Si può arrestare la marcia atopica?

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Responsabile U.O.C. Pediatria Bollate e Garbagnate
18.5.2012

NO!

- Ci sono fenotipi in cui si può arrestare?
- Ci sono fenotipi in cui si può rallentare l'evoluzione?

Di cosa parleremo

- Definizione
- Quanto è frequente la marcia atopica?
- L'identificazione precoce del bambino a rischio di marcia atopica
- La non utilità di alcuni interventi
- L'utilità di altri: ITS
- Il futuro

La marcia atopica: il timing

- Segni e sintomi allergici in sequenza temporale
- Esperienza comune di bambini e Pediatri
- Studi prospettici di coorte
- Manifestazioni rare nel primo mese di vita
- Picco di incidenza della dermatite atopica e dell'allergia alimentare nei primi 2 anni
- Inizio della sensibilizzazione agli inalanti intorno ai 3 anni
- Massima incidenza di asma nei primi 6 anni di vita

Come si esprime l'allergia

Gastrointestinali

Rinite

Asma

AEDS

AEDS persistente

Fischio

IgE

IgE

IgE

IgE

IgE

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Frequenza della marcia allergica

- Dati raccolti dal 1996 al 2008 da una coorte di bambini con malattia allergica.
- I dati erano resi disponibili dal “ National Health Insurance Research Database”.
- La diagnosi era sempre confermata da un medico rispetto alle definizioni internazionali.
- 10.729 bambini con età < 5 anni erano arruolati da un campione di 200.000 persone.
- Di questi 5866 (54,7%) avevano ricevuto, da un medico, diagnosi di almeno una malattia allergica (DA, AR, Asma).
- I dati dell’assicurazione sono fuorvianti sulle prevalenze: più sono malati più si assicurano. Talvolta patologie per rimborso

Sun HL et al. Coexistence of allergic diseases: patterns and frequencies. Allergy Asthma Proc 2012;33:e1-4.

Frequenza della marcia allergica

- Una sola delle tre patologie era diagnosticata nel 29.8% (3195)
- 2 erano presenti nel 18.8%
- 6.1% avevano tutte e 3 le malattie allergiche.
- I pz con più di una malattia avevano esordio più precoce rispetto a quelli che avevano una sola malattia (2.32 anni versus 2.79 e 4.17; $p < 0.05$).
- La marcia allergica completa era rappresentata solo nel 4,2%

Sun HL et al. Coexistence of allergic diseases: patterns and frequencies. Allergy Asthma Proc 2012;33:e1-4.

Lo studio MAS

- 1314 bambini seguiti per 12 anni
- 38% dei bambini erano ad alto rischio, con almeno 2 familiari atopici e/o IgE del cordone > 0.9kU/l
- 241 bambini hanno avuto AEDS nei primi 2 anni di vita
- il 69% dei pazienti con AEDS nei primi 3 mesi di vita, ha sviluppato sensibilizzazione ad aeroallergeni entro i 5 anni
- Il 50% dei pazienti con AEDS < 3 mesi e storia familiare ha avuto asma o allergie respiratorie contro il 12% dei bambini senza fattori di rischio

Lau S. The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). Paed Resp Rev 2002; 3:265–272.

Bisogna cominciare presto ma cosa succede tardi?

Asma a 16 anni

Asma a 22 anni

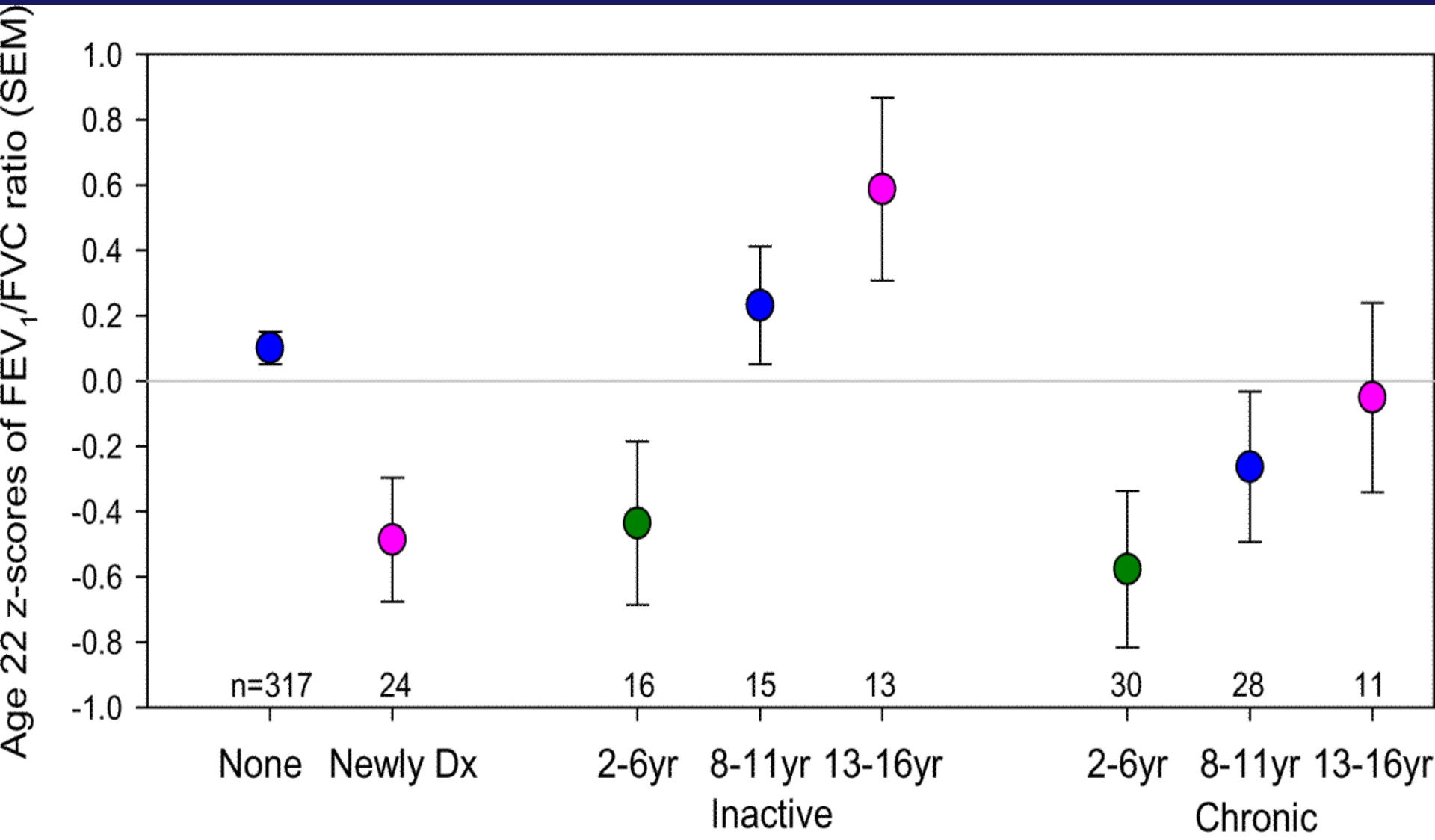
Asma a 33 anni

4 fenotipi temporali diversi

Physician Diagnosed Asthma and Current Symptoms		Asthma at
Between 2-16 Years	at 22 Years	Age 22 Years
-	-	No Asthma
+	-	Inactive
-	+	Newly Diagnosed
+	+	Chronic

Stern DA et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study.Lancet 2008;372:1058-64.

A 22 anni FEV_1/FVC basso se asma esordisce presto



Stern DA et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study.Lancet 2008;372:1058-64.

A 33 anni

Key messages

- About half of British people born in 1958 experienced one or more episodes of wheezing illness by 33 years of age. Less than two thirds of these recalled wheezing when interviewed at age 33.
- Incidence of wheezing illness at all ages was strongly and consistently related to a history of hay fever or eczema (atopy). Associations with maternal smoking during pregnancy, abdominal pain, and migraine were largely confined to those without atopy
- Active smoking was a powerful and potentially avoidable risk factor for wheeze starting in adult life among both atopic and non-atopic subjects
- A quarter of the children with a history of asthma or wheezy bronchitis by age 7 reported wheeze in the past year at age 33
- Recurrence of wheezing after prolonged remission during late adolescence was strongly associated with atopy and cigarette smoking.

Strachan DP et al. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195-9.

- Bisogna intervenire presto
- Intervenire presto su chi è a rischio di marcia

Di cosa parleremo

- Definizione
- Quanto è frequente la marcia atopica?
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Fattori di rischio significativi per lo sviluppo di asma

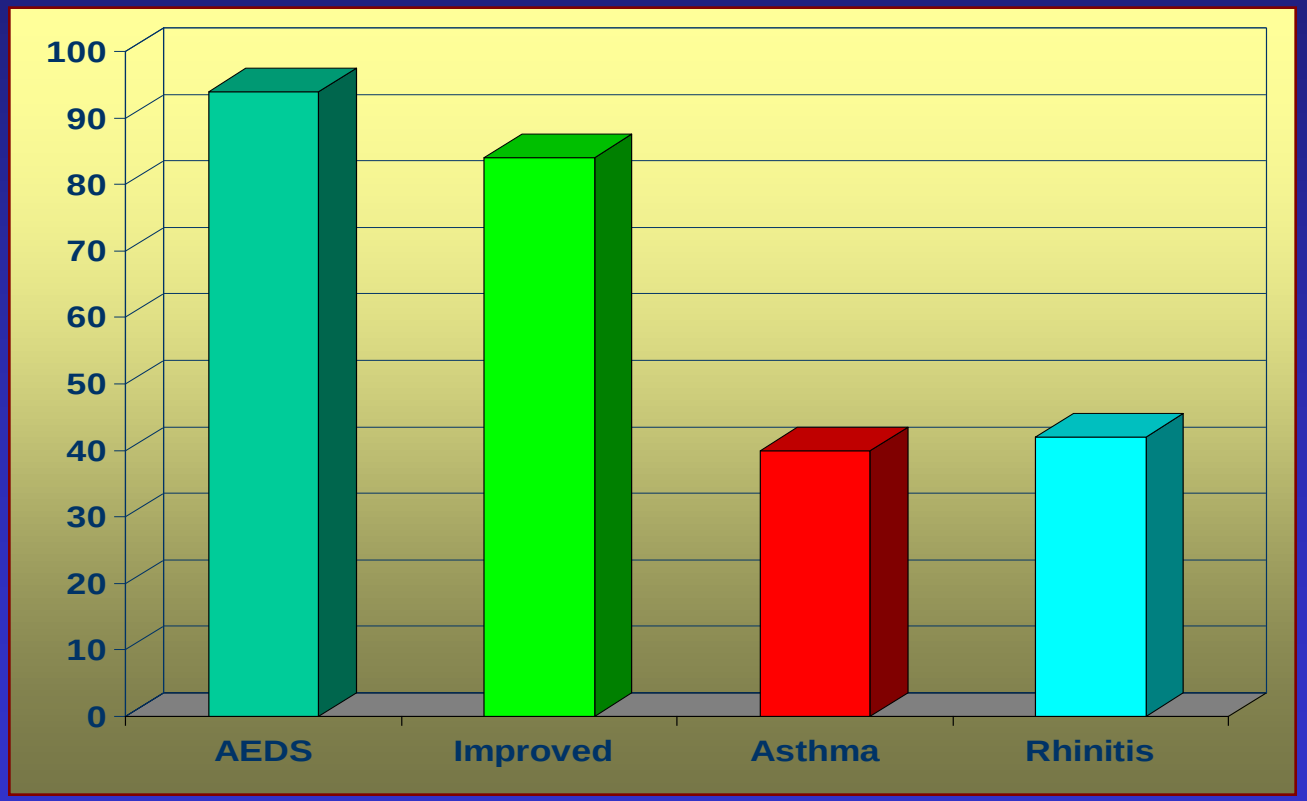
165 bambini a rischio seguiti per 7 anni.
All'età di 7 anni la prevalenza di asma e rinite era doppia nei bambini che a 4 anni avevano allergie alimentari (n=31) rispetto agli altri (n=134)

- rinite 64,5% vs 33,6, p=001
- asma 48,4% vs 26,1, p<0,05
- rinite o asma 77,4% vs 45,5, p<0,001
- allergeni in causa erano uovo, latte ed arachidi

Zeiger RS. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance J Allergy Clin Immunol 1995;95:1179-90

Development of allergies and asthma in infants and young children with atopic dermatitis

A prospective follow-up to 7 years of age



Gustafsson D. Development of allergies and asthma in infants and young children with atopic dermatitis - a prospective follow-up to 7 years of age. Allergy 2000; 55:240-5

Development of allergies and asthma in infants and young children with atopic dermatitis

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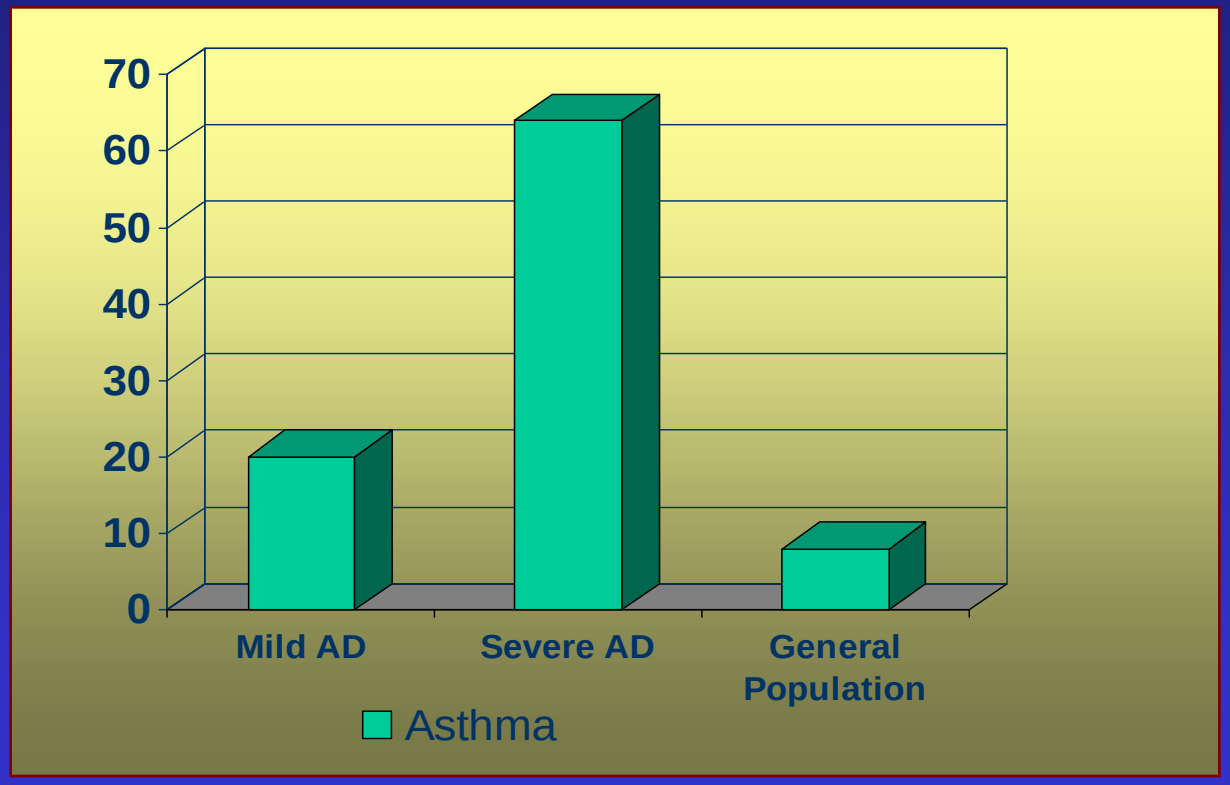


Gustafsson D. Development of allergies and asthma in infants and young children with atopic dermatitis--a prospective follow-up to 7 years of age. Allergy 2000; 55:240-5

Sensibilizzazione ad alimenti ed asma a 7 anni

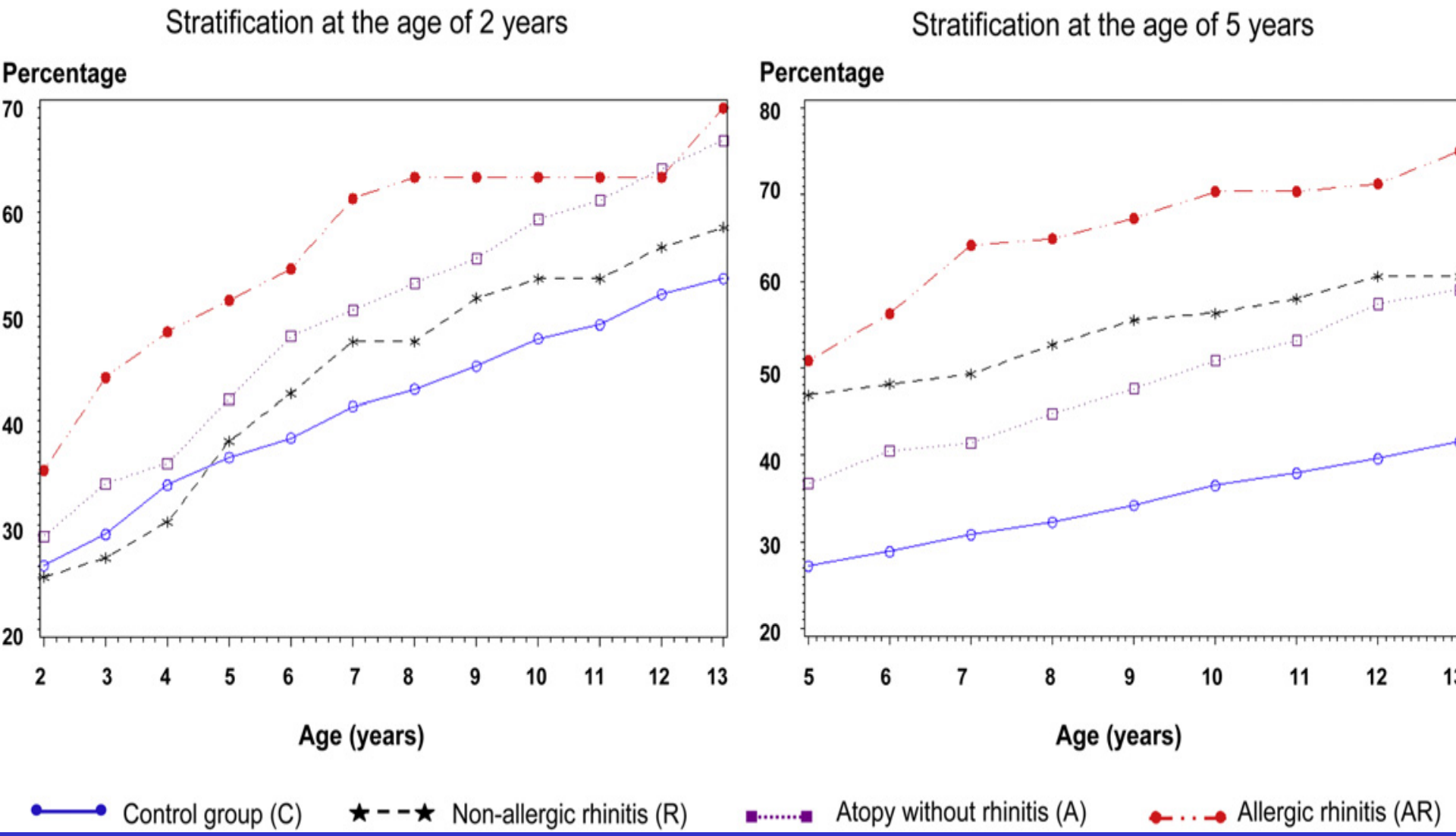
Illi S. The pattern of atopic sensitization is associated with the development of asthma in childhood. J Allergy Clin Immunol. 2001;108:709-14

DA con sensibilizzazione a rischio di asma

	Group			
	Non-atopic eczema	Atopic eczema	Asymptomatic	Asymptomatic-sensitized
Unadjusted associations				
6 years % (*n*)	21.8 (17/78)	47.8 (53/111)	14.3 (19/133)	30.3 (23/76)
7 years % (*n*)	17.4 (12/69)	44.6 (45/101)	13.6 (16/118)	42.0 (29/69)
OR (95% CI)*	1	3.52 (1.88–6.59)	0.63 (0.31–1.27)	2.19 (1.11–4.32)
P	–	< 0.001	0.201	0.025
Adjusted associations†				
OR (95% CI)*	1	2.60 (1.32–5.14)	0.73 (0.35–1.54)	2.36 (1.14–4.90)
P	–	0.006	0.410	0.021
Unadjusted associations after excluding infants with early wheeze‡				
6 years % (*n*)	14.8 (8/54)	31.0 (18/58)	8.2 (8/97)	16.0 (8/50)
7 years % (*n*)	12.2 (6/49)	30.8 (16/52)	5.8 (5/86)	23.3 (10/43)
OR (95% CI)*	1	2.92 (1.22–7.00)	0.50 (0.18–1.36)	1.52 (0.58–3.99)
P	–	0.016	0.174	0.395

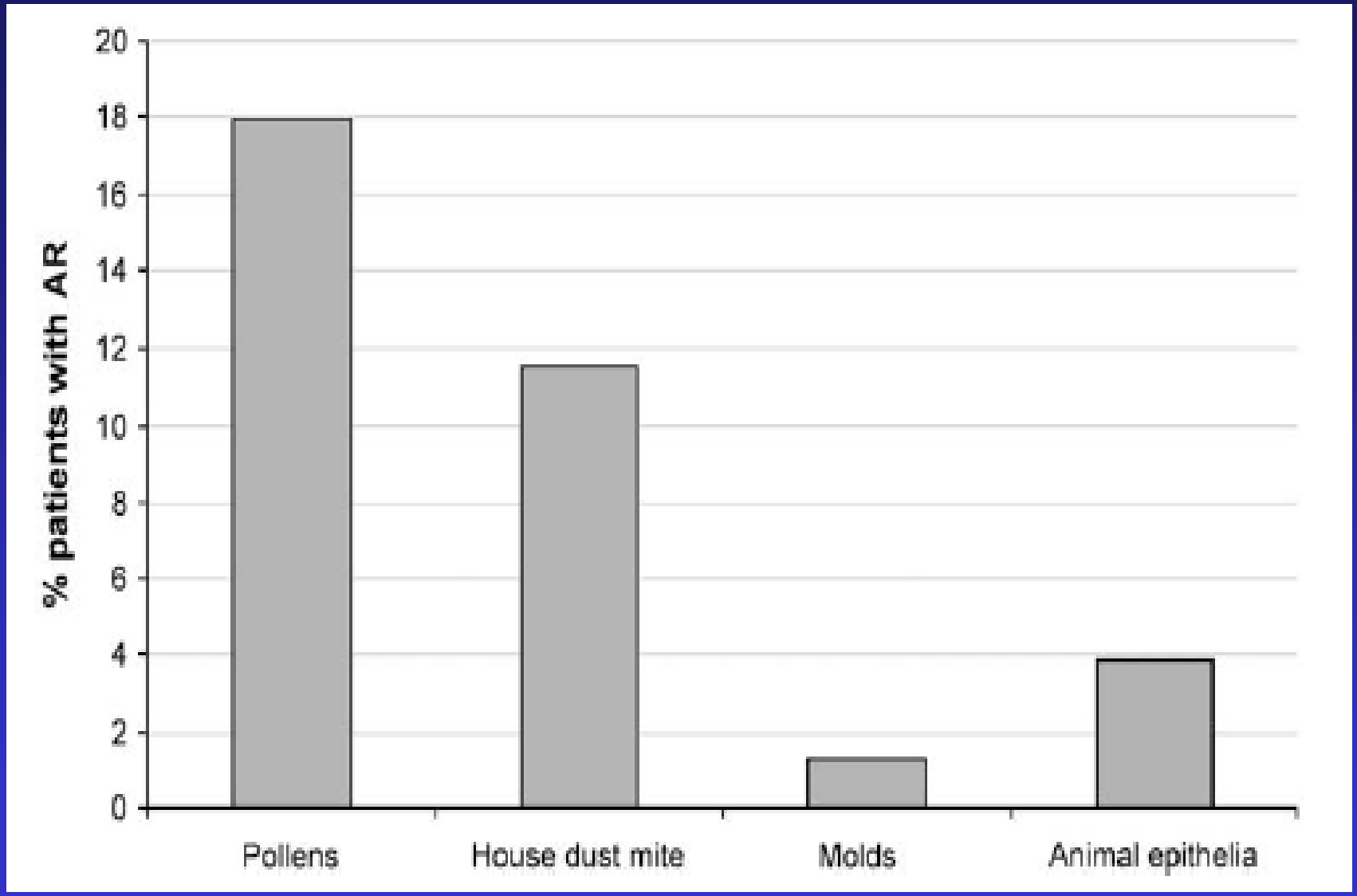
Lowe AJ et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. Clin Exp Allergy 2007;37:1624-31.

Prevalenza di wheezing in 4 fenotipi



Rochat M et al. Multicentre Allergy Study (MAS) group. Allergic rhinitis as a predictor for wheezing onset in school-aged children. J Allergy Clin Immunol 2010;126:1170-5.

Nuove sensibilizzazione nei NAR a distanza



Rondón C, et al. Evolution of patients with nonallergic rhinitis supports conversion to allergic rhinitis. J Allergy Clin Immunol 2009;123:1098-102.

Prick inalanti in 824 bambini di età < 2 anni

Allergen	*N* (percentage of children tested)	Positive, in percentage of children demonstrating atopy
Any allergen	326 (39.6)	
Any aeroallergen	231 (28.0)	70.9
Egg	141 (17.1)	43.3
Dermatophagoides pteronyssinus	91 (11.0)	27.9
Grass pollen	58 (7.0)	17.8
Feathers	48 (5.8)	14.7
Dog	48 (5.8)	14.7
Cat	45 (5.5)	13.8
Dermatophagoides farinae	44 (5.3)	13.5
Milk	36 (4.4)	11.0
Fish (cod)	36 (4.4)	11.0
Peanut	31 (3.8)	9.5

de Bilderling G. et al. Early skin sensitization to aeroallergens. Clin Exp Allergy 2008; 38:643-8.

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Probiotici e prebiotici

Probiotics

- In initial studies using *Lactobacillus* GG in a randomised human trial (159 mothers supplemented before delivery and infants supplemented for 6 months), analysis showed a 50% reduction in eczema at age 2 years; the protective effect persisted up to 7 years of age [117, 118]; the prevalent eczema was very low and not different from the probiotic-treated group
- While there are a number of recognised effects of gut microflora on immune development, the mechanism of the clinical effect seen in this study is not clear; there was no effect on allergic sensitisation, or other allergic outcomes
- Subsequent studies of the same strain in other populations have shown no effect [45]
- The effects of probiotics are variable and appear to depend on the strain, the timing, method of administration, host and other environmental factors [reviewed in ref. 42]

Summary: The revised Cochrane meta-analysis concludes that there is some evidence that a probiotic or a synbiotic containing *L. rhamnosus* may reduce the incidence of eczema in infants at high risk of allergic disease, but that there are no reproducible data for other probiotics; there is no evidence that any probiotic prevents other allergic conditions or sensitisation; they also advised caution based on methodological concerns with some of the included studies

Prebiotics

- Initial studies using prebiotics in cow-milk-based formula showed reduced cumulative incidence of allergic outcomes in high-risk children including atopic dermatitis, recurrent wheezing and allergic urticaria in the treatment group compared with the placebo at 2 years; there were also reduced respiratory tract infections, fever episodes and antibiotic prescriptions reported [48]
- Subsequent studies have also found a reduced risk of atopic dermatitis in children at low risk of allergic disease [50]
- Mechanisms of effect are likely to include effects in promoting favourable colonisation with healthy commensal bacteria, as well as direct effects on the immune system [63, 64]

Summary: There is encouraging evidence that prebiotics have a number of health-promoting effects, including immune effects, which may reduce the risk of allergic and infectious outcomes; the results of several large multicentre studies are awaited with interest as there are still relatively few studies to report on allergy outcomes

Prescott S. et al. Strategies to prevent or reduce allergic disease. Ann Nutr Metab 2011;59 Suppl 1:28-42.

Serve eliminare l'acaro?

CONCLUSIONS: Trials have tended to be small and of poor methodological quality, making it difficult to offer any definitive recommendations. Interventions that achieve substantial reductions in HDM load may offer some benefit in reducing rhinitis symptoms. Isolated use of HDM impermeable bedding is unlikely to prove effective.

Nurmatov U. et al. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. Allergy 2012;67:158-65.

Efficace prevenzione “multipla”

- Interventi multifattoriali
- Questo si esprime in un NTT di 17 (NNT).

Maas T, et al. Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006480.

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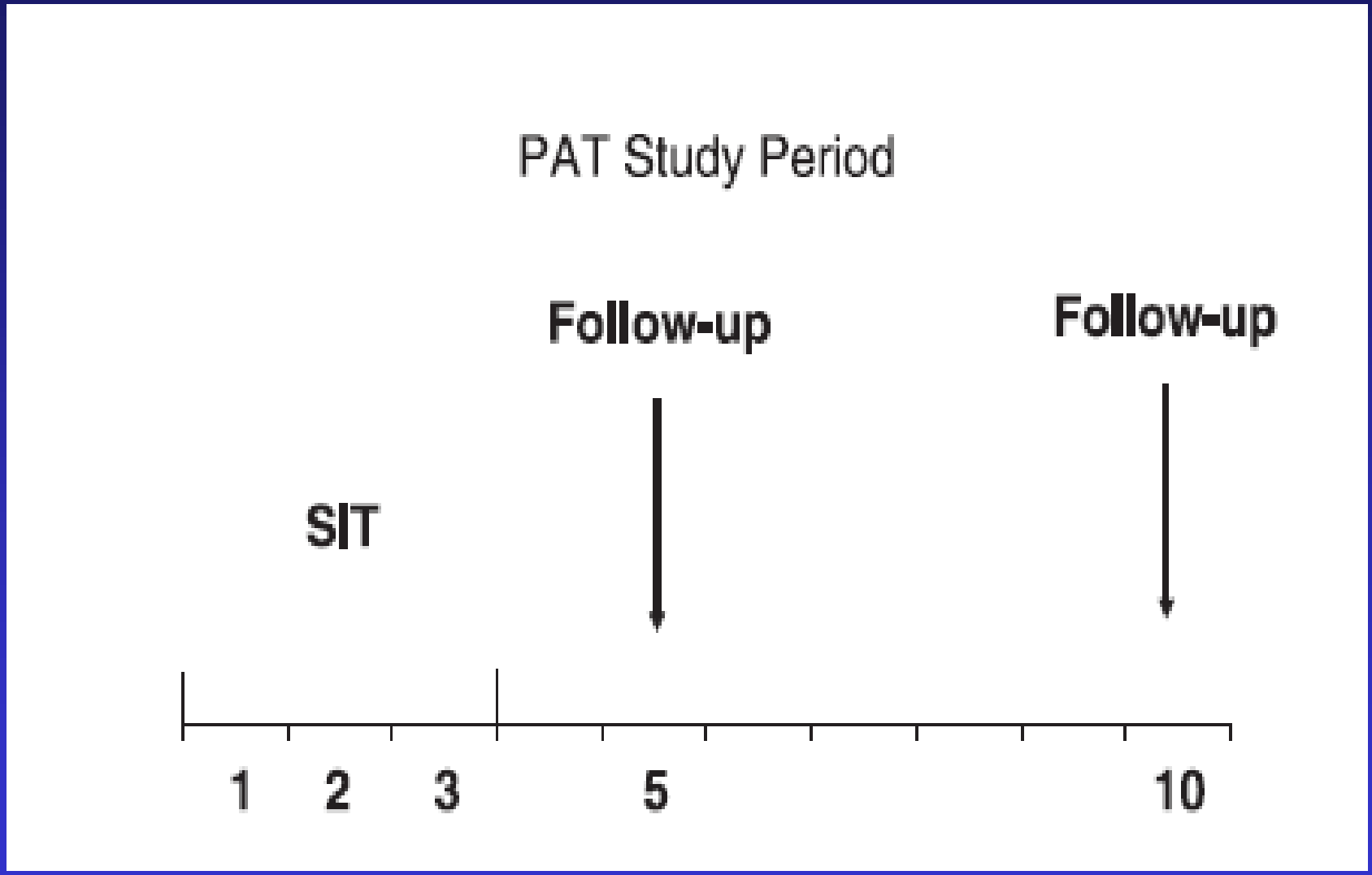
PAT = preventive allergy treatment



SCIT per 3 anni riduce asma nella rinocongiuntivite stagionale

- Studio multicentrico (6 centri allergologici pediatrici)
- 205 bambini randomizzati di 6-14 anni (età media 10.7 aa)
- Storia di rinocongiuntivite allergica da betulla e/o graminacee con SPT e test di provocazione congiuntivale +
- Test di provocazione bronchiale con metacolina durante la stagione di esposizione e in inverno
- Prima della SCIT, 20% presentavano asma lieve durante la stagione pollinica
- Gruppo controllo: antistaminici generali e locali, DSCG e budesonide nasale

Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Criteri d'esclusione

- Pregressa SIT
- Altre sensibilizzazioni
- Asma che richiedeva terapia quotidiana

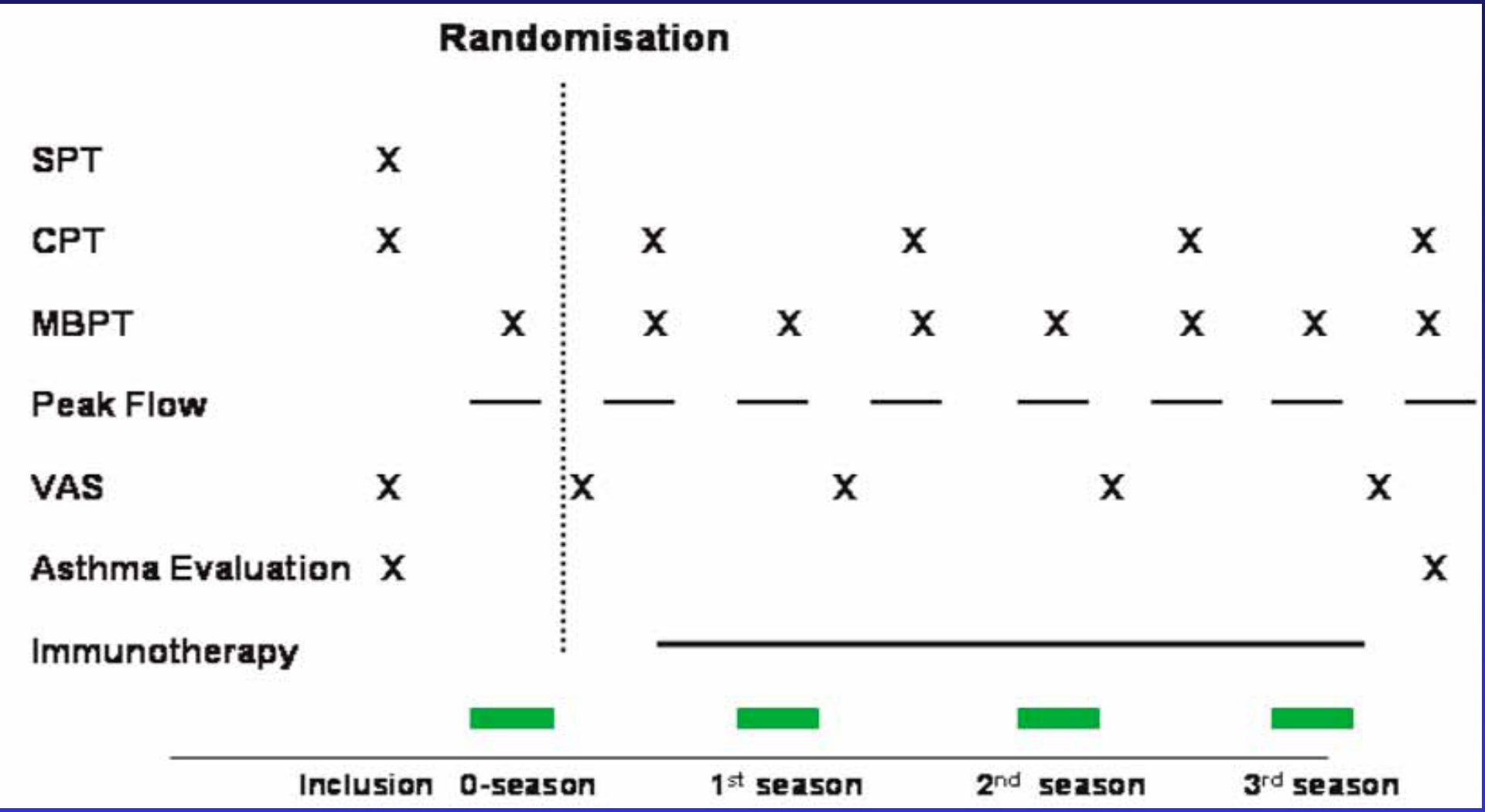
Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Limiti del PAT

- Studio in aperto
- Metodo di randomizzazione non precisato

Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Il prospetto dello studio



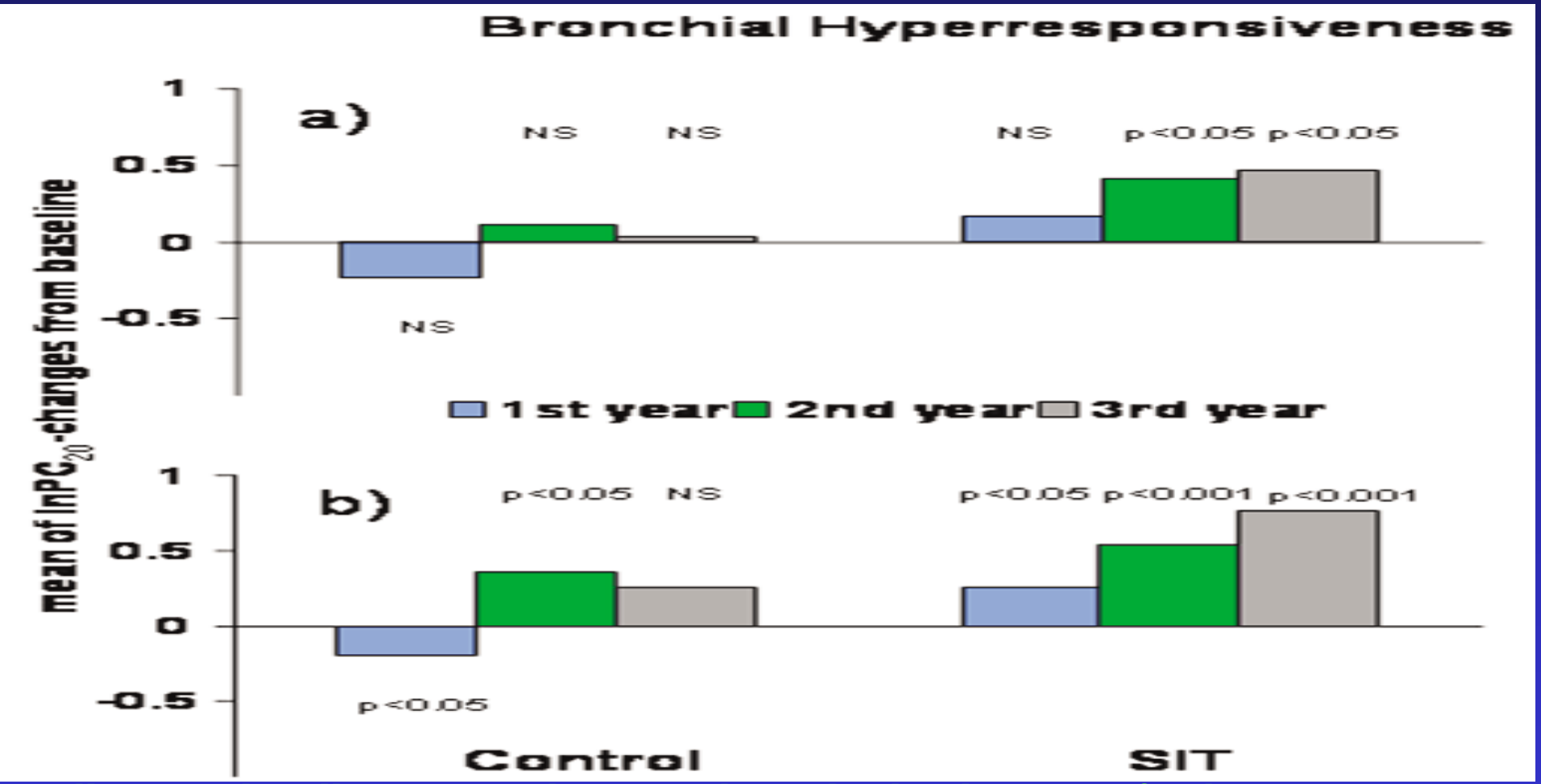
Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Asma era definito dalla ricorrenza di 2 su 3 segni nei 12 mesi precedenti

- Cough
- Wheeze
- Shortness of breath

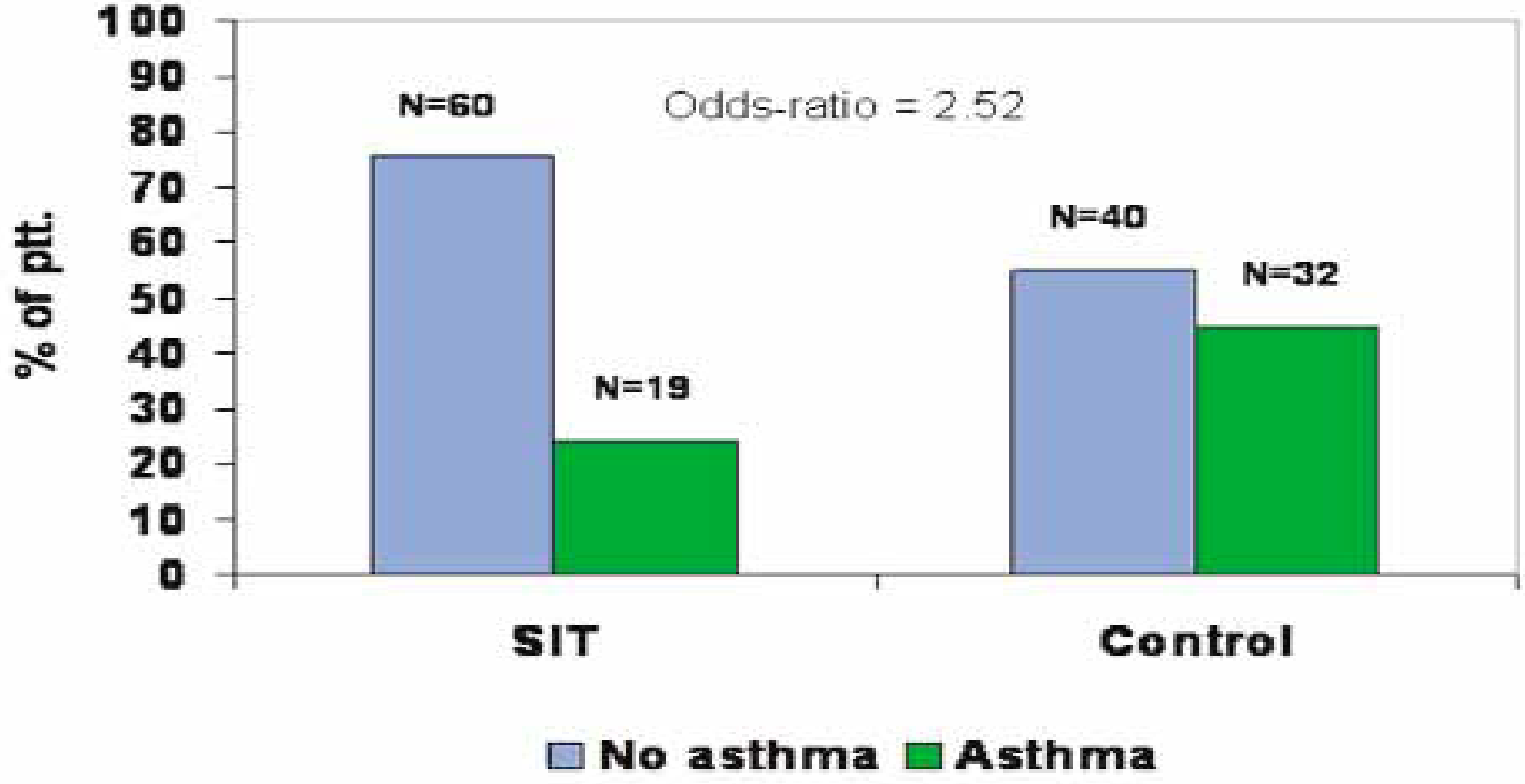
Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Miglioramento di IRB sia durante stagione pollinica (a) che durante l'inverno (b)



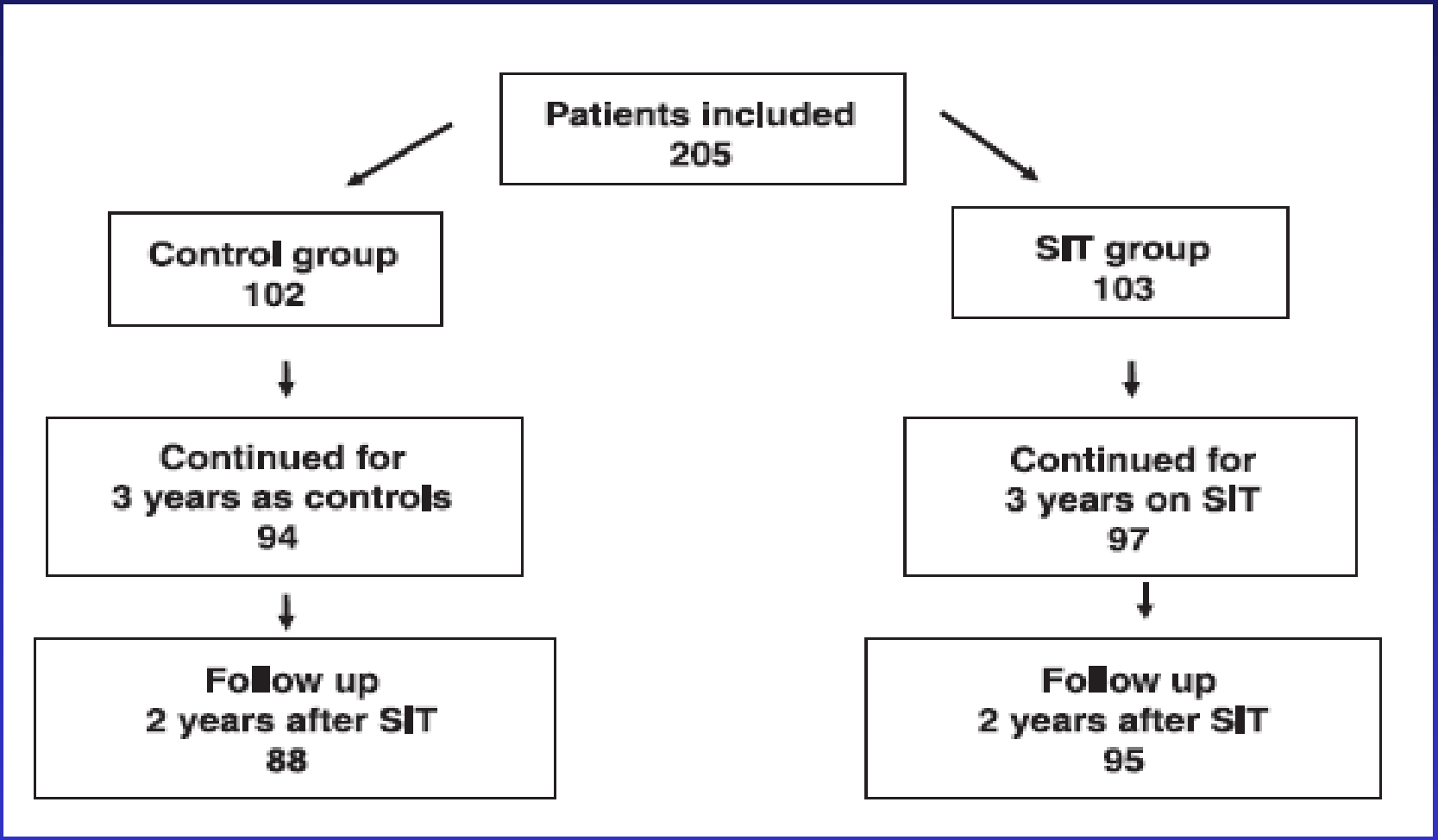
Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Incidenza d'asma dopo i 3 anni di SCIT in 151 bambini con sola RA



Möller C et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.

Flow chart dei bambini a 5 anni



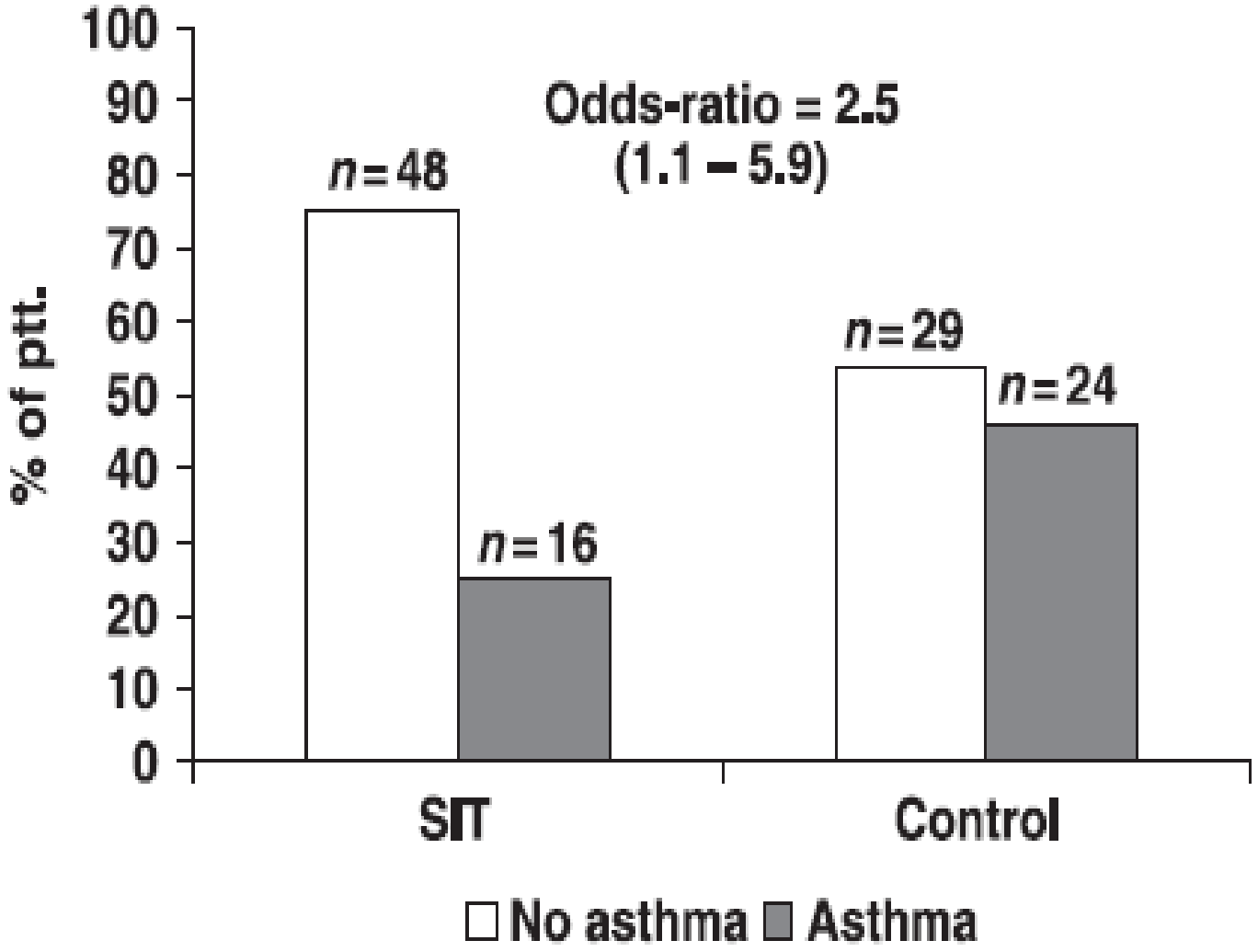
Niggemann B et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006 ;61:855-9.

Cosa accade a 5 anni

- Due anni dopo la sospensione della SCIT
- 183 bambini erano valutati a 2 anni dalla sospensione della SCIT con il gruppo controllo
- Asma con valutazione clinica
- CPT e metacolina eseguiti durante la stagione e in inverno dopo 5 anni
- Miglioramento della RA persiste anche a 5 anni.
- Non differenze nella metacolina
- I trattati con ITS avevano meno asma rispetto ai controlli

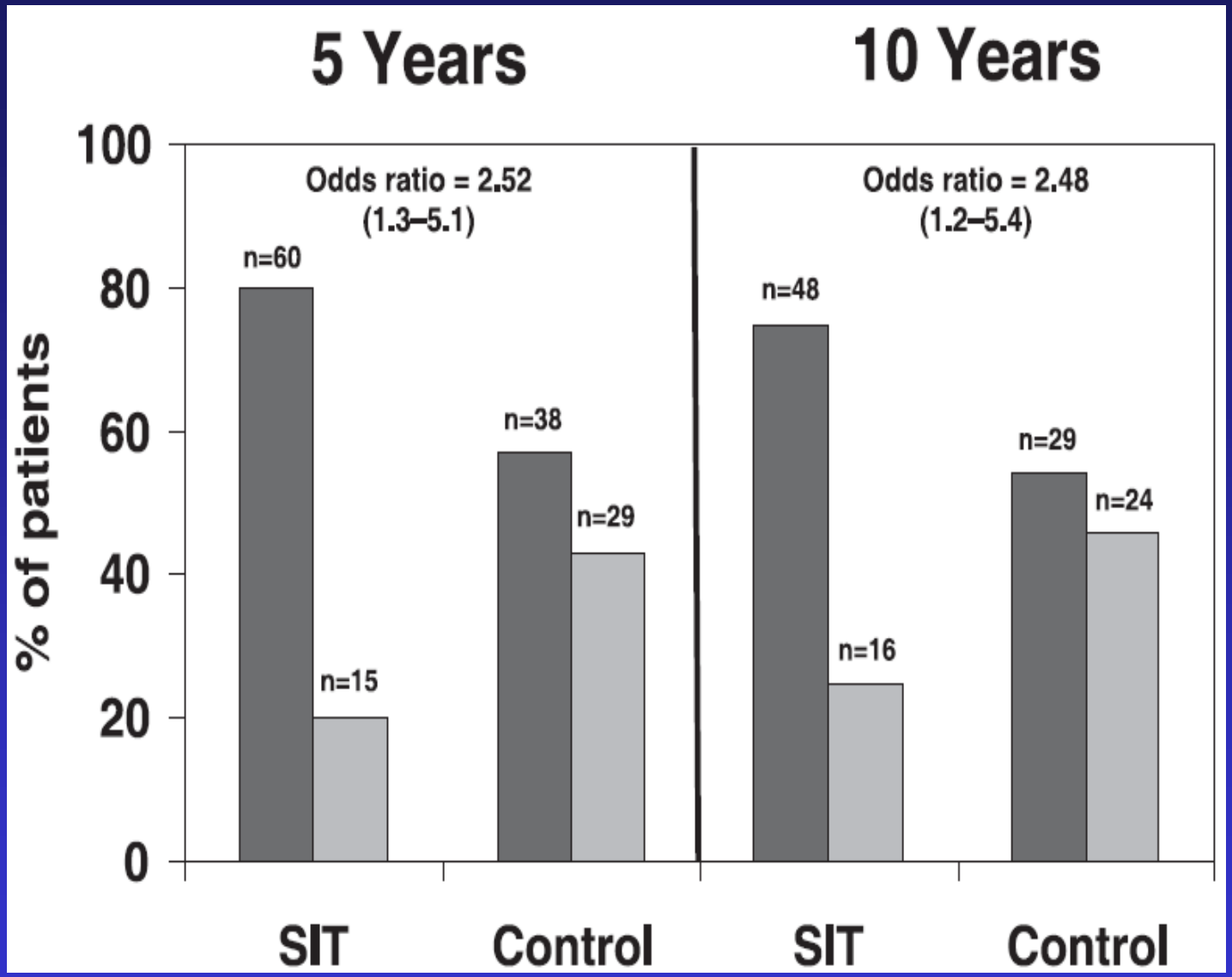
Niggemann B et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006 ;61:855-9.

Cosa accade a 10 anni : dropout elevato



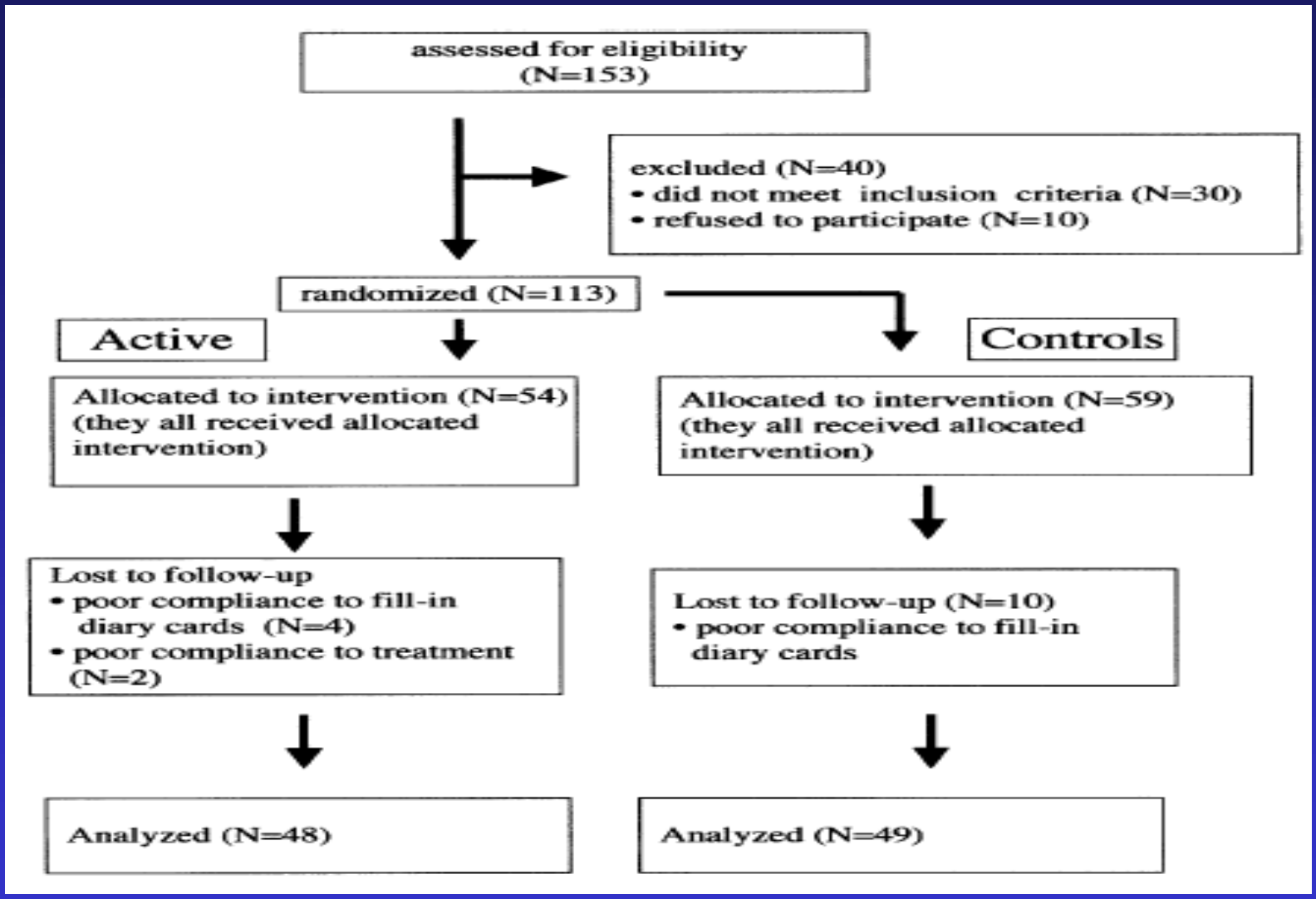
Jacobsen L et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007;62:943-8.

Cosa accade a 10 anni



Jacobsen L et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007;62:943-8.

Flow chart dei partecipanti alla SLIT



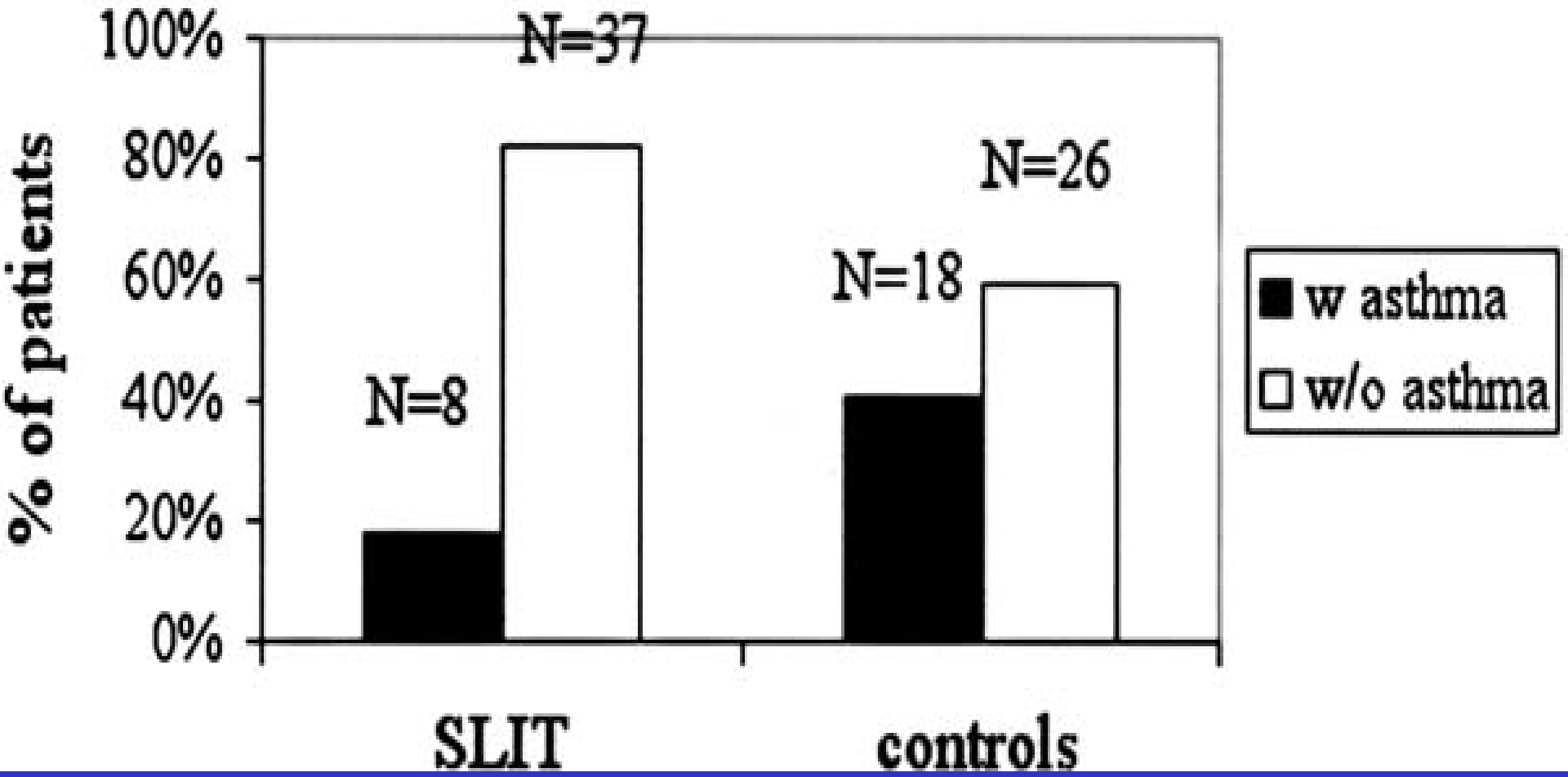
Novembre E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114:851-7.

SLIT, come la SCIT, riduce i sintomi di RA e riduce rischio di asma?

- Studio randomizzato in aperto
- Età media 7,7 aa (5-14)
- RA per graminacee
- Non asma all'arruolamento
- SLIT (ALK) Graminacee
- Trattamento pre-costagionale (15 feb-15 giu) x 3 aa

Novembre E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114:851-7.

% di bambini con e senza asma dopo 3 anni SLIT



Novembre E et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114:851-7.

SLIT preventiva?

- 216 bambini con RA con o senza asma intermittente
- Randomizzati per soli farmaci (72) o farmaci + SLIT (144) in aperto per 3 anni
- Clinical score durante esposizione allergenica, PFR, Metacolina, SPT a inizio e fine dello studio
- Valutati esordio di asma persistente, nuove sensibilizzazioni, sintomi clinici, IRB.

Marogna M et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol 2008;101:206-11.

SLIT preventiva: i risultati

SLIT + Drug

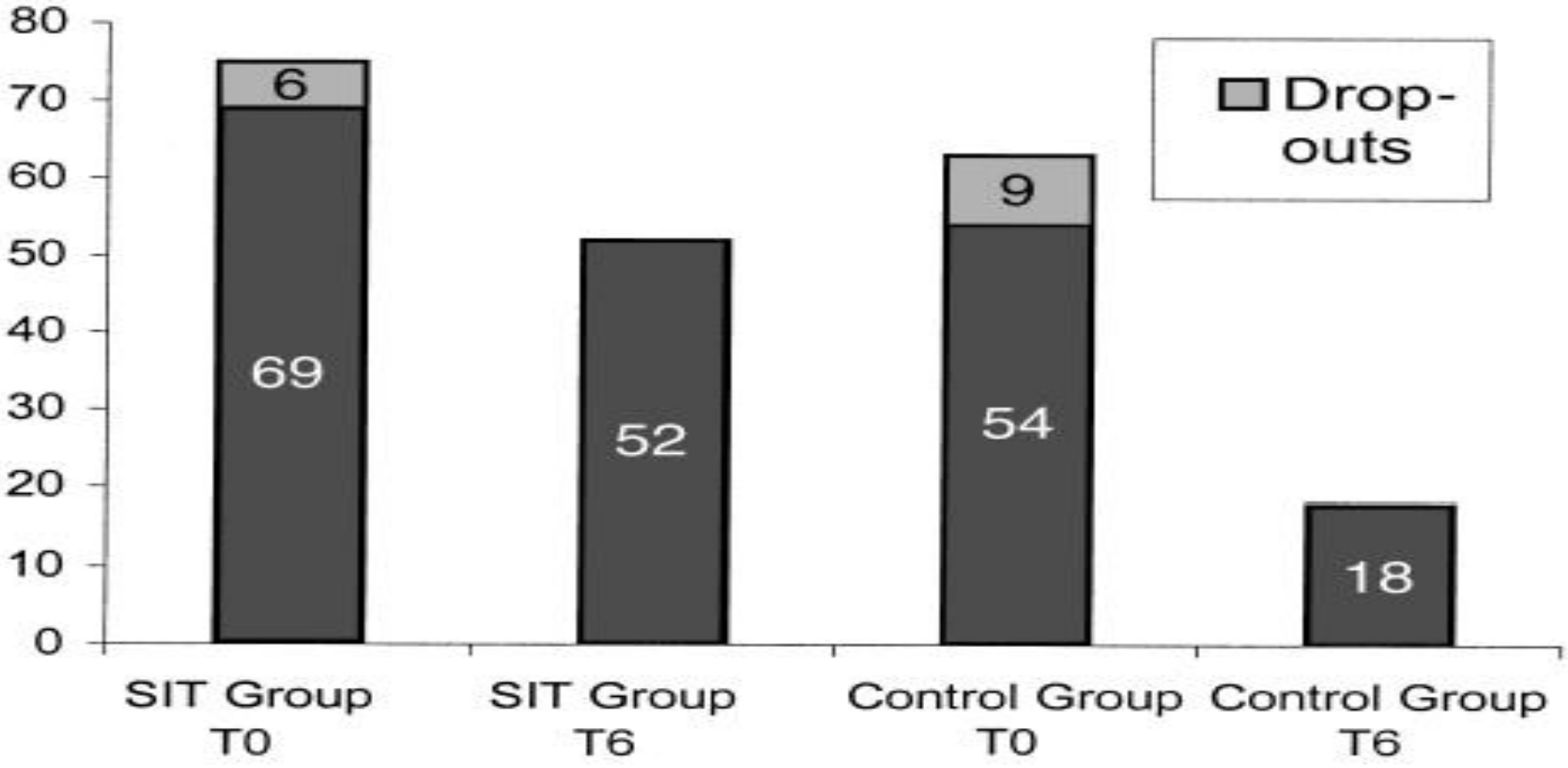
- Dropout 9,7%
- Nuove sensibilizzazioni 3,1%
- Asma lieve persistente ↓
- Ridotto “clinical score”
- Test alla metacolina + ridotti a 3 anni di SLIT

Drug

- Dropout 8,3%
- Nuove sensibilizzazioni 34,8%
- Asma lieve persistente ↑ Elevato “clinical score”
- Test alla metacolina + invariati a 3 anni

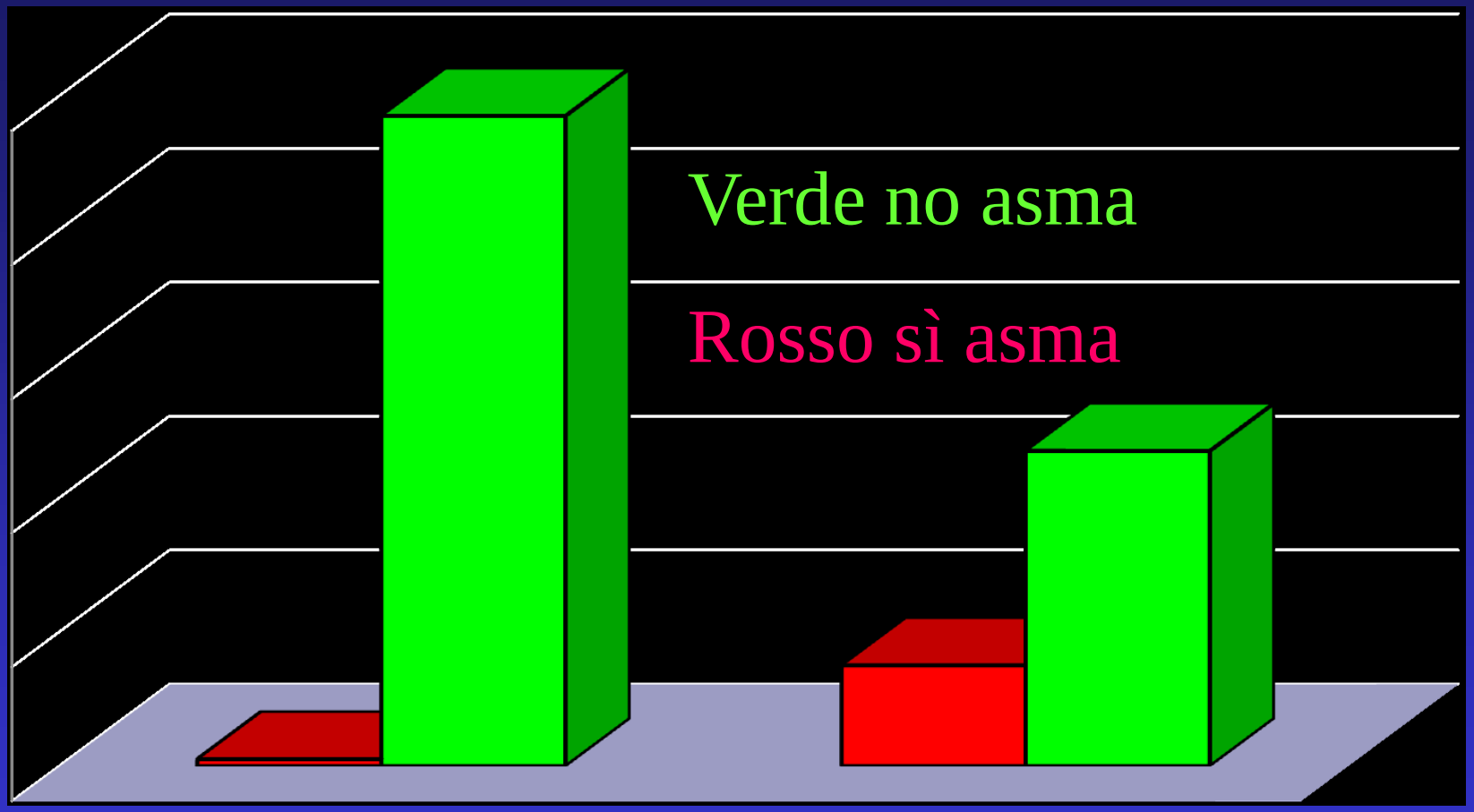
Marogna M et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol 2008;101:206-11.

SIT inibisce nuove sensibilizzazioni in chi è già asmatico e monosensibilizzato



Pajno GB et al. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31:1392-7.

Sviluppo di asma persistente a 3 anni nei bambini sensibilizzati agli acari



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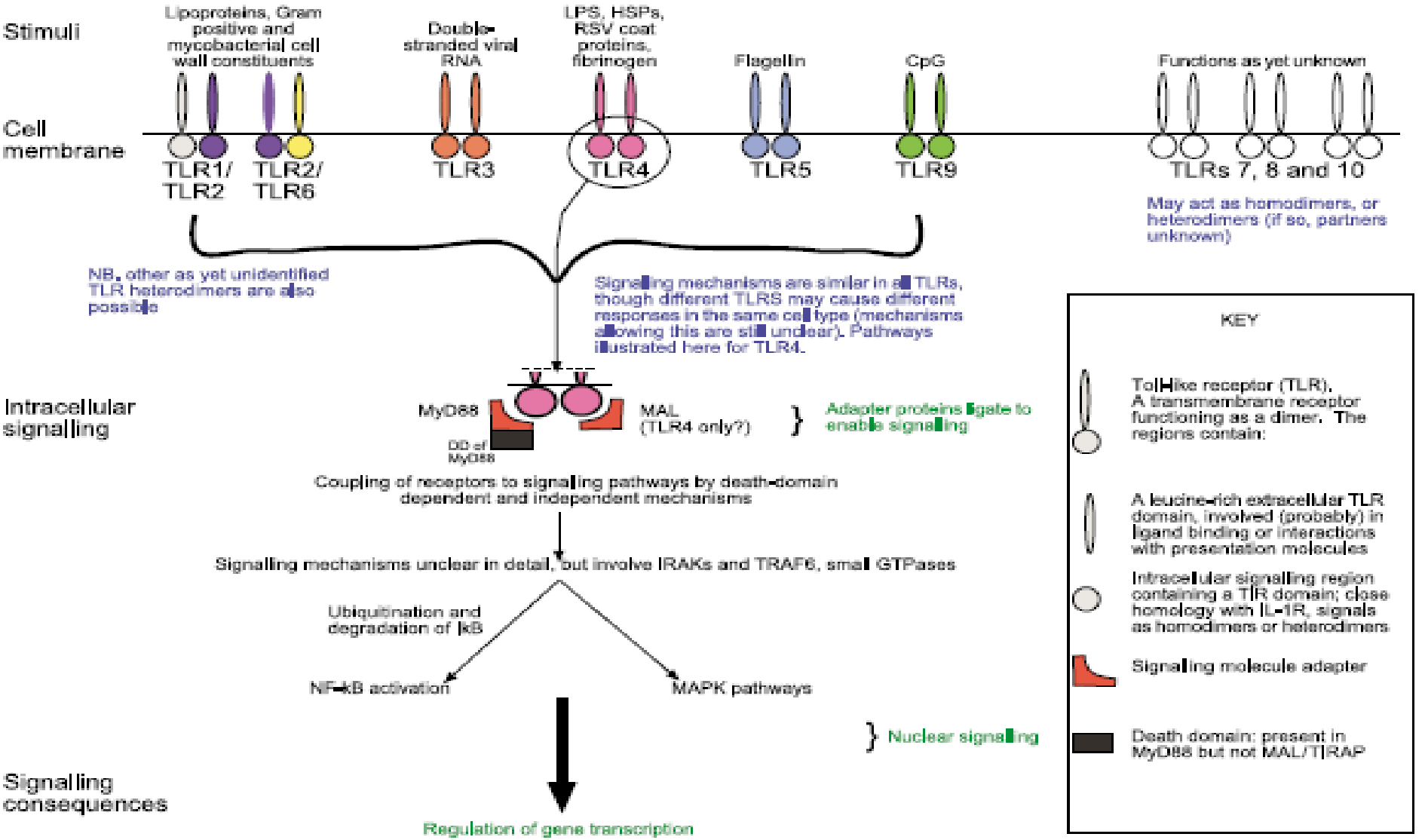
ITS: TLR 9 e CpG



Sabroe I et al. Toll-like receptors: their role in allergy and non-allergic inflammatory disease. Clin Exp Allergy 2002;32:984-9.

CpG ed applicazioni nell'ITS

Type	Allergens	Probable advantages	Outcomes [Reference]
Type A ISS ODN	Mite extract	Short course Rapid action Persisting activity Increased efficacy	Promising results in safety trial [1]
Type B ISS ODN	Amb a 1 for ragweed allergy	Short course Persisting activity Reduced adverse reactions	Discontinued ([7], press release by Dynavax Corp.)
Intralymphatic injections	Grass pollen extract	Short course Rapid action Persisting activity Increased efficacy Decreased adverse reactions Increased patient uptake	Promising results with similar efficacy to subcutaneous injection [22]
Intradermal peptides	Peptides representing Fel d 1 for cat allergy	Short course Decreased local adverse reactions	Equivocal results with new regimens to be trialed [19]
Recombinant allergen	Bet v 1	Standardized medicament No induction of IgE to new specificities	Efficacy similar to birch extract [19]
Recombinant allergen cocktail	Group 1,2,5A, 5B and 6 Timothy grass allergens	Standardized medicament No induction of IgE to new specificities Optimal therapeutic dose for all allergens	Efficacy similar to grass extract [18]
MPL adjuvant	Tyrosine-absorbed glutaraldehyde treated grass extract	Short course Rapid action Persisting activity Increased efficacy Reduced adverse reactions	Short course produces rapid improvement similar to traditional subcutaneous injection ([23], Internet press release by Allergy Therapeutics Corp.)
BCG	Mite extract	Increased efficacy for subcutaneous and sublingual immunotherapy	Not effective [26, 27]

Thomas WR. Innovation in immunotherapy. Clin Exp Allergy 2009;39:450-4.

Le mutazioni della filaggrina

- Il ripristino della barriera cutanea con creme alla fillaggrina potrebbero giocare un ruolo non solo per la cura della DA ma anche per ripristinare la barriera cutanea e ridurre il rischio di sensibilizzazione

Heimall J et al. Filaggrin mutations and atopy: consequences for future therapeutics. Expert Rev Clin Immunol 2012;8:189-97.

Conclusioni

- I giochi si fanno nei primi mesi di vita
- Non possiamo sperare di prevenire le allergie interferendo con la marcia atopica
- E’ possibile identificare con discreta precisione il bambino a rischio di marcia atopica
- Possiamo più facilmente dire cosa non serve (probiotici) ed è inutile
- Poiché è difficile prevenirla, rimane un cardine la cura appropriata delle singole allergopatie
- Lo strumento più efficace: ITS.

Grazie

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Conclusioni

a. Non possiamo sperare di prevenire le allergie interferendo con la marcia atopica
b. I casi più gravi a pochi mesi sono già “marciati”!
c. Gli allergeni sono offendenti universali
d. I giochi si fanno nei primi mesi di vita
e. In questa finestra possiamo proporre un approccio proibizionista
f. Ogni approccio promozionista deve fare i conti con i buchi dell’ipotesi igienica

- Da cosa nasce l'idea che la SOTI possa modificare la marcia allergica?
- Dalla valutazione dei molteplici effetti immunologici che la SOTI induce

Fattori perinatali e asma

- neonato con grave prematurità
- neonato con pneumopatia
- ventilazione neonatale con somministrazione di O_2

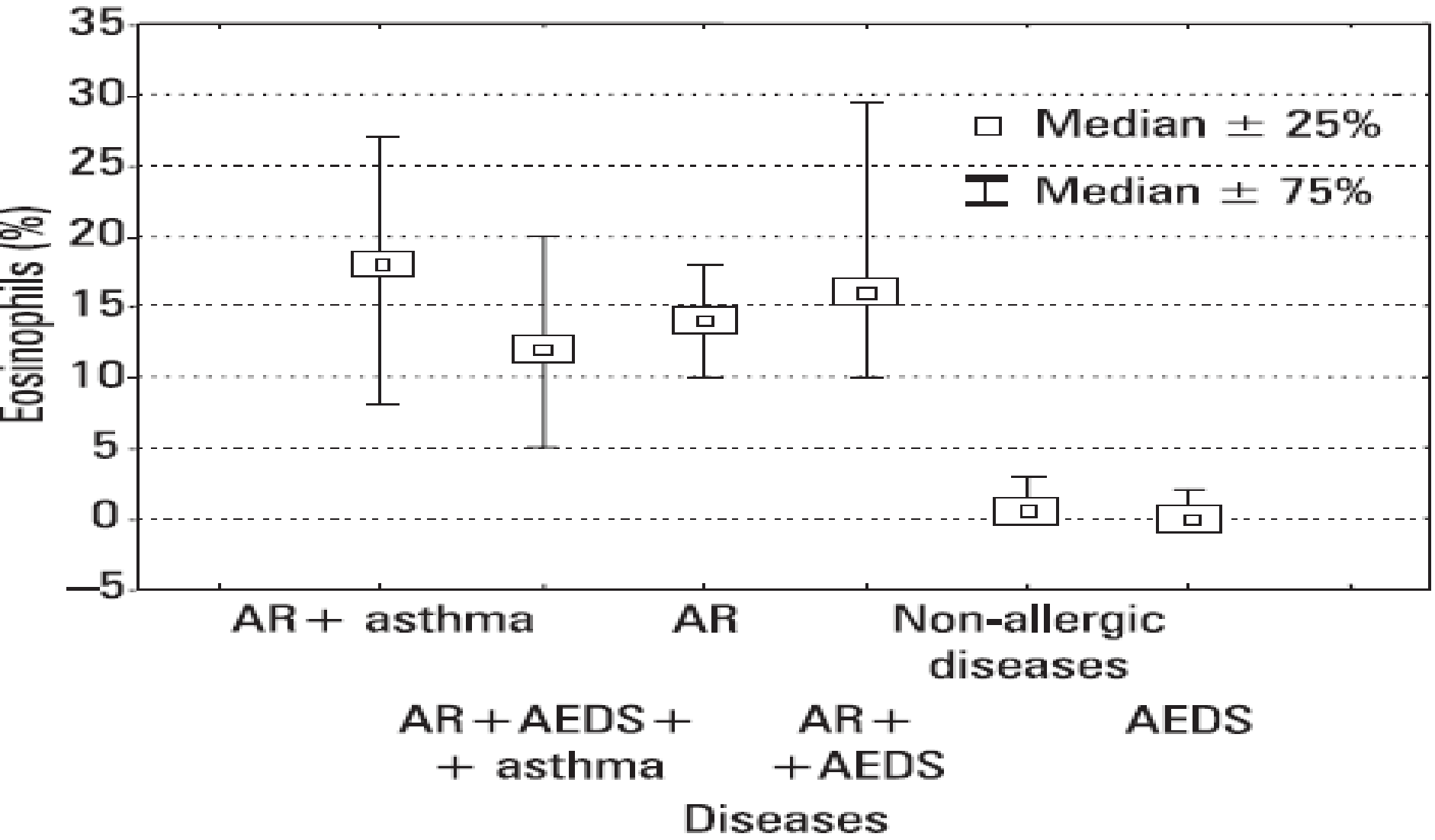
Frey U. Maternal atopic disease modifies effects of prenatal risk factors on exhaled nitric oxide in infants. Am J Respir Crit Care Med. 2004;170:260-5
Li YF. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest. 2005;127:1232-41

Ipotesi non confermate

Conclusions: In children below 4 years nasal eosinophilia ≥ 8% was predictive for AR development. Allergic march was observed in children with AEDS or/and gastrointestinal allergy symptoms present at the beginning of observation. Nasal eosinophilia in small children might be predictive for the risk of allergic march.

Nowacki Z et al. Is prediction of the allergic march possible on the basis of nasal cytology?. Pneumonol Alergol Pol 2010;78:263-70.

La citologia nasale predice



Nowacki Z et al. Is prediction of the allergic march possible on the basis of nasal cytology?. Pneumonol Alergol Pol 2010;78:263-70.

Criteri per definire il rischio di asma

Table 1: A clinical index to define asthma risk (from Castro-Rodriguez et al, 2000)

Major Criteria	Minor Criteria
1. Parental asthma*	1. allergic rhinitis*
2. eczema*	2. Wheezing apart from colds
	3. Eosinophilia (> 4%)

*Physician diagnosis of asthma, eczema or allergic rhinitis.

Criteri di previsione di asma in età adulta modificati

Guilbert TW, IACI 2004;114:1282-7

Criteri maggiori:

- ✓ Storia familiare di asma
- ✓ Dermatite atopica
- ✓ Sensibilizzazione ≥ 1 aeroallergene

Criteri minori:

- ✓ Sensibilizzazione a latte, uovo o arachidi
- ✓ Rinite allergica diagnosticata dal medico
- ✓ Rinorrea non associata a raffreddore
- ✓ Respiro sibilante non associato ad "influenza"
- ✓ Conta eosinofili > 4%

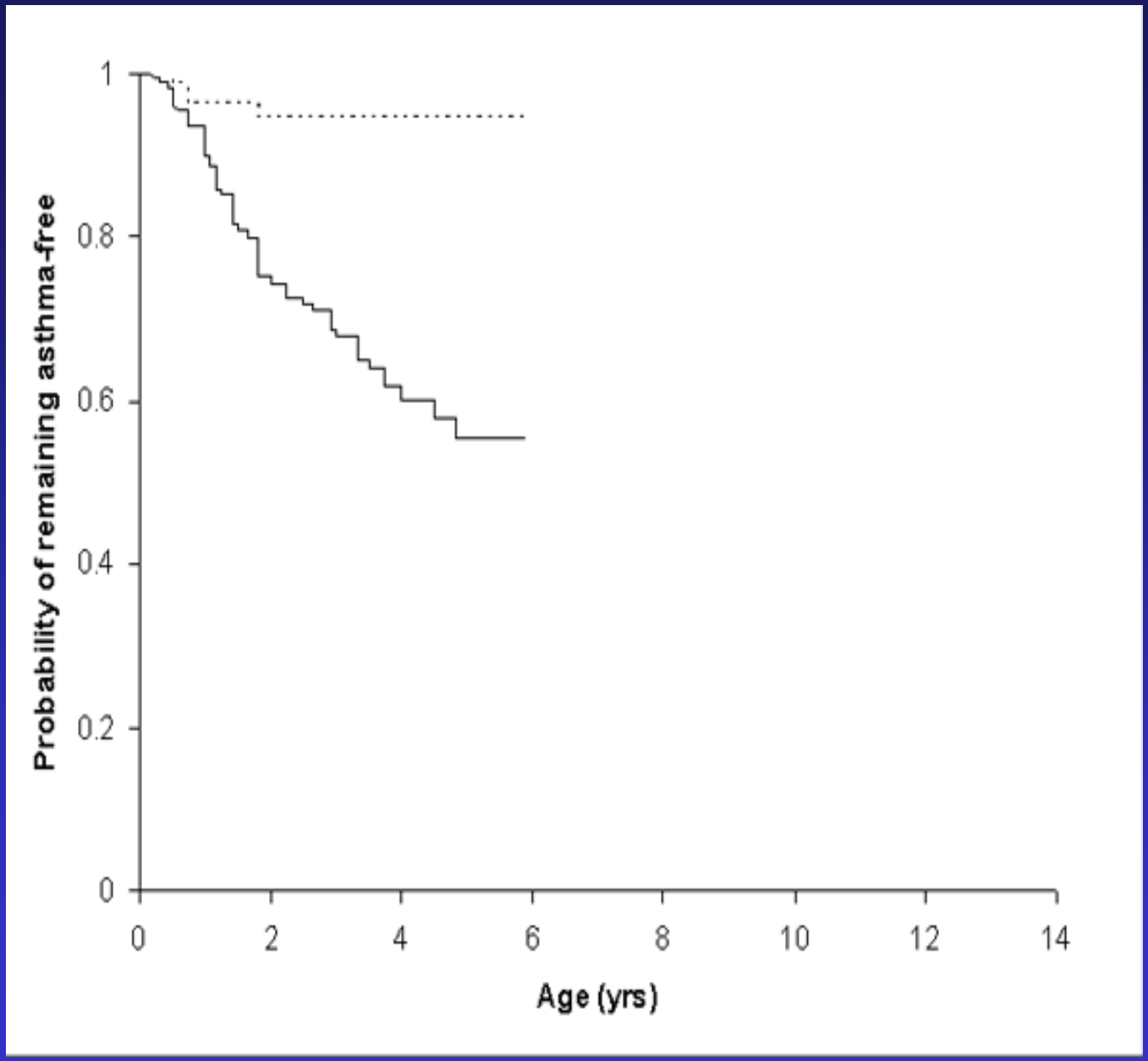
Il b. deve avere una storia di ≥ 4 episodi di wheezing con almeno 1 diagnosticato/confermato da un medico.

asma in età adulta

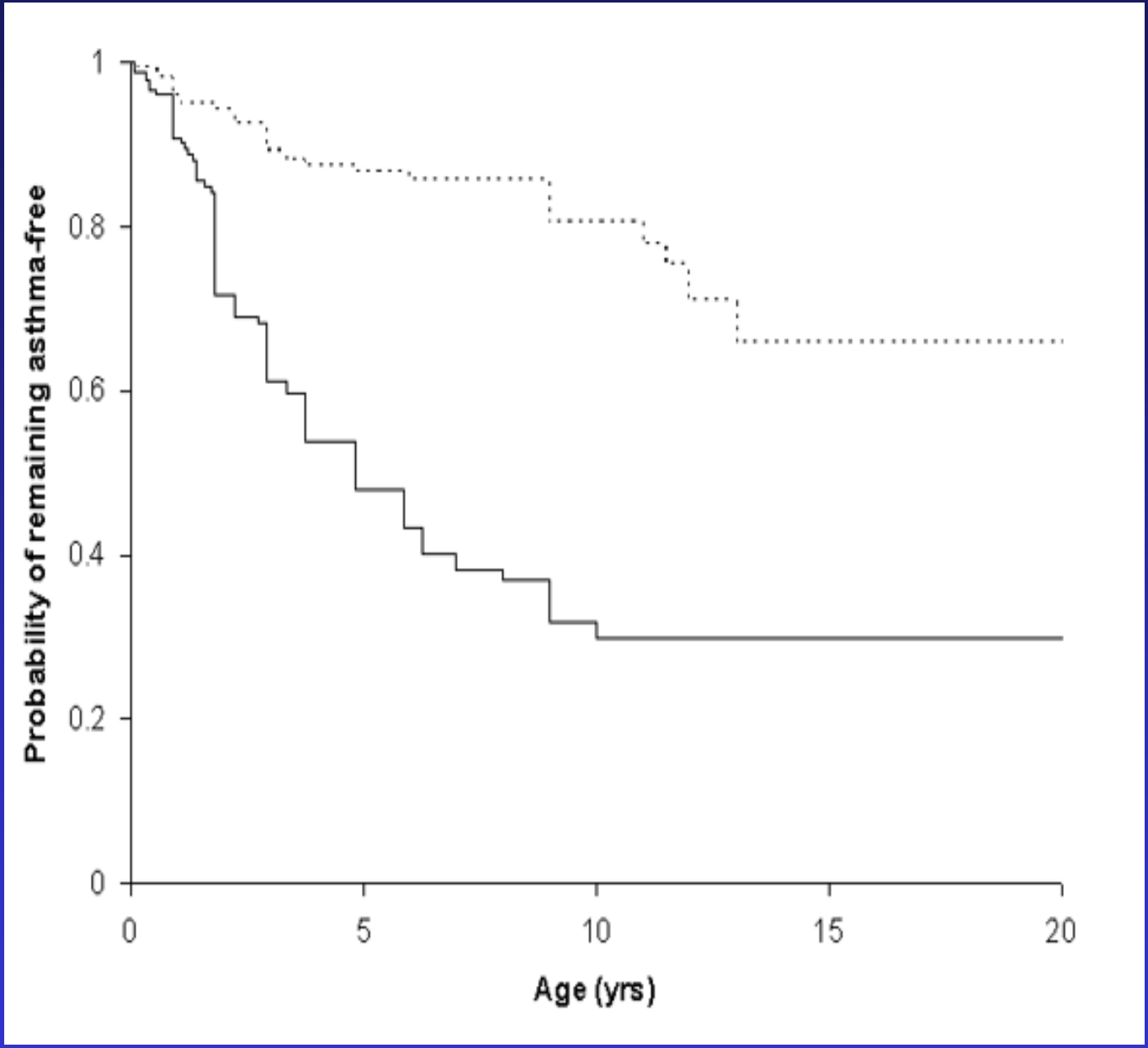
Fenotipi nei primi 8 anni di vita

- Birth cohort seguita nel tempo con questionari a 2 mesi e 1, 2, 4 e 8 anni di età.
- Dati completi per 3.014 bambini
- Fenotipi divisi in transitori, intermittenti, tolleranza tardiva e persistenti.
- Concomitanti sintomi clinici + diagnosi pediatrica nel 3.1% a 1 anno fino al 7.6% a 8 anni di vita.
- L'incremento a 8 anni probabilmente riflette l'aumento dell'allergia alla frutta secca e la "pollen-related reactions to foods"
- Reattività precoce per uovo, arachide, frutta secca o IgE specifiche per alimenti a 4 anni incrementavano il rischio di reattività ad alimenti, eczema, rinite e asma a 8 anni.

Ostblom E et al. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. Clin Exp Allergy 2008;38:1325-32.



Schroeder A et al. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy 2009;39:261-70.



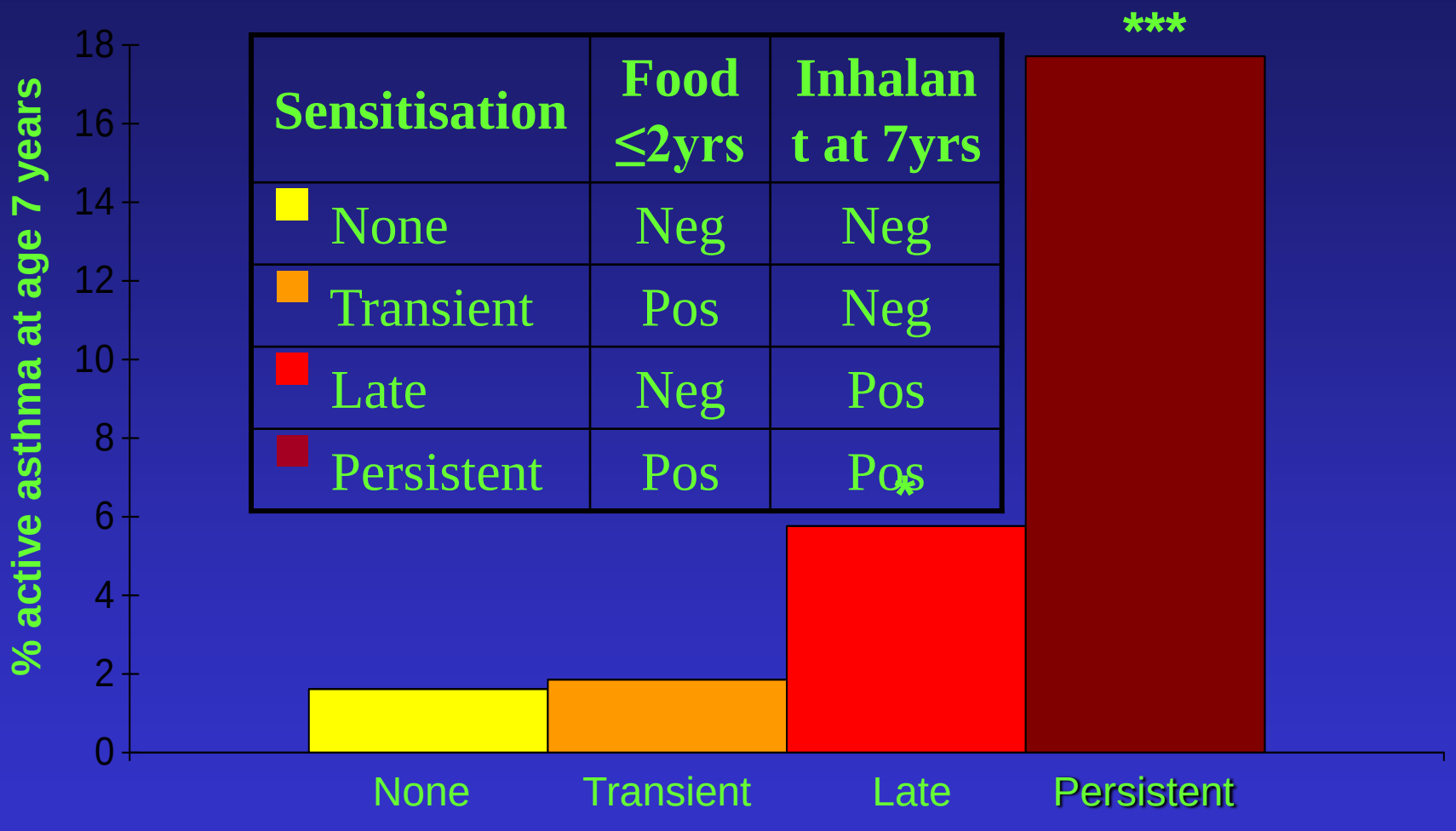
Schroeder A et al. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy 2009;39:261-70.

Risk Factors for the Development of Food Allergy

- Immature mucosal immune system
- Early introduction of solid food
- Hereditary increase in mucosal permeability
- IgA deficiency or delayed IgA production
- Impaired enteric nervous system
- Immune alterations, e.g. low levels of TGF-beta
- Gastrointestinal infections

Bischoff SC & Crowe S, Gastroenterology 2005;128:1089–1113

Pattern di sensibilizzazione e asma



Sensitisation	Food ≤2yrs	Inhalant at 7yrs
None	Neg	Neg
Transient	Pos	Neg
Late	Neg	Pos
Persistent	Pos	Pos

* p<0.05 *** p<0.0001

Illi S. The pattern of atopic sensitization is associated with the development of asthma in childhood. J Allergy Clin Immunol 2001;108:709-14.

- Prevenzione primaria (deficit di filaggrina), secondaria e **terziaria**
- Quali bambini con allergia alimentare sono più a rischio di sviluppare la marcia?
- Se non è possibile prevenirla è utile identificarlo?
- L'eliminazione dell'acaro previene il passaggio rinite/asma?
- Quali sono le tappe: sensibilizzazione A/AA, AA/ASMA; rinite/asma
- Quali strumenti possiamo considerare per provare ad interromperla?
- Poiché l'asma è un fattore di rischio per anafilassi fatale, non averla aiuta
- Chi fa la SOTI per allergia alimentare ha più o meno probabilità di sviluppare la marcia?
- Il futuro

Frequenza elevata dell'eczema nelle visite

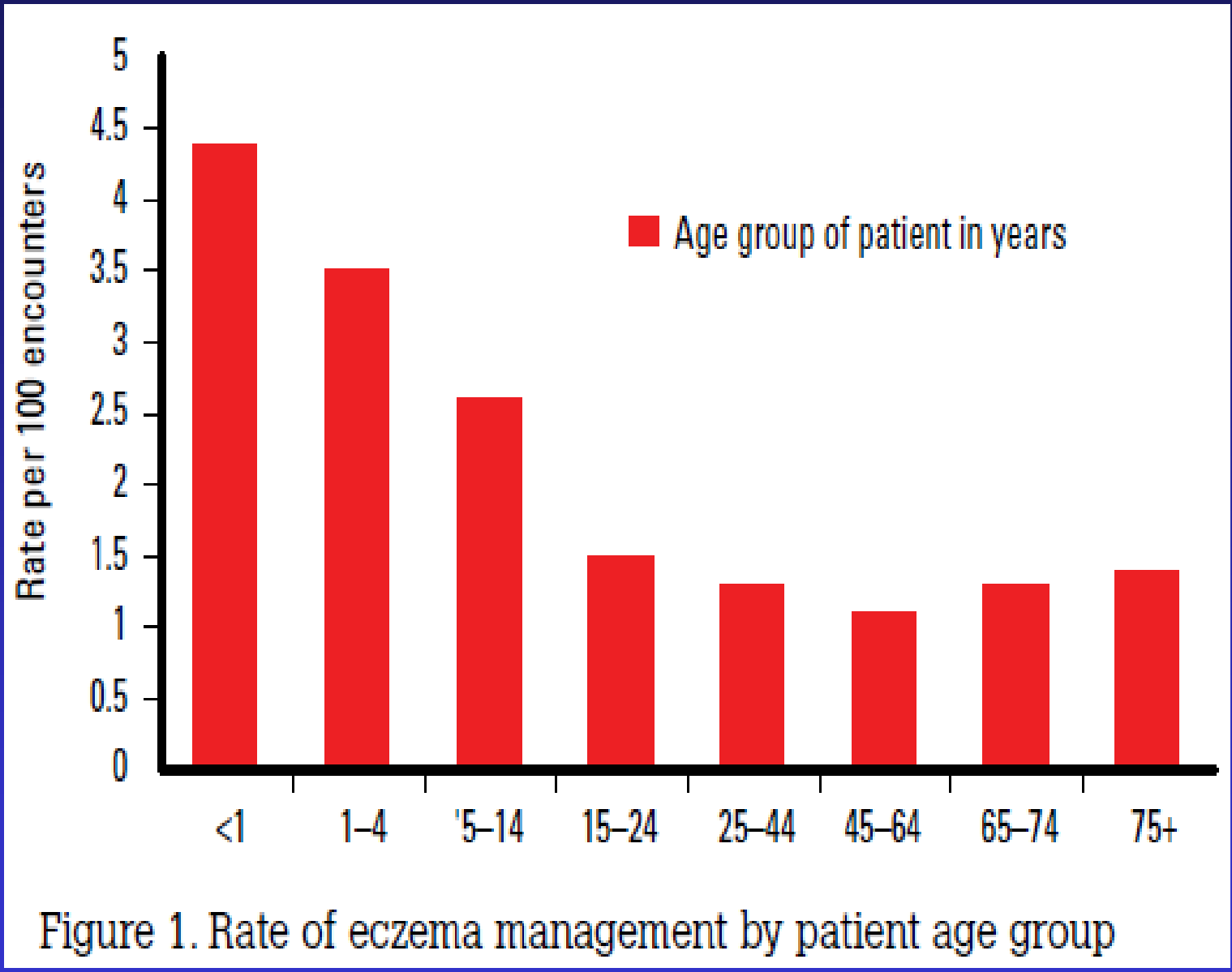
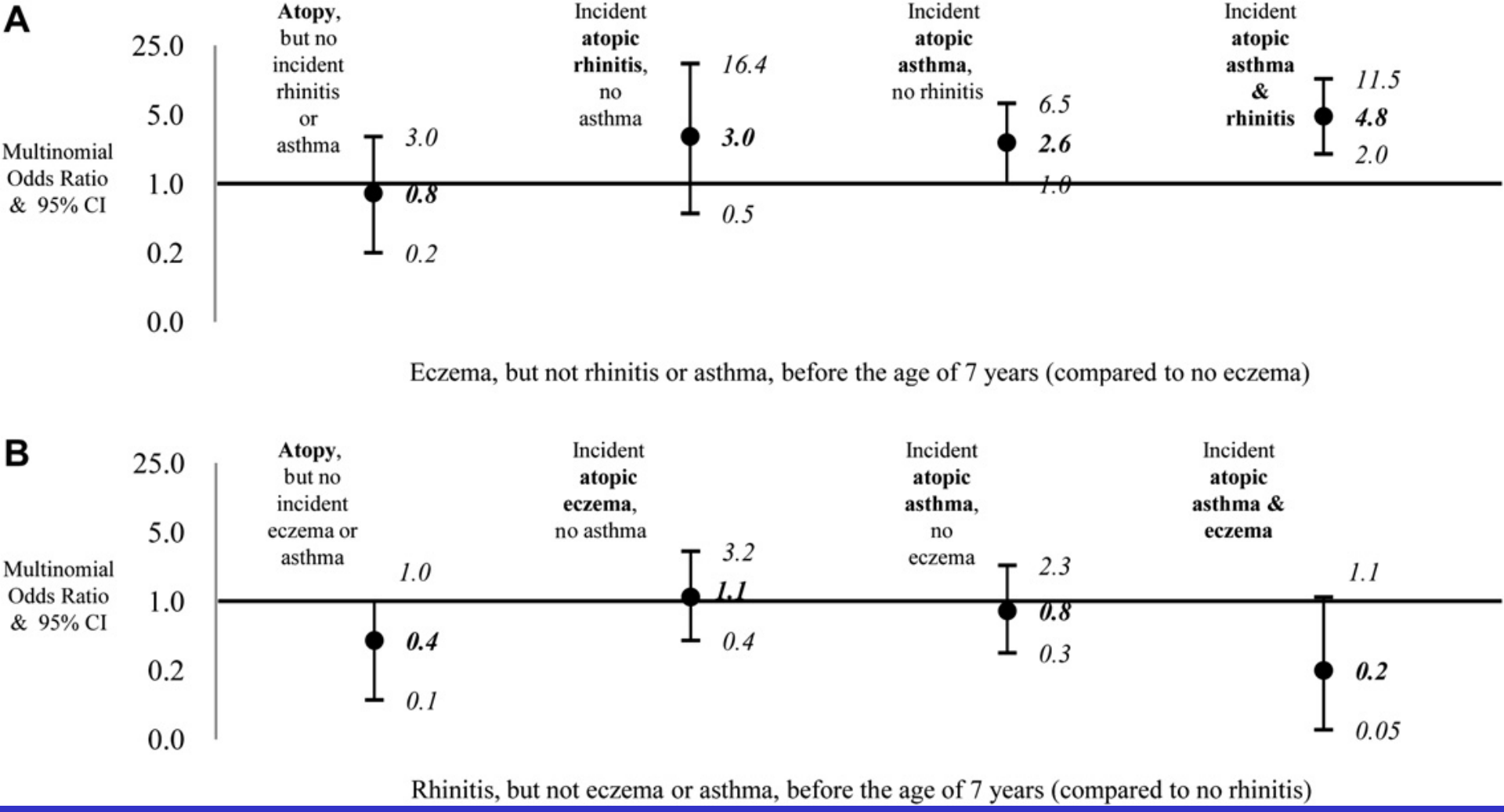


Figure 1. Rate of eczema management by patient age group

Charles J et al. Eczema. Aust Fam Physician 2011;40:467.

DA e rinite predicono asma atopico a 40 anni



Martin PE et al. Childhood eczema and rhinitis predict atopic but not nonatopic adult asthma: a prospective cohort study over 4 decades. J Allergy Clin Immunol 2011;127:1473-9.

Fumo materno e paterno deleteri

Characteristics *		Adult Data % (n+/n total)	No Adult Data % (n+/n total)	p-value
Male		47.8 (410/858)	52.3 (203/388)	0.14
Ethnicity		64.6 (554/858)	46.4 (180/388)	<0.0001
Early Wheezing Phenotypes				
Never		51.7 (355/687)	50.4 (70/139)	
Transient		20.1 (138/687)	18.7 (26/139)	
Late		15.7 (108/687)	11.5 (16/139)	
Persistent		12.5 (86/687)	19.4 (27/139)	0.1, 3df
Any skin test, age 6yr		39.0 (260/667)	35.8 (34/95)	0.6
Alternaria skin test, age 6yr		17.1 (114/666)	20.0 (19/95)	0.5
Parental Characteristics:				
Asthma	Maternal	10.7 (90/845)	11.9 (37/310)	0.5
	Paternal	12.1 (98/812)	12.1 (34/282)	0.9
Smoking	Maternal	14.9 (128/858)	23.9 (92/385)	<0.001
	Paternal	27.8 (235/846)	39.5 (150/380)	<0.001
Ed>12yrs	Maternal	74.7 (640/857)	53.9 (207/384)	<0.001
	Paternal	76.5 (644/842)	56.5 (212/375)	<0.001

Stern DA et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study.Lancet 2008;372:1058-64.

Fattori di rischio per sensibilizzazione agli inalanti

- precoci reazioni avverse ad alimento
- ereditarietà per eczema
- esordio dell'eczema < 4 m
- severità dell'eczema

Gustafsson D. Development of allergies and asthma in infants and young children with atopic dermatitis. A prospective follow-up to 7 years of age. Allergy 2000; 55:240-5.

Probiotici non utili nella terapia della DA

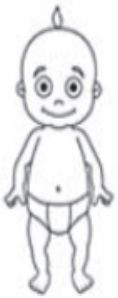
- AUTHORS' CONCLUSIONS: The evidence suggests that probiotics are not an effective treatment for eczema, and probiotic treatment carries a small risk of adverse events.

Boyle RJ et al. Probiotics for treating eczema. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006135.

Fattori di rischio ed interventi possibili

Risk factors

- Tobacco smoke[A]
- Environmental pollutants[A]
- Abnormal intestinal flora colonisation[A]
- Decreased exposure to sunlight[B]
- Early introduction of solid foods before 3–4 months of age[B]
- Formula feeding?[B]
- Diet low in n–3 PUFA, antioxidants and soluble fibre[B]
- Delayed introduction of solid foods[B]
- Vitamin D deficiency[C]



Before conception	Pregnancy	Perinatal	1st year of life	Older than 1 year
Interventions				
?	• Healthy, balanced died[c] • Pro- and prebiotics[b] • n–3 PUFA[b] • Vitamin D[a]	• Breastfeeding for ≥6 months[c] • Hypoallergenic infant formula in the first 6 months if breastfeeding is not possible[c] • Introduction of solid foods at 4–6 months[c] • Pro- and prebiotics[b] • n–3 PUFA[a]		• Healthy and balanced died[a] • Pro- and prebiotics[b] • n–3 PUFA[c]

Prescott S. et al. Strategies to prevent or reduce allergic disease. Ann Nutr Metab 2011;59 Suppl 1:28-42.

Perché?

SCIENTIFIC REPORTS

OPEN

The Role of TSLP in IL-13-Induced Atopic March

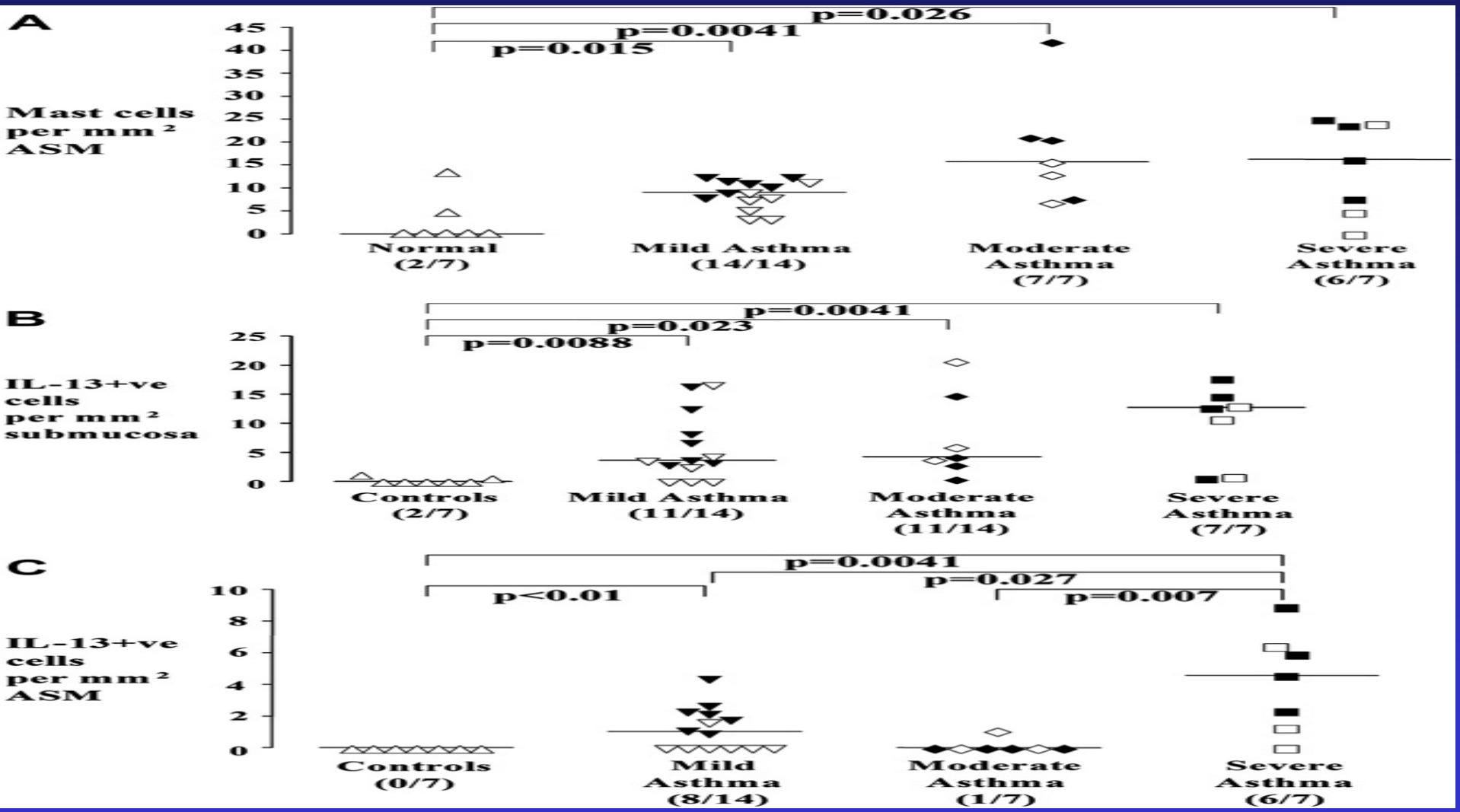
SUBJECT AREAS:
DISEASES
CYTOKINES
MODELLING
IMMUNITY

Zhou Zhu[1], Min-Hee Oh[1], Jinho Yu[1], Yong Jun Liu[2] & Tao Zheng[1]

[1]Division of Allergy & Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, 1A-38, Baltimore, MD 21224, [2]Department of Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030.

Zhu Z et al. The Role of TSLP in IL-13-Induced Atopic March. Sci Rep. 2011;1:23. Epub 2011 Jul 15.

IL 13 nell'escreato e nella mucosa come marker di gravità dell'asma severo



Saha SK, et al. Increased sputum and bronchial biopsy IL-13 expression in severe asthma. J Allergy Clin Immunol 2008;121:685-91.

SIT e prevenzione dell'asma

- AA marzo 2008 pag 32

Vit E in gravidanza e wheezing

- BACKGROUND: Two previous cohort studies showed inverse relationships between maternal vitamin E and zinc intake during pregnancy and the risk of wheeze and/or asthma in the offspring. We investigated the association between maternal intake of vegetables, fruit, and selected antioxidants during pregnancy and the risk of wheeze and eczema in the offspring aged 16-24 months.
- METHODS: Subjects were 763 Japanese mother-child pairs. Data on maternal intake during pregnancy were assessed with a diet history questionnaire. Data on symptoms of wheeze and eczema were based on criteria of the International Study of Asthma and Allergies in Childhood.
- RESULTS: Higher maternal intake of green and yellow vegetables, citrus fruit, and beta-carotene during pregnancy was significantly associated with a reduced risk of eczema, but not wheeze, in the offspring {adjusted odds ratios (ORs) between extreme quartiles [95% confidence intervals (CIs)] = 0.41 (0.24-0.71), 0.53 (0.30-0.93), and 0.52 (0.30-0.89), respectively}. Maternal vitamin E consumption during pregnancy was significantly inversely related to the risk of infantile wheeze, but not eczema [adjusted OR (95% CI) = 0.54 (0.32-0.90)]. No statistically significant exposure-response associations were observed between maternal intake of total vegetables, vegetables other than green and yellow vegetables, total fruit, apples, alpha-carotene, vitamin C, or zinc and the risk of wheeze or eczema in the children.
- CONCLUSIONS: **Higher maternal consumption of green and yellow vegetables, citrus fruit, and beta-carotene during pregnancy may be protective against the development of eczema in the offspring. Higher maternal vitamin E intake during pregnancy may reduce the risk of infantile wheeze.**

Miyake Y, et al. Allergy 2010;65:758-65.

Cesareo facilita asma

- **BACKGROUND: Caesarean section might be a risk factor for asthma because of delayed microbial colonisation, but the association remains controversial. A study was undertaken to investigate prospectively whether children born by caesarean section are more at risk of having asthma in childhood and sensitisation at the age of 8 years, taking into account the allergic status of the parents.**
- **METHODS: 2917 children who participated in a birth cohort study were followed for 8 years. The definition of asthma included wheeze, dyspnoea and prescription of inhaled steroids. In a subgroup (n = 1454), serum IgE antibodies for inhalant and food allergens were measured at 8 years.**
- **RESULTS: In the total study population, 12.4% (n = 362) of the children had asthma at the age of 8 years. Caesarean section, with a total prevalence of 8.5%, was associated with an increased risk of asthma (OR 1.79; 95% CI 1.27 to 2.51). This association was stronger among predisposed children (with two allergic parents: OR 2.91; 95% CI 1.20 to 7.05; with only one: OR 1.86; 95% CI 1.12 to 3.09) than in children with non-allergic parents (OR 1.36; 95% CI 0.77 to 2.42). The association between caesarean section and sensitisation at the age of 8 years was significant only in children of non-allergic parents (OR 2.14; 95% CI 1.16 to 3.98).**
- **CONCLUSIONS: Children born by caesarean section have a higher risk of asthma than those born by vaginal delivery, particularly children of allergic parents. Caesarean section increases the risk for sensitisation to common allergens in children with non-allergic parents only.**

Roduit C, et al. Thorax. 2009 ;64:107-13.

I parametri del peri-partum

- BACKGROUND: To investigate the associations between clinical obstetric factors during birth and doctor-diagnosed wheezing and allergic sensitization during early childhood.
- METHODS: We followed 410 Finnish women from late pregnancy until 18 months age of their children. All children were delivered at term. Doctor-diagnosed wheezing among children was established by questionnaires, while specific immunoglobulin E antibodies to inhalant and food allergens were measured in 388 children at 1 year of age. Data on maternal obstetric variables were recorded at the time of delivery.
- RESULTS: Children of mothers with longer duration of ruptured fetal membranes before birth had significantly higher risk of doctor-diagnosed wheezing during early childhood compared to those children with shorter period of ruptured fetal membranes (III vs I quartile; aOR 6.65, 95% CI 1.99-22.18; $P < 0.002$ and IV vs I quartile; aOR 3.88, 95% CI 1.05-14.36, $P < 0.043$). Children who were born by Cesarean delivery had significantly less allergic sensitization at the age of 1 year compared to those who were born by vaginal route (16.0%vs 32.2%; aOR 0.34, 95% CI 0.14-0.80; $P < 0.013$). Furthermore, allergic sensitization tended to be more common in children with longer duration of labor before birth. No other birth-related obstetric factors, such as induction, the type of fetal membrane rupture during birth or quality of amniotic fluid were associated significantly with the examined outcomes.
- CONCLUSION: **The longer duration of the ruptured fetal membranes possibly reflected the higher risk of intrapartum infection at birth, and further increased the risk of doctor-diagnosed wheezing among offspring.**

Keski-Nisula L,et al. Allergy 2010 ;65:1116-25.

- **Regulatory T cells and asthma**
- D. S. Robinson *†
- Clin Exp Allergy. 2009 Sep;39(9):1314-23. Epub 2009 Jun 17.

- **ABSTRACT**
- Airway inflammation in asthma is characterized by activation of T helper type-2 (Th2) T cells, IgE production and eosinophilia. In many cases, this process is related to an inappropriate T cell response to environmental allergens, and other T cell-dependent pathways may also be involved (such as Th17). Regulatory T cells (Tregs) are T cells that suppress potentially harmful immune responses. Two major subsets of Treg are CD25hi, Foxp3+Tregs and IL-10-producing Tregs. There is evidence that the numbers or function of both subsets may be deficient in patients with atopic allergic disease. Recent work has extended these findings into the airway in asthma where Foxp3 expression was reduced and CD25hi Treg-suppressive function was deficient. In animal models of allergic airways disease, Tregs can suppress established airway inflammation and airway hyperresponsiveness, and protocols to enhance the development, recruitment and function of Tregs have been described. Together with studies of patients and *in vitro* studies of human T cells, these investigations are defining potential interventions to enhance Treg function in the airway in asthma. Existing therapies including corticosteroids and allergen immunotherapy act on Tregs, in part to increase IL-10 production, while vitamin D3 and long-acting β-agonists enhance IL-10 Treg function. Other possibilities may be enhancement of Treg function via histamine or prostanoid receptors, or by blocking pro-inflammatory pathways that prevent suppression by Tregs (activation of Toll-like receptors, or production of cytokines such as IL-6 and TNF-α). As Tregs can also suppress the potentially beneficial immune response important for controlling infections and cancer, a therapeutic intervention should target allergen- or site-specific regulation.

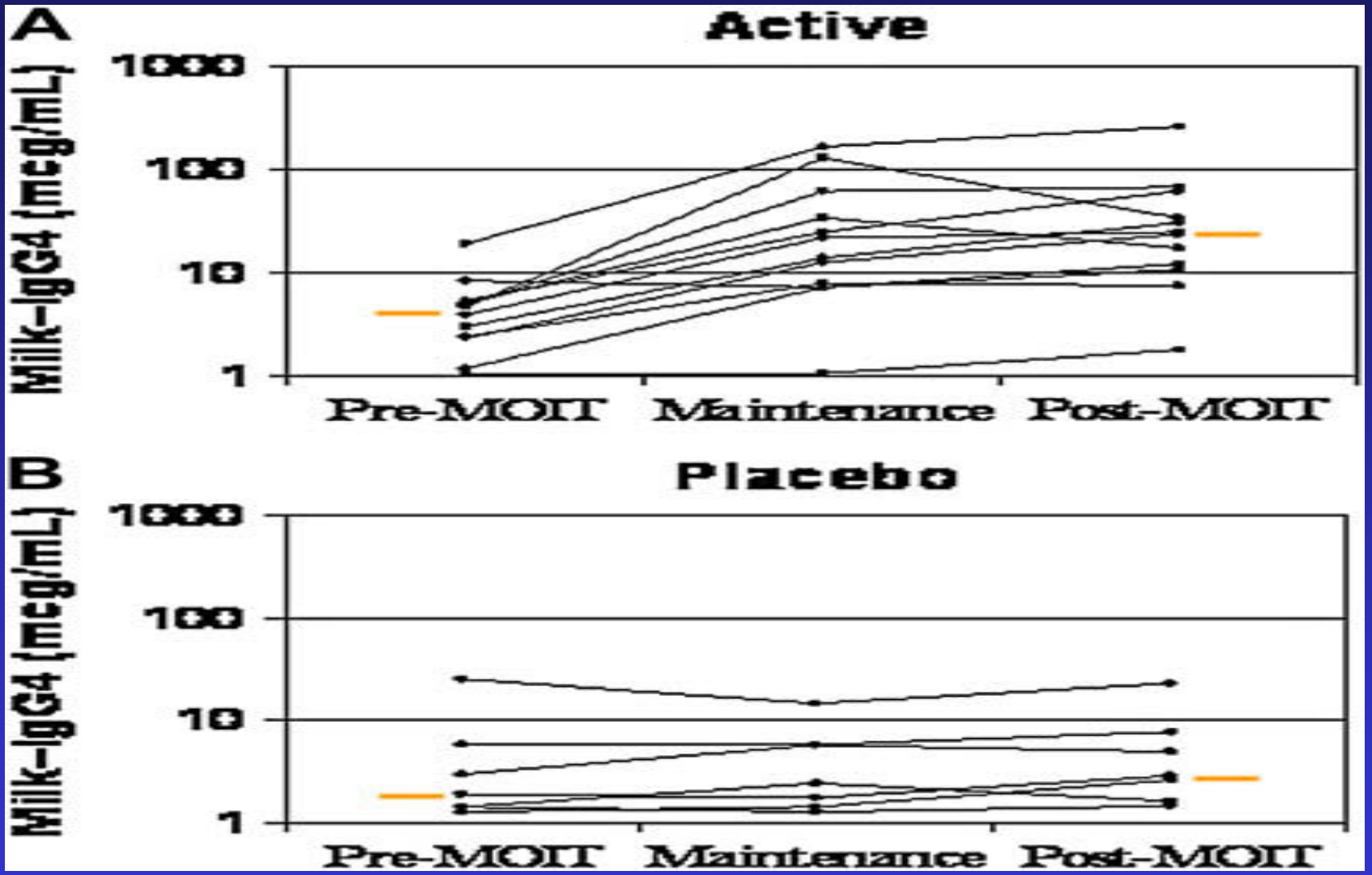
Asma fattore di rischio per morte

Patient no.	Age (y)	M/F	Date	Culprit	Asthma	Previous history	Food	Location	Timely epinephrine
1	32	M	3/11/2001	Nuts	Yes	Yes	Nut bowl	Restaurant	No
2	16	M	5/9/2001	Walnut	Yes	Yes	Chinese food	School, cooking class	Probably
3	9	M	5/18/2001	Peanut	Yes	Yes	Cookie	School outing	No
4	24	F	11/26/2001	Peanut	Yes	Yes	Chinese food	Home	No
5	25	F	10/30/2001	Nut meats	Yes	Yes	Candy	Home of friends	No
6	16	M	11/5/2002	Milk	Yes	Yes	Bread	Home	Unk
7	31	M	12/13/2002	Peanut	Yes	Yes	Catered food	Office party	No
8	50	M	12/24/2002	Nut	Yes	Yes	Cookie	Home	No
9	12	F	3/14/2003	Peanut	Unk	Unk	Egg roll	Unk	Unk
10	18	M	6/21/2003	Peanut	Unk	Unk	Wrap	Unk	Unk
11	32	M	3/15/2003	Shrimp	Yes	Yes	Meal	Restaurant	No
12	29	M	6/13/2003	Peanut	Yes	Yes	Meal	Restaurant	No
13	29	M	4/24/2000	Almond	Yes	Yes	Candy	Office	Yes
14	17	F	12/26/1986	Nuts	Yes	Yes	Cookie	Home of friends	No
15	21	F	10/9/2003	Peanut	Yes	Yes	Brownie	College	No
16	18	M	1/20/2004	Shrimp roll	Yes	Unk	Shrimp roll	Restaurant	No
17	27	M	2/1/2004	Peanut	Unk	Yes	Baked clam	Home	No
18	17	M	2/8/2004	Hazelnut	Yes	Yes	Candy	Home of friends	No
19	17	F	4/6/2004	Peanut	Yes	Yes	Peanut butter	Camp	No
20	34	F	5/29/2004	Peanut	Unk	Yes	Thai dish	Home	No
21	5	M	8/1/2004	Peanut	Unk	No	Peanuts	Home	No
22	9	M	7/22/2004	Milk	Unk	Unk	Milk	Camp	Yes
23	22	F	10/29/2004	Peanut	Yes	Yes	Dessert	Restaurant	No
24	14	F	1/22/2005	Peanut	Yes	Yes	Egg roll	Restaurant	No
25	36	M	3/21/2001	Peanut	Yes	Yes	Brownie	Work	No
26	17	M	3/5/2005	Milk/whey	Yes	Yes	Protein shake	Home	No
27	7	F	3/2/2005	Milk	Yes	Yes	Chocolate mix	Home	Unk
28	11	F	5/31/2005	Peanut	Unk	Yes	Candied apple	Carnival	Unk
29	40	M	2/8/2006	Tree nut	Unk	Yes	Cookie	Work	Yes
30	13	F	4/13/2006	Peanut	Yes	Yes	Wrap	Fast food in mall	No
31	16	M	8/1/2006	Peanut	Yes	Yes	Cookie	Home of friends	No

F, Female; *M*, male; *Unk*, unknown.

Bock SA et al. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007;119:1016-8.

IgG4 si incrementano negli attivi ma non nei placebo



Skripak JM, et al. A randomized, double-blind, placebocontrolled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008; 122:1154–1160.

Immunologic effects of selected immunomodulatory therapies for food allergy

Investigators	Therapy	Route	Model	Allergen	Immunologic effects
Li *et al.*	"Engineered" recombinant proteins	Rectal	Mouse	Peanut	Protection from anaphylaxis Increased IFN-γ, TGF-β Decreased Th2 cytokines
Li *et al.*	Traditional Chinese medicine	Oral	Mouse	Peanut	Protection from anaphylaxis Reduced PN-specific IgE Increased IgG2a levels Reduced Th2 cytokines Increased IFN-γ by CD8+ T-cells
Mondoulet *et al.*	Epicutaneous immunotherapy	Epicutaneous	Mouse	Peanut Egg Aeroallergens (dust mite, pollen)	Reduced airway hyper-responsiveness Increased IgG2a Reduced IgE/IgG2a ratio
Yang *et al.*	Peptide immunotherapy	Subcutaneous	Mouse	Egg	Protection from anaphylaxis Decreased histamine Decreased OVA-specific IgE Increased IFN-γ (spleen) Decreased Th2 cytokines Increased TGF-β, FOXP3 mRNA (intestine)
Patriarca *et al.*	OIT	Oral	Human	Milk Egg Fish Other	Decreased IgE Increased IgG4
Buchanan *et al.*	OIT	Oral	Human	Egg	Increased egg-specific IgG, IgE unchanged
Staden *et al.*	OIT	Oral	Human	Milk Egg	Decreased IgE
Skripak *et al.* Narisety *et al.*	OIT	Oral	Human	Milk	Decreased PST (IgE mediated) Increased IgG4
Jones *et al.*	OIT	Oral	Human	Peanut	Decreased basophil activation Increased IgG4 Decreased IgE Increased FOXP3+ Tregs Downregulation of apoptosis genes

Scurlock AM et al. Pediatric food allergy and mucosal tolerance. Mucosal Immunol 2010;3:345-54.

Summary of selected SLIT and OIT studies

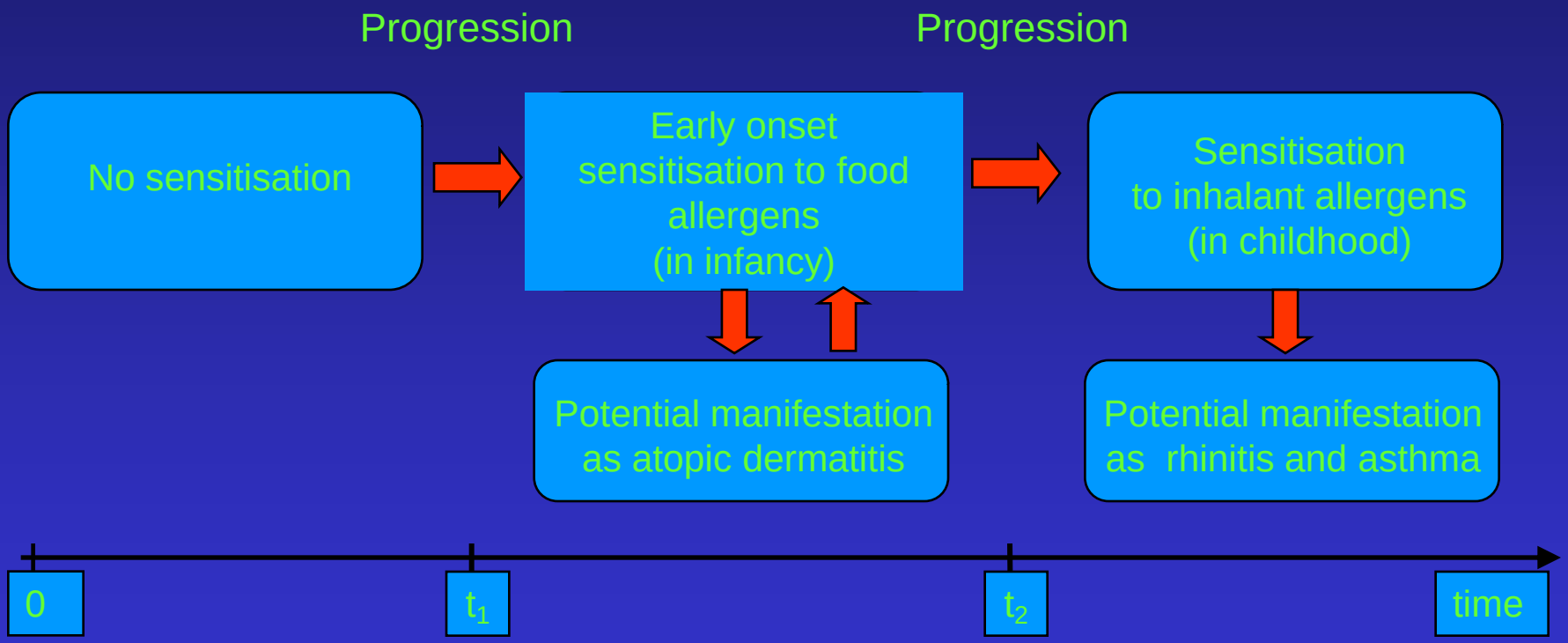
Investigator	Allergen	Route	Results
Enrique *et al.** (*Oral Allergy Syndrome)	Hazelnut	Sublingual	Increased maximal threshold dose Increased IgG4, IL-10
Mempel *et al.* Kerzl *et al.*	Kiwi	Sublingual	Reduced skin test reactivity Prolonged desensitization after discontinuation
Patriarca *et al.*	Milk Egg Fish Other	Oral	Effective desensitization (77%) Decreased IgE Increased IgG4
Meglio *et al.*	Milk	Oral	Effective desensitization (71%) Increased threshold dose
Buchanan *et al.*	Egg	Oral	Increased threshold dose at food challenge Increased egg-specific IgG No significant change in IgE
Staden *et al.*	Milk Egg	Oral	Overall response 64% (36% completely tolerant of dose) Increased threshold dose Decreased IgE
Longo *et al.*	Milk	Oral	In treatment group: 36% completely tolerant to milk protein 54% consume limited amounts 10% unable to complete protocol Elimination diet group: Positive DBPCFC in all 30 subjects
Skripak *et al.* Narisety *et al.*	Milk	Oral	Increased threshold dose Increased milk-specific IgG4 Decreased skin prick test reactivity
Jones *et al.*	Peanut	Oral	Increased threshold dose Decreased PST reactivity Decreased basophil activation Increased IgG4 Decreased IgE Increased FOXP3 + T-cells T-cell Microarray: downregulation of apoptosis genes
Clark *et al.*	Peanut	Oral	Increased threshold dose

Scurlock AM et al. Pediatric food allergy and mucosal tolerance. Mucosal Immunol 2010;3:345-54.

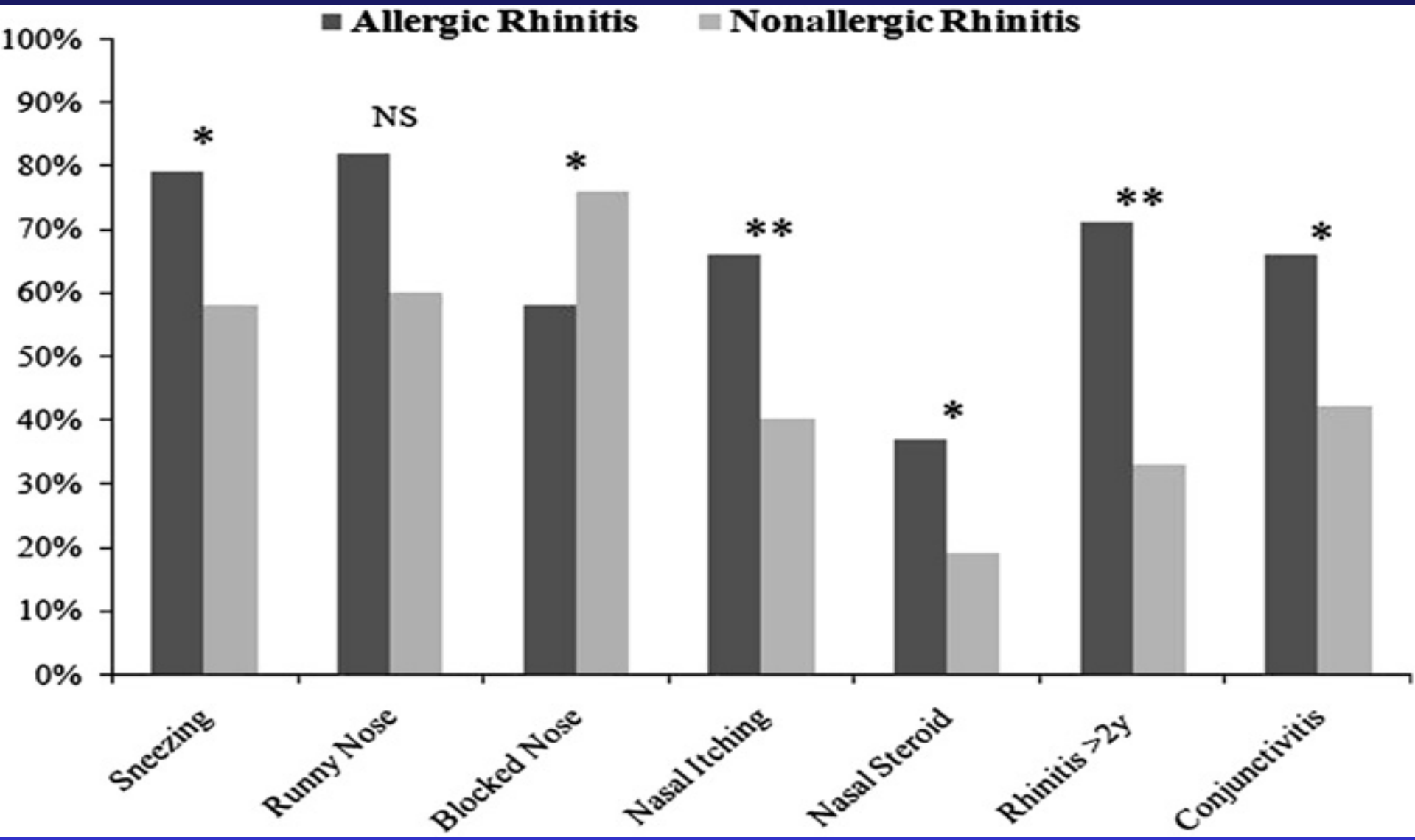
- Un motivo in più per eseguire una buona prevenzione della prematurità

Current understanding of atopy:

the atopic march



Diagnosi differenziale clinica fra AR e NAR



Chawes BL, et al. Children with allergic and nonallergic rhinitis have a similar risk of asthma. J Allergy Clin Immunol 2010;126:567-73.