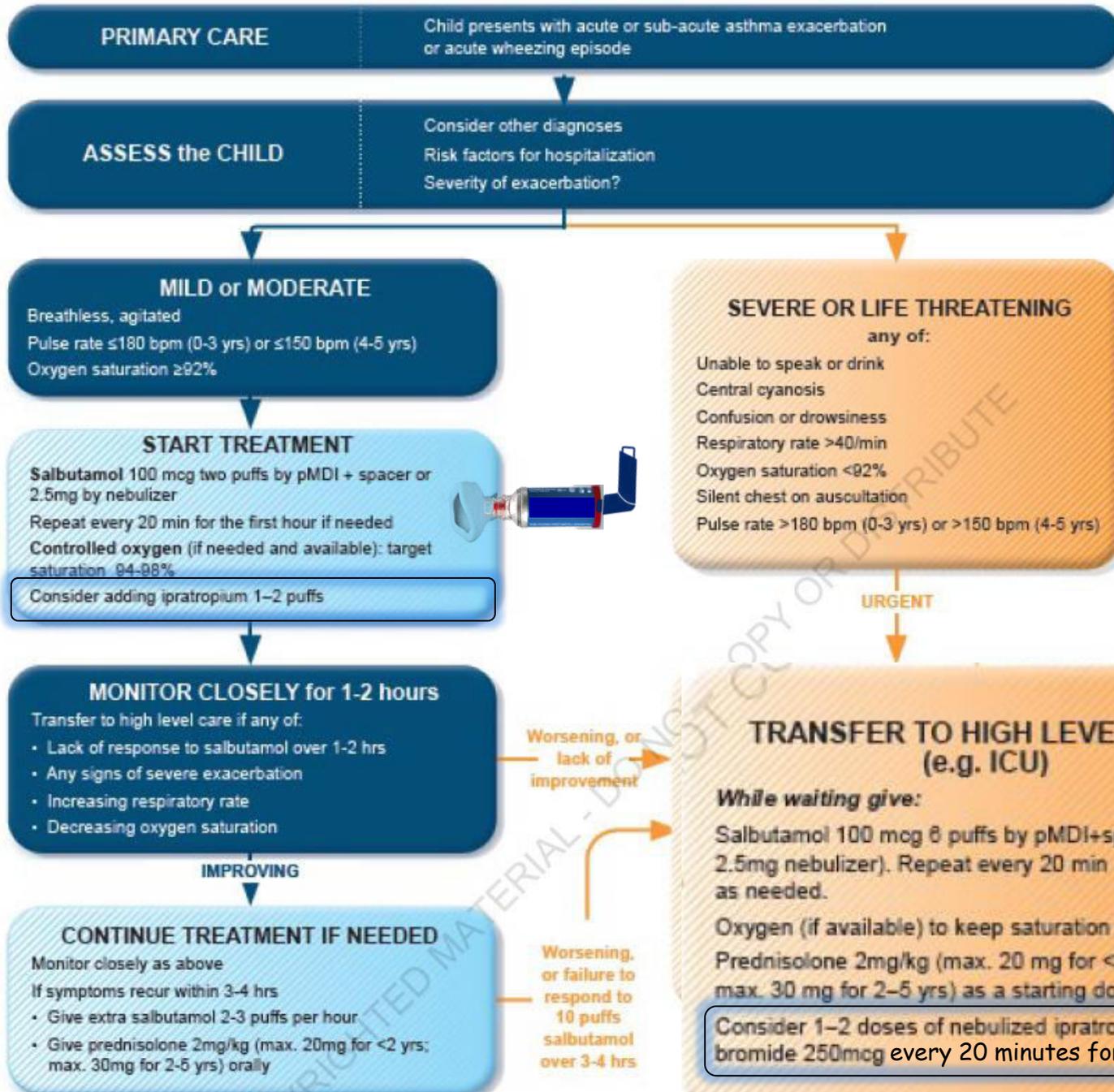
What's new in GINA 2021?

Management of acute asthma or wheezing in children 5 years and younger



What's new in GINA 2021?

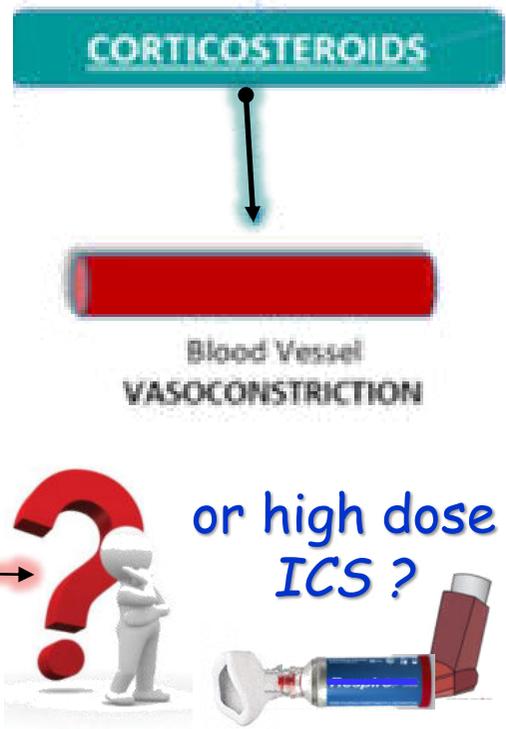
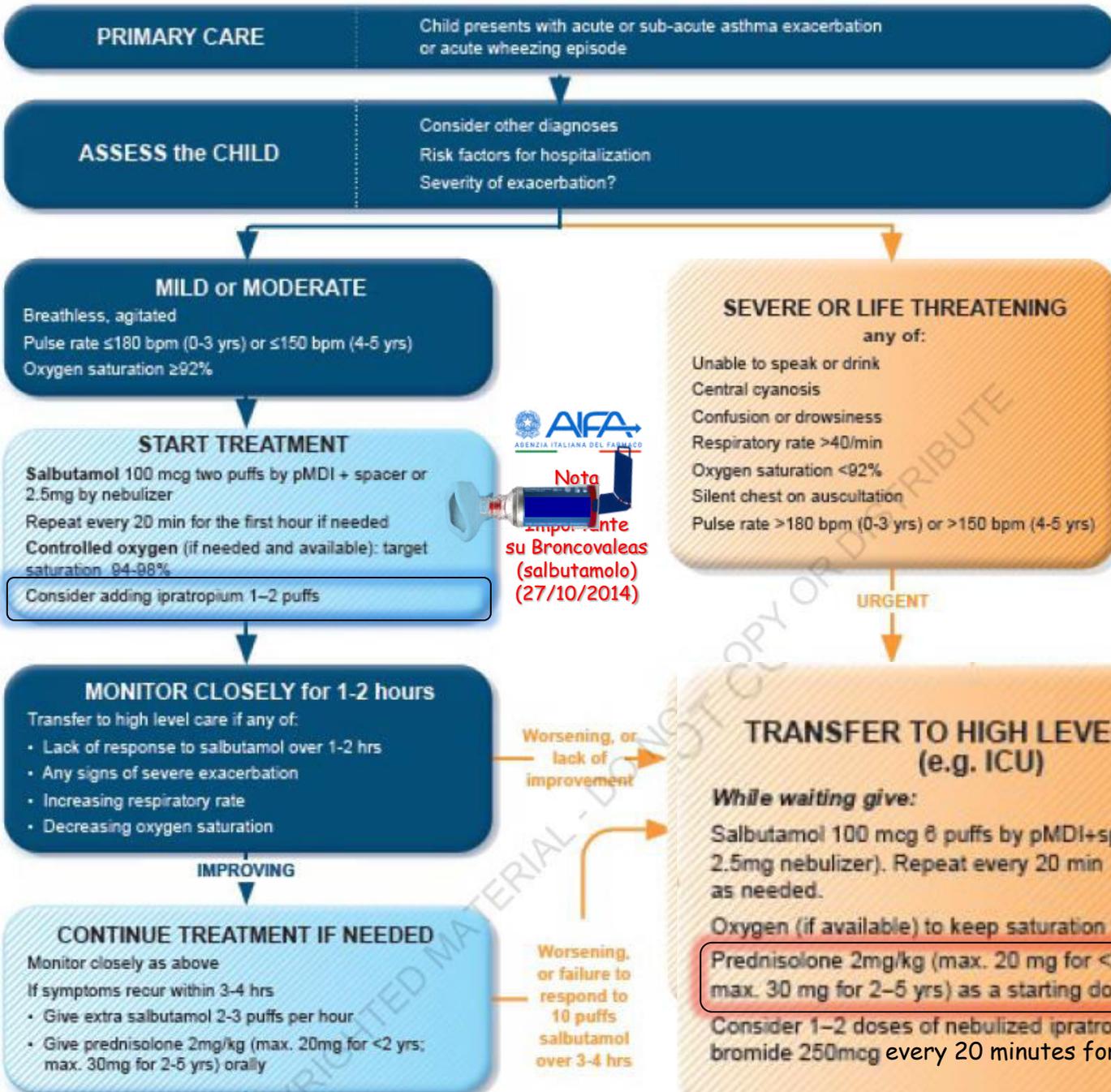
Management of acute asthma or wheezing in children 5 years and younger



DELAYED

What's new in GINA 2021?

Management of acute asthma or wheezing in children 5 years and younger



Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: Randomized clinical trial.

Iramain R, Pediatr Pulmonol. 2019;54(4):372-377.

✓ 103 children
(2-14 years of age)
with severe asthma exacerbations
(defined by the
Pulmonary Score ≥ 7)

• salbutamol and ipratropium
(2 puff every 10 min for 2 h and
then every 30 min for 2 h more)
by MDI with a valved-holding
chamber and mask along with
oxygen by a cannula separately
(MDI-SIB);

vs

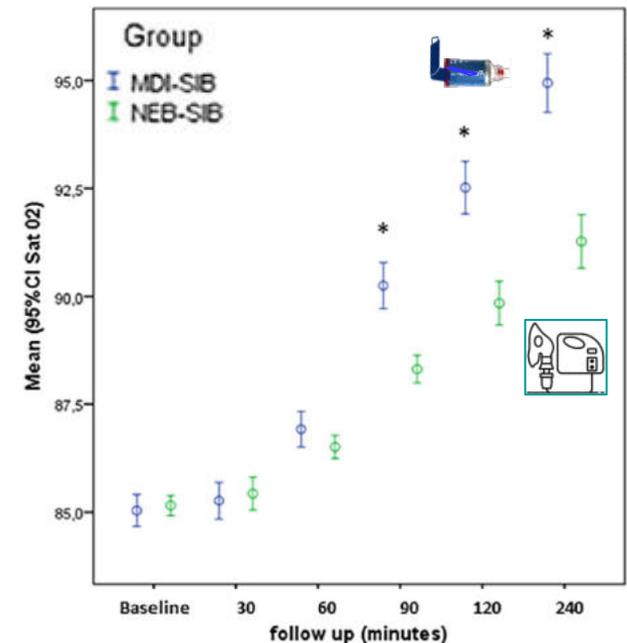
• nebulization with oxygen
(NEB-SIB) of salbutamol and
ipratropium (1 every 20 min for 2 h
and then every 30 min for 2 h
more)

TABLE 1 Pulmonary score¹²

Score	Respiratory rate (breaths/min)		Wheezing	Accessory muscle use-sternocleidomastoid
	<6 yrs	≥ 6 yrs		
0	<30	<20	None	No apparent increase
1	31-45	21-35	Terminal expiration with stethoscope	Mild increase
2	46-60	36-50	Entire expiration with stethoscope	Increase
3	>60	>50	Inspiration & expiration without stethoscope	Maximal activity

The Pulmonary Score ranges from 0 (no or very mild exacerbation) to 9 (severe exacerbation).

Oxygen saturation
(mean and 95%CI)
during the treatment
between groups
(*P < 0.0001)



Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: Randomized clinical trial.

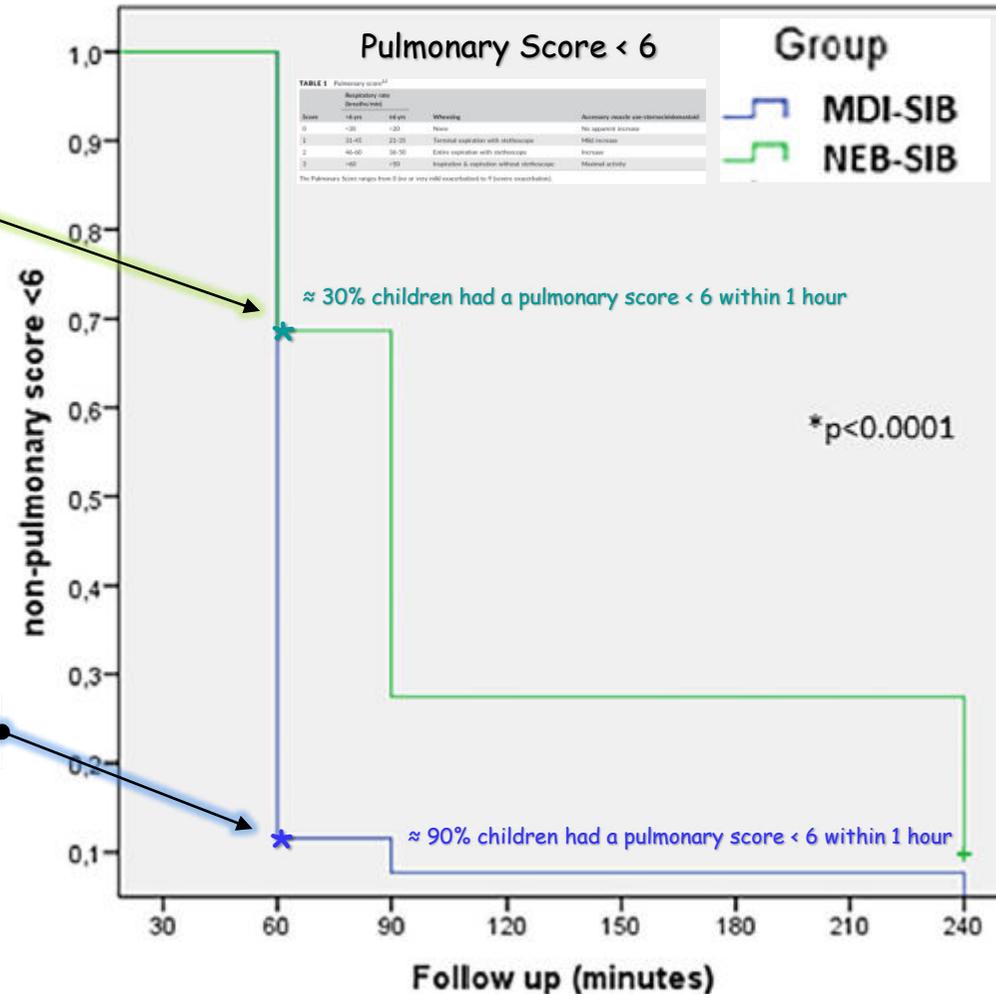
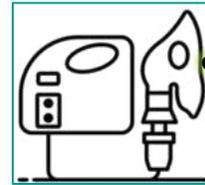
Iramain R, Pediatr Pulmonol. 2019;54(4):372-377.

✓ 103 children (2-14 years of age) with severe asthma exacerbations (defined by the **Pulmonary Score ≥ 7**)

- salbutamol and ipratropium (2 puff every 10 min for 2 h and then every 30 min for 2 h more) by MDI with a valved-holding chamber and mask along with oxygen by a cannula separately (MDI-SIB);

vs

- nebulization with oxygen (NEB-SIB) of salbutamol and ipratropium (1 every 20 min for 2 h and then every 30 min for 2 h more)



What's new in GINA 2021?

Box 6-7. Choosing an inhaler device for children 5 years and younger

Age	Preferred device	Alternate device
0–3 years	Pressurized metered dose inhaler plus dedicated spacer with face mask	Nebulizer with face mask
4–5 years	Pressurized metered dose inhaler plus dedicated spacer with mouthpiece	Pressurized metered dose inhaler plus dedicated spacer with face mask or nebulizer with mouthpiece or face mask



❖ Young children can use spacers of all sizes, but theoretically a lower volume spacer (<350 mL) is advantageous in very young children.



- Bisgaard H, A non-electrostatic spacer for aerosol delivery. *Arch Dis Child.* 1995 Sep;73(3):226-30.
- Kenyon CJ, The effects of static charge in spacer devices on glucocorticosteroid aerosol deposition in asthmatic patients. *Eur Respir J.* 1998 Mar;11(3):606-10.
- Wildhaber JH, Reducing electrostatic charge on spacer devices and bronchodilator response. *Br J Clin Pharmacol.* 2000 Sep;50(3):277-80.

Inhaler Errors in the CRITIKAL Study: Type, Frequency, and Association with Asthma Outcomes

Price DB, JACI Pract 2017; 5:1071-1081

➤ The CRITIKAL study is the first study to observe associations between specific inhaler errors and poorer asthma outcomes, including increased likelihood of having uncontrolled symptoms and increased exacerbation rate.

➤ Over the past 40 years the frequency and type of inhaler errors have not changed.



➤ Generic errors, such as not exhaling, not holding the breath, insufficient speed of inhalation, dose preparation errors for DPIs, and coordination problems with MDIs, were the most common.

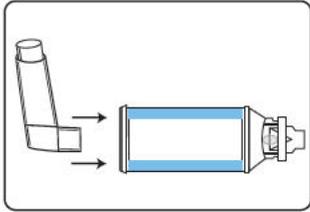
➤ One critical error in this study was insufficient inspiratory effort when using a DPI. All DPIs demonstrate flow-dependent dose emission and therefore the generic instruction when using these is to inhale as fast as possible.

How to use an MDI with a spacer



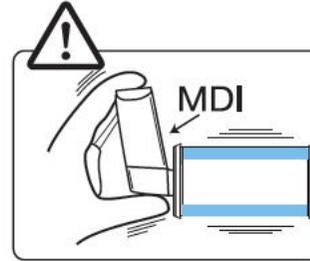
FASE 1:

Inserire lo spray nel distanziatore Respiro®



FASE 2:

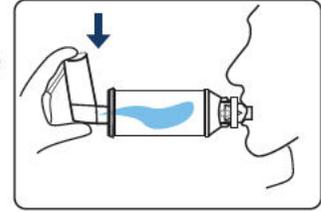
Agitare bene lo spray inserito nel distanziatore prima di ogni spruzzo.



FASE 3:

Espirare profondamente.

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



FASE 4:

RIPETERE QUESTI PASSAGGI PER 2 VOLTE

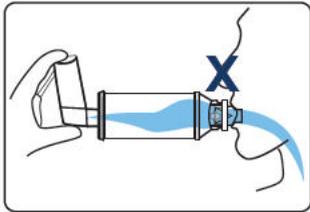
FASE 5:

FASE 5:

(per soggetti non collaboranti)

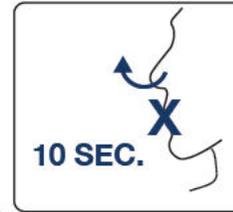
Inspirare profondamente

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



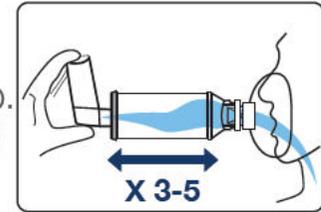
Trattenere il respiro per 10 secondi

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



Per i bambini in età prescolare

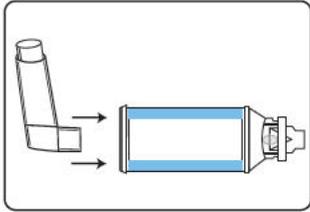
si deve usare una mascherina che aderisca bene al viso. Far eseguire 3-5 atti respiratori.



How to use an MDI with a spacer

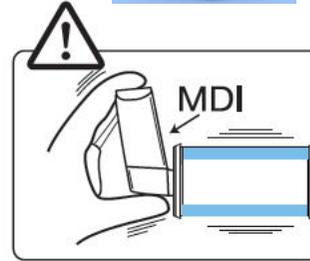
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Inserire lo spray nel distanziatore Respiro®



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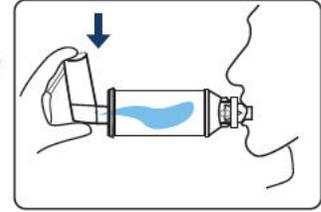
Agitare bene lo spray inserito nel distanziatore prima di ogni spruzzo.



FASE 3:

Espirare profondamente.

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

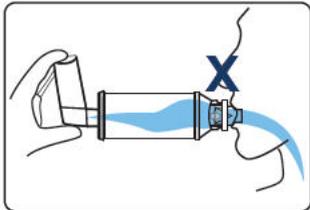


FASE 4:

RIPETERE QUESTI PASSAGGI PER VOLTE

Inspirare profondamente

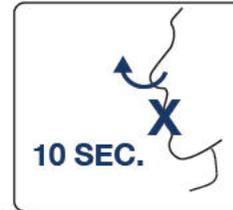
e lentamente dalla bocca, tenendo le labbra chiuse sul boccaglio fino alla fine dell'inspirio.



FASE 5:

Traferire il respiro per 10 secondi

ed espirare lentamente dalla bocca. Ripetere con il farmaco ogni 10 secondi. So...

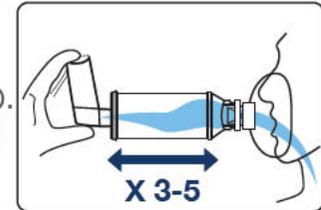


FASE 5:

(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.



.....spray

1 + 1 (2) spruzzi al mattino

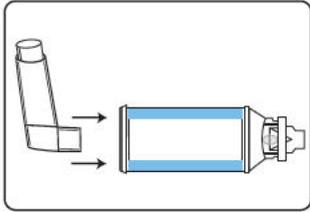
1 + 1 (2) spruzzi alla sera



How to use an MDI with a spacer

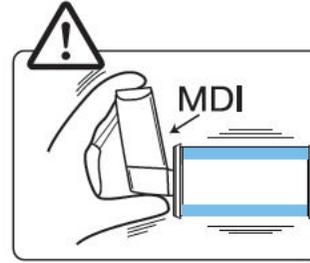
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FASE 2:

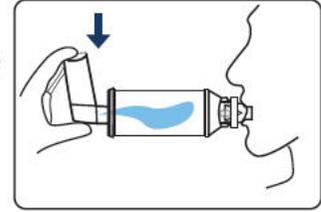
Agitare bene lo spray inserito nel distanziatore prima di ogni spruzzo.



FASE 3:

Espirare profondamente.

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



FASE 4:

RIPETERE QUESTI PASSAGGI PER 2 VOLTE

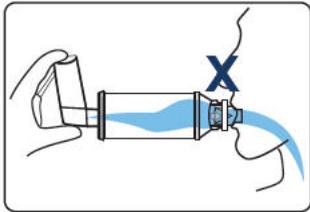
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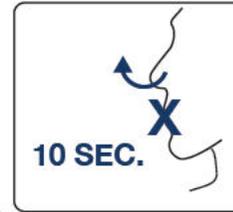
Inspirare profondamente

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



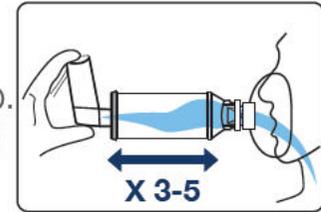
Trattenere il respiro per 10 secondi

ed espirare lentamente dal naso per ridurre i sintomi della tosse. Il farmaco non andrebbe sciaccolato.



Per i bambini in età prescolare

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



Tira su, tira su, tira su

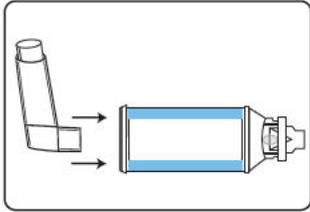
.....
... tira su.



How to use an MDI with a spacer

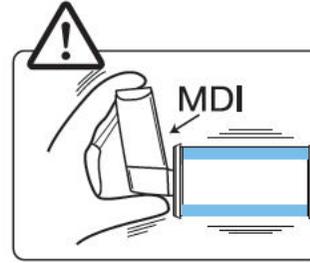
FASE 1:

Inserire lo spray nel distanziatore Respiro®



FASE 2:

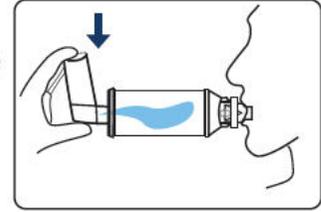
Agitare bene lo spray inserito nel distanziatore prima di ogni spruzzo.



FASE 3:

Espirare profondamente.

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



FASE 4:

RIPETERE QUESTI PASSAGGI PER 2 VOLTE

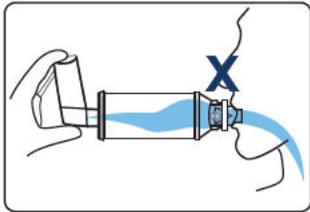
FASE 5:

FASE 5:

(per soggetti non collaboranti)

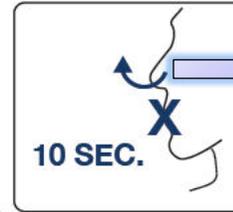
Inspirare profondamente

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



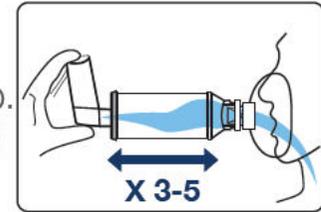
Trattenere il respiro per 10 secondi

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



Per i bambini in età prescolare

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



Development and cross-sectional validation of the Childhood Asthma Control Test.

Liu AH, *J Allergy Clin Immunol.* 2007 Apr;119(4):817-25.

- ✓ A 21 item questionnaire was administered to 343 patients with asthma and their caregivers
- ✓ 7 items were selected from regression analyses to comprise the C-ACT

A score ≤ 19 indicated inadequately controlled asthma (specificity 74%, sensitivity 68%)

Have your child complete these questions.

SCORE

1. How is your asthma today?

				<input type="checkbox"/>
Very bad 0	Bad 1	Good 2	Very good 3	

2. How much of a problem is your asthma when you run, exercise or play sports?

				<input type="checkbox"/>
It's a big problem, I can't do what I want to do. 0	It's a problem and I don't like it. 1	It's a little problem, but it's okay. 2	It's not a problem. 3	

3. Do you cough because of your asthma?

				<input type="checkbox"/>
Yes, all of the time. 0	Yes, most of the time. 1	Yes, some of the time. 2	No, none of the time. 3	

4. Do you wake up during the night because of your asthma?

				<input type="checkbox"/>
Yes, all of the time. 0	Yes, most of the time. 1	Yes, some of the time. 2	No, none of the time. 3	

Please complete the following questions on your own

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

<input type="checkbox"/>					
5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

<input type="checkbox"/>					
5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

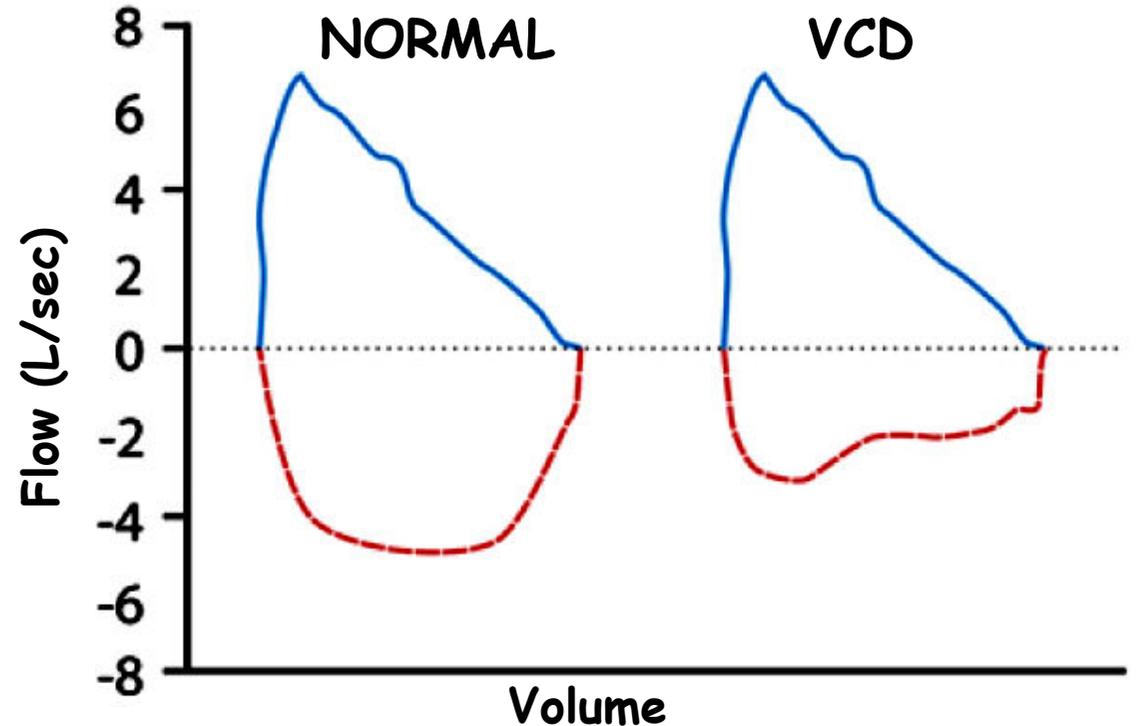
<input type="checkbox"/>					
5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

TOTAL

Use of videography in the diagnosis of exercise-induced vocal cord dysfunction: a case report with video clips.

Davis RS, J Allergy Clin Immunol. 2007 Jun;119(6):1329-31.

➤ In evaluating for EIVCD, an exercise challenge with flow-volume loops may show the characteristic pattern of a **flattening or clipping** of the **inspiratory loop** when the patient is symptomatic.



The effort on the right reveals blunting or flattening of the inspiratory portion of the loop.

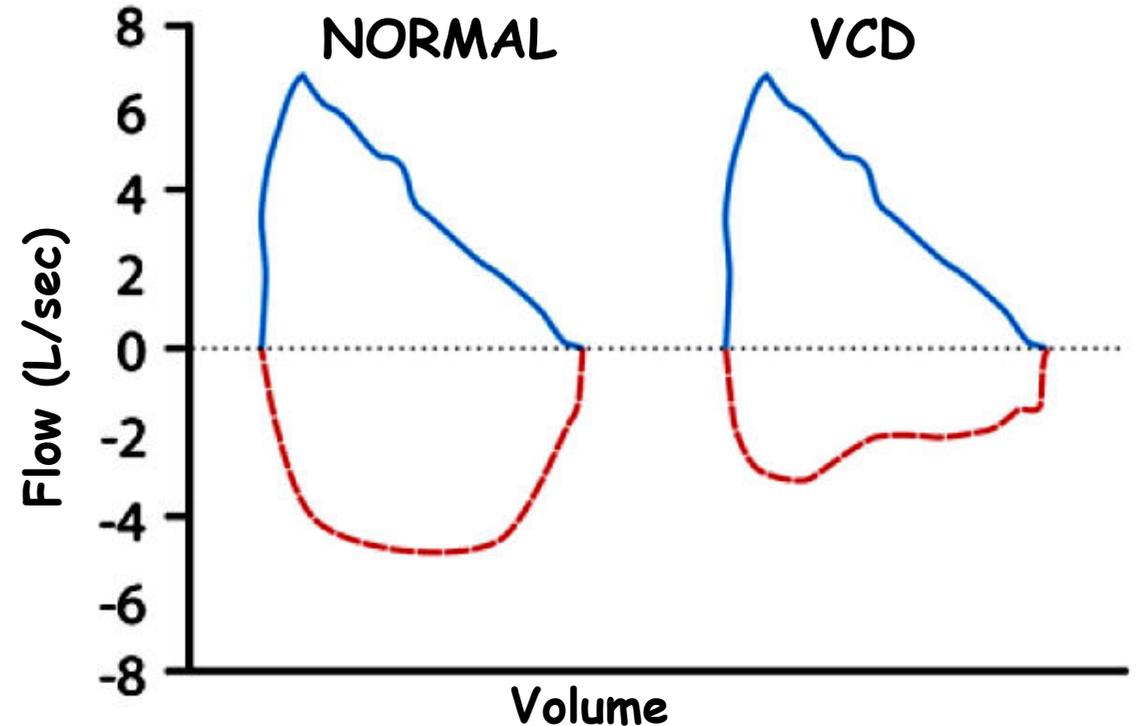
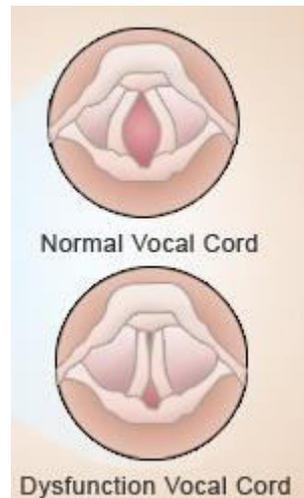
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➤ In evaluating for EIVCD, an exercise challenge with flow-volume loops may show the characteristic pattern of a **flattening or clipping** of the **inspiratory loop** when the patient is symptomatic.

❖ However, a negative challenge test does not rule it out.

➤ The gold standard for the diagnosis of VCD is visualization of the vocal cords in the symptomatic patient.



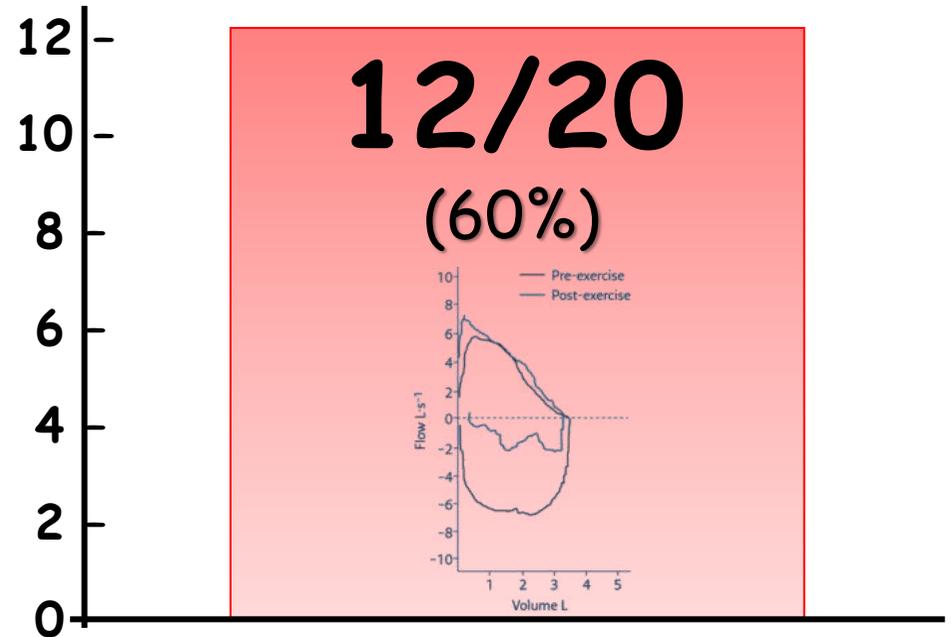
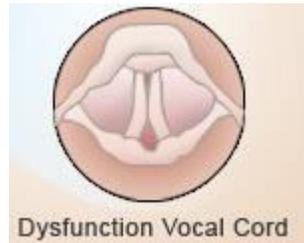
The effort on the right reveals blunting or flattening of the inspiratory portion of the loop.

Pulse oximetry coupled with spirometry in the emergency department helps differentiate an asthma exacerbation from possible vocal cord dysfunction.

Nolan PK, Pediatr Pulmonol. 2007 Jul;42(7):605-9.

n° patients with spirometric evidence of VCD

- ✓ In 20 patients persistently symptomatic with acute respiratory distress and room air oxygen saturations $\geq 97\%$ after treatment.



What's new in GINA 2021?

➤ "The relevance of managing **co-morbid conditions** to ensure optimal asthma control has been increasingly stressed in successive versions".

• Some of these conditions can mimic asthma or contribute to symptoms e.g.:

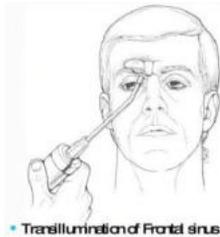
○ vocal cord dysfunction



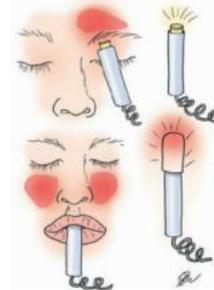
○ anxiety disorders

○ hyperventilation S.

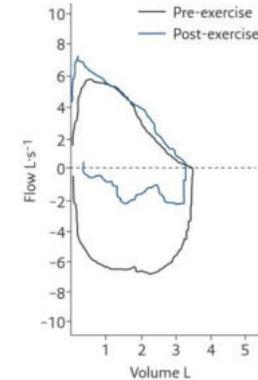
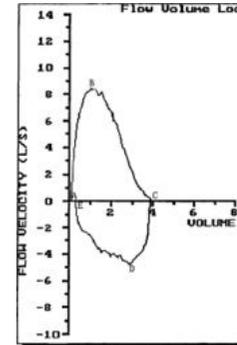
○ upper airways disease



• Transillumination of Frontal sinus



• others may reduce responsiveness to treatment (e.g. smoking and concurrent COPD)".



and

	NEVER 0	RARE 1	SOMETIMES 2	OFTEN 3	VERY OFTEN 4
Chest pain					
Feeling tense					
Blurred vision					
Dizzy spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in chest					
Bloated feelings in stomach					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers or arms					
Tight feelings around mouth					
Cold hands or feet					
Palpitations					
Feelings of anxiety					

Nijmegen questionnaire score > 23 out of 64 = HS

Evaluation of association between exercise-induced bronchoconstriction and childhood asthma control test questionnaire scores in children

Chinellato I. and Boner AL Pediatr Pulmonol 2012;47:226-32

- ✓ 92 asthmatic children.
- ✓ EIB evaluated by exercise challenge.
- ✓ C-ACT score.



The two single questions showing a significant association with EIB were those focusing on nocturnal asthma.



Evaluation of association between exercise-induced bronchoconstriction and childhood asthma control test questionnaire scores in children

Chinellato I. and Boner AL *Pediatr Pulmonol* 2012;47:226-32



If you want to identify EIB ask for:

- 1) Nocturnal symptoms,
- 2) If the child fatigues earlier than his peers during exercise.

The two single questions showing a significant association with EIB were those focusing on nocturnal asthma.



Increase in atopic sensitization rate among Dutch children with symptoms of allergic disease between 1994 and 2014.

Koet LBM, Pediatr Allergy Immunol. 2018 Feb;29(1):78-83.



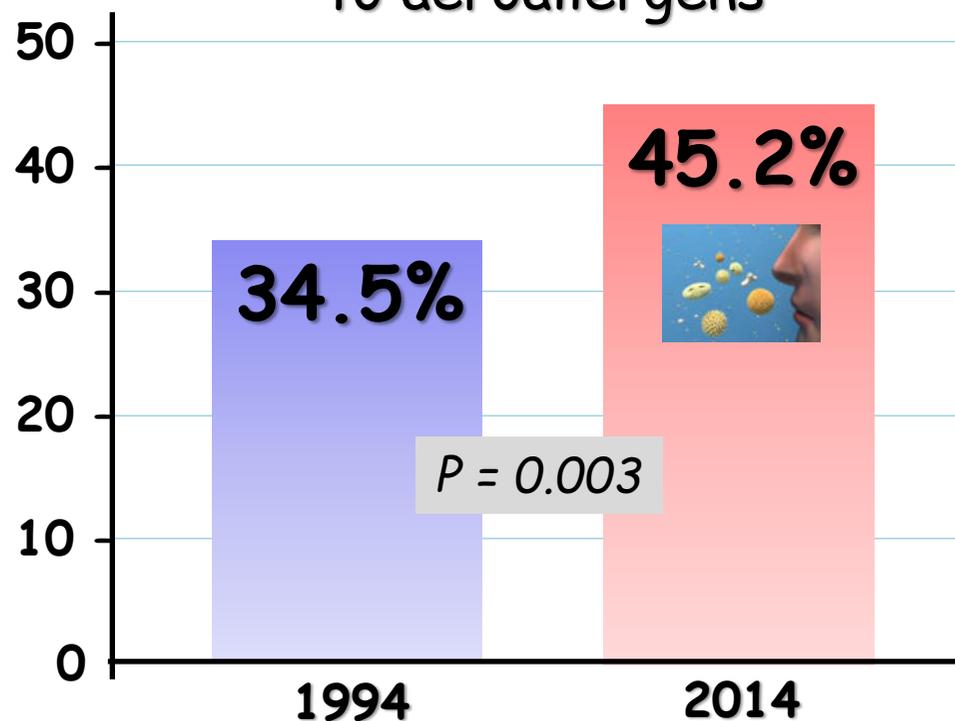
✓ Sensitization data of all children tested in our clinical laboratory during 1994-2014 (18,199 children)

✓ Sensitization using the ImmunoCAP system and defined as a specific IgE level of ≥ 0.35 kU/L.

✓ Trends in sensitization rates to 5 food and 5 aeroallergens for different age categories

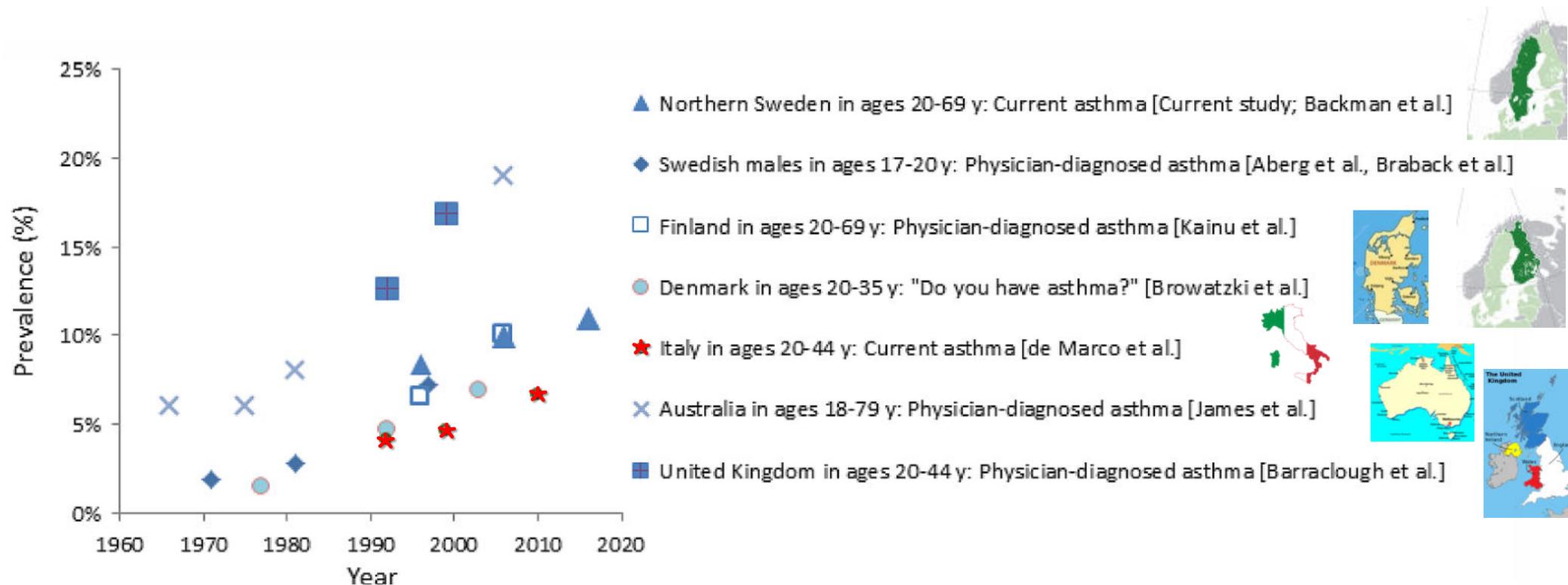


sensitization rate to aeroallergens



Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016 - results from three population surveys. *H Backman, CEA 2017;47:1426-1435*

Repeated surveys of **asthma prevalence among adults in the general population**, with the same methods within the same age-span and area.



Environmental changes could enhance the biological effect of Hop J pollens on human airway epithelial cells.

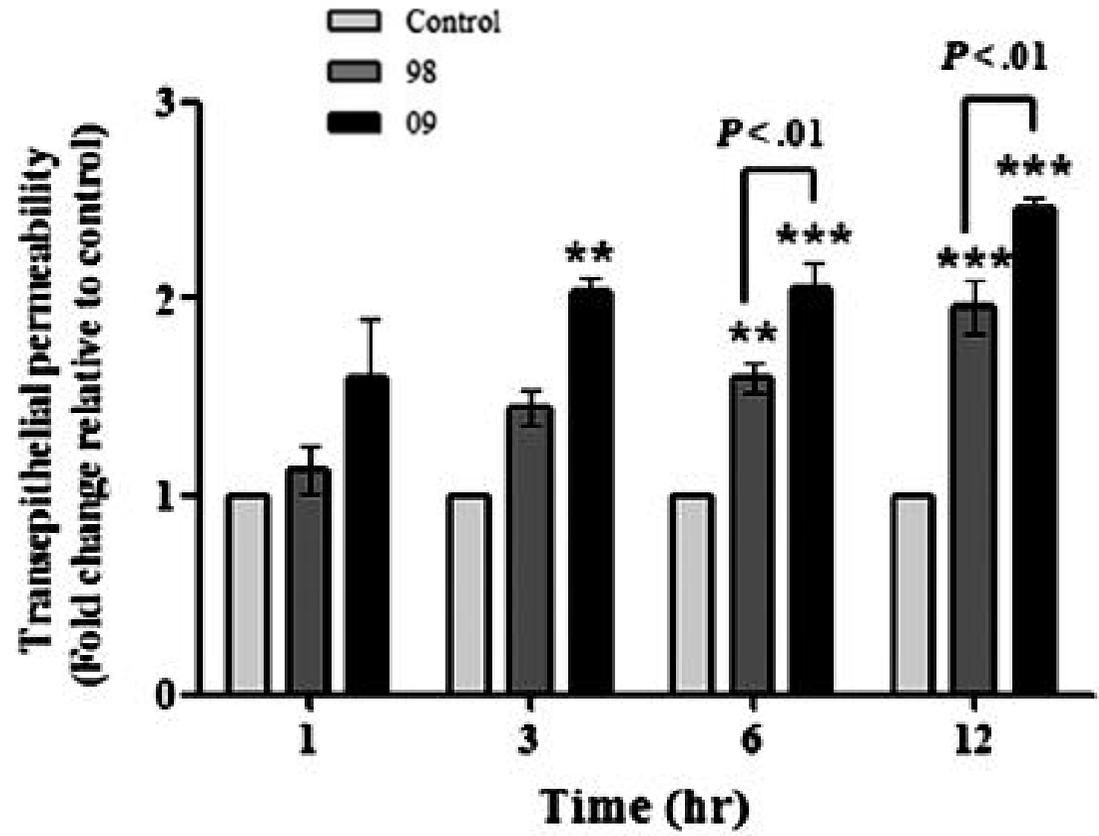
Lee SI, *J Allergy Clin Immunol* 2014;134:470-72

✓ Collected Hop J pollens in 1998 and 2009.

✓ Prepared 2 pollen extracts (the 1998 and 2009 extracts).



Transepithelial permeability of Calu-3 cells induced by the 2 pollen extracts



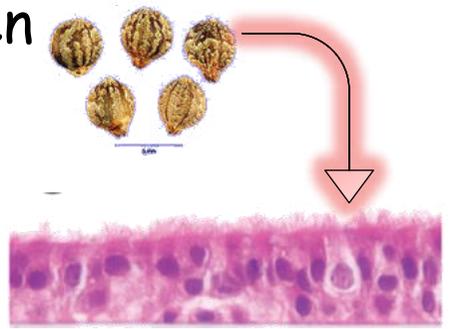
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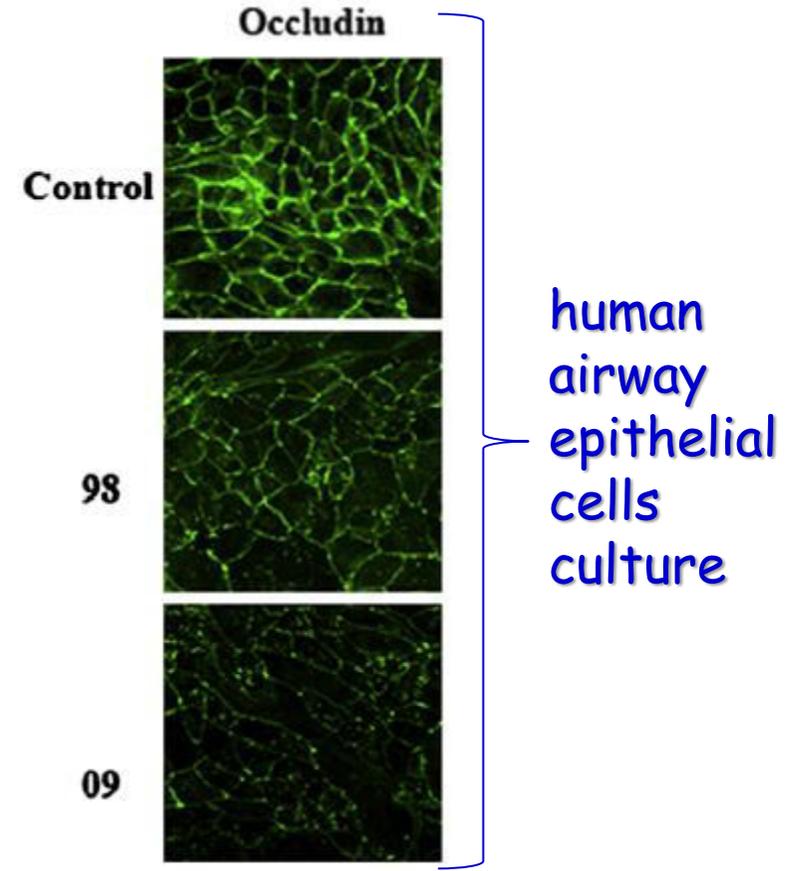
✓ Collected Japanese hop *luppolo del Giappone* (Hop J) pollens in 1998 and 2009.



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Occludin degradations induced by **protease activity** of Hop J pollen extracts



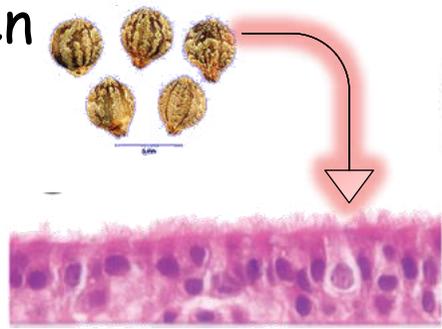
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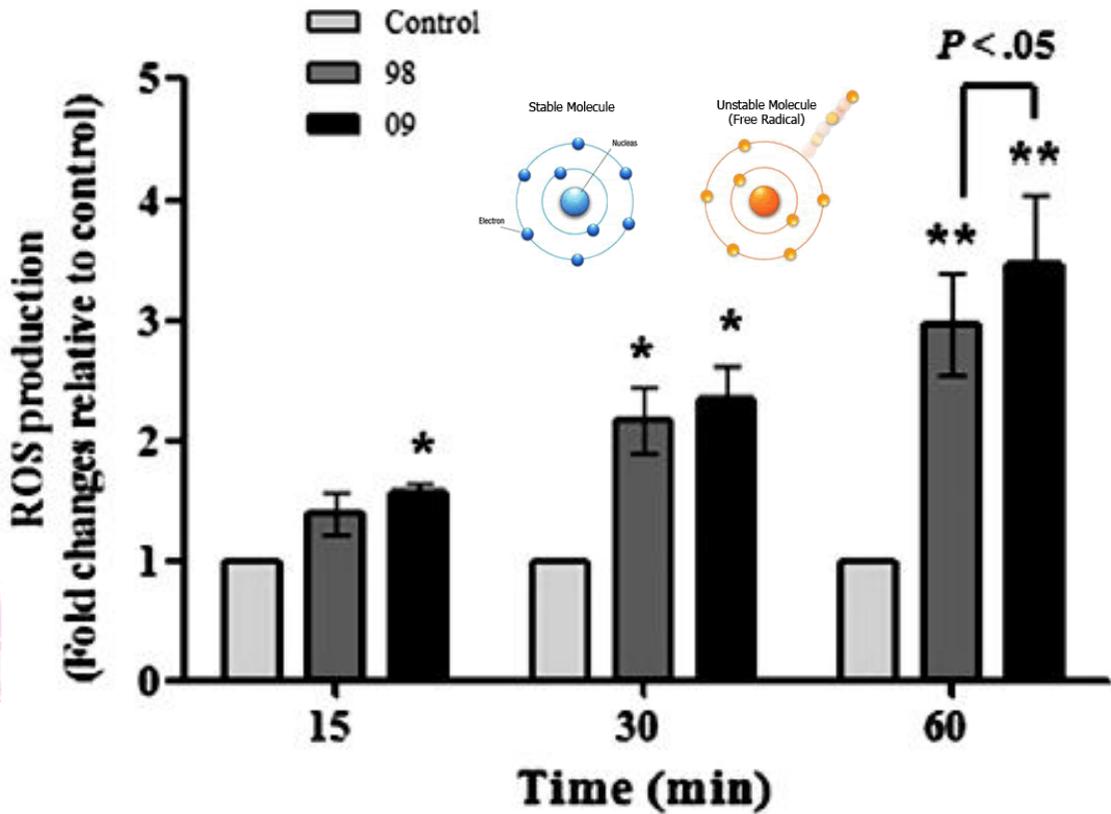
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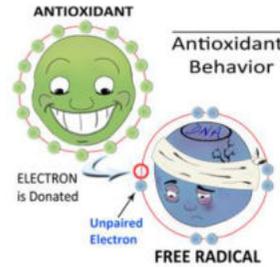


ROS production (oxidase activity) in human airway epithelial cells induced by the 98 and 09 extracts

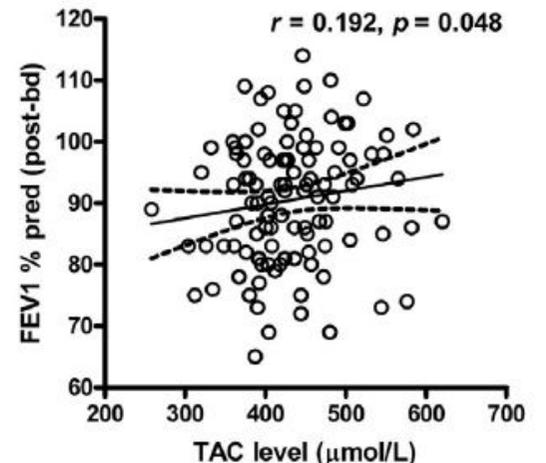
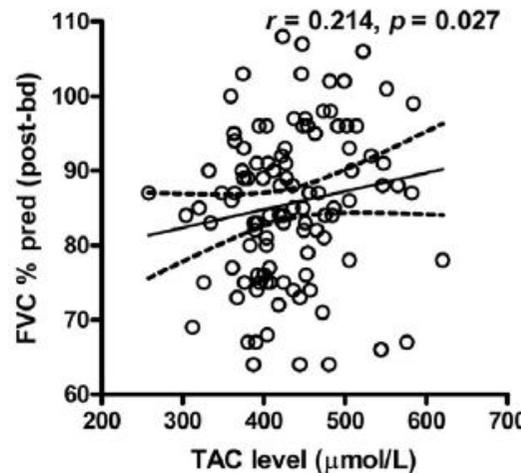
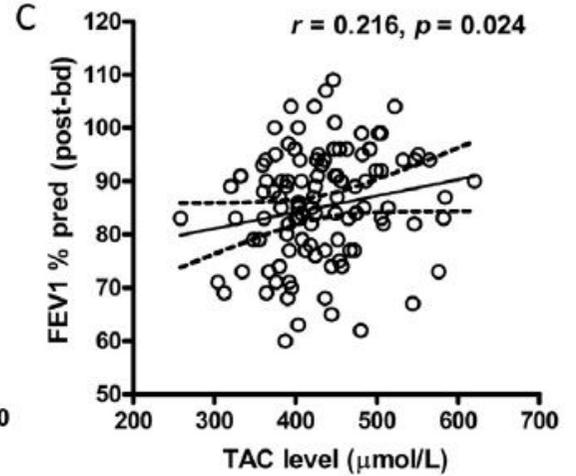
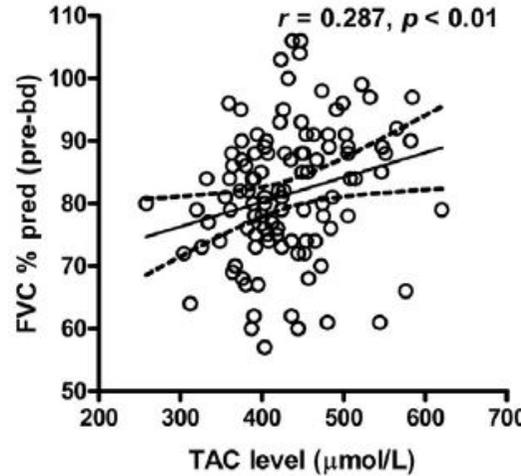


Oxidative stress is associated with atopic indices in relation to childhood rhinitis and asthma.

Wei Choo CY, *J Microbiol Immunol Infect.* 2021 Jun;54(3):466-473.



TAC levels were (+) associated with FVC and FEV₁% predicted



✓ 132 children who completed a 7-years follow-up in a birth cohort.

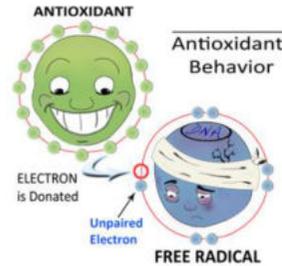
- glutathione peroxidase (GPx),
- myeloperoxidase (MPO),
- total anti-oxidant capacity (TAC),
- 8-hydroxy-2'-deoxyguanosine (8-OHdG) urine levels

✓ Lung function,



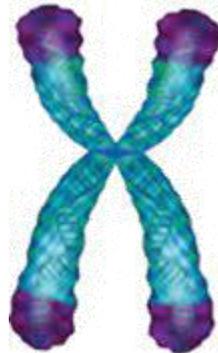
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✓ Lung function,

Prof. Dacher Keltner at UC Berkeley



• Born to Be Good:
The Science of a Meaningful Life,

• The Compassionate Instinct



Berkeley
UNIVERSITY OF CALIFORNIA

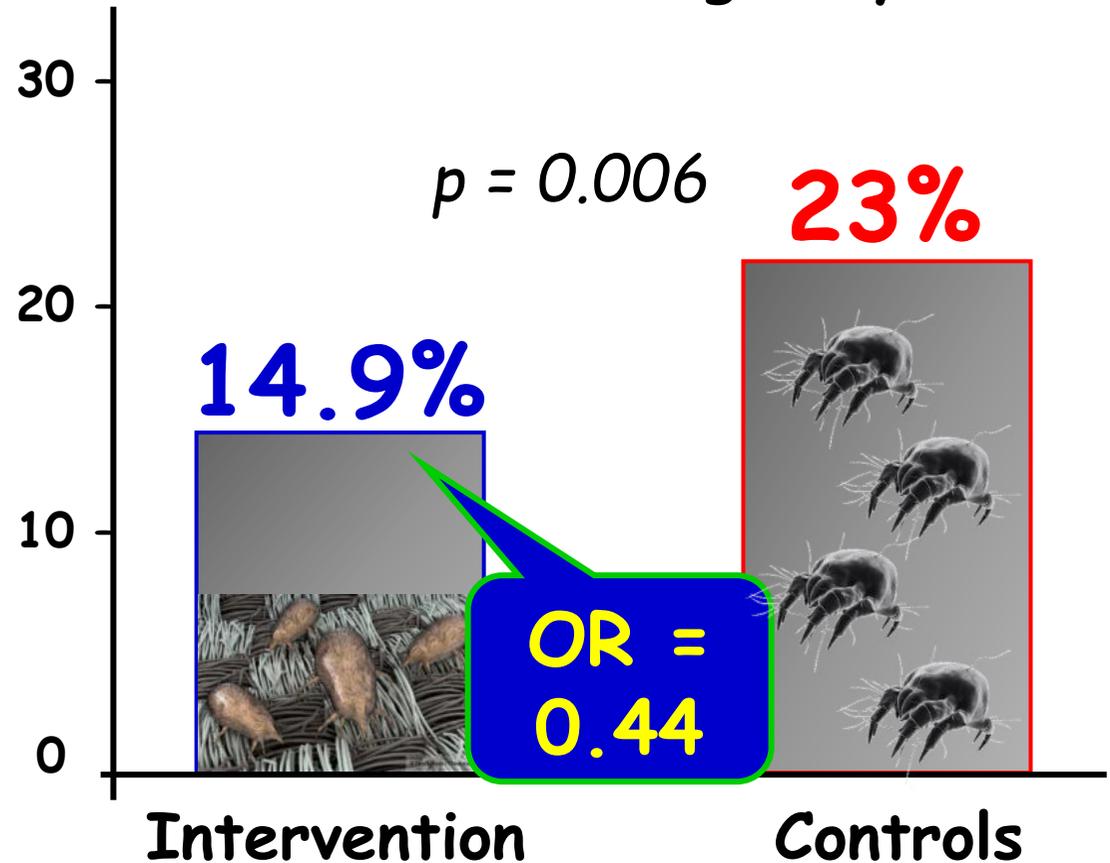
The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age.

Chan-Yeung M, *J Allergy Clin Immunol*. 2005;116(1):49-55.



- ✓ 545 high-risk infants with immediate FH of asthma and allergies
- ✓ Intervention (avoidance of house dust) or control groups
- ✓ Outcomes at 7 years

% ch. with pediatric diagnosis of asthma at age 7 yrs



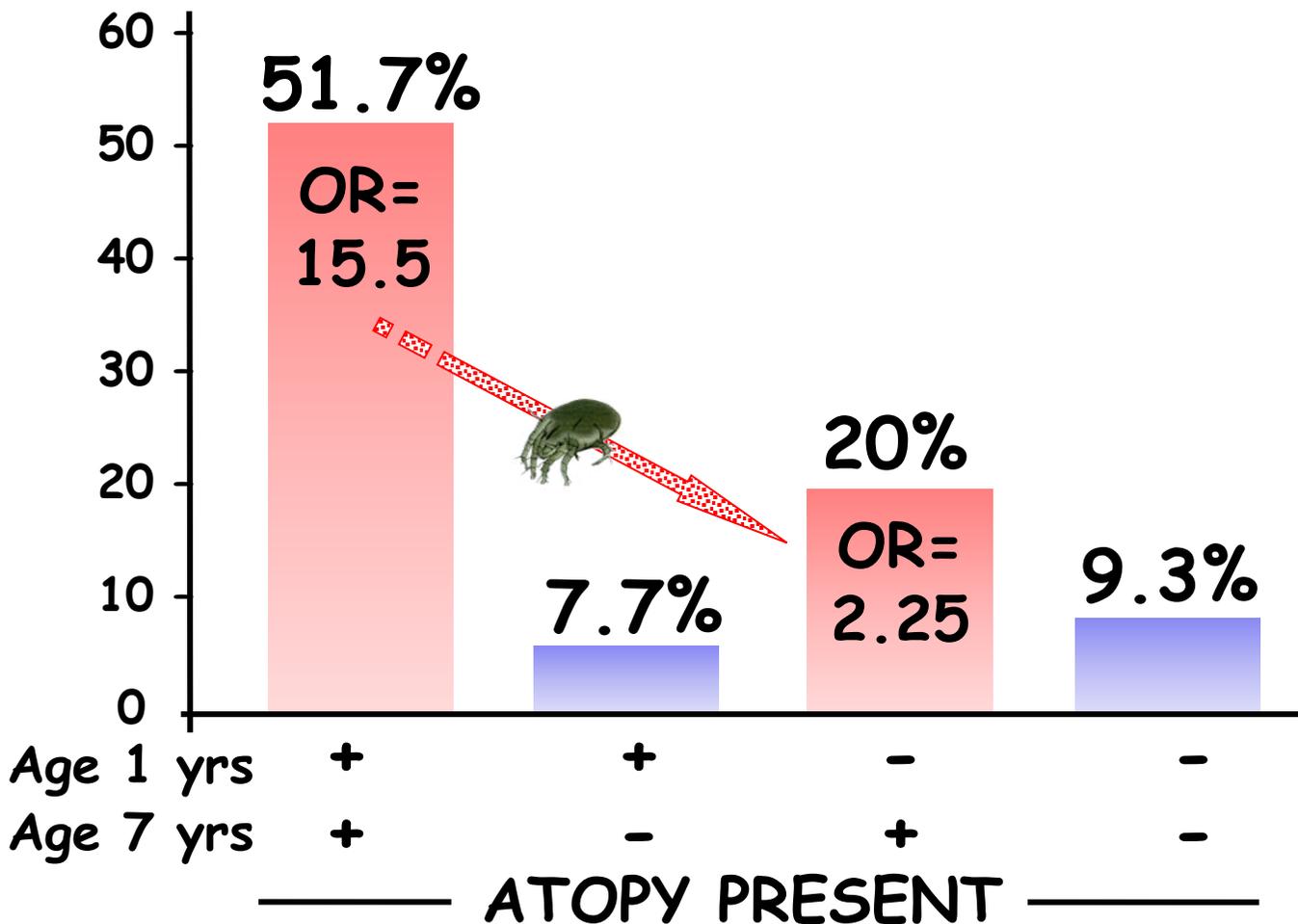
Atopy in early life and effect of a primary prevention program for asthma in a high-risk cohort.

Chan-Yeung M, *J Allergy Clin Immunol*. 2007;120(5):1221-3.



- ✓ Infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases.
- ✓ Intervention group (N=279) or the control group (N=266) before the child's birth.

PREVALENCE OF ASTHMA AT AGE 7 YEARS



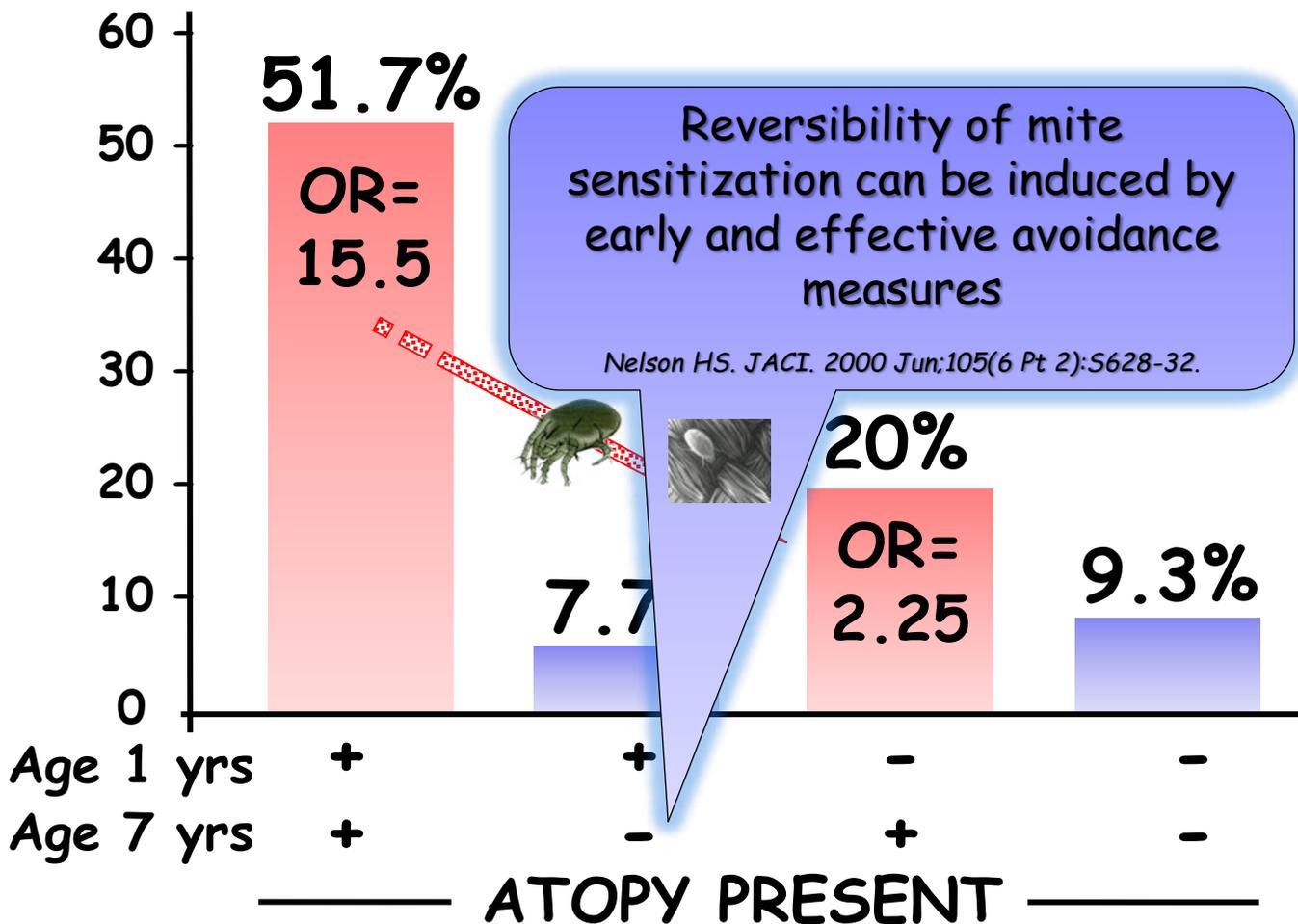
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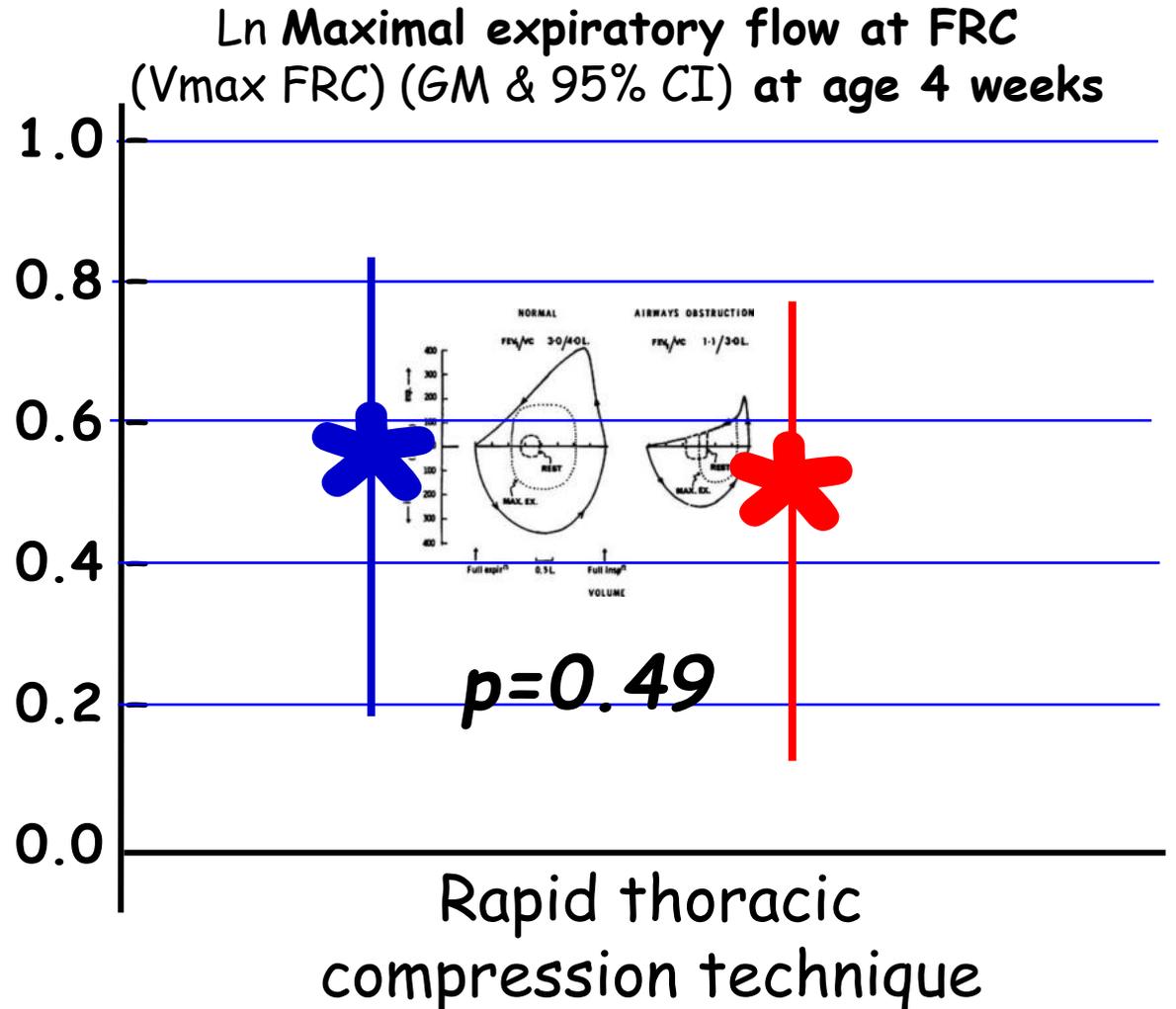


Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years.

Woodcock A, *Am J Respir Crit Care Med.* 2004;170(4):433-9.



- ✓ Manchester cohort
- ✓ 128 active group
- ✓ 111 control group
- ✓ Allergen level, symptoms, sensitization and lung function at 3 years of age



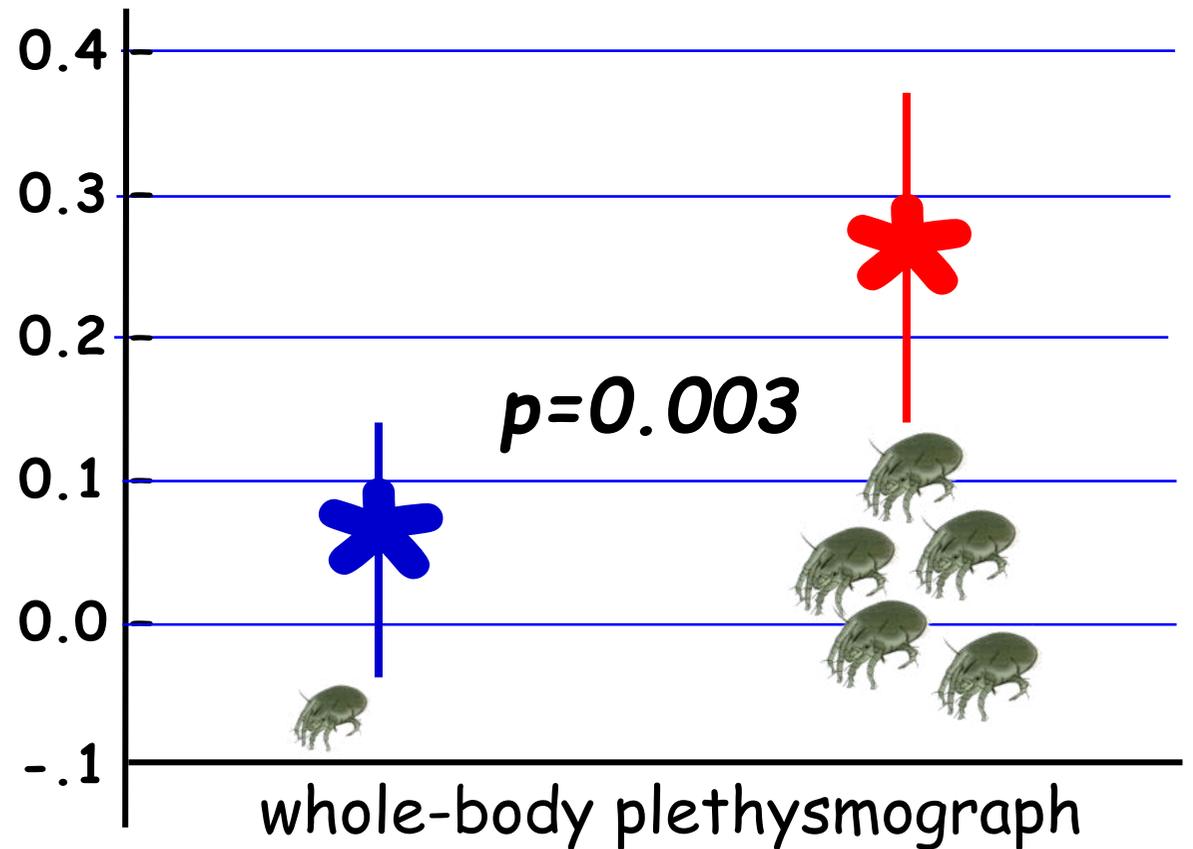
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Ln sRaw GM & 95% CI
(kiloPascal/second) at age 3 years



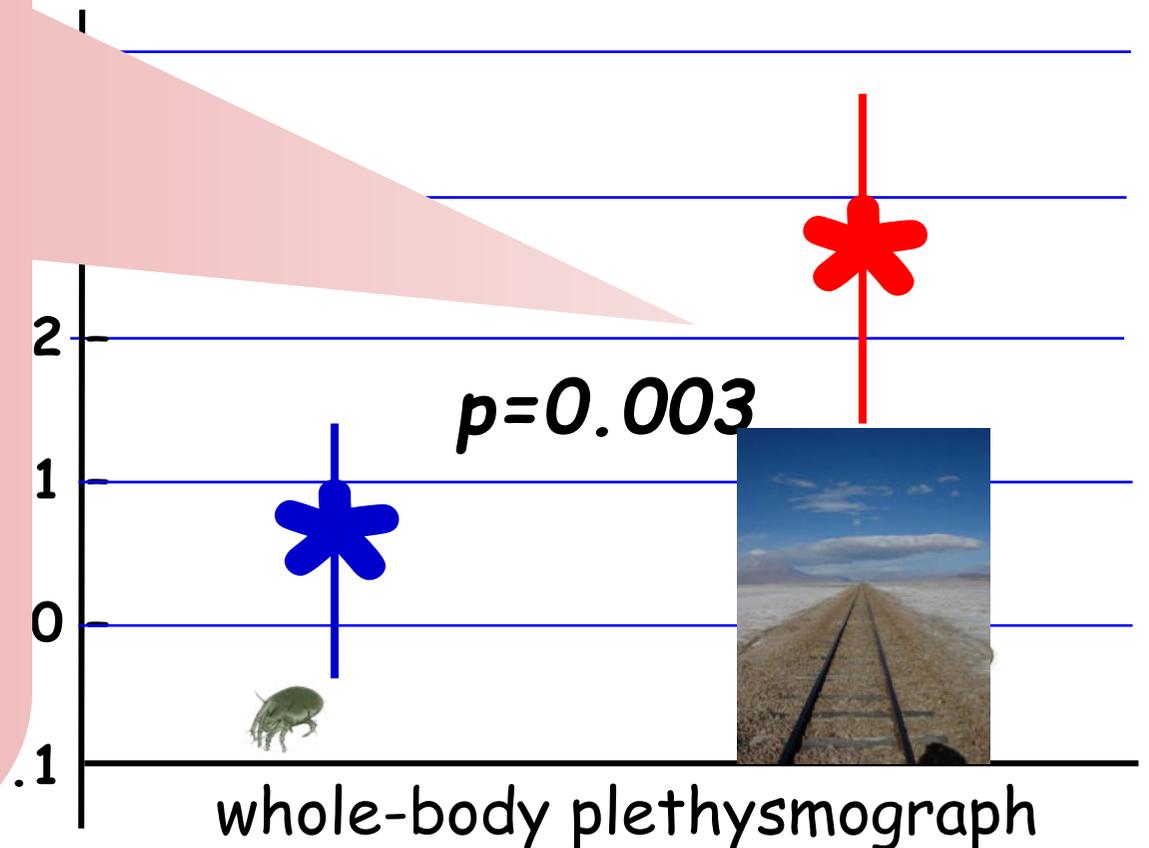
ALB

Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years.

Woodcock A, *Am J Respir Crit Care Med.* 2004;170(4):433-9.

This may be an important factor in relation to the tracking effect of lung function

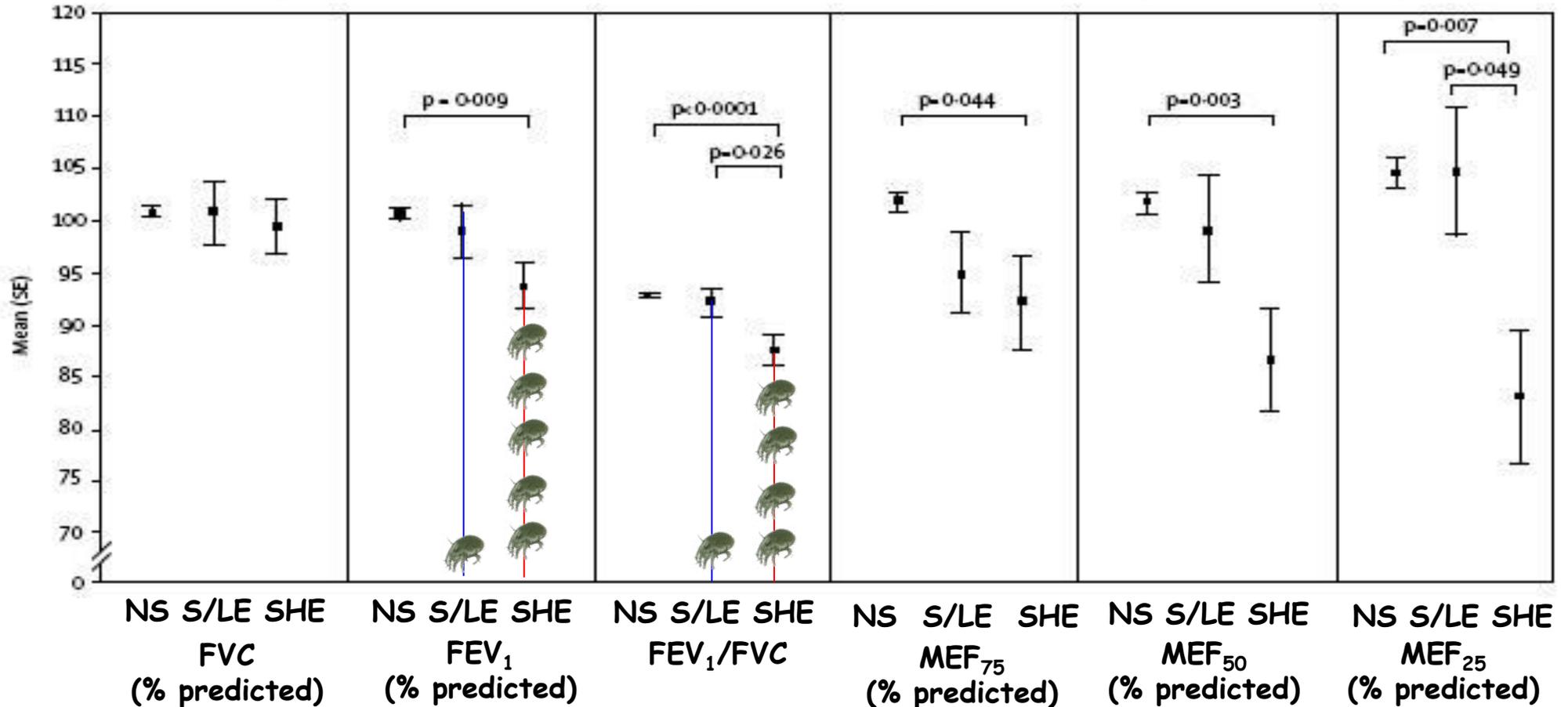
Ln sRaw GM & 95% CI
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Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study.

Illi S, Lancet. 2006;368(9537):763-70.

Effect of allergen sensitisation and exposure at ≤ 3 years on lung function at age 7 years.



NS= Not sensitised to dust mites or cat dander. S/LE= sensitised to dust mites cat dander and low exposure to these allergens. S/HE= Sensitised to dust mites or cat dander and high exposure to these allergen.

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

Murray CS, Am J Respir Crit Care Med. 2017;196(2):150-158

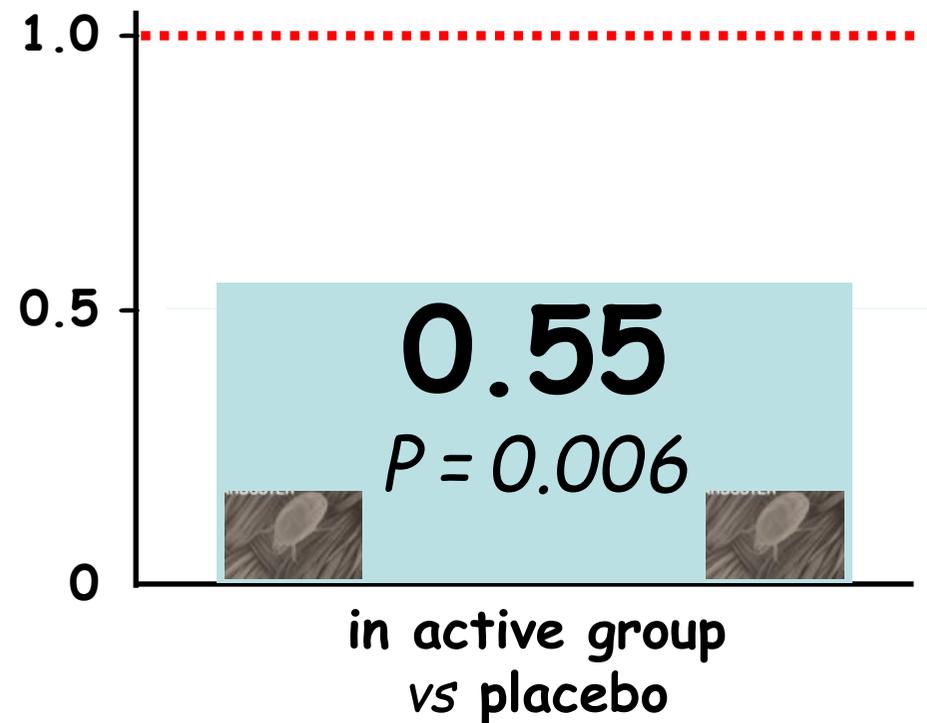
✓ mite-sensitized children with asthma (ages 3-17 yr) after an emergency hospital attendance with an asthma exacerbation to receive mite-impermeable (active group n°= 146) or control (placebo group n°= 138) bed encasings.



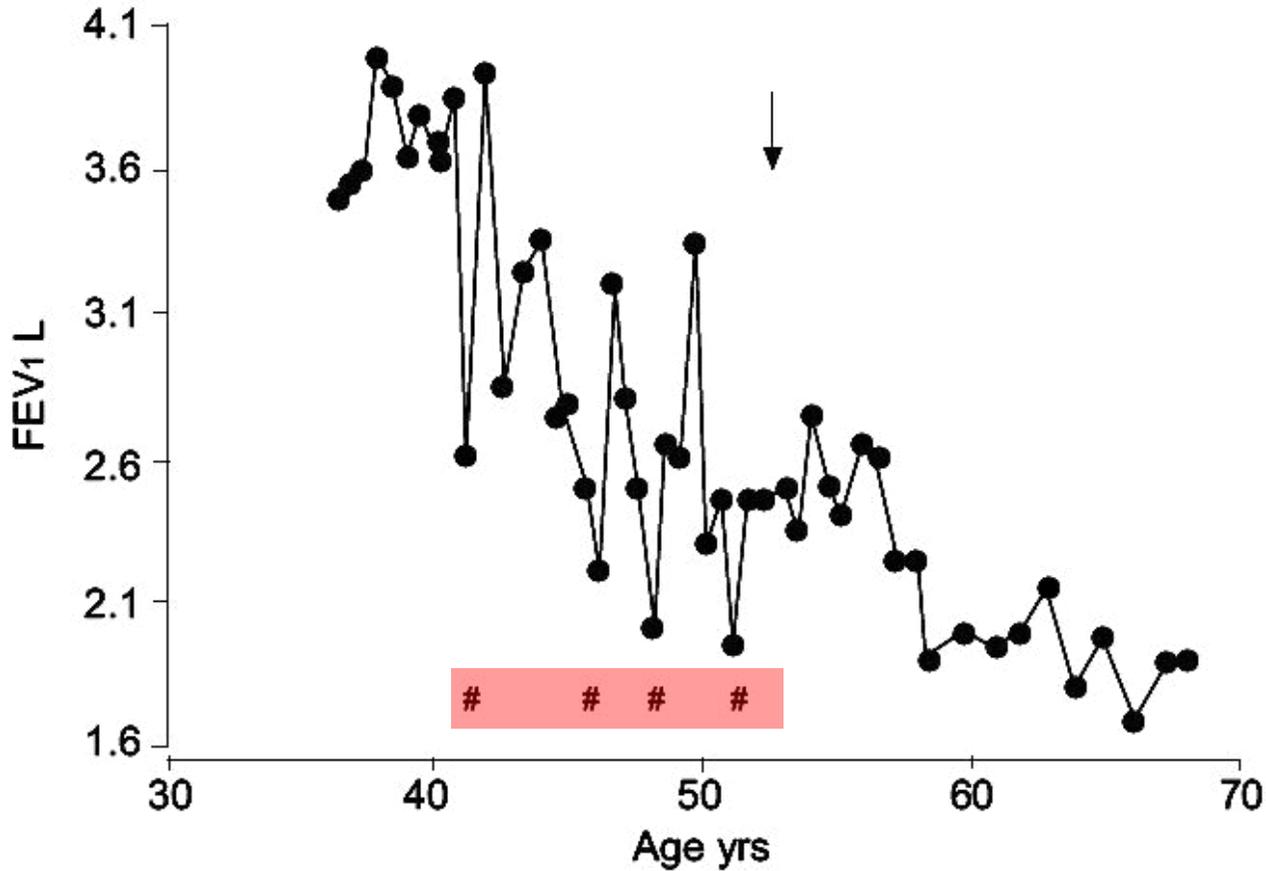
✓ Follow-up 12 months



*HR of emergency
hospital attendance*



Severe exacerbations predict excess lung function decline in asthma. Bai TR, Eur Respir J. 2007;30(3):452-6.

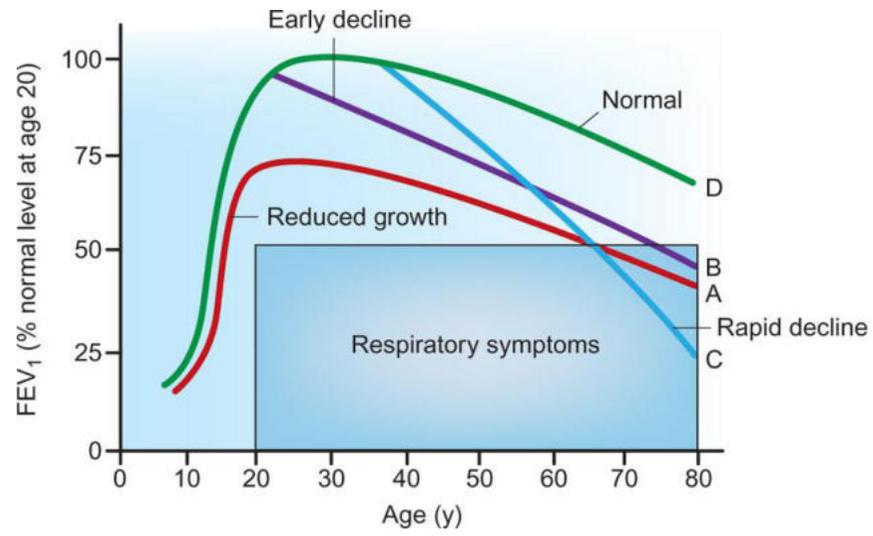
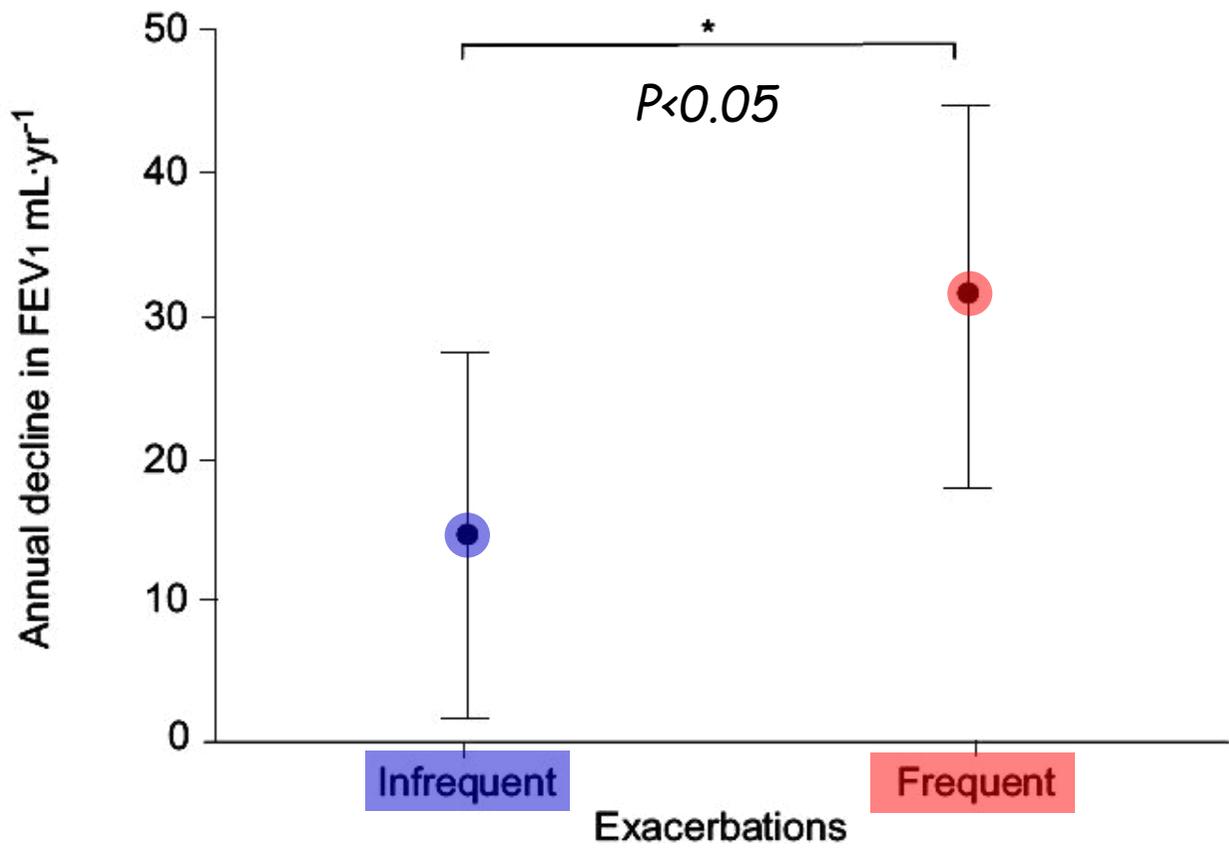


FEV₁ records over a 35-yr period in a subject with 4 exacerbations.

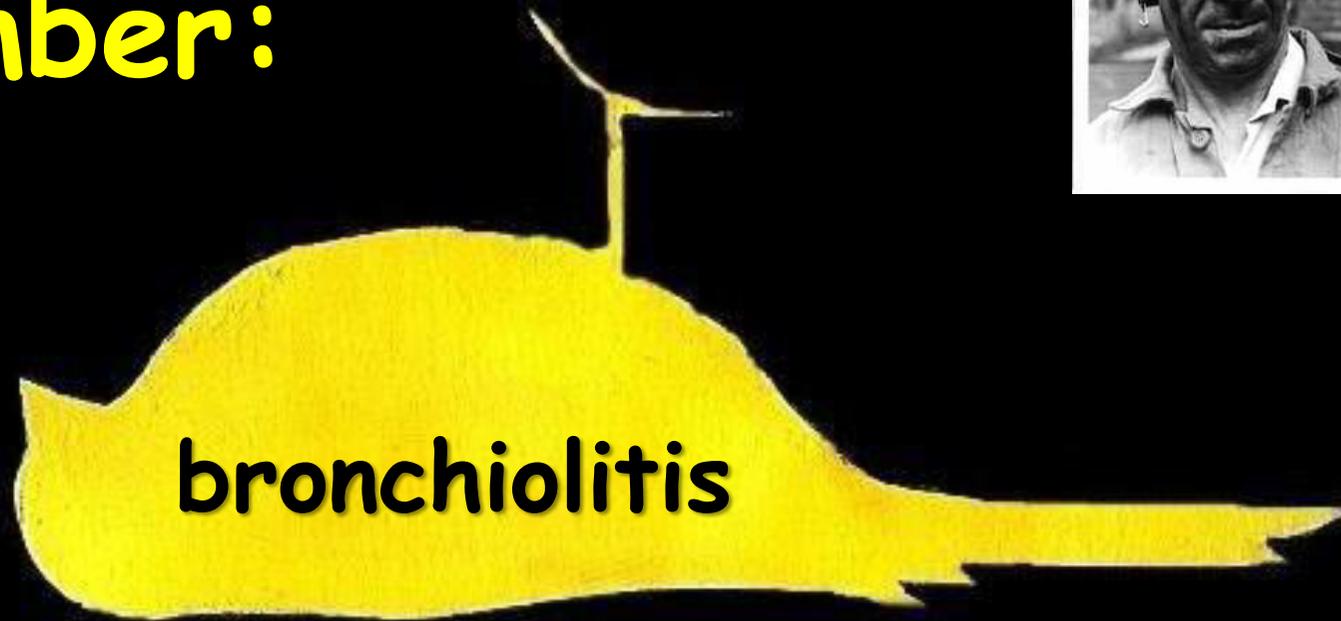
#: time-point of exacerbation

Severe exacerbations predict excess lung function decline in asthma. Bai TR, Eur Respir J. 2007;30(3):452-6.

Estimated annual decline in FEV₁ in patients with infrequent or frequent asthma exacerbations



Remember:



**is our canary in the hospital
to suggest predisposition to:
wheezy bronchitis, asthma and COPD**

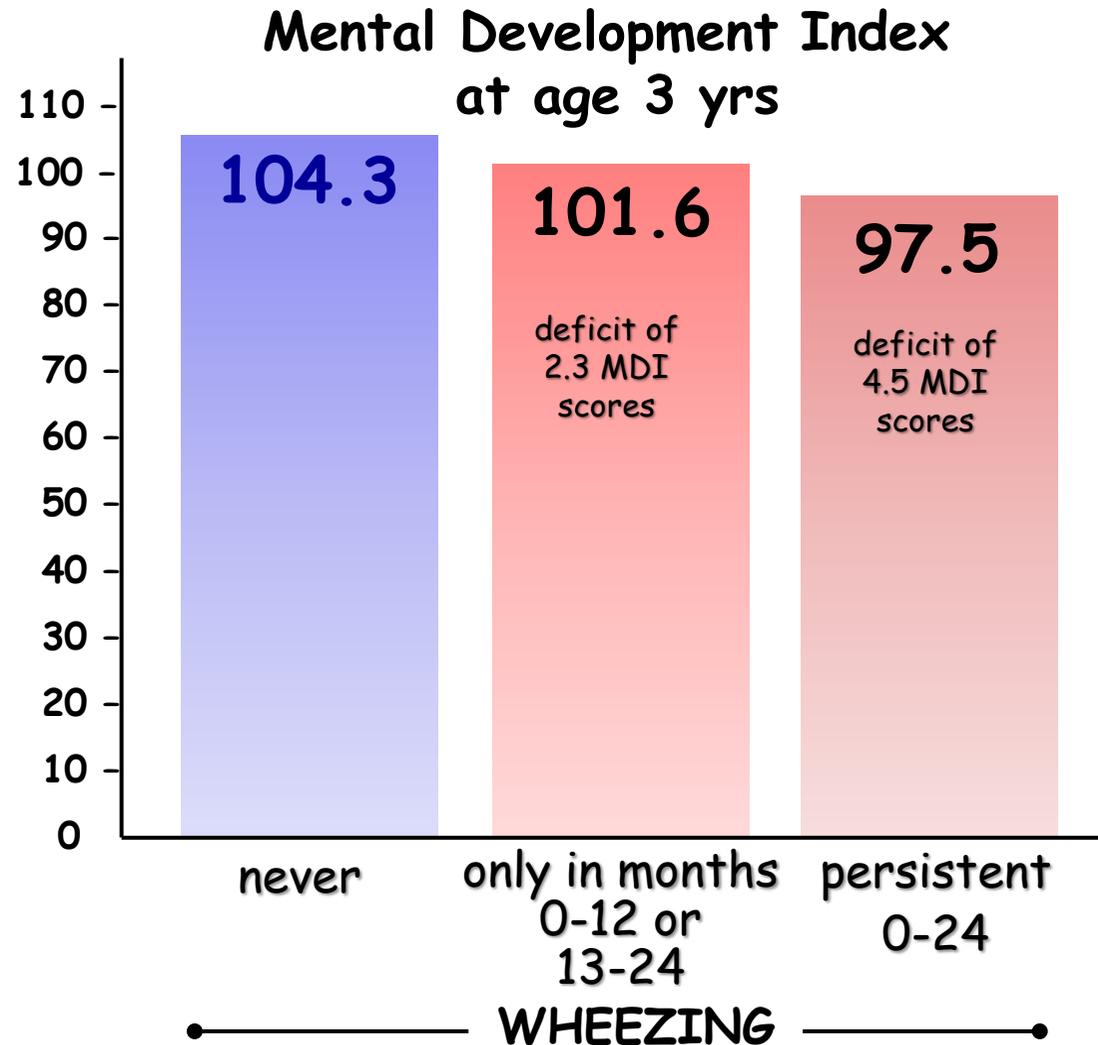
Early wheezing phenotypes and cognitive development of 3-yr-olds. Community-recruited birth cohort study

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

✓ Birth cohort (n=468).

✓ Wheezing symptoms over first two years.

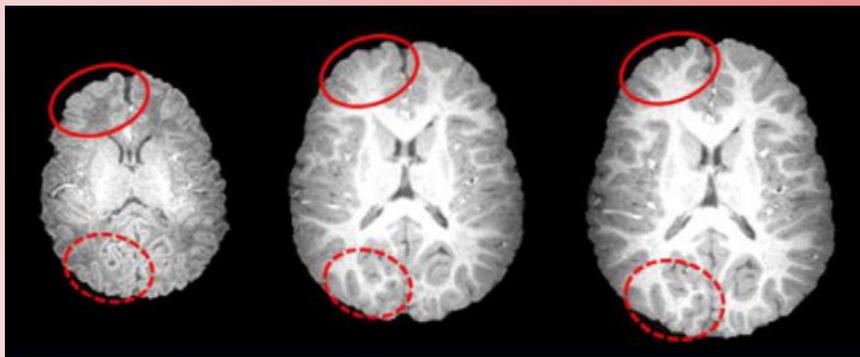
✓ Cognitive status of children at the age of 3 yr with the Bayley Mental Development Index (MDI).



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.



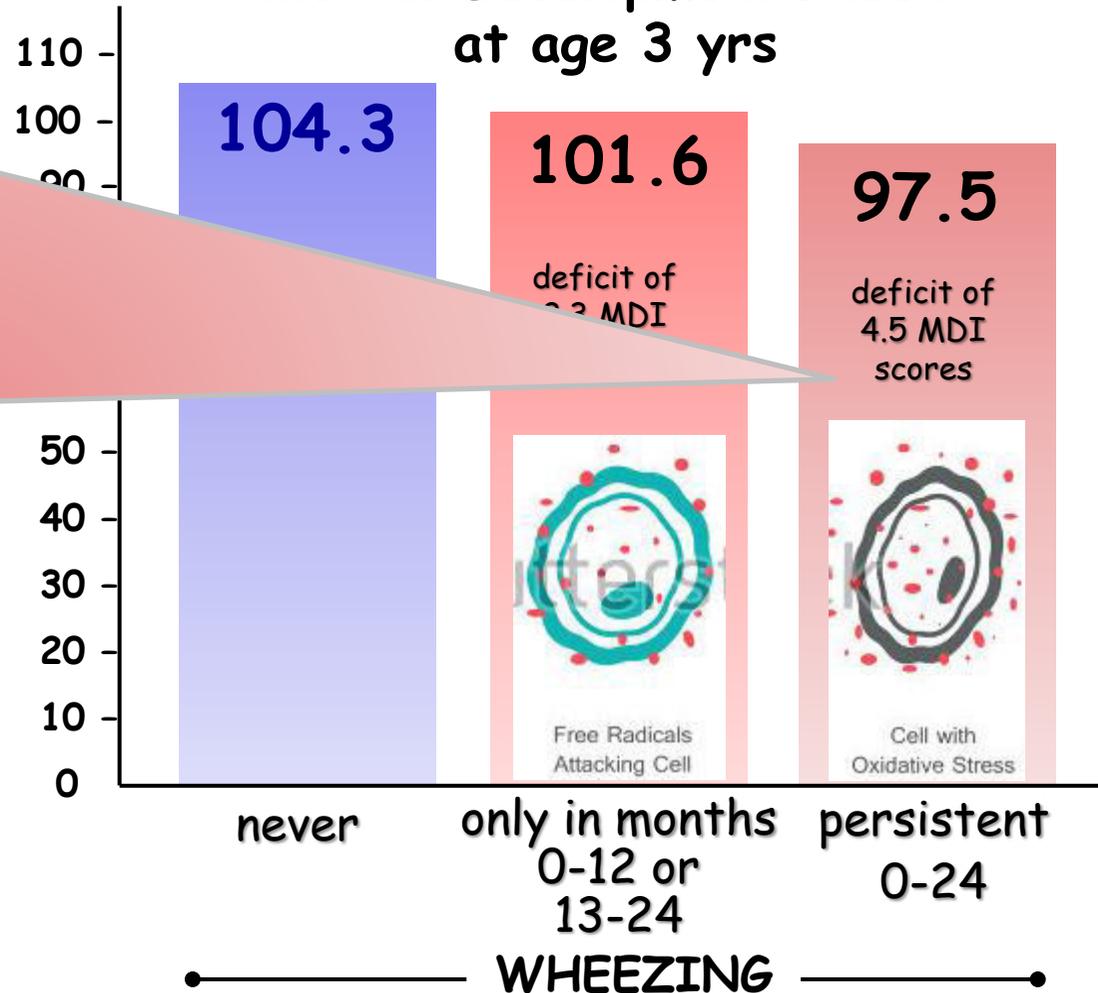
Two weeks

One year

Two years

Selenium may be protective

Mental Development Index at age 3 yrs



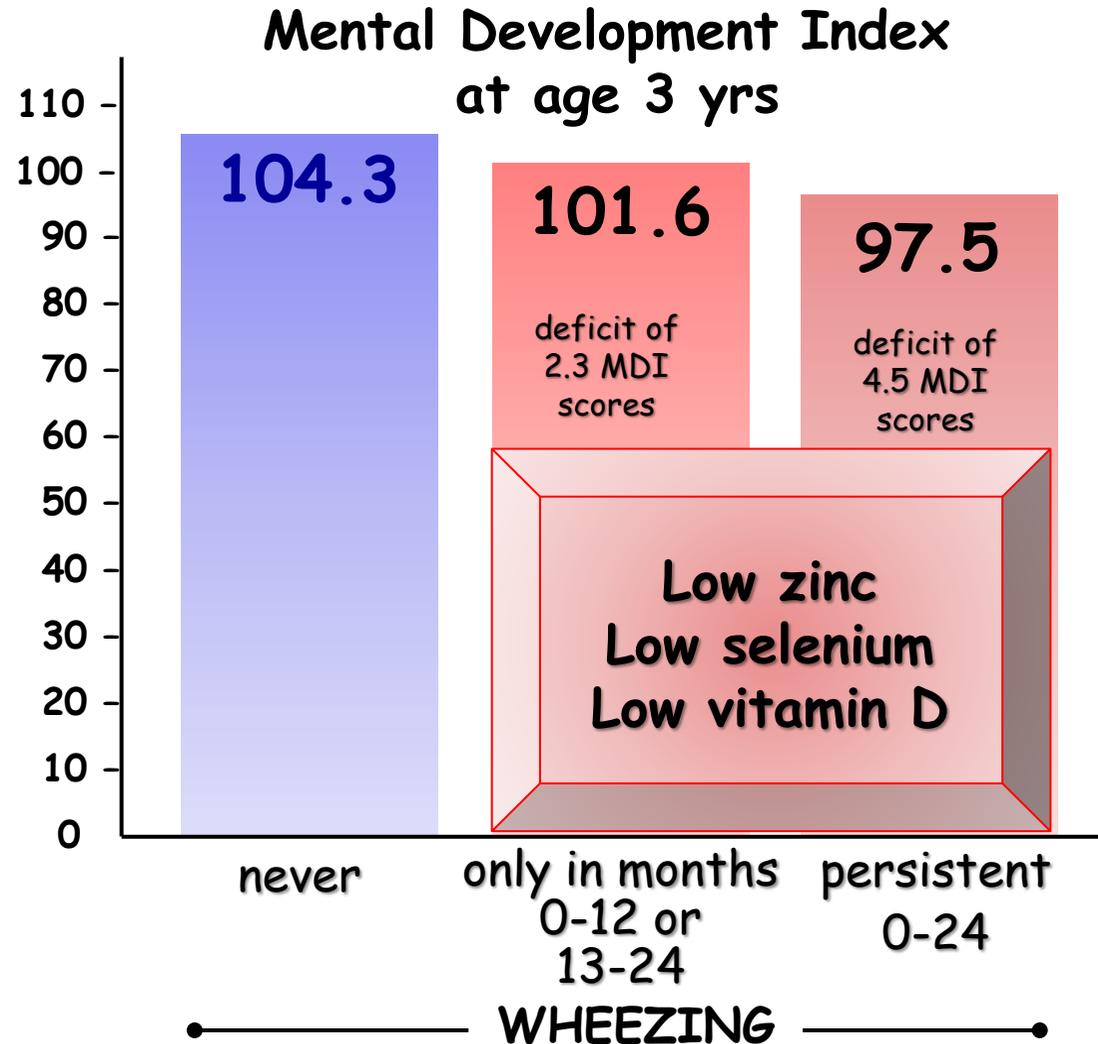
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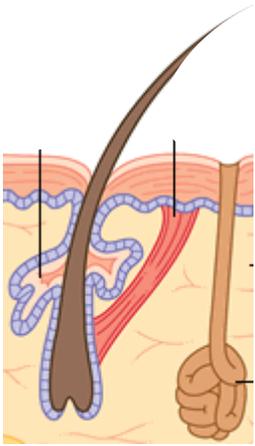
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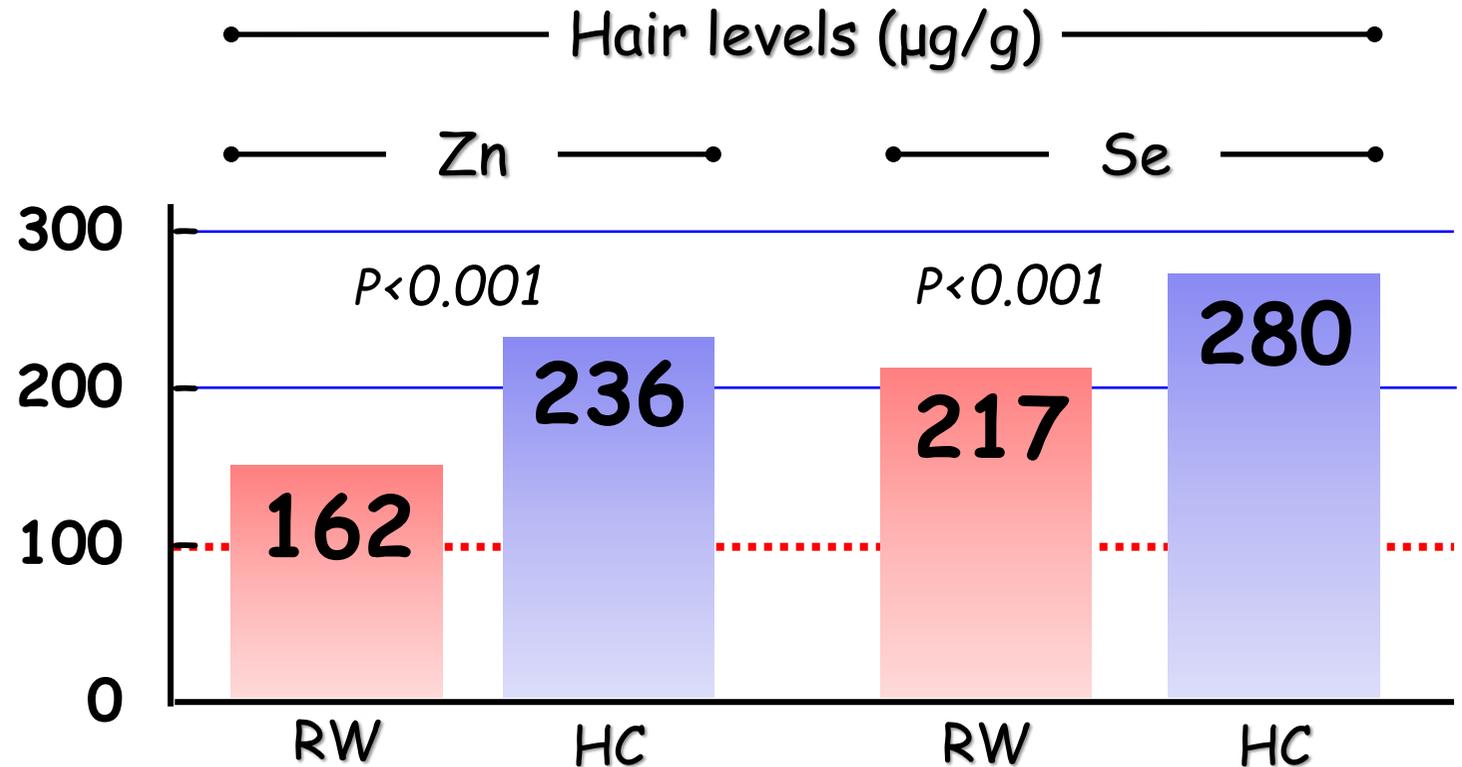


Hair Zinc and Selenium Levels in Children With Recurrent Wheezing

Razi C. H., *Pediatr Pulmonol* 2012;47:1185-1191



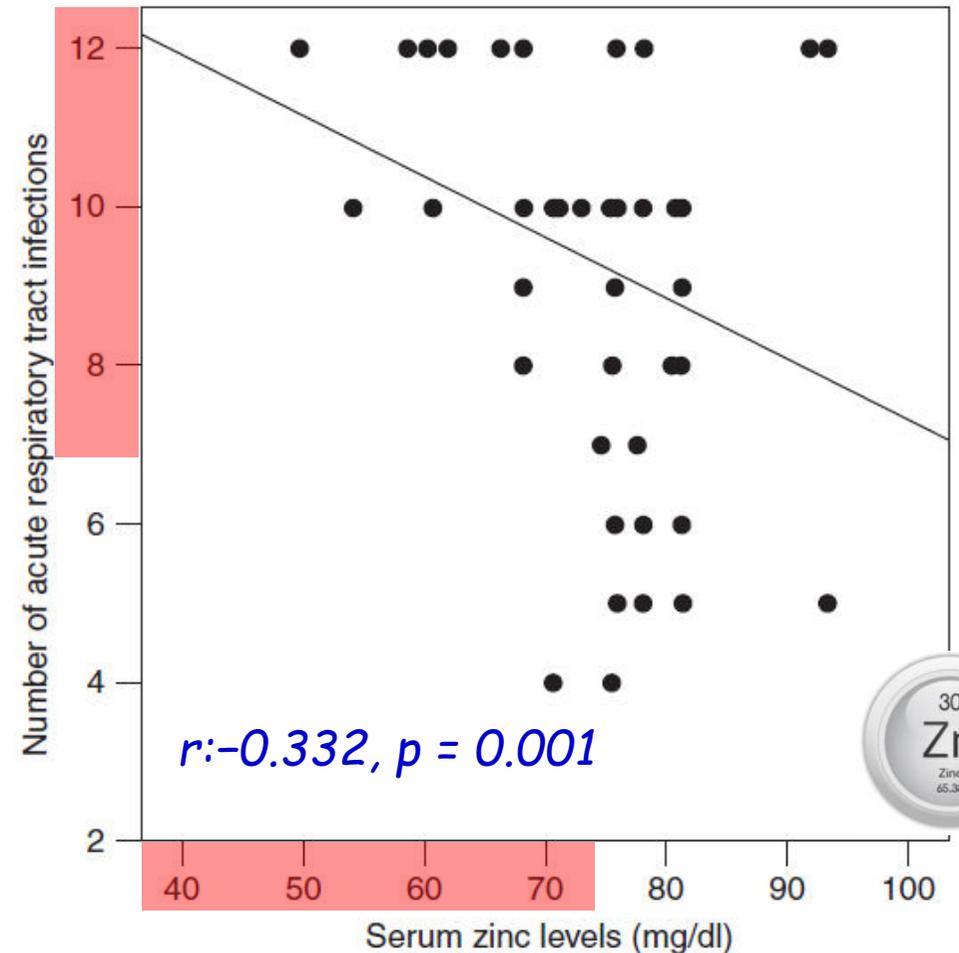
- ✓ Zn and Se hair levels
- ✓ Total antioxidant capacity (TAC) (mmol/L)
- ✓ 65 patients with recurrent wheezing (RW)
- ✓ 65 healthy children (HC)



Serum heavy metal and antioxidant element levels of children with recurrent wheezing.

Razi CH, *Allergol Immunopathol (Madr)*. 2011;39:85-9.

Correlation between serum zinc levels and n° of **Acute Respiratory Tract Infections**.



✓ 100 children with recurrent wheezing from 1 to 6 years

✓ 116 age- and sex-matched healthy children.

✓ serum mercury, lead, aluminium, zinc, selenium, and copper levels in blood

Serum heavy metal and antioxidant element levels of children with recurrent wheezing.

Razi CH, *Allergol Immunopathol (Madr)*. 2011;39:85-9.

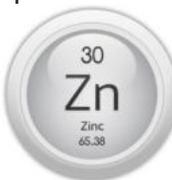
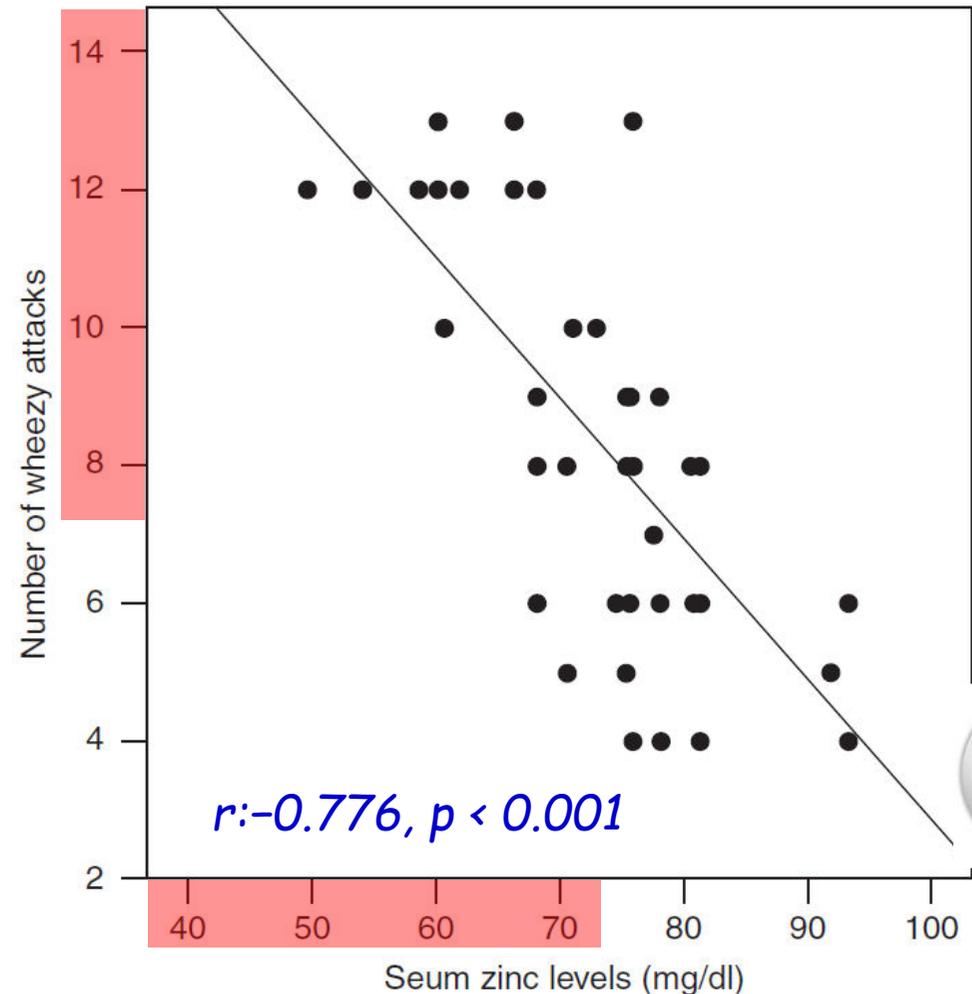
✓ 100 children with recurrent wheezing from 1 to 6 years

✓ 116 age- and sex-matched healthy children.

✓ serum mercury, lead, aluminium, zinc, selenium, and copper levels in blood



Correlation between serum zinc levels and n° of wheezy attacks during the previous year

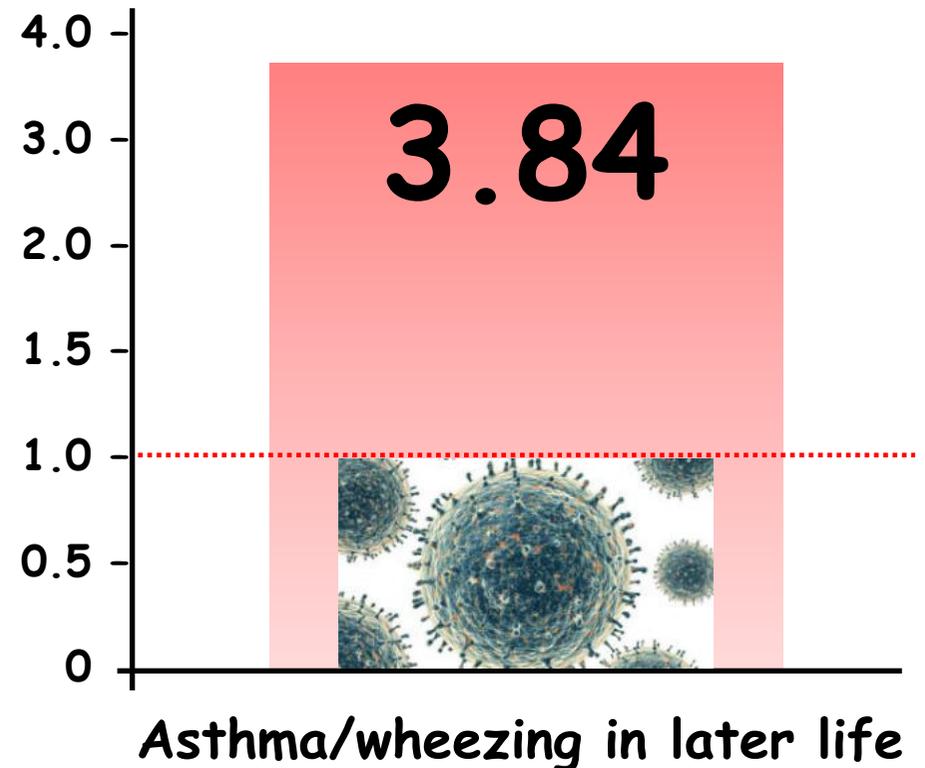


Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis

Régnier SA, *Pediatr Infect Dis* 2013;32:820-826

- ✓ 15 studies assessed the association between RSV-confirmed hospitalization for up to 3 years of age and asthma/wheezing later in life.
- ✓ 82,008 unique individuals (including 1533 with RSV-confirmed hospitalization)

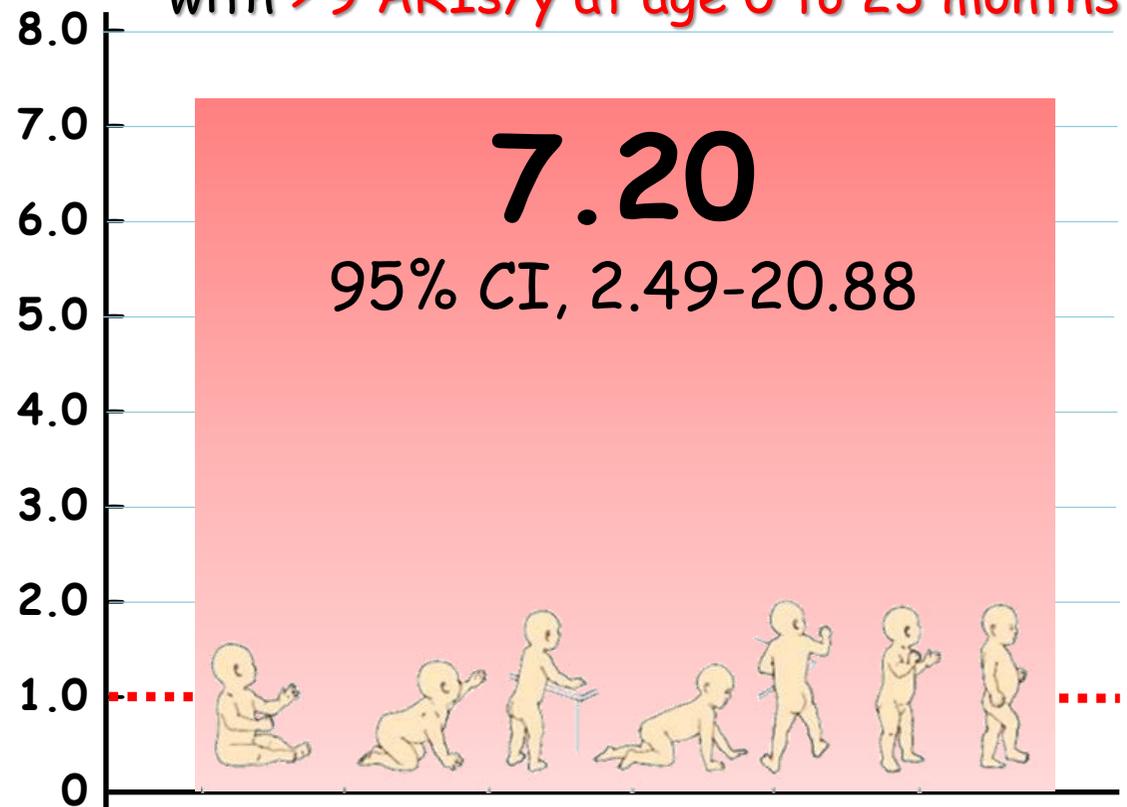
In children who had RSV disease in early life *OR* for



Acute respiratory infections in early childhood and risk of asthma at age 7 years.

Toivonen L, *Allergy Clin Immunol.* 2019 Jan;143(1):407-410.e6.

OR of asthma at age 7 years in children with **> 9 ARI's/y at age 0 to 23 months**



compared with children with **< 5 ARI's/y at age 0 to 23 months**

✓ a prospective, population-based birth cohort study (n= 923) to investigate the association between acute respiratory infections (ARIs) during the first 24 months of life and asthma at age 7 years.

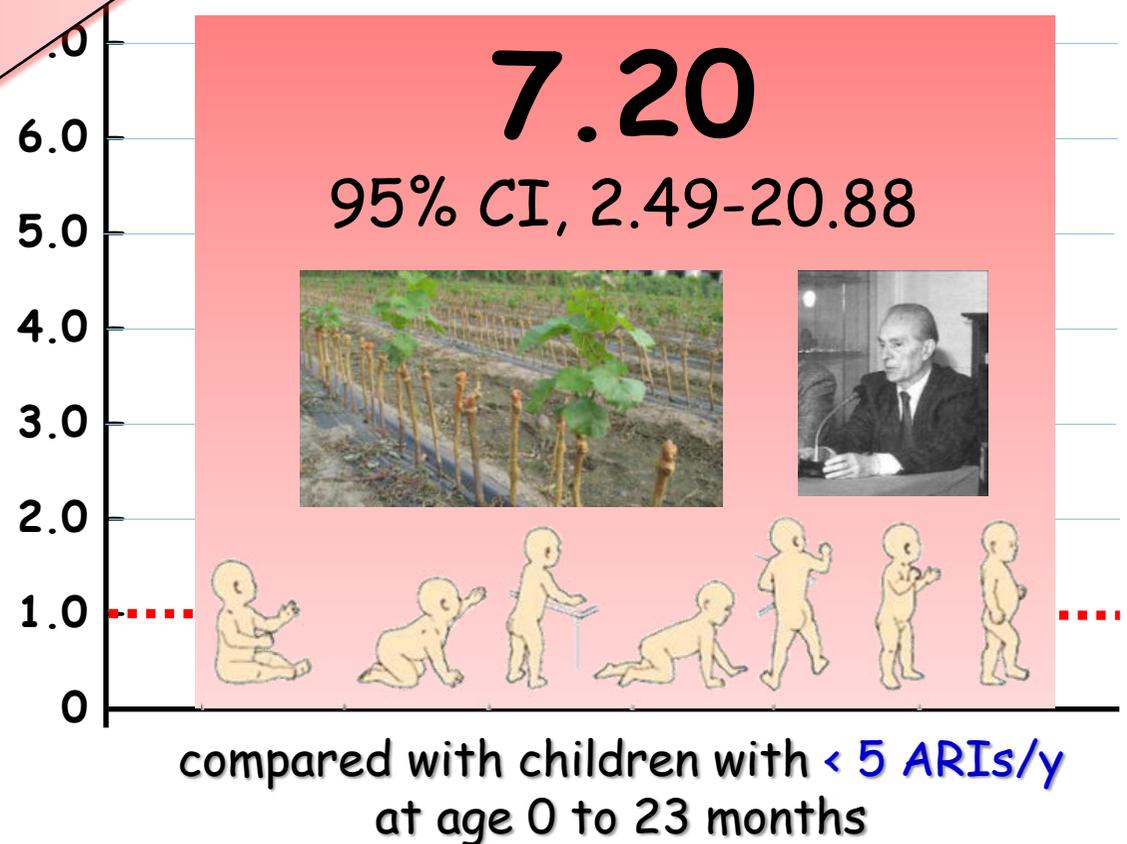
Acute respiratory infections in early childhood and risk of asthma at age 7 years.

Toivonen L, *Allergy Clin Immunol.* 2019 Jan;143(1):407-410.e6.

The mean duration of ARI's was longer and measures of severity were higher in children with asthma at age 7 years compared with those without asthma.

These findings may reflect poorer immunological responses in children who later develop asthma.

OR of asthma at age 7 years in children with **> 9 ARI's/y at age 0 to 23 months**



Nasopharyngeal wash in preventing and treating upper respiratory tract infections: Could it prevent COVID-19?

Singh S, Lung India. 2020;37(3):246-251.

Rajasthan Hospital, Jaipur,
Rajasthan, India.



The technique of nasopharyngeal wash to prevent the virus

from inhabiting and replicating in the nasal and pharyngeal mucosa has been suggested to be useful in reducing symptoms, transmission, and viral shedding in cases of viral acute respiratory tract infections.

In rapid systematic review, we found studies showing some improvement in prevention and treatment of upper respiratory tract infections.

We postulate that hypertonic saline gargles and nasal wash may be useful in prevention and for care of patients with COVID-19.



✓ 8 studies on viral infections



✓ hypertonic saline nasal irrigations & gargling



✓ **Primary outcomes**

- Change in onset or severity of acute URTI-related symptoms (e.g. nasal discharge, congestion, sneezing, headache, sore throat, and fever) over periods up to 28 days
- Time to resolution of symptomatic illness.

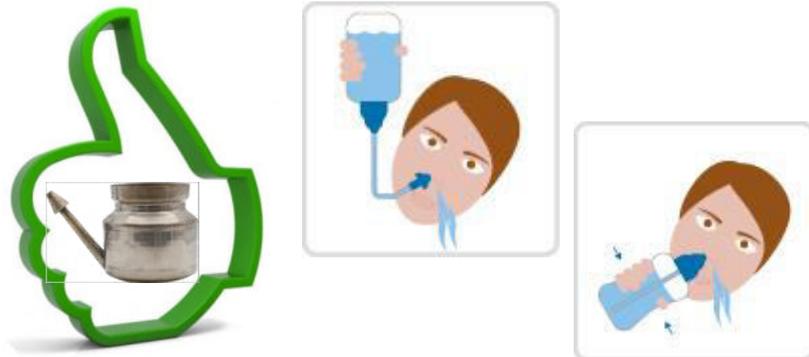
✓ **Secondary outcomes**

- Viral shedding
- Transmission to household contacts
- Adverse events associated with treatment.
- Days or work or school.
- Antibiotic and URTI medication use.

Nasopharyngeal wash in preventing and treating upper respiratory tract infections: Could it prevent COVID-19?

Singh S, Lung India. 2020;37(3):246-251.

- ✓ 8 studies on viral infections
- ✓ hypertonic saline nasal irrigations & gargling



✓ Primary outcomes

- Change in onset or severity of acute URTI-related symptoms (e.g. nasal discharge, congestion, sneezing, headache, sore throat, and fever) over periods up to 28 days → ○ reduced incidence of fever
○ reduced nasal congestion, weakness, rhinorrhea, and improved sleep quality
- Time to resolution of symptomatic illness. → ○ duration of illness lower by 1.9 days

✓ Secondary outcomes

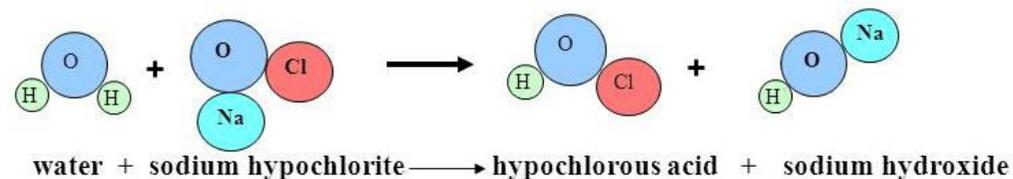
- Viral shedding → ○ lesser transmission and viral shedding
- Transmission to household contacts → ○ reduced incidence of influenza by 35%
- Adverse events associated with treatment. → ○ none
- Days or work or school. → ○ increased attendance
- Antibiotic and URTI medication use. → ○ less use of over-the-counter medications

Nasopharyngeal wash in preventing and treating upper respiratory tract infections: Could it prevent COVID-19?

Singh S, Lung India. 2020;37(3):246-251.

- In pathogenesis of COVID-19, hands play an important role by transporting virus from fomites mainly to nose and mouth.
- From mouth and nose virus spreads in the body.
- Saline wash of the nasal passage, mouth, and throat would probably eliminate or reduce viral load in the body mechanically at least in the initial stage of the pathogenesis as it does with handwashing.
- The possible mechanism of action of hypertonic saline gargles and nasal wash is the chlorite ion; which the cells in nasal and pharyngeal mucosa convert to **hypochlorous acid (HOCl)**, which has anti-viral properties.

Ramalingam S, Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. Sci Rep. 2018 Sep 11; 8(1):13630.



Nasopharyngeal wash in preventing and treating upper respiratory tract infections: Could it prevent COVID-19?

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➤ In pathogenesis of COVID-19, hands play an important role by transporting virus from fomites mainly to nose and mouth.

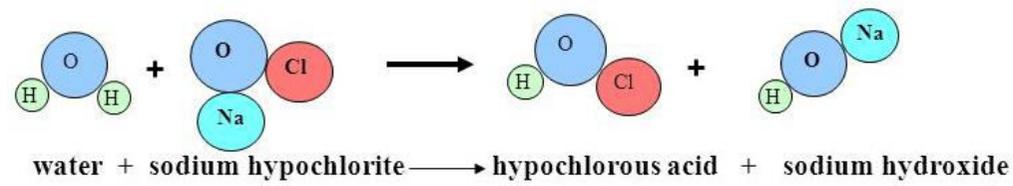
➤ From m

Since hypertonic saline gargles and nasal wash have been shown to work for a multitude of common viruses, logically, they should work for SARS-CoV-2 as well.



➤ The possible mechanism of action of the gargles and nasal wash is the chlorite ion; which the cells in nasal and pharyngeal mucosa convert to **hypochlorous acid (HOCl)**, which has anti-viral properties.

Ramalingam S, Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. *Sci Rep.* 2018 Sep 11; 8(1):13630.



Upper Respiratory Tract Diseases

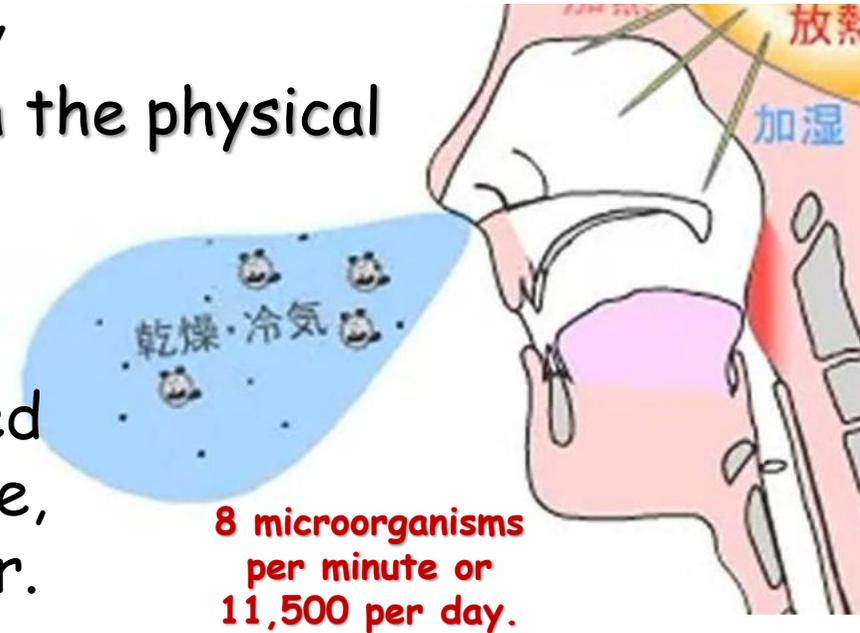
http://www.ariatlas.org/data_research/appendis_b

I. The respiratory tract is the most common site for infection by pathogens.

A. This site becomes infected frequently because it comes into direct contact with the physical environment and is exposed to microorganisms in the air.

B. The human respiratory tract is exposed to many potential pathogens via the smoke, soot, and dust that is inhaled from the air.

C. It has been calculated that the average individual inhales about 8 microorganisms per minute or 11,500 per day.

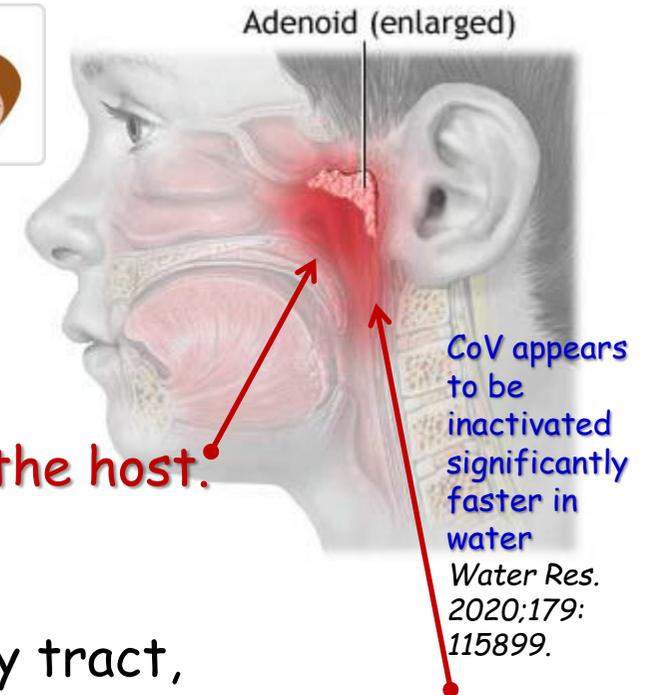


Upper Respiratory Tract Diseases

Mechanisms Used By Respiratory Tract Pathogens To Initiate Disease.

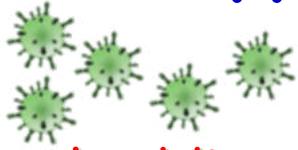
A. Before a respiratory disease can be established, the following conditions need to be met:

- There must be a sufficient number or **sufficient "dose"** of infectious agent inhaled.
 - The infectious particles must be airborne.
 - The infectious organism must **remain alive** and viable.
 - The organism must be deposited on susceptible tissue in the host.**
- B. Once a respiratory tract pathogen is in the respiratory tract, **it is essential that it colonize these surfaces before it can cause obvious disease.**



CoV appears to be inactivated significantly faster in water
Water Res. 2020;179:115899.

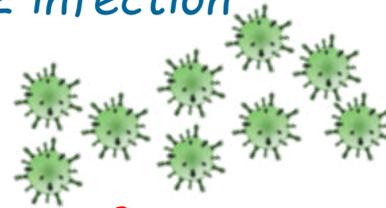
Upper Respiratory Tract Diseases and Covid 19



➤ **Shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease,**

• Yu P, A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. *J Infect Dis.* 2020.

• Huang R, A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China. *Lancet Infect Dis.* 2020;20(5):534-5.

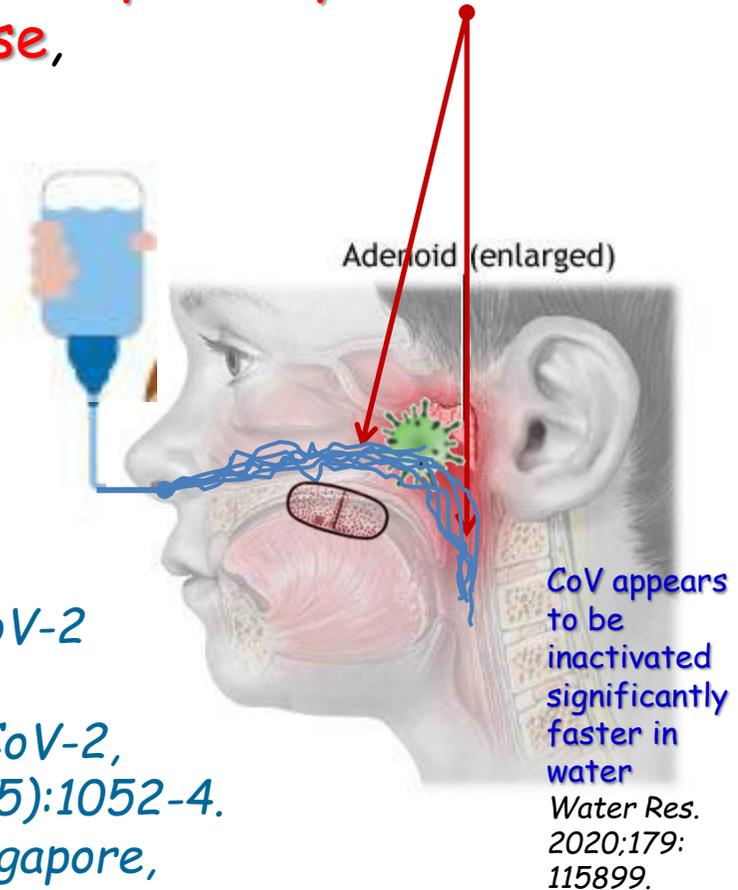


➤ **within the first 3 days from onset of symptoms.**

• Pan X, Asymptomatic cases in a family cluster with SARS-CoV-2 infection. *Lancet Infect Dis.* 2020;20(4):410-1.

• Tong ZD, Potential Presymptomatic Transmission of SARS-CoV-2, Zhejiang Province, China, 2020. *Emerg Infect Dis.* 2020;26(5):1052-4.

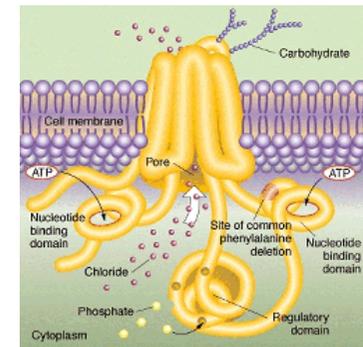
• Wei WE, Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(14):411-5.



Nasal irrigations with baby shampoo 1%

<https://www.youtube.com/watch?v=eyfvPggW7tw&t=304s>

- Nasal irrigations with dilute (1%) baby shampoo increase mucociliary clearance time in healthy subjects.
The effect of dilute baby shampoo on nasal mucociliary clearance in healthy subjects. Isaacs S, Am J Rhinol Allergy. 2011;25(1):e27-e29.
- Baby shampoo nasal irrigation (1%) disrupted preformed bacterial biofilms and inhibited biofilm formation in symptomatic patients after post-functional endoscopic sinus surgery.
Chiu AG, Baby shampoo nasal irrigations for the symptomatic post-functional endoscopic sinus surgery patient. Am J Rhinol. 2008;22(1):34-37.
- Chronic rhinosinusitis is highly prevalent in patients with cystic fibrosis, postoperative meticulous daily nasal irrigations may prevent mucus retention and bacterial recolonization.
Hamilos DL. Chronic Rhinosinusitis in Patients with Cystic Fibrosis. J Allergy Clin Immunol Pract. 2016;4(4):605-612.



Lowering the transmission and spread of human coronavirus.

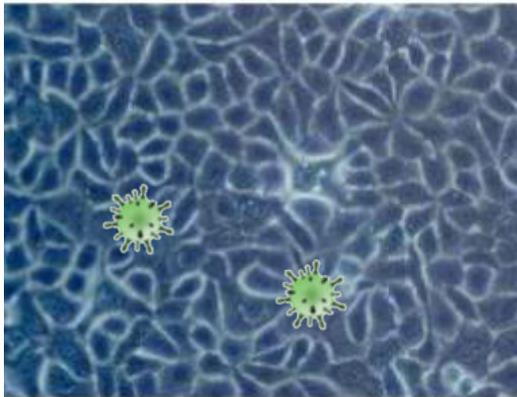
Meyers C, J Med Virol. 2020 Sep 17.



✓ Common over-the-counter nasal rinses and mouthwashes/gargles

✓ ability to inactivate high concentrations of HCoV using contact times of 30 s, 1 min, and 2 min

✓ using the tissue culture



❖ A 1% baby shampoo nasal rinse solution inactivated HCoV greater than 99.9% with a 2-min contact time.

❖ Several over-the-counter mouthwash/gargle products including Listerine and Listerine-like products were highly effective at inactivating infectious virus with greater than 99.9% even with a 30-s contact time.



* La formulazione prevede oli essenziali ([mentolo](#) 0,042%, [timolo](#) 0,064%, [eucaliptolo](#) 0,092% e [metil salicilato](#) 0,06%) ed [etanolo](#) al 26,9 %^[7].

Lowering the transmission and spread of human coronavirus.

Meyers C, J Med Virol. 2020 Sep 17.



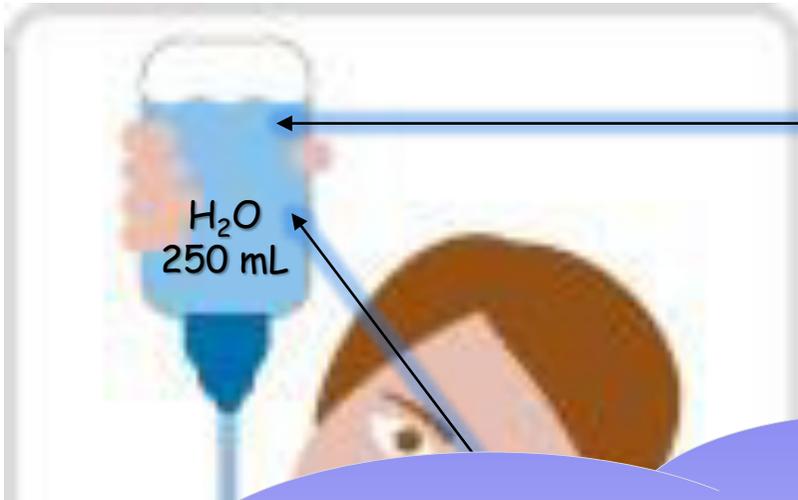
Nasal rinses and mouthwashes, which directly impact the major sites of reception and transmission of human coronaviruses (HCoV), may provide an additional level of protection against the virus.

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H₂O
250 mL

+ 2.5 mL
baby shampoo
1% solution

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Identifier: NCT04347538

**Impact of Nasal Saline Irrigations
on Viral Load in Patients With COVID-19.**

*"nasal saline with baby shampoo irrigations may
decrease viral shedding/viral load and viral
transmission"*

half a teaspoon of baby shampoo (which acts as
a surfactant, potentially helping to kill the virus)

Cloruro di sodio, Bicarbonato
Acido ialuronico, Pantenolo



hypertonic
Solution
3%



Isotonic solution

Benefits and Safety of Nasal Saline Irrigations in a Pandemic-Washing COVID-19 Away.

Farrell NF, JAMA Otolaryngol Head Neck Surg. 2020 Jul 23.

Topical nasal rinses take advantage of this secretory lining in multiple ways:

- 1) removing the mucus and its associated particulate matter.
- 2) increasing hydration of the deeper aqueous layer,
- 3) improving the underlying ciliary beat frequency
- 4) reducing local inflammatory mediators.



➤ Hypertonic saline nasal irrigations should be encouraged for:

- patients
- and
- health care workers especially

From 1996 to 2021: what has change in pediatric allergology in the last 25 years



Attilio Boner
University of
Verona, Italy

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335 6274799

- ✓ Atopic march
- ✓ Atopic Dermatitis
- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ Meta-analysis vs Biological Plausibility

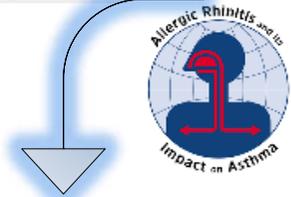


Allergic rhinitis and Its Impact on Asthma. ARIA. In collaboration with the World Health Organization.

Bousquet J, *J Allergy Clin Immunol* 2001;108:S150-S153.

Allergic rhinitis: **tradizione...**

- **seasonal** (SAR)
- and
- **perennial** (PAR),



➤ a new classification for AR based on duration profile: rather than on seasonal profile,

- **intermittent** symptoms < 4 days a week and < 4 wk
- **persistent** symptoms > 4 days a week and > 4 wk

and

➤ a further grading of severity: according to symptom intensity and impairment in patient's QoL.

- **mild**
- **moderate**
- **severe**

- (i) sleep disturbance,
- (ii) impairment of daily activities, leisure, and/or sports,
- (iii) impairment of school performance,
- (iv) bothersome symptoms

Allergic rhinitis and Its Impact on Asthma. ARIA.

In collaboration with the World Health Organization.

Bousquet J, *J Allergy Clin Immunol* 2001;108:S150-S153.

Allergic rhinitis:

- seasonal (SAR)
- and
- perennial (PAR),



➤ a new classification

rather than

and

➤ a focus on quality of life, according to symptoms and impairment

➤ Symptoms are assessed using the Total Four Symptoms Score (T4SS) by calculating the sum of scores for:

○nasal obstruction, (4 wk)

○rhinorrhea,

○nasal itching,

○sneezing

➤ Each nasal symptom is scored on a scale from 0 to 3:

○0, no symptoms

○1, mild

○2, moderate

○3, severe

resulting in a T4SS ranging from 0 to 12.

performance, (some symptoms)

Optimal management of allergic rhinitis

Scadding GK. Arch Dis Child 2015;100:576-582.

A

1. Shake bottle well
2. Look down
3. Using RIGHT hand for LEFT nostril put nozzle just inside nose aiming towards outside wall
4. Squirt once or twice (2 different directions ↗ ↘)
5. Change hands and repeat for other side
6. DO NOT SNIFF HARD

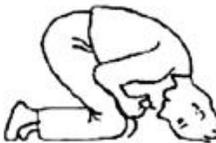


shake

B



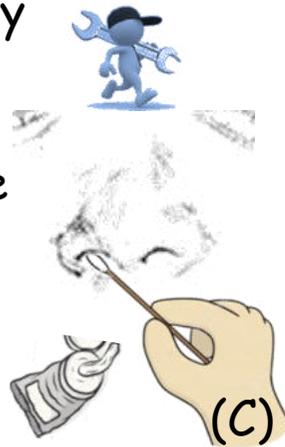
Wrong



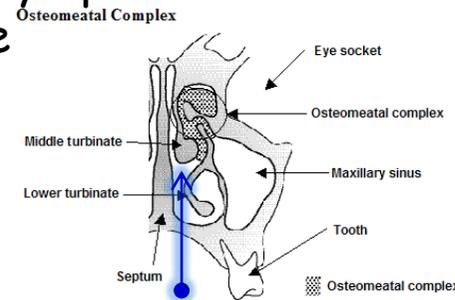
Choose any position you feel comfortable with

A) Shows how to use a nasal spray so as to avoid the septum and spray as much of the lateral wall mucosa as possible, allowing subsequent mucociliary clearance to distribute the liquid all over the mucosa.

....and let it stay there longer (C)



B) Shows how nasal drops (superior for rhinosinusitis) should be used with the head completely upside down so that drops reach the ostiomeatal complex in the upper nose where sinuses drain and ventilate.



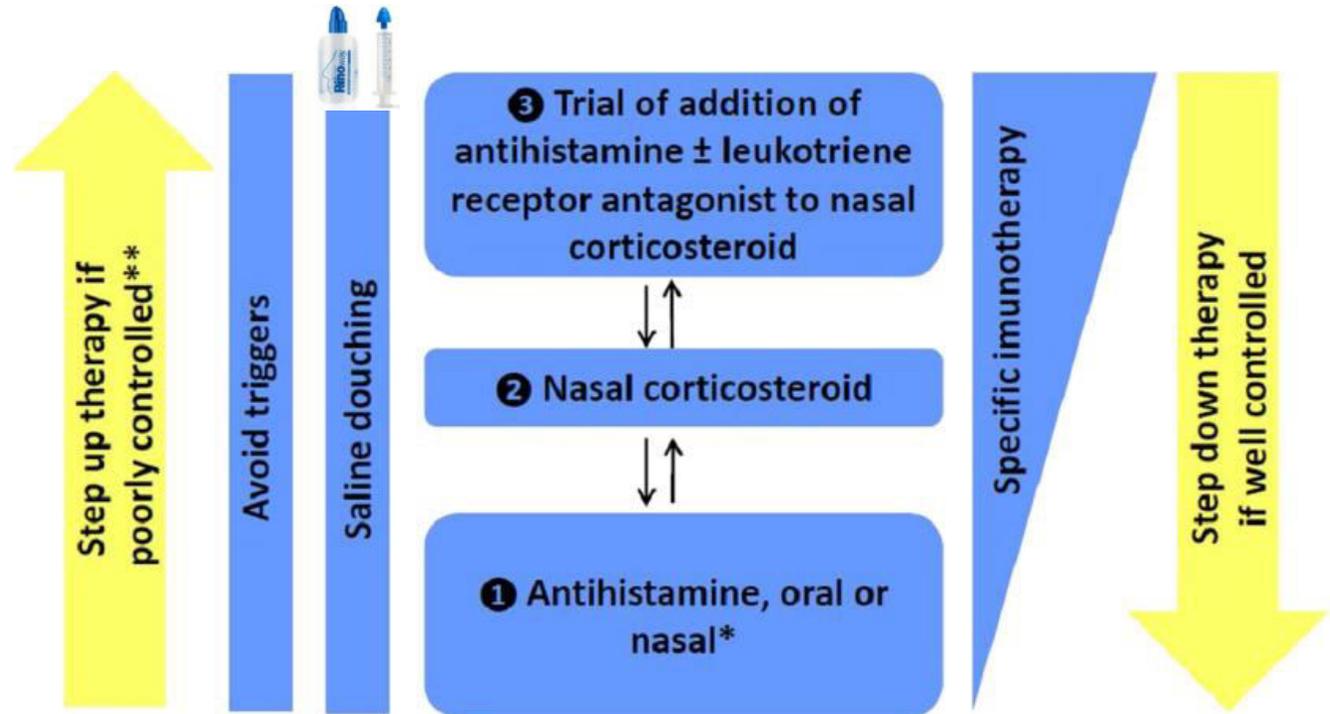
Optimal management of allergic rhinitis

Scadding GK. Arch Dis Child 2015;100:576-582.

Entry to therapy can occur at 1, 2 or 3 year, depending on severity of presenting symptoms.

Poor control should lead to a step up, good control to a step down, so that the minimum therapy necessary is used.

For seasonal disease, regular therapy should be commenced 2 weeks before the anticipated start of symptoms.

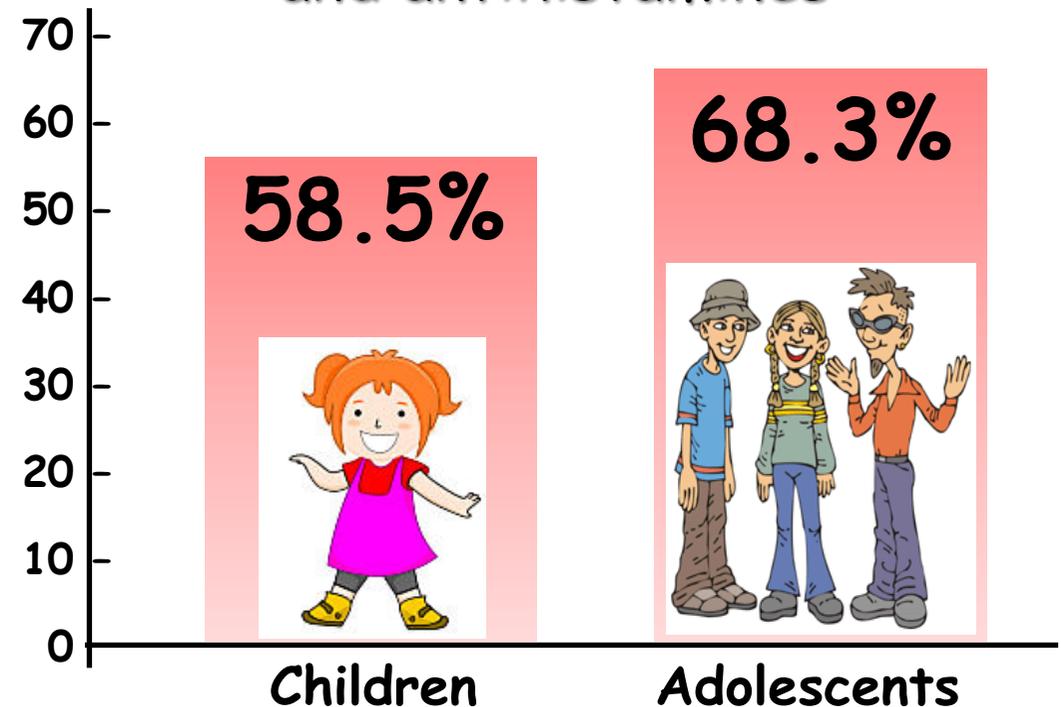


*Oral antihistamines may be better tolerated, while intranasal antihistamines have a more rapid onset of action.
**Reconsider diagnosis if not controlled within 1-2 weeks. If <2 years of age and unresponsive to antihistamine within a week, reconsider diagnosis before stepping up therapy. If poorly controlled, consider a short rescue course of a decongestant or low-dose oral prednisolone to gain symptom control; topical ipratropium may be useful for rhinorrhoea.

Nasal obstructive disorders impair health-related quality of life in adolescents with persistent allergic rhinitis: A real-life study. *M Valls-Mateus, PAI 2017;28:438-445*

- ✓ 142 patients (41 children, 6-11 years old and 101 adolescents, 12-17 years old) with moderate and severe persistent allergic rhinitis (PER).
- ✓ After 2 months of intranasal steroids and antihistamines, patients were asked whether their symptoms had improved (yes/no) and classified accordingly in R, responders and NR, non-responders.

% pts non responding to intranasal steroids and antihistamines



Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study.

Garavello W. *Pediatr Allergy Immunol.* 2003;14(2):140-143.

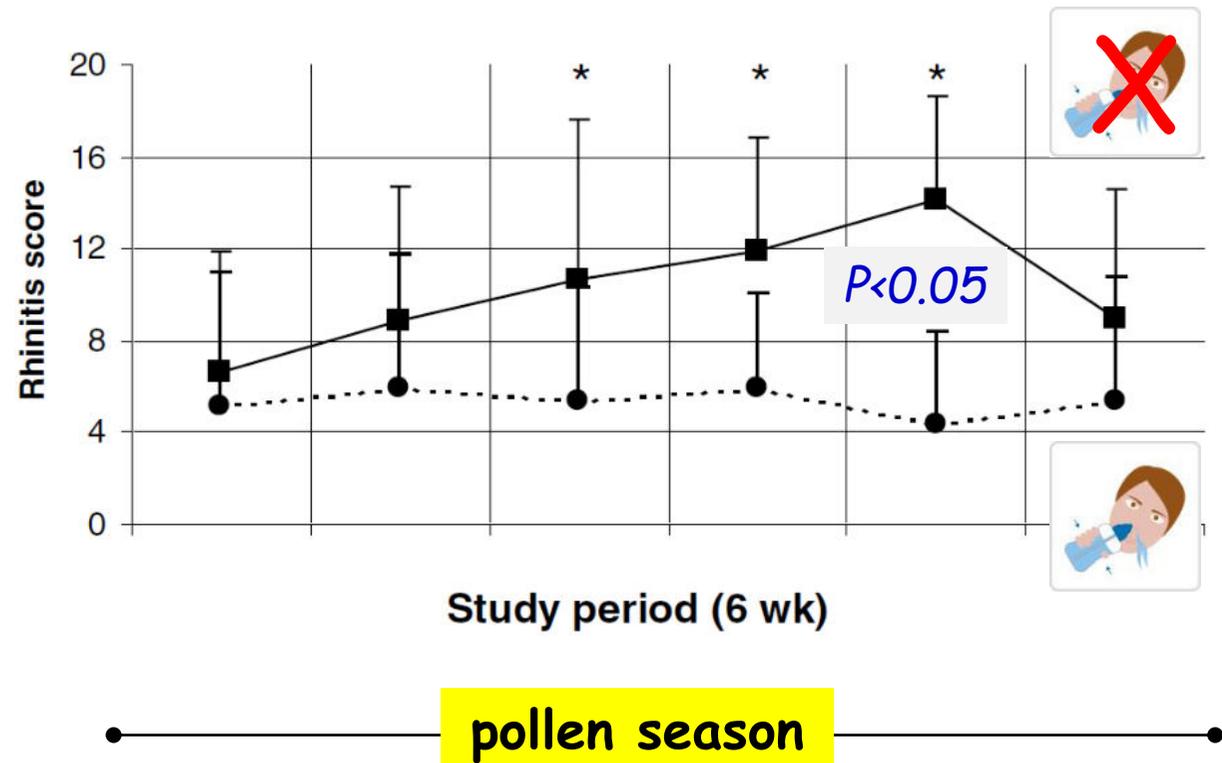


✓ 20 children with seasonal allergic rhinitis to *Parietaria*.

✓ 10 children were randomized to receive three-times daily nasal irrigation with hypertonic saline for the entire pollen season, which had lasted 6 weeks.

✓ 10 patients were allocated to receive no nasal irrigation and were used as controls.

RHINITIS SCORE during the 6-week period of the pollen season for both patients treated with nasal irrigation (dotted line) and controls (solid line).



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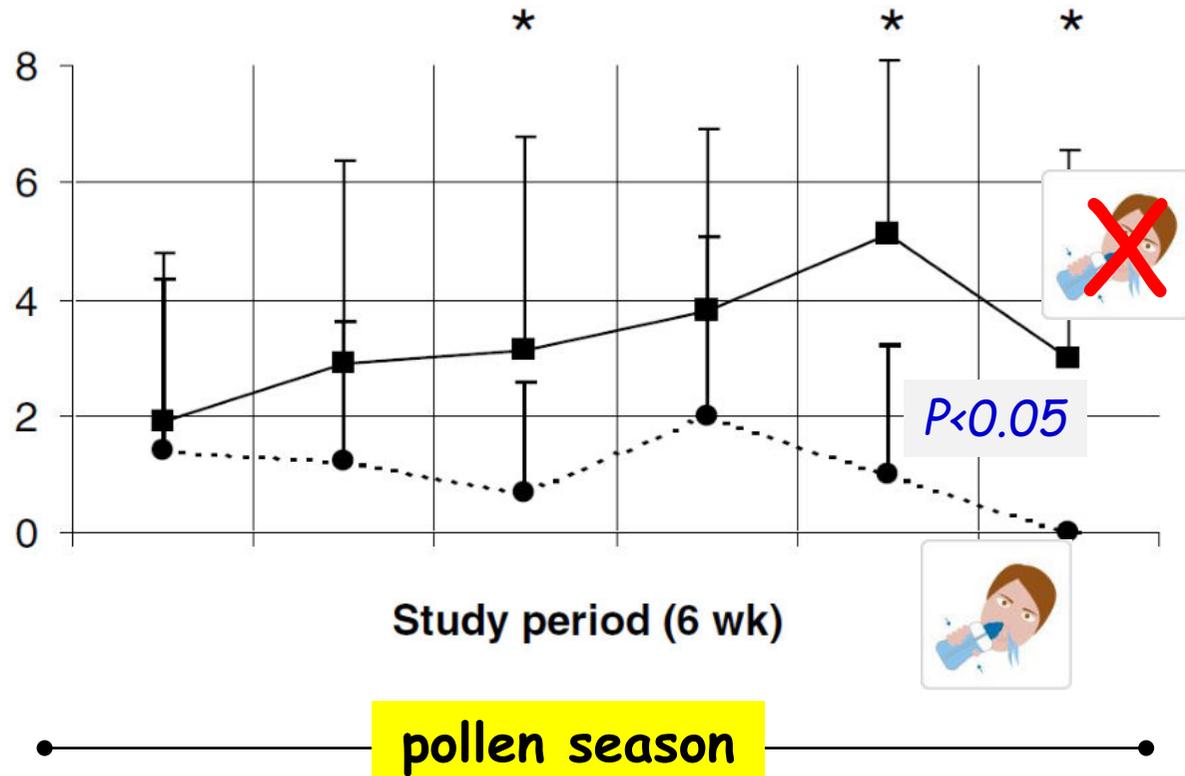


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- ✓ 10 patients were allocated to receive no nasal irrigation and were used as controls.

number of oral intake of antihistamines per week for each week of the pollen season in both patients treated with nasal irrigation (dotted line) and controls (solid line).



Number of tablets of antihistamines



Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis.

Hermelingmeier KE, Am J Rhinol Allergy. 2012;26(5):e119-25.

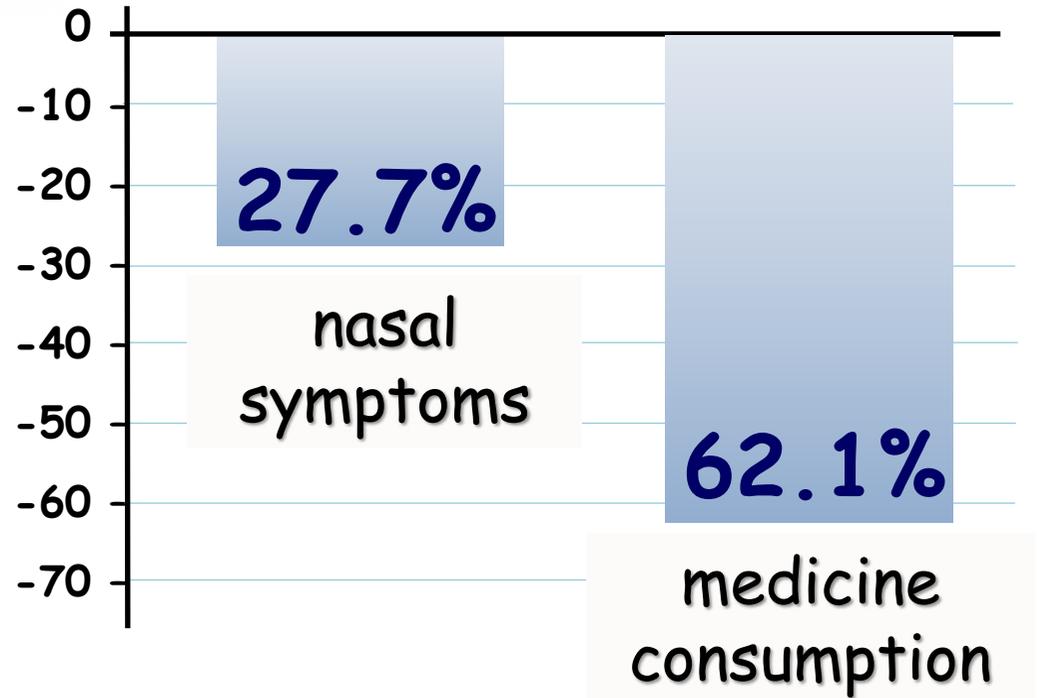
✓ 10 randomized, controlled trials (>400 participants total)

✓ primary (symptom score) and secondary parameters (medicine consumption, mucociliary clearance, and quality of life).

✓ Saline nasal irrigation (SNI) performed regularly over a period of up to 7 weeks



With Saline Nasal Irrigation
% reduction in



Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis.

Hermelingmeier KE, Am J Rhinol Allergy. 2012;26(5):e119-25.

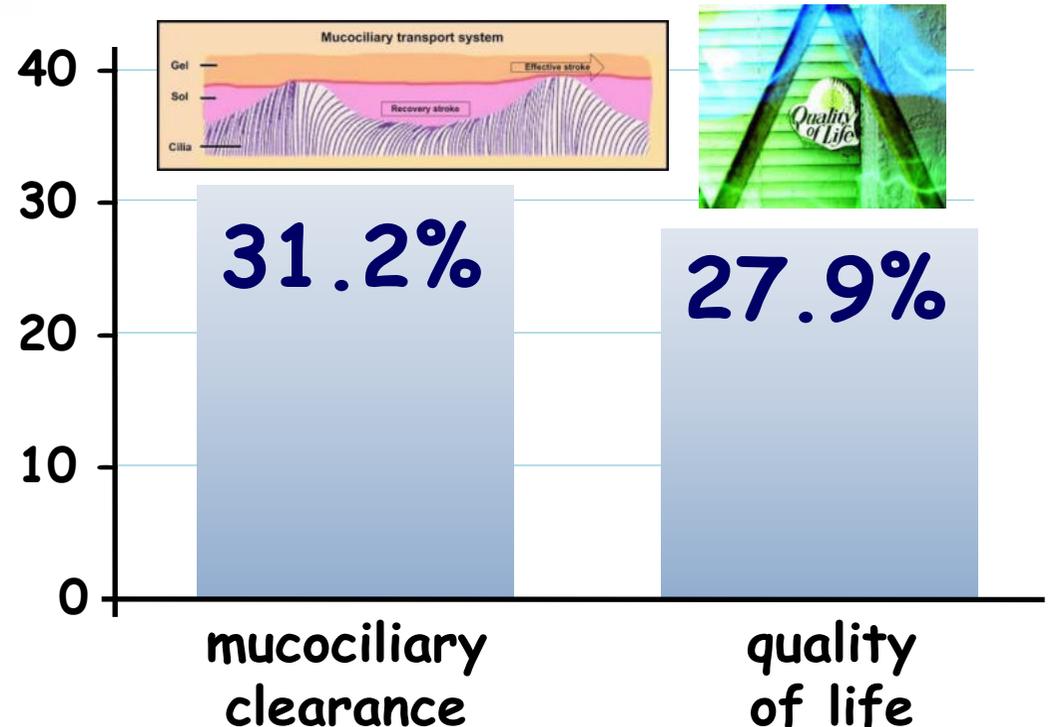
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With Saline Nasal Irrigation % improvement in



Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis.

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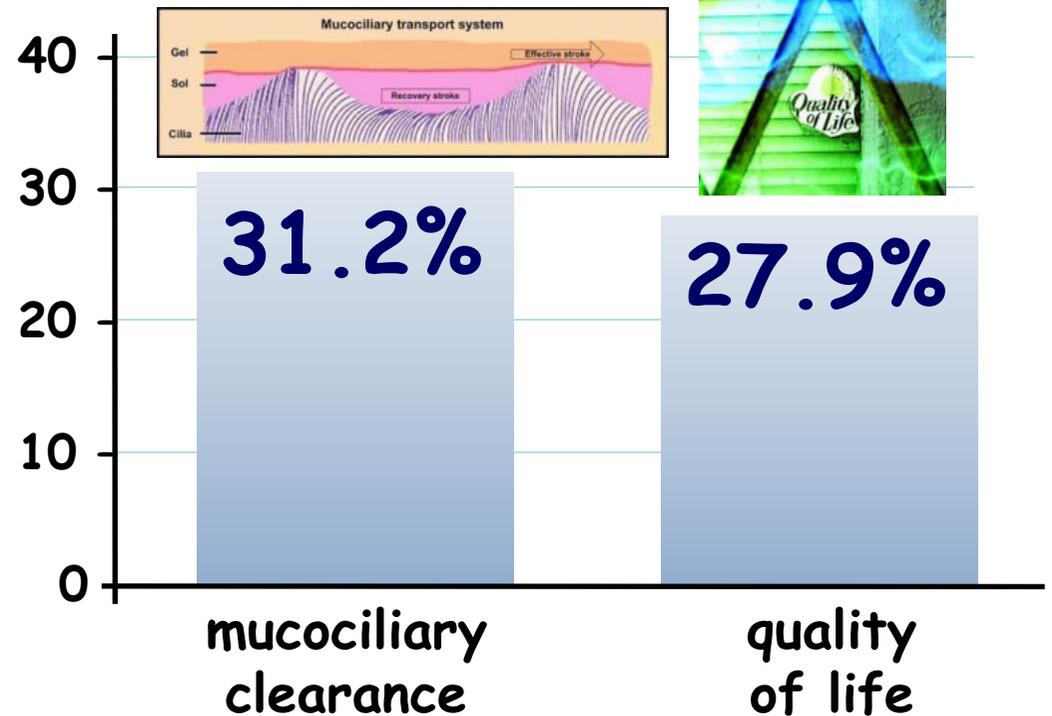
SNI using isotonic, or better hypertonic, saline solution can be recommended as complementary therapy in AR.



1000 grains pollens



With Saline Nasal Irrigation % improvement in



Nasal irrigation as an adjunctive treatment in allergic rhinitis: a systematic review and meta-analysis.

Hermelingmeier KE, Am J Rhinol Allergy. 2012;26(5):e119-25.

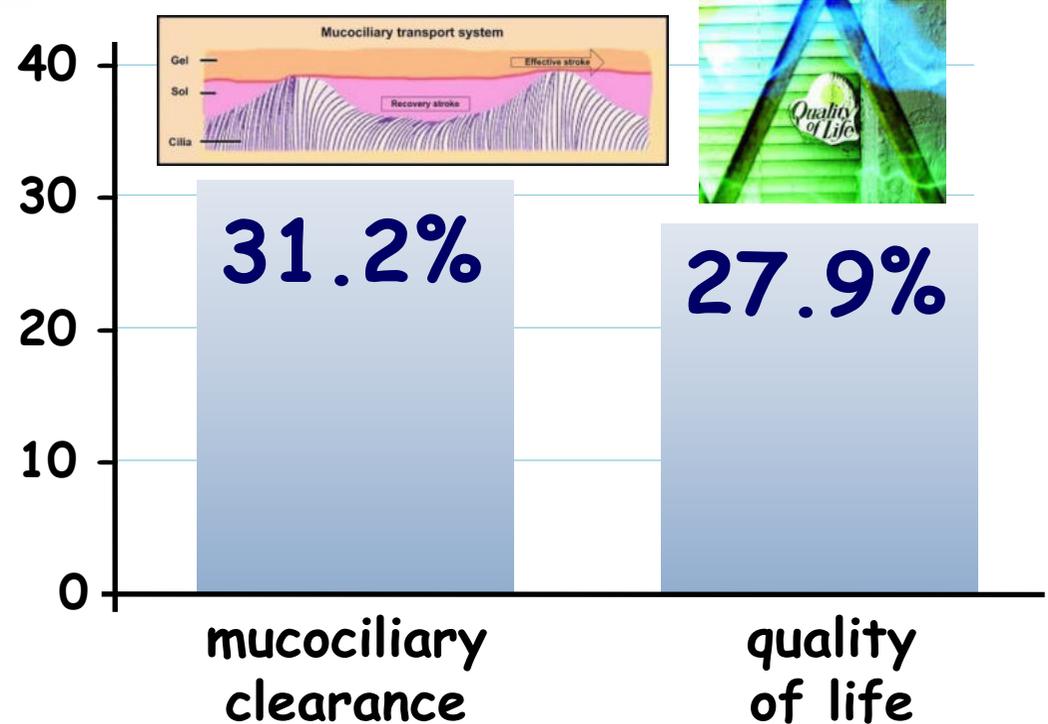
Saline irrigation is well tolerated, inexpensive, easy to use, and there is no evidence showing that regular, daily SNI adversely affects the patient's health or causes side effects.



1000 grains pollens



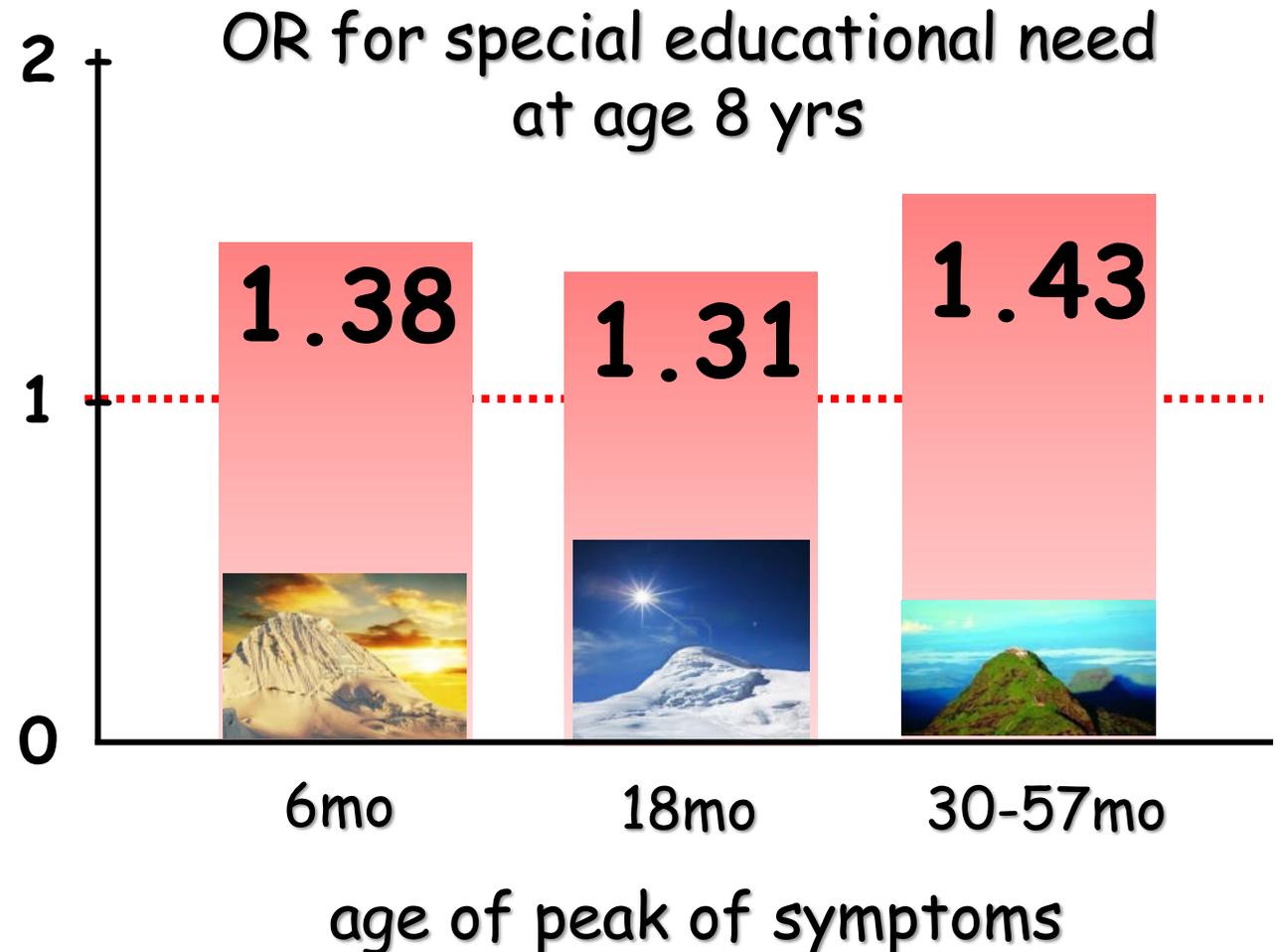
With Saline Nasal Irrigation % improvement in



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

Bonuck K. *Pediatrics* 2012;130:634

- ✓ 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.

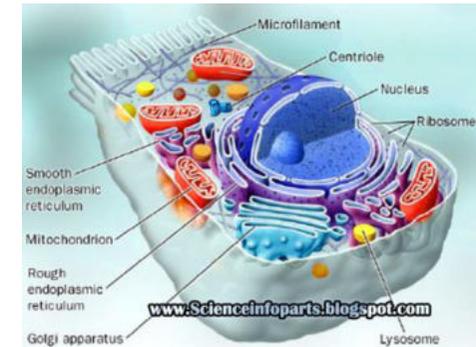


Role of Oxidative Stress in the Neurocognitive Dysfunction of Obstructive Sleep Apnea Syndrome.

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

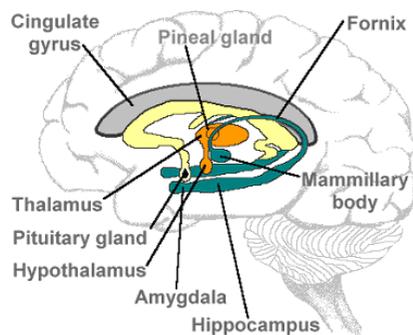
repetitive hypoxia and reoxygenation

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.

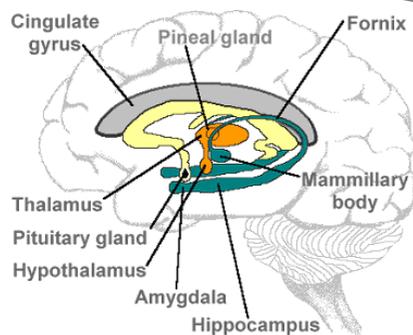
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repetitive hypoxia
and reoxygenation

mitochondria and
endoplasmic reticulum
dysfunction



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



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cognitive dysfunction

(memory, executive function, attention/vigilance)

From 1996 to 2021: what has change in pediatric allergology in the last 25 years



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335 6274799

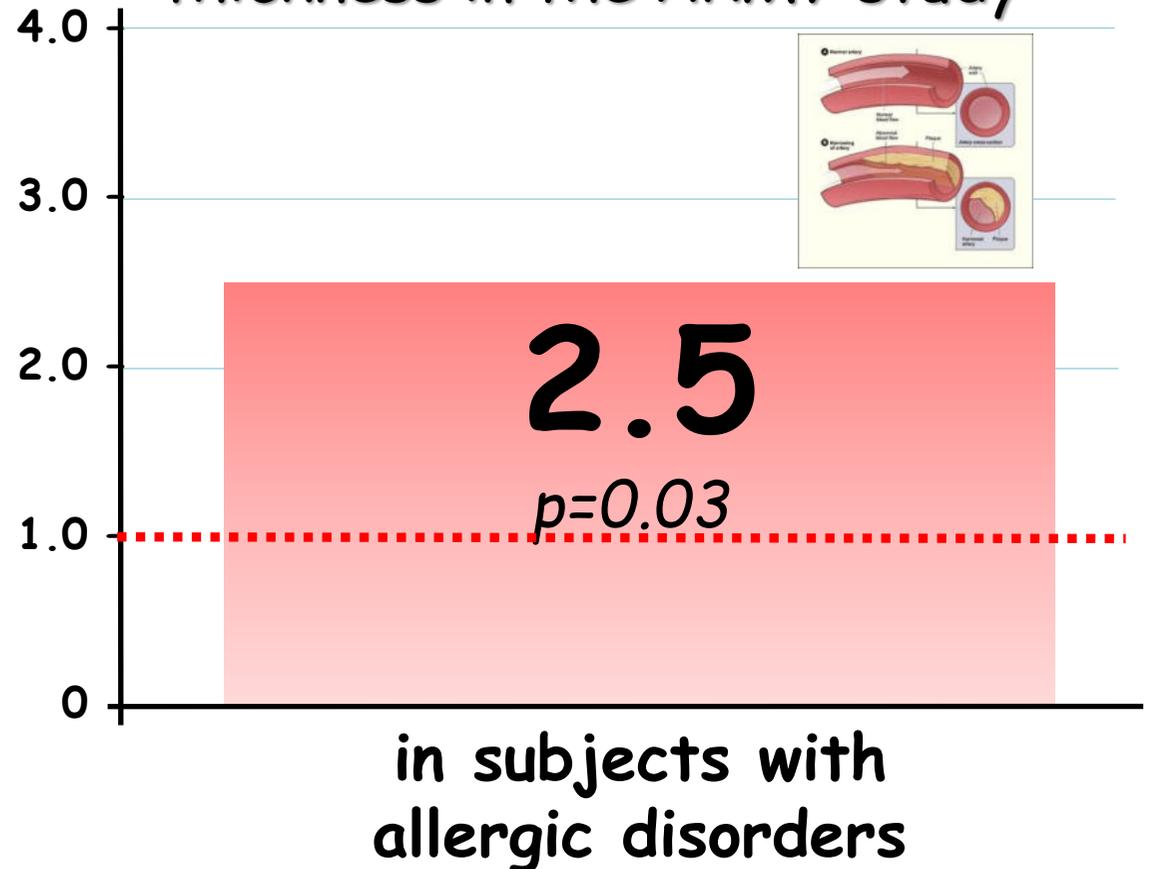
- ✓ Atopic march
- ✓ Atopic Dermatitis
- ✓ Food Allergy
- ✓ Asthma
- ✓ Allergic Rhinitis
- ✓ **Meta-analysis vs Biological Plausibility**



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

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

OR for high intima-media thickness in the ARMY study



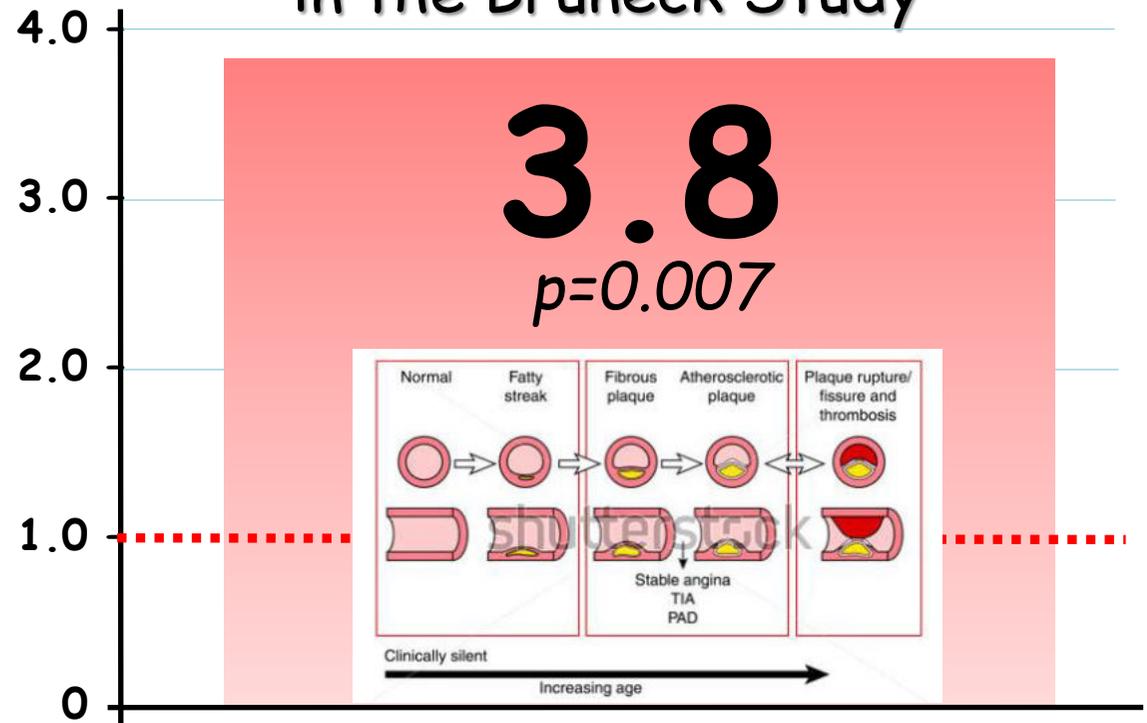
✓ The ARMY study is a cross-sectional evaluation of 141 men aged 17 or 18 years

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

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in subjects with allergic disorders

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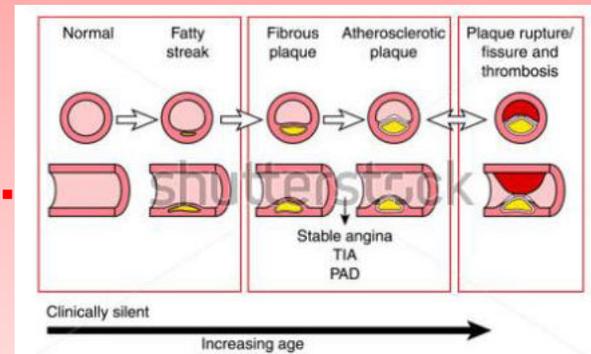
Knoflach M, Arch Intern Med 2005;165:2521-6.

Our findings fit well with the emerging concept that key components of allergies, such as leukotrienes or mast cells, are active in human atherogenesis



OR for atherosclerosis development and progression in the Bruneck Study

3.8
p=0.007



in subjects with allergic disorders

ALLERGIC DISEASES EPIDEMIOLOGY

- The prevalence of allergic disease has increased substantially over the past 50 years and is now estimated to affect up to **40% of the population in industrialised countries.**

40%

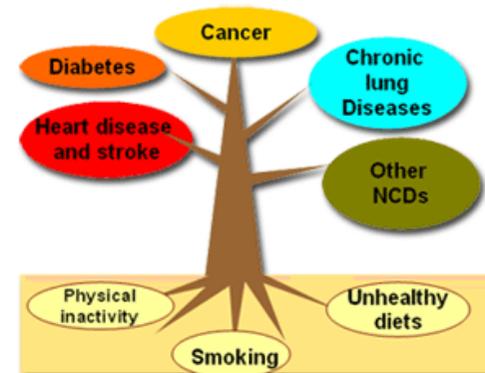


Pawankar R, Canonica GW, Holgate ST, Lockey RF. Allergic diseases and asthma: a major global health concern. Curr. Opin. Allergy Clin. Immunol. 2012;12:39-41.

- Allergic disease is now regarded as one of the most common and earliest onset 'modern' so-called noncommunicable diseases (NCDs).

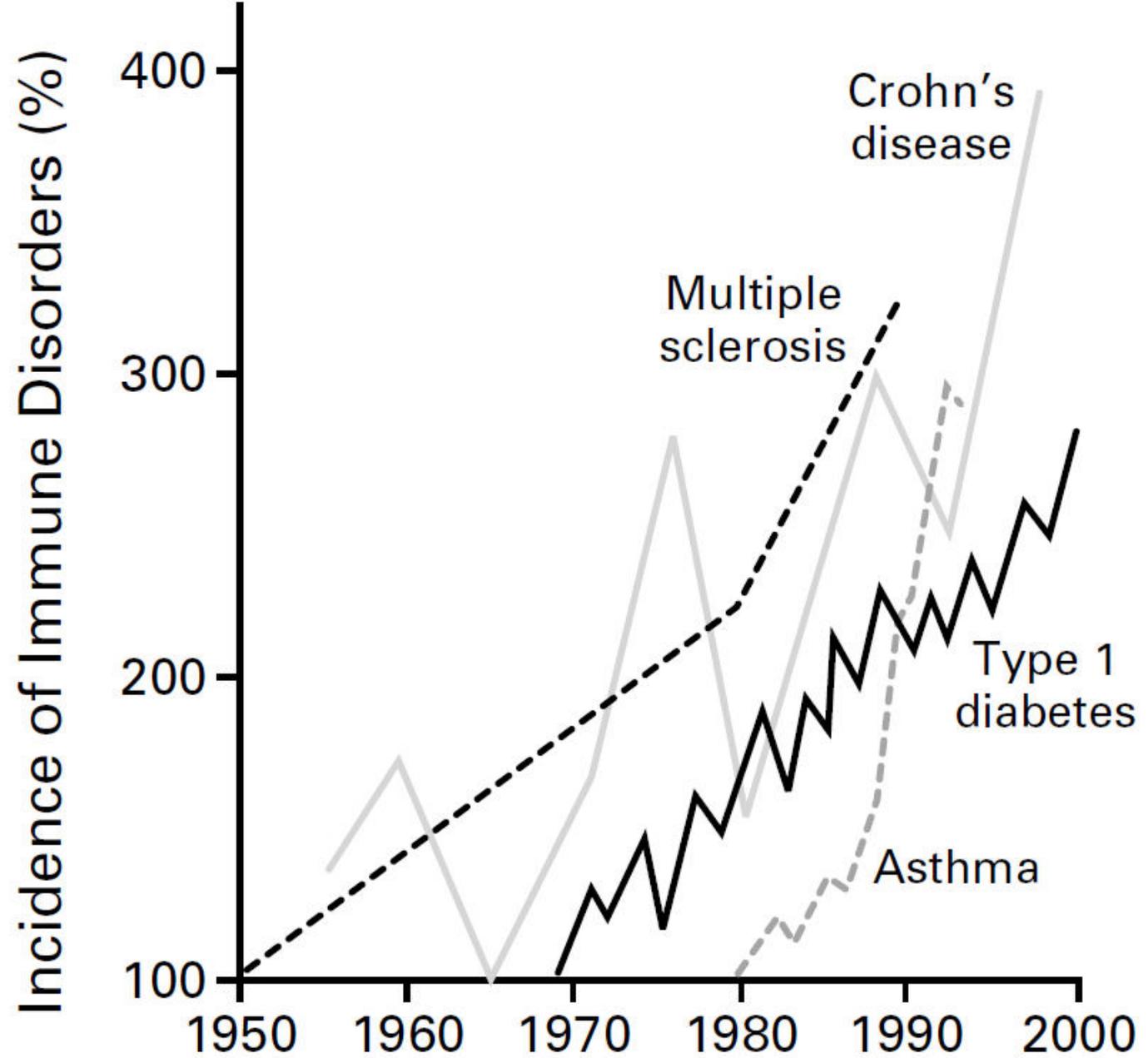
Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature 2011; 474:327-36.

- Although genetic factors play an important role in individual susceptibility, only environmental change can explain the recent rapid increase in allergic diseases.



The increased Incidence of Immune Disorders from 1950 to 2000 in different part of the world.

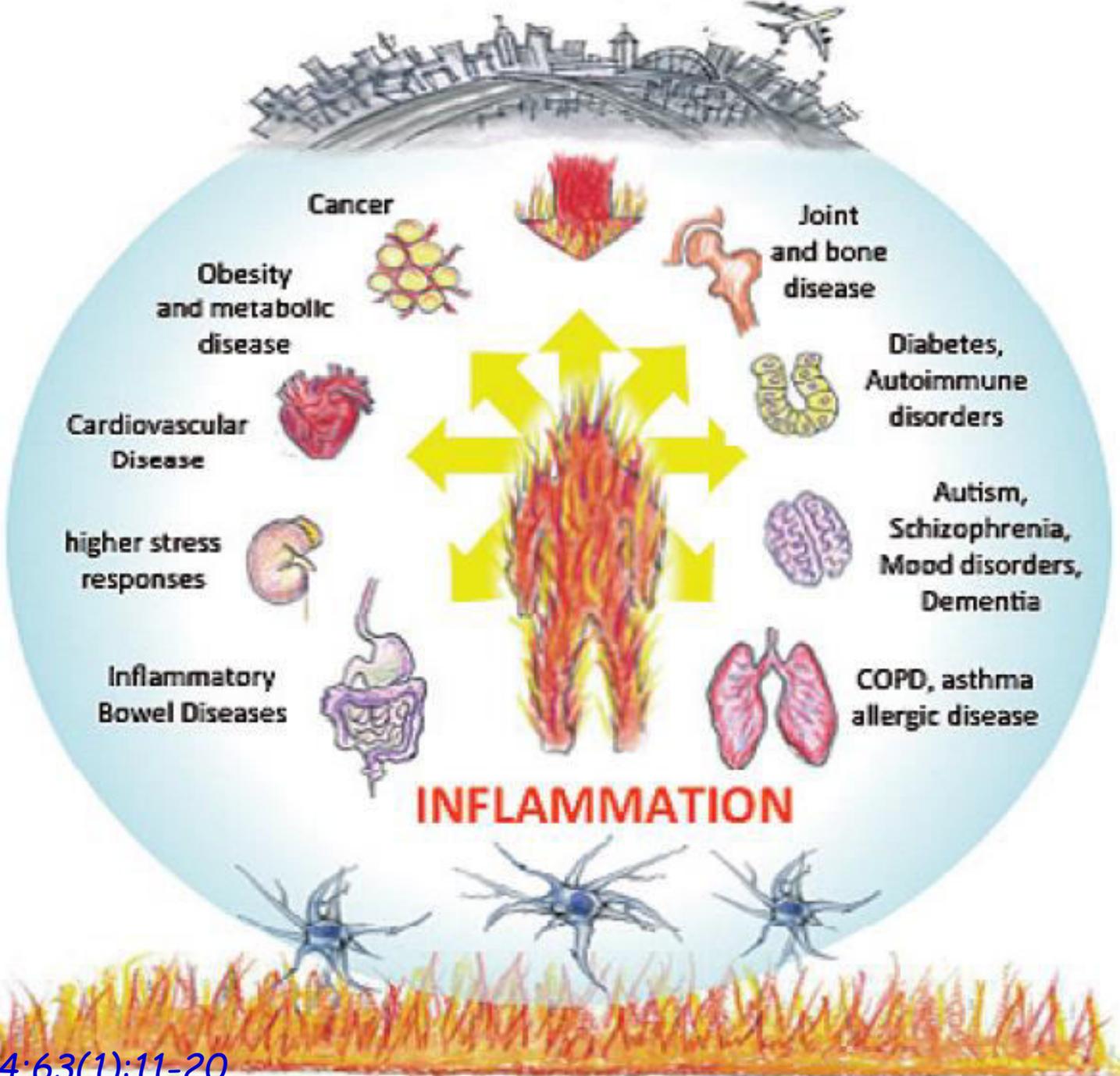
Bach JF.
N Engl J Med.
2002;347(12):911-20



by a courtesy of Prof. Hans Bisgaard

A rising propensity for inflammation is implicated in the parallel rise of virtually all NCDs.

There was little doubt that modern environmental changes promote inflammation and, as a paediatricians, we could already see the first hand effects of this in the first years of life in the epidemic allergic inflammation.

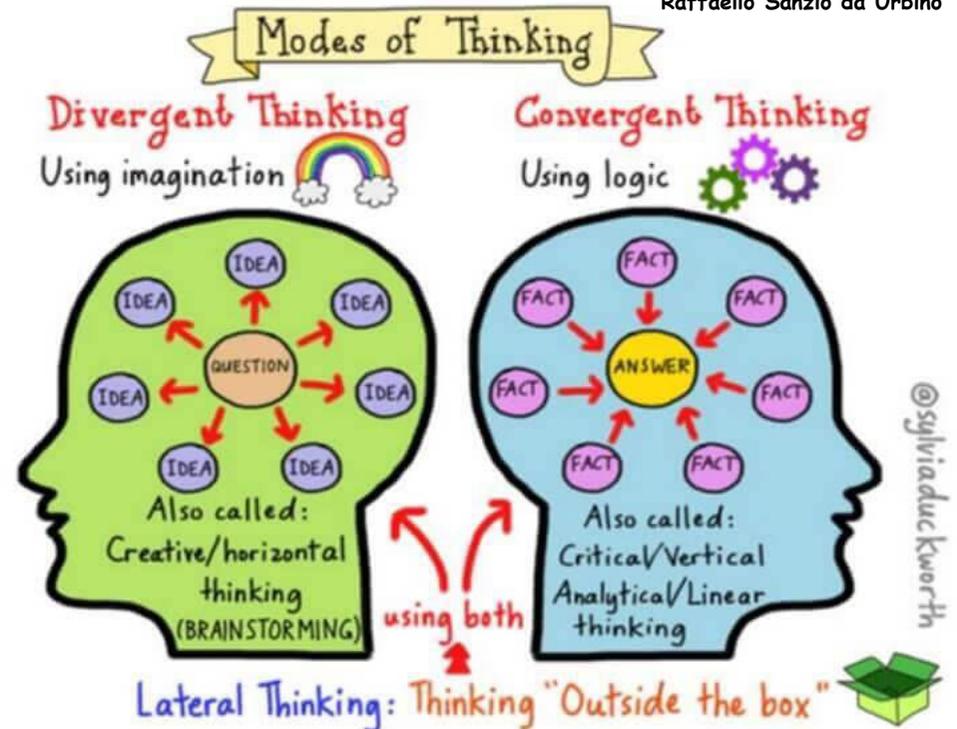
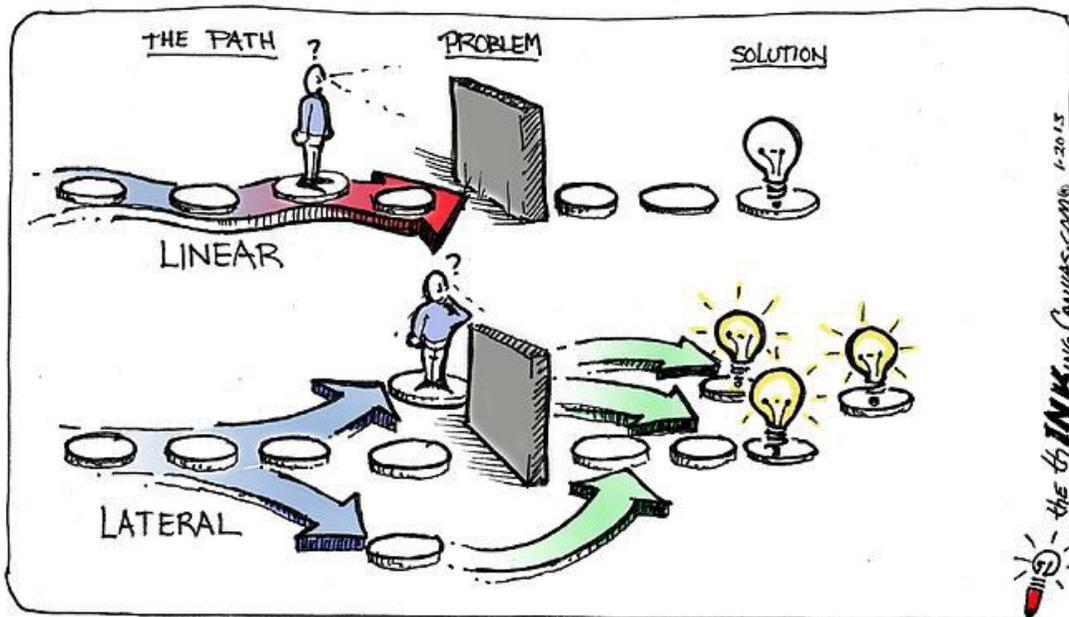


What is Lateral Thinking?

- **Lateral thinking** is a manner of solving problems using an indirect and creative approach via reasoning that is not immediately obvious.
- It involves ideas that may not be obtainable using only traditional step-by-step logic.
- The term was promulgated in 1967 by Edward de Bono. He cites the Judgment of Solomon as an example.



Raffaello Sanzio da Urbino



Fruits and vegetables in general health



curcumin



soy



sulforaphane



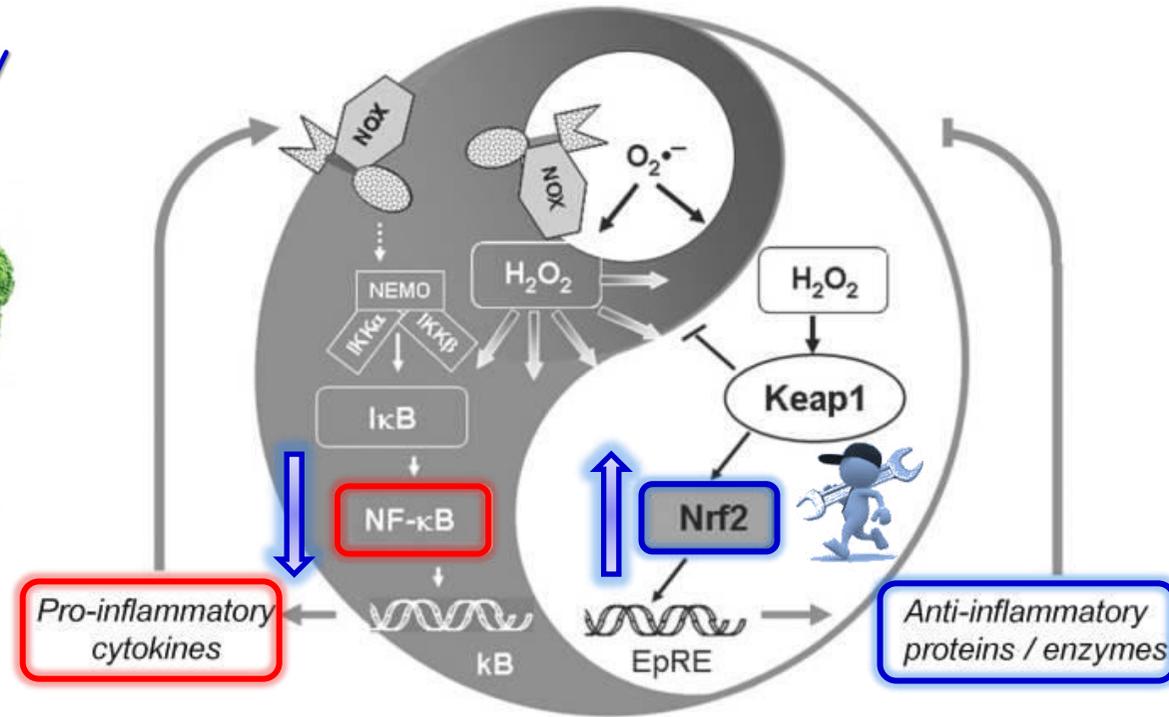
quercetin



resveratrol

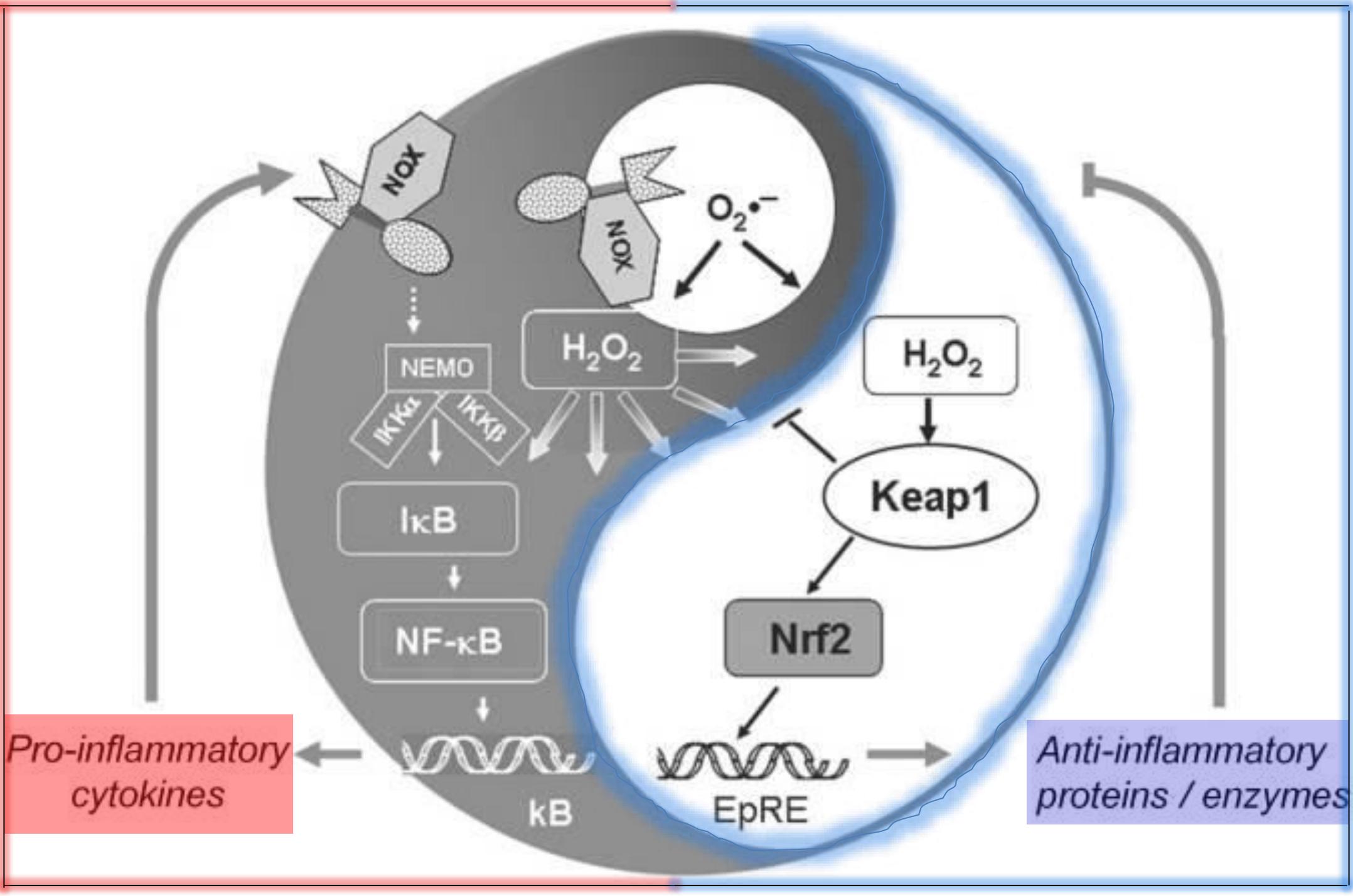


Transcription factors involved in the process of converting, or transcribing, DNA into RNA.



NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells

Nrf2 = Nuclear factor (erythroid-derived 2)-like 2



Thank you
for your
attention
in those
last 25 years!



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