

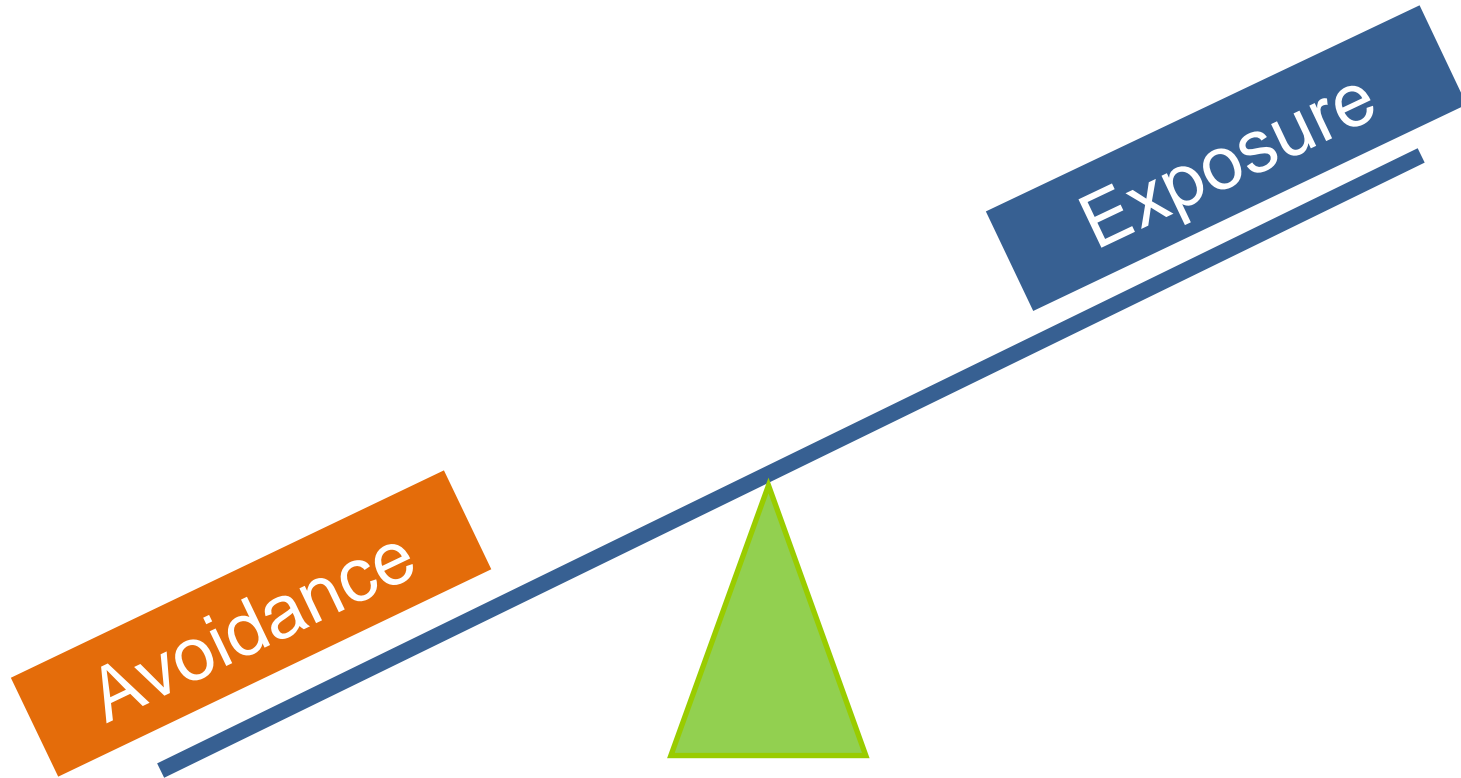
Induction de Tolérance: Est-ce Toujours d'Actualité?

Gideon Lack

KING'S
College
LONDON

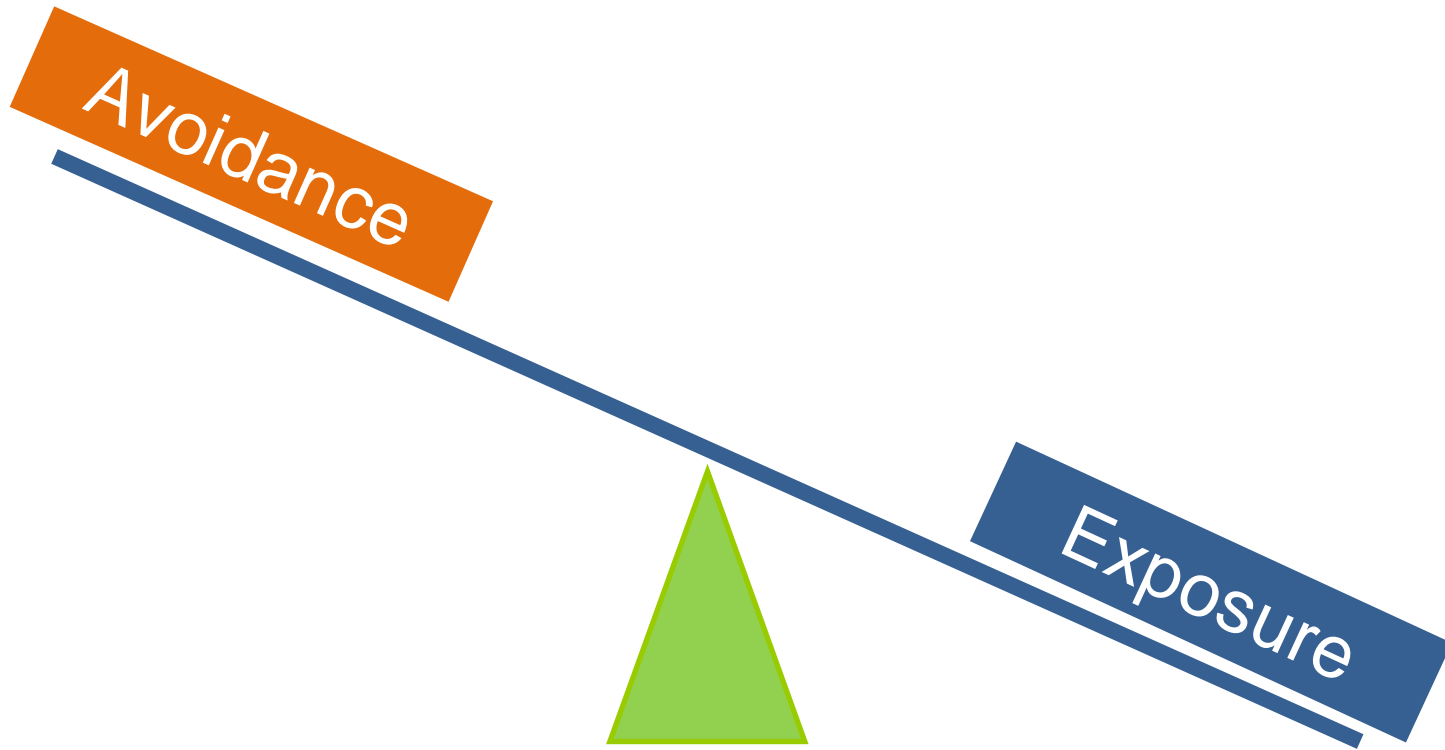
University of London

Guy's and St Thomas' 
NHS Foundation Trust



Avoidance

Exposure



Childhood exposure to pets including cats was associated with **lower sensitization to cats** in adulthood, particularly among those with a positive family history of atopy (OR 0.68 95%CI 0.51 to 0.93).



Roost HP. J Allergy Clin Immunol 1999; 104: 941-7.

Dog ownership in early childhood **protects against the development of inhalant sensitisation** and this effect cannot be attributed to the simultaneous exposure to endotoxin.



Chen CM. Eur Respir J 2008; 31: 963–973

Exposure to 2 or more dogs or cats in the first year of life may **reduce subsequent risk of allergic sensitization to multiple allergens** during childhood.



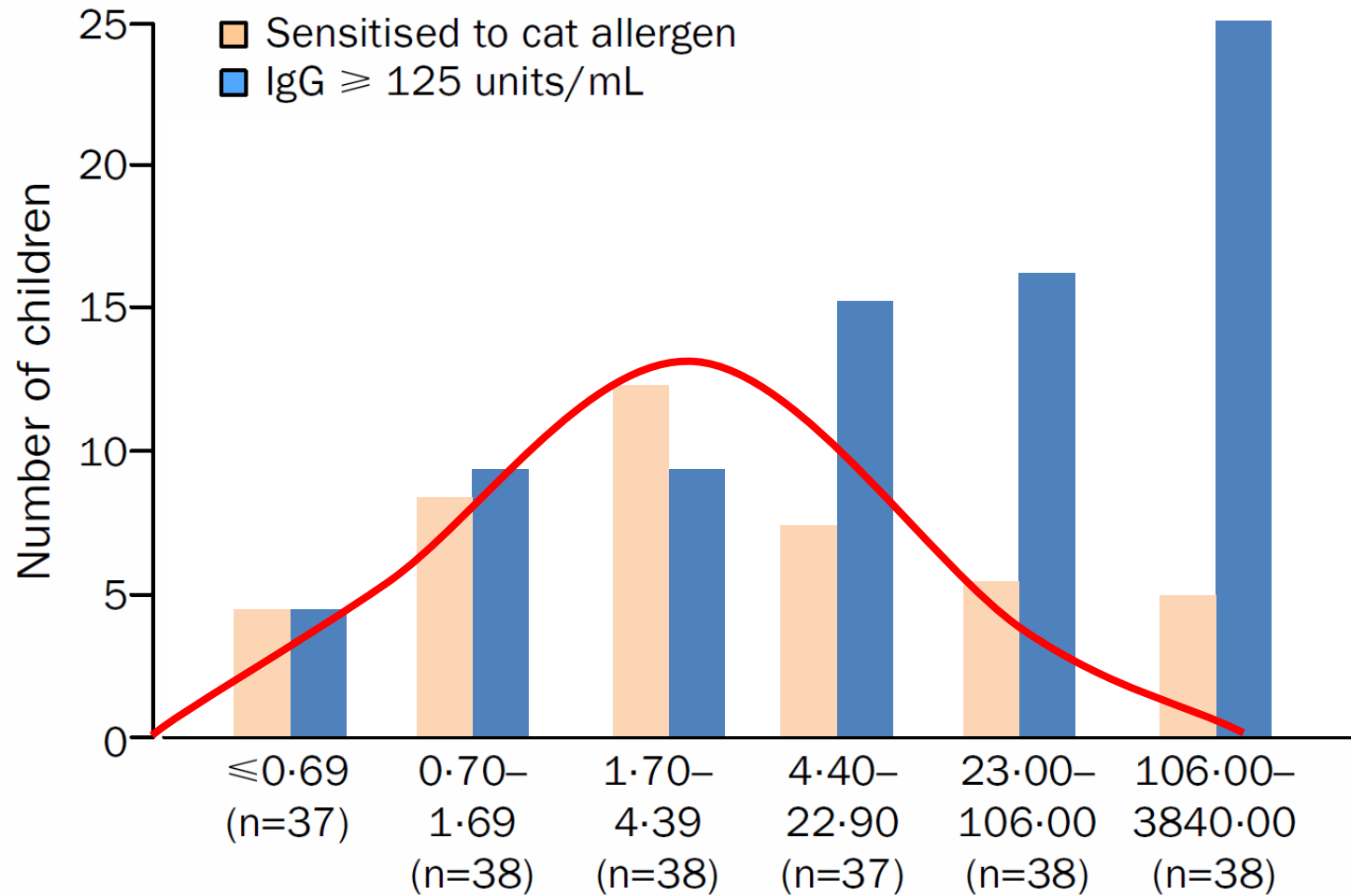
Ownby DR. JAMA 2002; 288: 963-972.

Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study

■ Methods

- Population cross - sectional study of 226 children (aged 12 – 14 years).
- 47 of whom had asthma.
- Dust samples were obtained from four different areas within the children's homes and assayed for cat allergen and dust mite.
- Antibodies to cat and mite allergens measured by isotype (IgG and IgG4).
- Sensitization/Specific IgE/SPT.

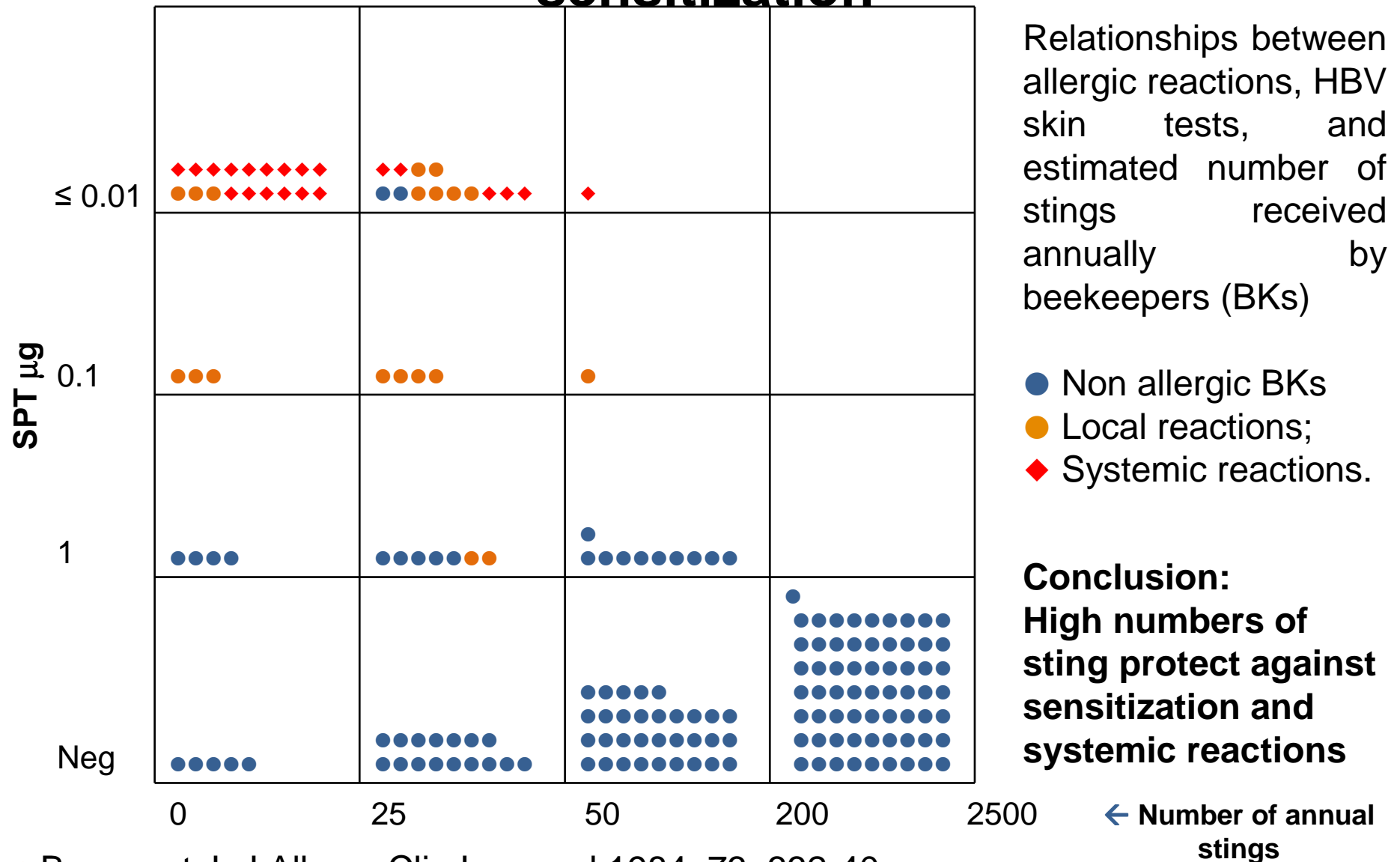
Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study



Prevalence of sensitisation to cat allergens and of IgG antibody to Fel d 1 ≥125 units/mL for six equal-exposure groups for cat allergen

→ Platts-Mills TA. Lancet 2001; 357: 752-56.

Clinical and immunologic survey in beekeepers (n = 200) in relation to their sensitization



→ Bousquet J. J Allergy Clin Immunol 1984; 73: 332-40.

Randomised controlled avoidance studies

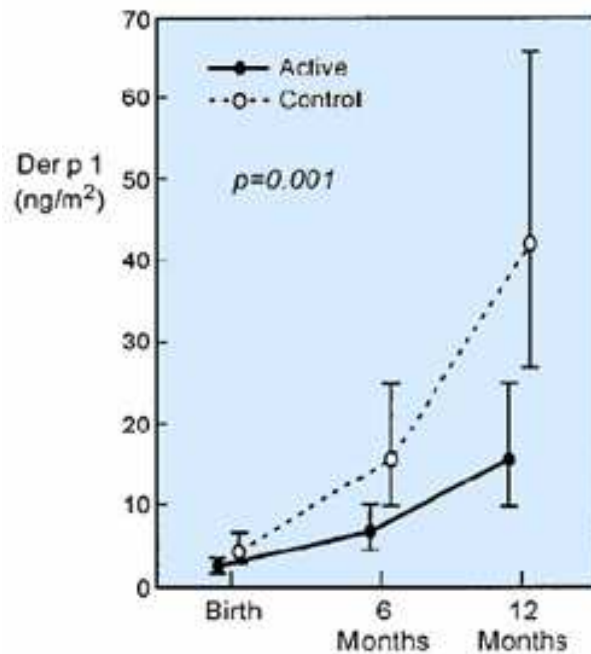


High-risk children (n = 251) were prenatally randomized to stringent environmental control [active (n = 133) or no intervention [control (n = 118)].

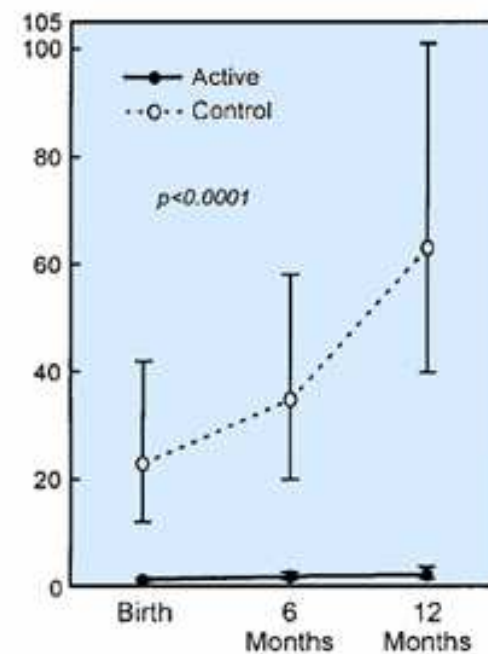
→ Woodcock A. Am J Respir Crit Care Med; 170: 433–439.

Manchester Asthma and Allergy Study: Low-allergen environment can be achieved and maintained during pregnancy and in early life

House dust mite allergen levels (GM and 95% CI) in nursery room at birth, 6 months, and 12 months

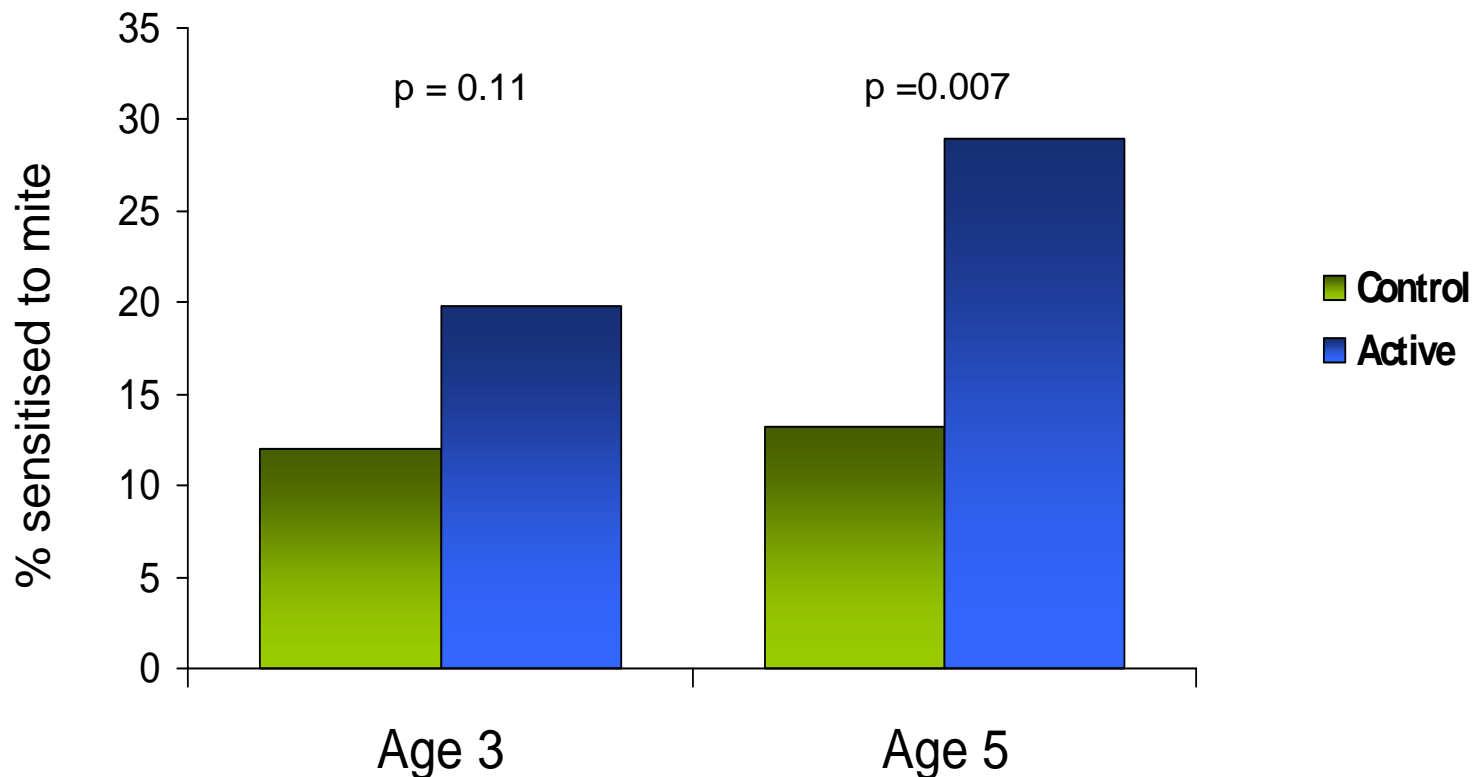


Crib mattress, total allergen recovered



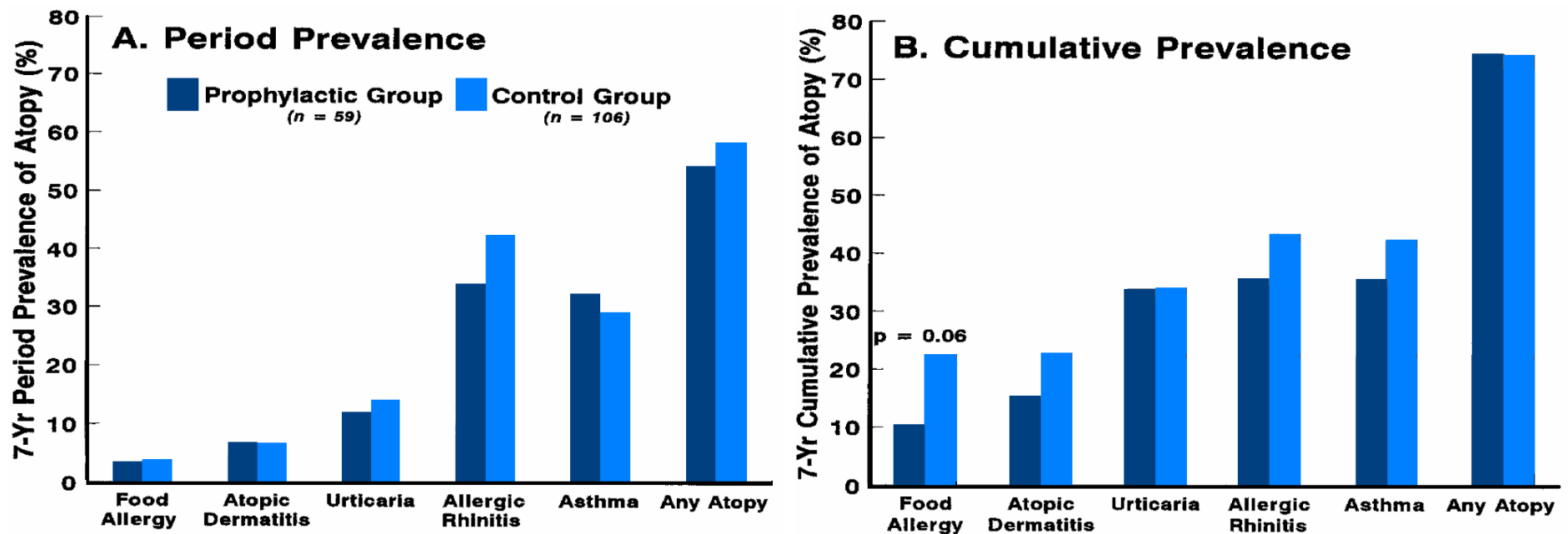
Crib mattress, allergen concentration

Higher Prevalence of Mite Sensitisation with Stringent Environmental Control



→ Woodcock A. Am J Respir Crit Care Med; 170: 433–439.

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



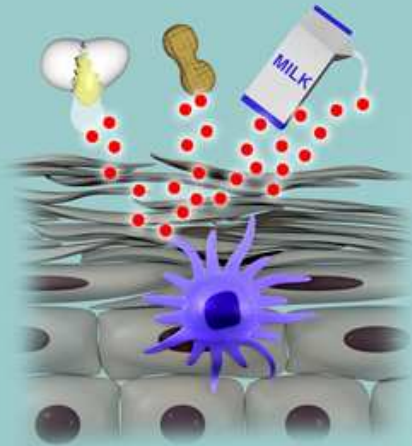
→ Zeiger RS. J Allergy Clin Immunol 1995;95:1179-90.

Why have avoidance studies failed?

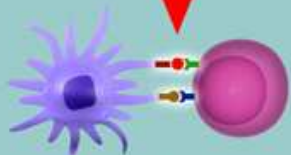
1. Development of allergy or tolerance is unrelated to allergen.
2. Avoidance measures have been insufficient.
3. The concept of avoidance is wrong

DUAL ALLERGEN EXPOSURE HYPOTHESIS

CUTANEOUS EXPOSURE



Skin



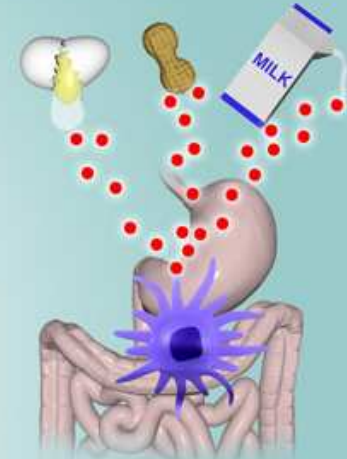
Skin-draining lymph nodes



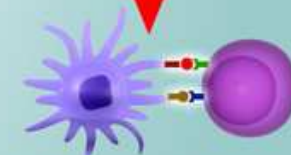
Th2 memory

ALLERGY

ORAL EXPOSURE



GI Track

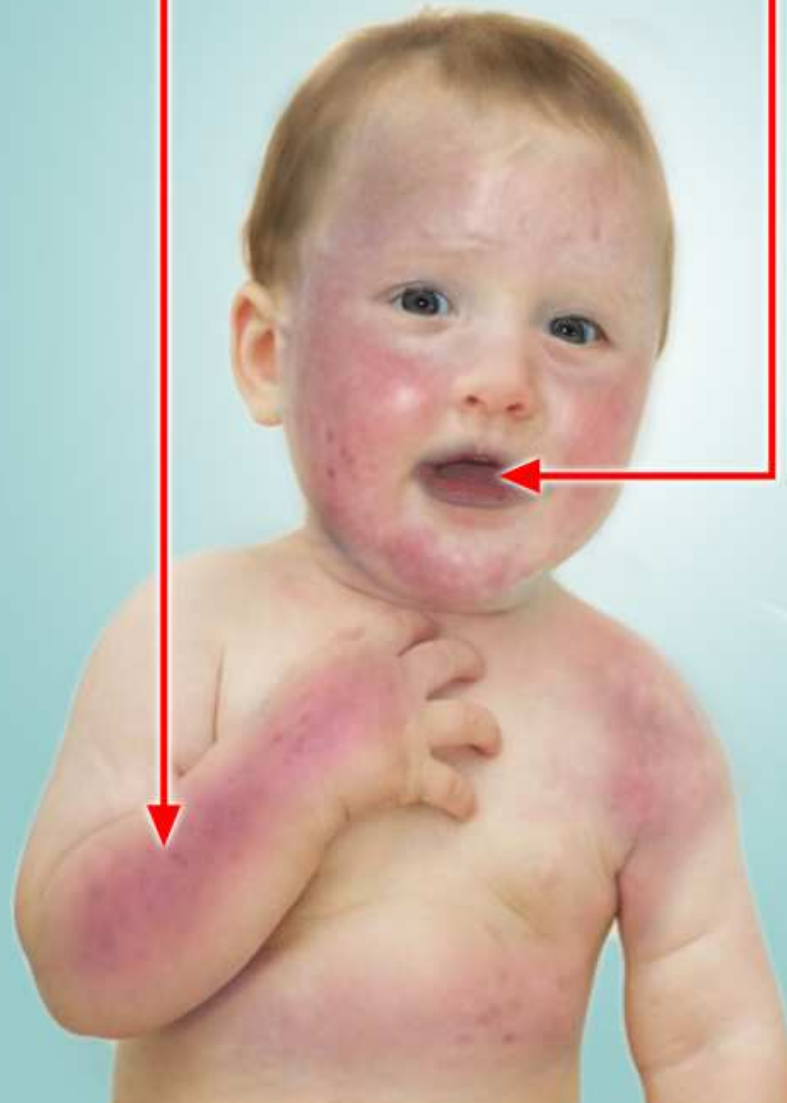


Mesenteric lymph nodes



Th1 memory Treg memory

TOLERANCE



Should we expose infants to
food allergens?

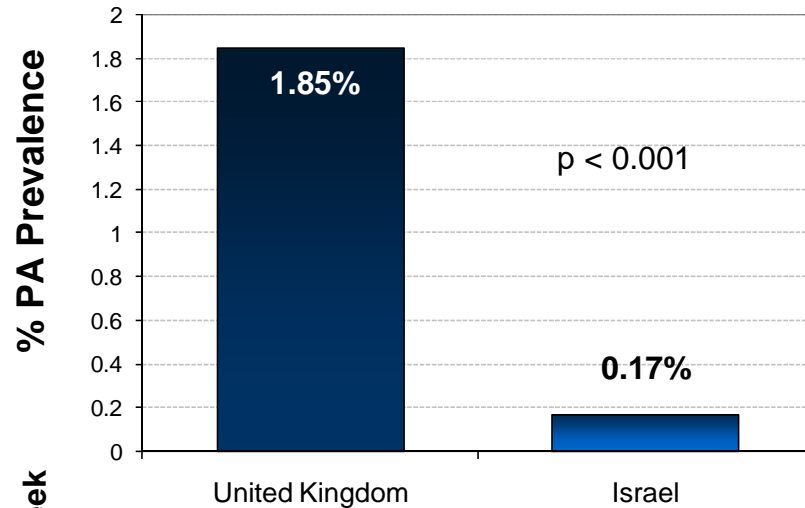
Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy



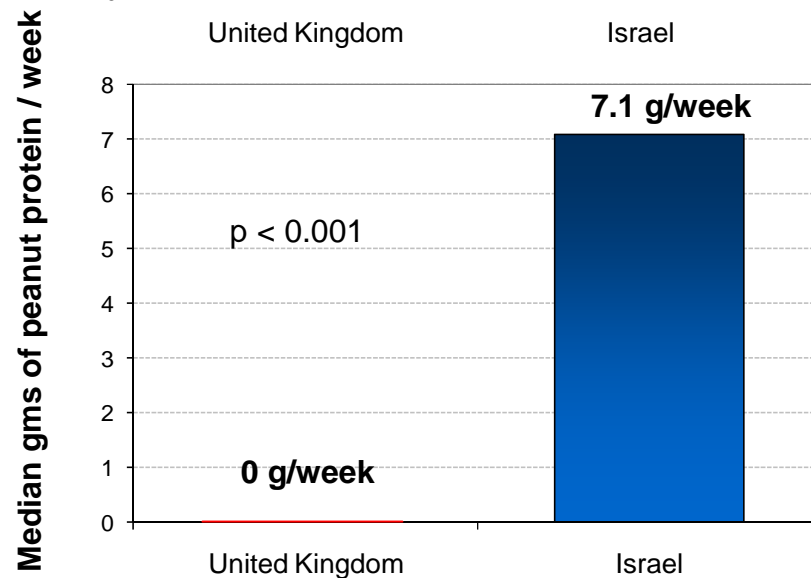
Methods

- 5171 Jewish school children in UK and 5615 Jewish school children in Israel were compared for food allergies and apoty.
- Questionnaire based assessment of peanut allergy validated by challenges.
- Infant weaning for peanut and other foods was determined in infants using a validated FFQ.

Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy



Prevalence of Peanut Allergy in Children 4-18yrs



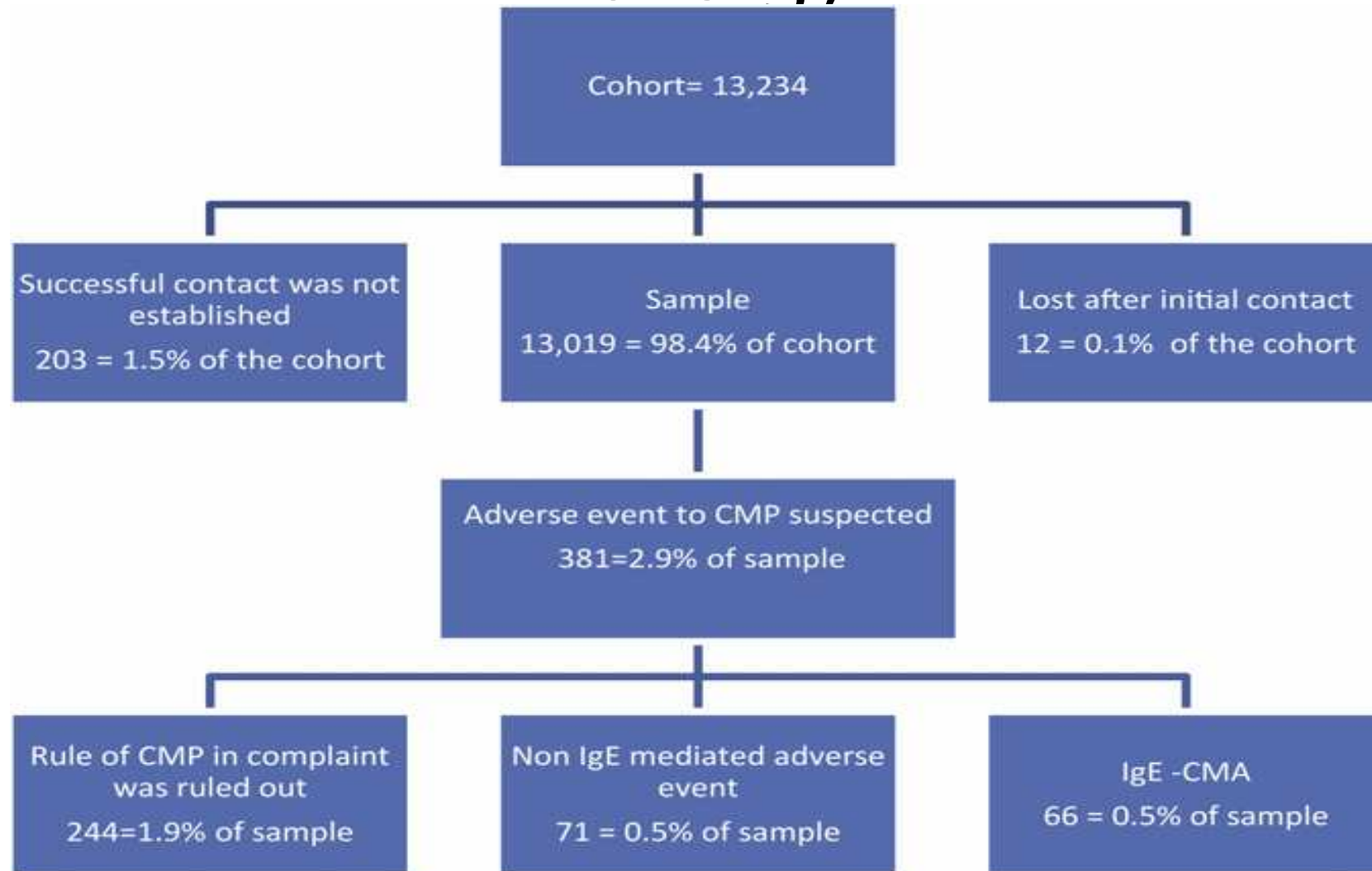
Peanut Protein Consumption 8-14 month

United Kingdom 5171

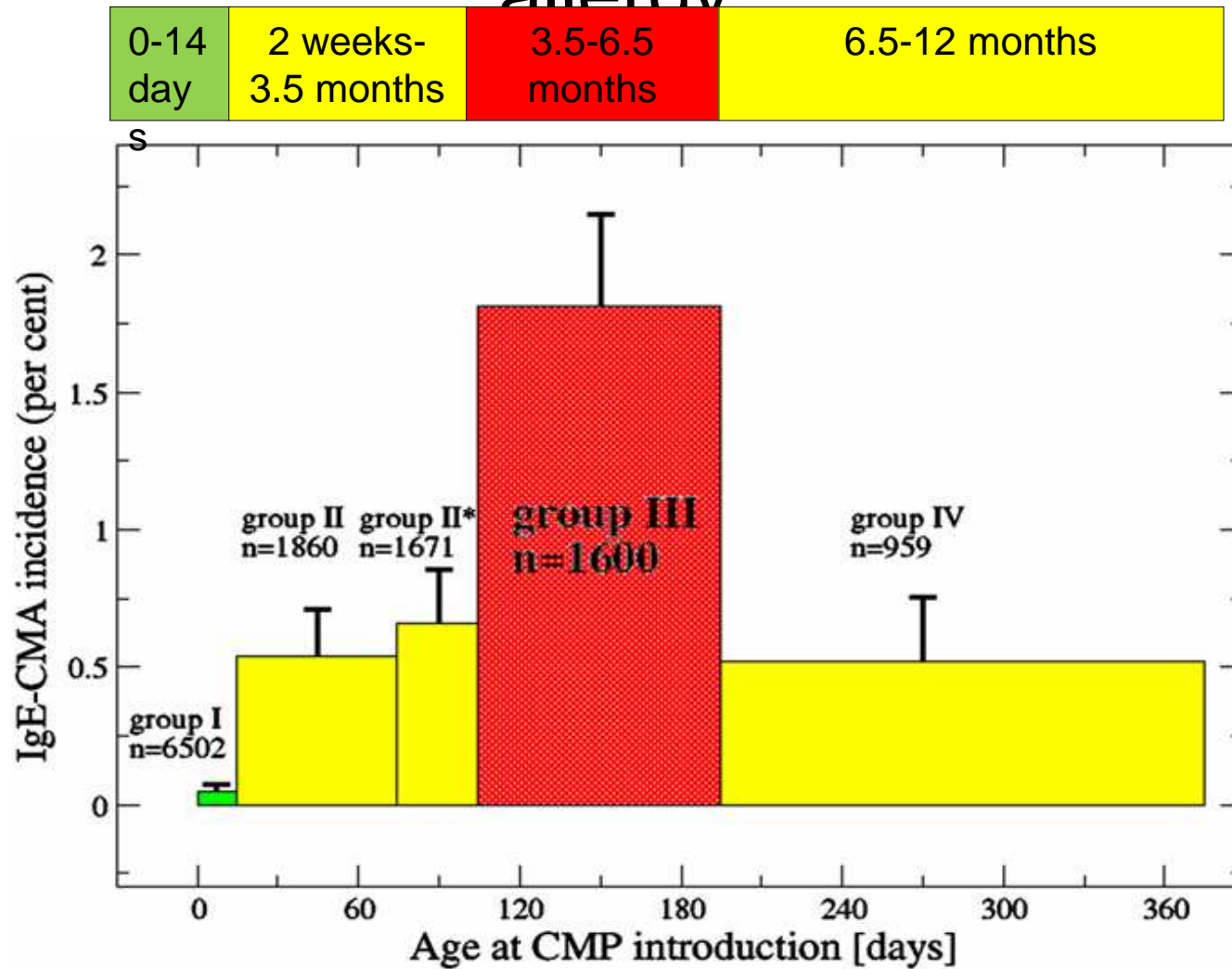
Israel 5615

How early is early?

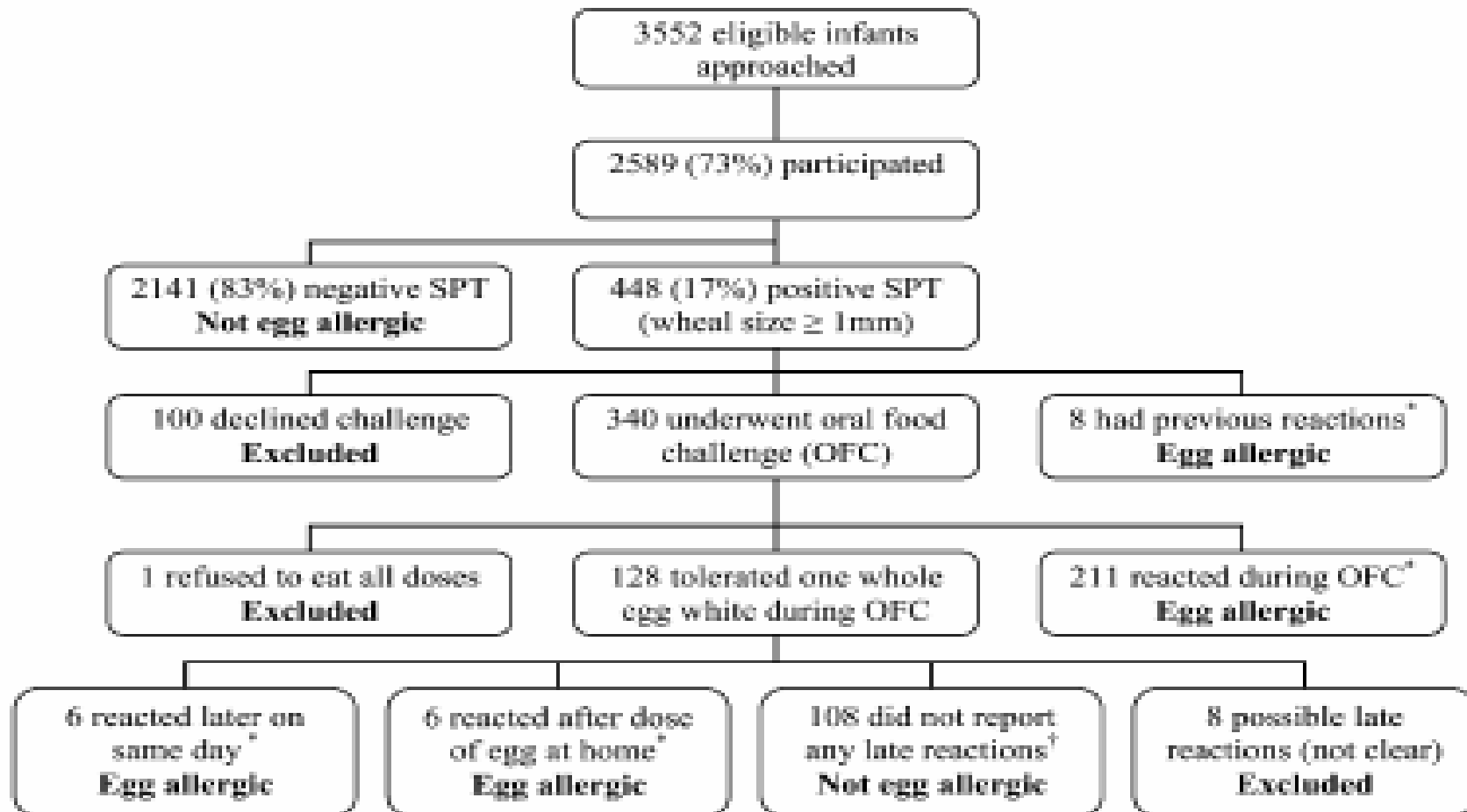
Cohort analysis for cow's milk allergy



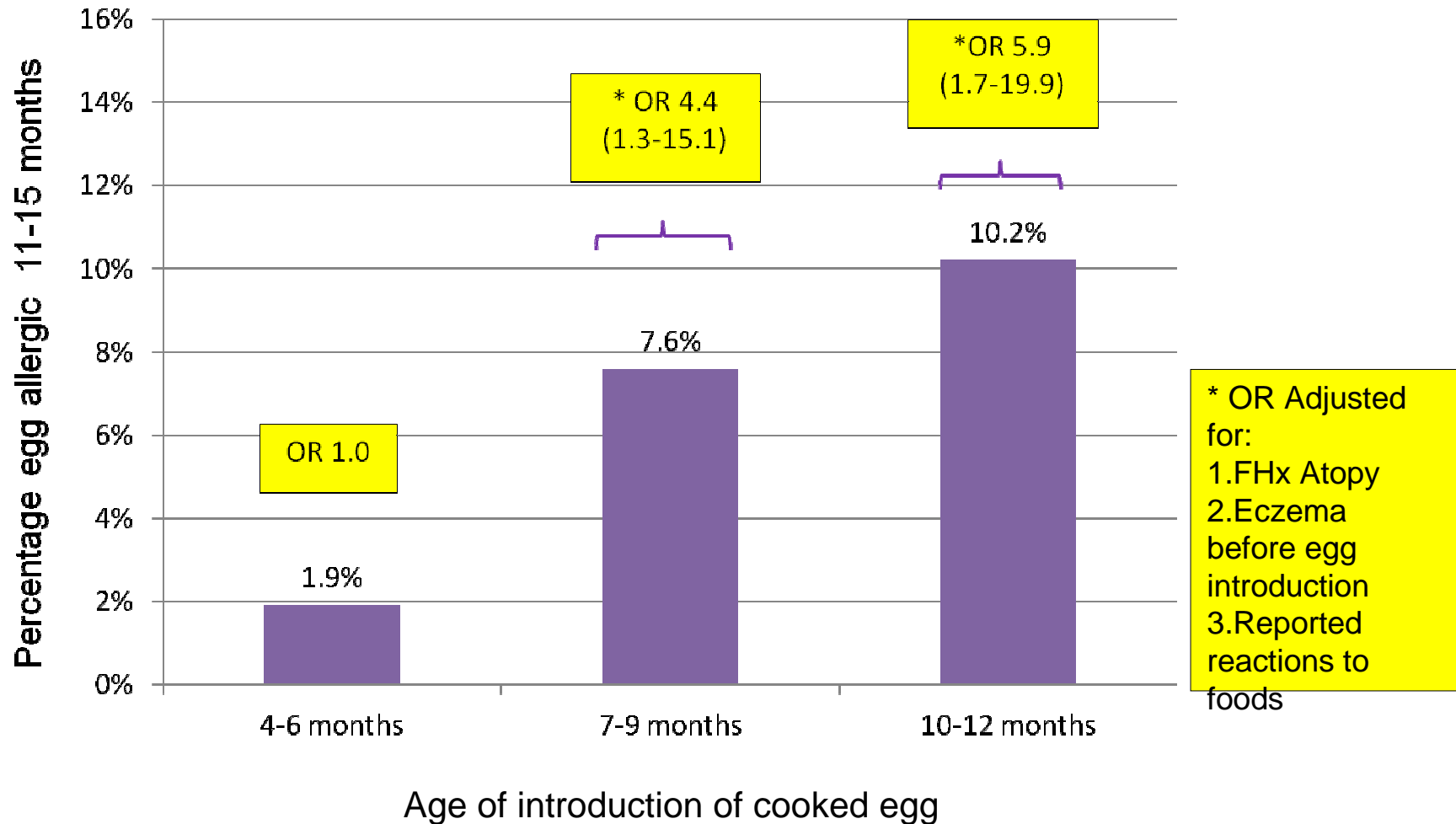
Early cow's milk introduction associated with reduced incidence of cow's milk protein allergy



Cohort analysis for egg allergy

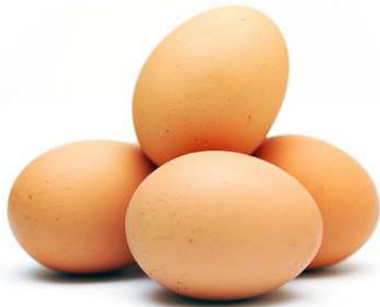


Introduction of cooked egg at 4-6 months is associated with reduction in egg allergy



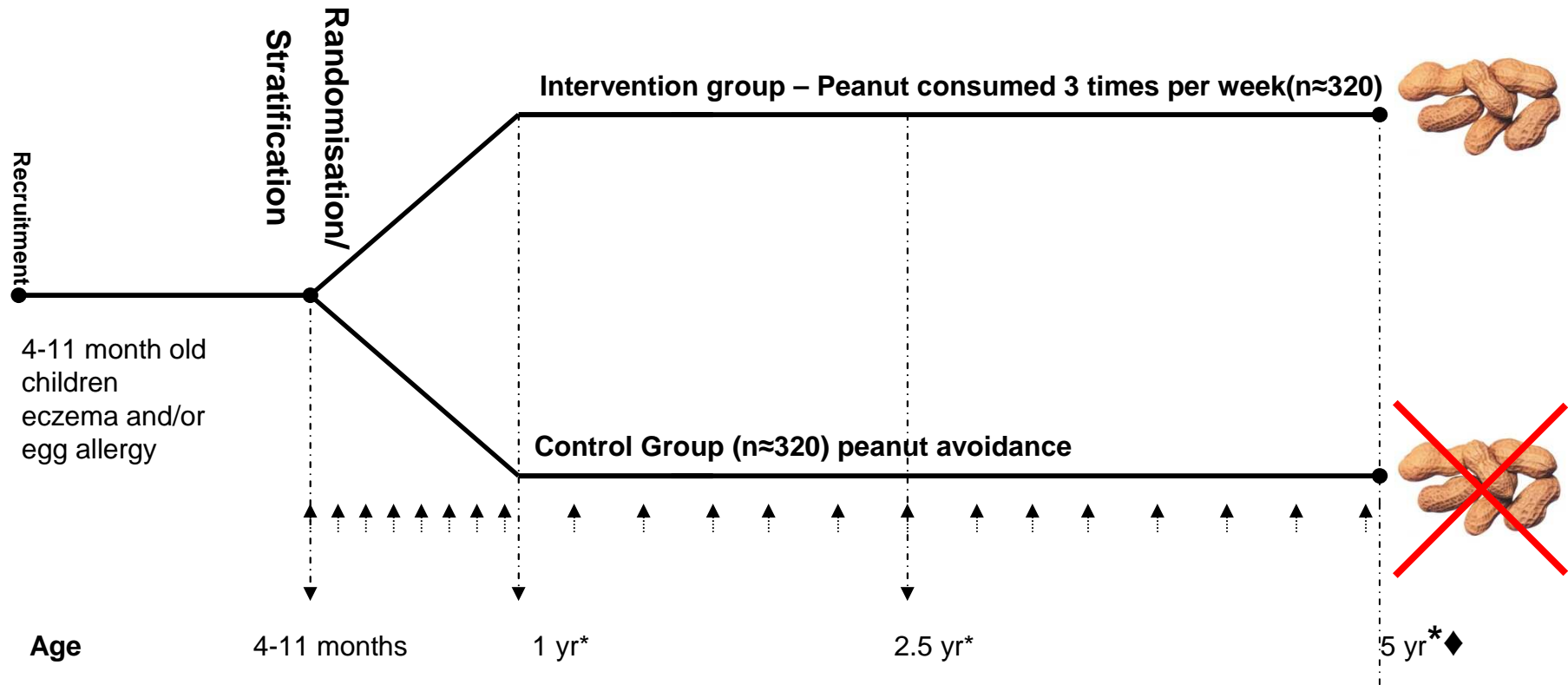
Koplin J et al. J Allergy Clin Immunol 2010;126:807-13.

Randomised controlled exposure studies



Food allergens

LEAP Study – Immune Tolerance Network



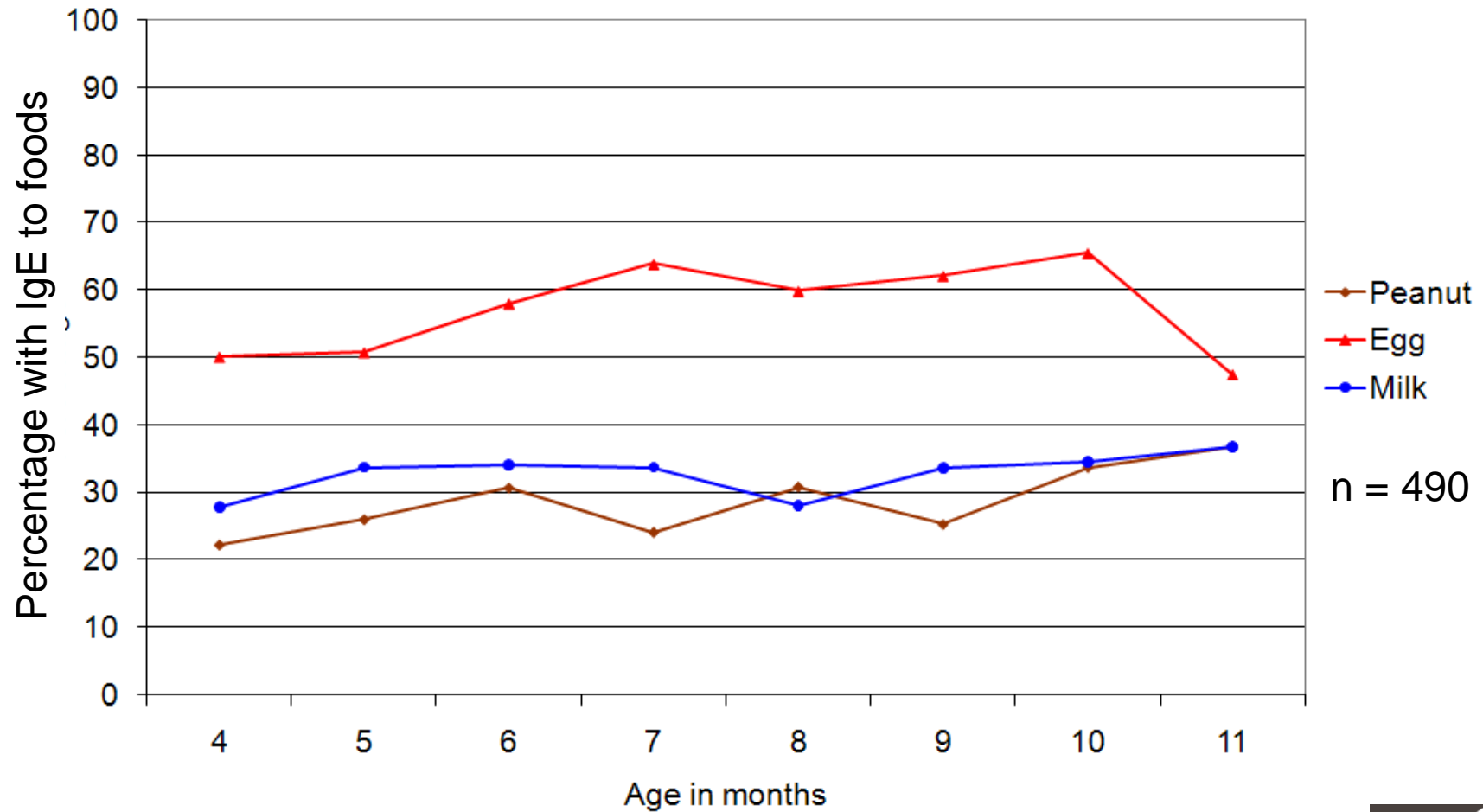
Primary Endpoint

- The proportion of participants with peanut allergy at 60 months of age. Peanut allergy is defined by the Double Blind Placebo Controlled Food Challenge

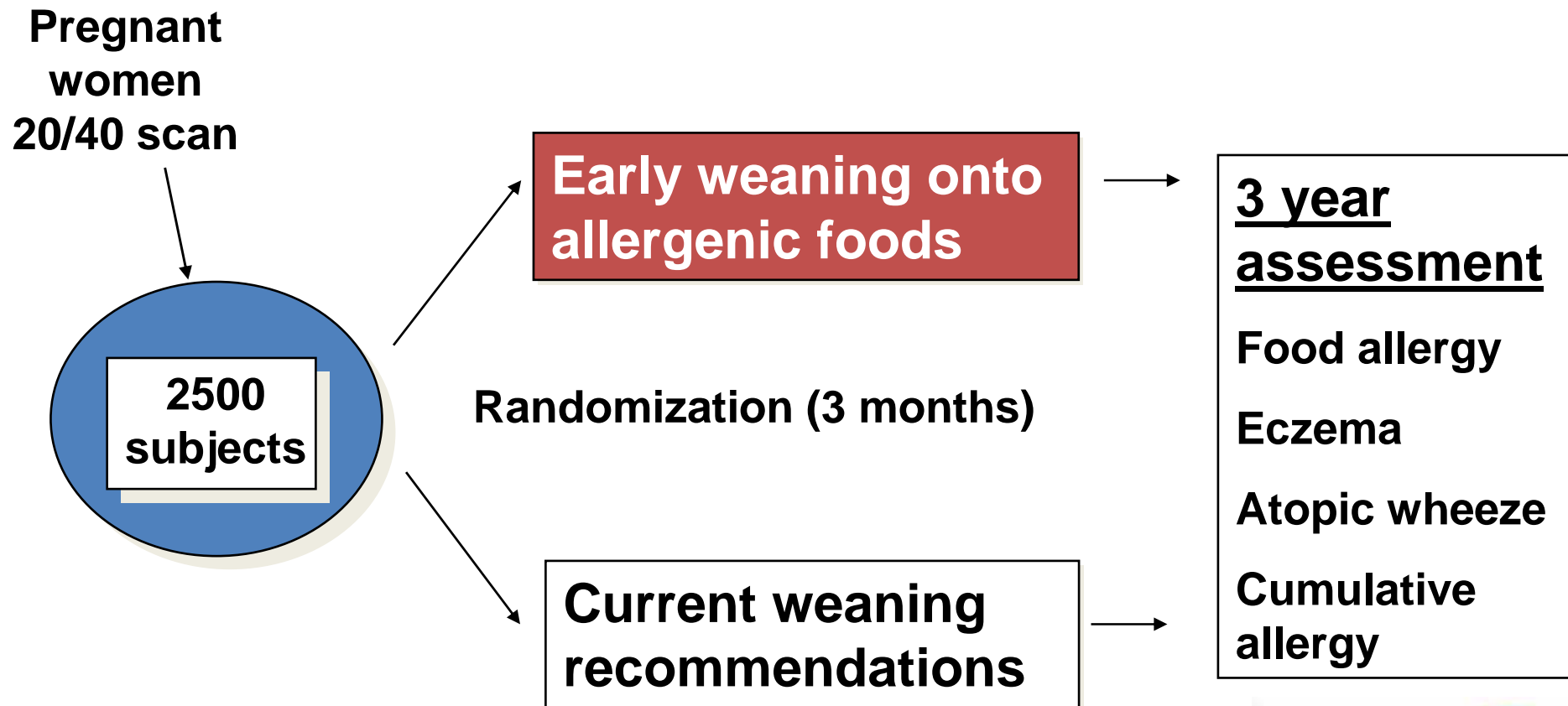
Secondary Endpoints

- The proportion of participants with allergic sensitisation to food allergens (30 and 60 months)
- The proportion of participants with allergic rhinoconjunctivitis and asthma (30 and 60 months)
- The proportion of participants with food allergy at 60 months
- Incidence of adverse events, laboratory anomalies, and nutritional evaluations
- Results of cellular and humoral immune response to peanut and other specific allergens

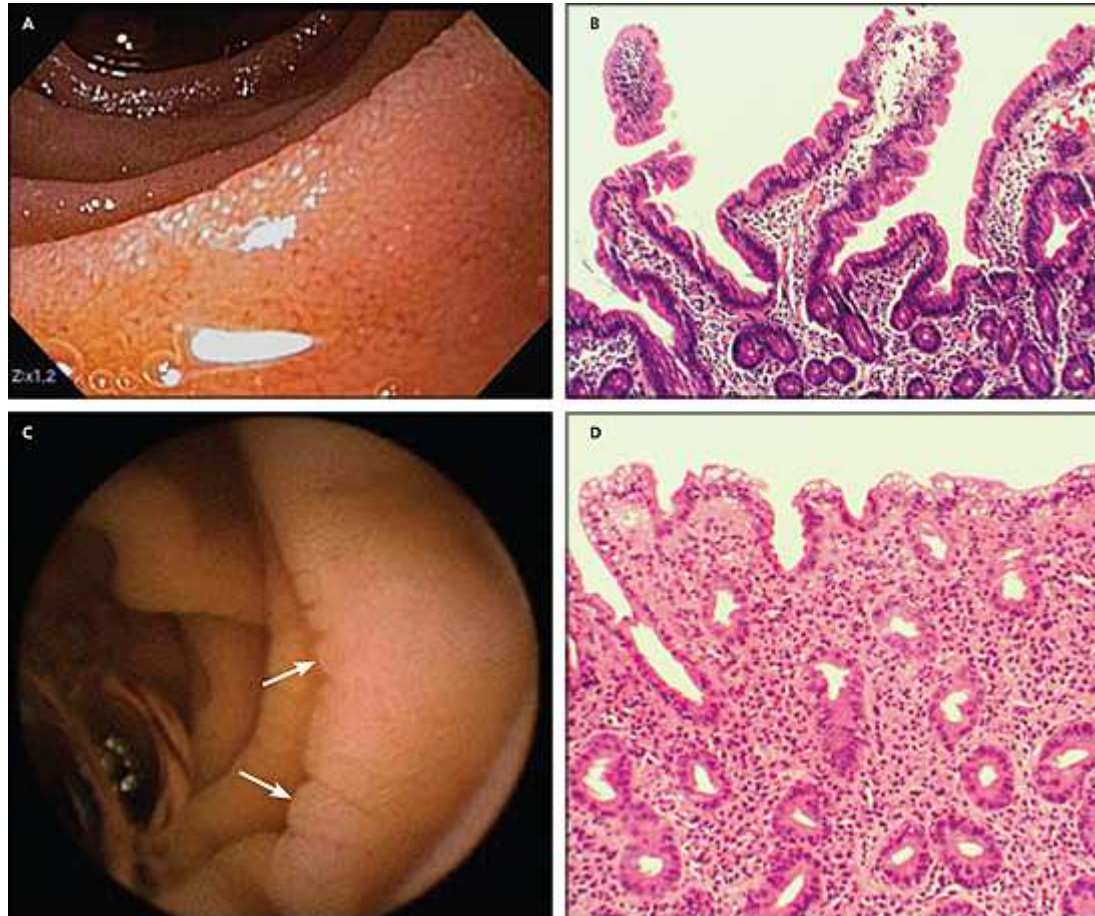
Is Oral Tolerance Induction a Primary or Secondary Prevention Strategy?



EAT Study - Early Weaning Trial

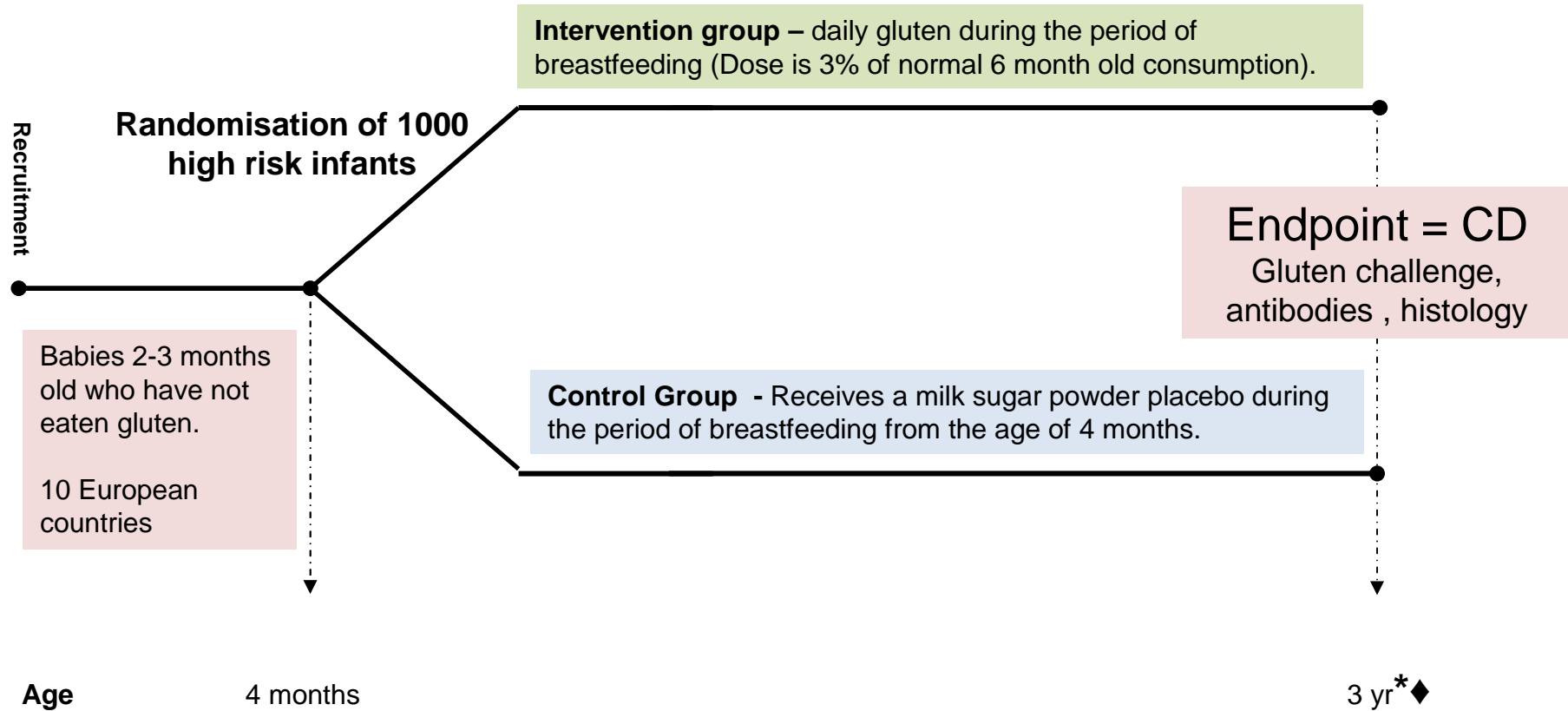






Endoscopic and biopsy findings in patients with and without celiac disease. (A) High-definition endoscopic photo of normal small intestine. The villi are clearly visible with no evidence of atrophy or scalloping of the folds. (B) Biopsy specimen of normal small intestine (hematoxylin-eosin; original magnification, $\times 100$). (C) PillCam image of small intestine in a patient with celiac disease, showing scalloping of the mucosal folds (arrows) characteristic of a malabsorption pattern. There is also evidence of villous atrophy compared with normal. (D) Biopsy specimen of small intestine in a patient with celiac disease (hematoxylin-eosin; original magnification, $\times 100$). Note the loss of villous architecture.

Prevent CD



'High-risk': First degree family member has coeliac disease.



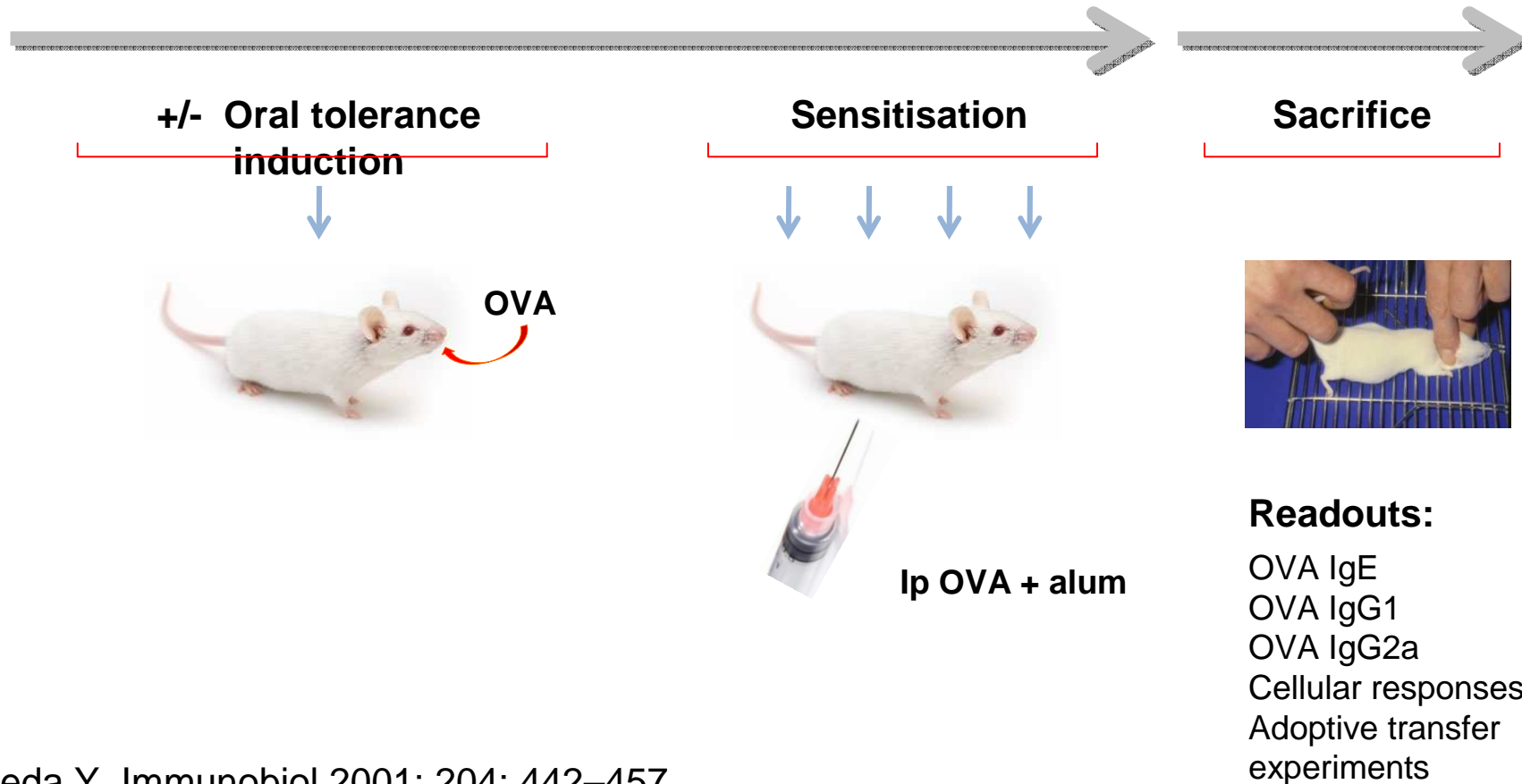
The failure of oral tolerance induction is functionally coupled to the absence of T Cells in Peyer's patches under germfree conditions

Specific pathogen free

Germ free

Gnotobiotic:

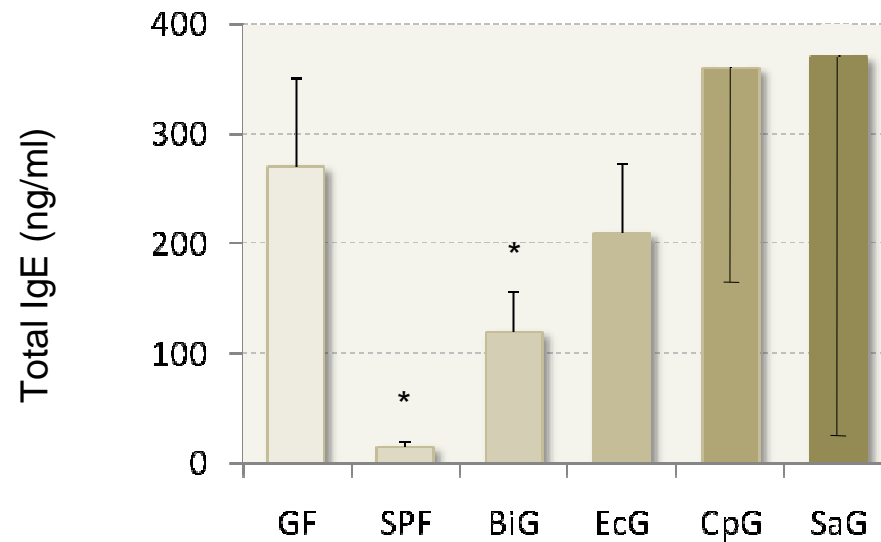
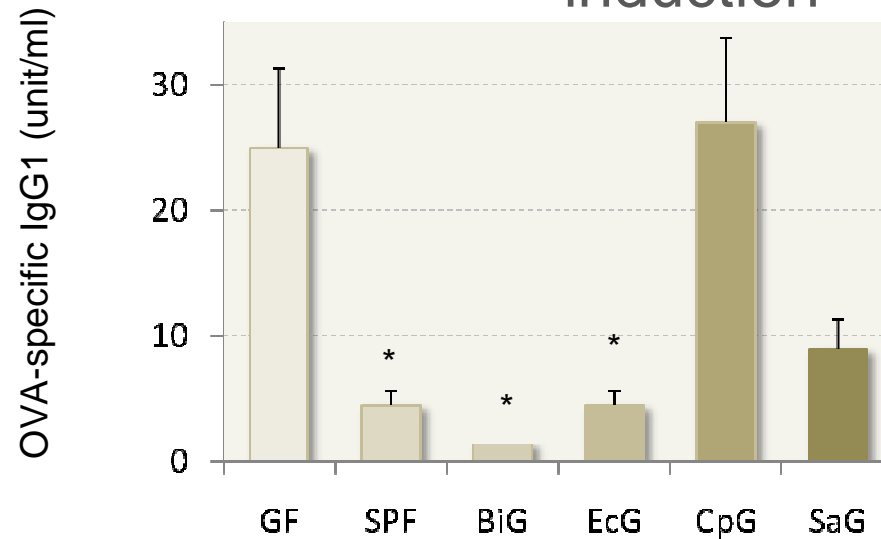
Bifidobacterium infantis
Escherichia coli
Clostridium perfringens
Staphylococcus aureus



Readouts:

OVA IgE
OVA IgG1
OVA IgG2a
Cellular responses
Adoptive transfer experiments

Serum Ab titer in the mice that underwent oral tolerance induction

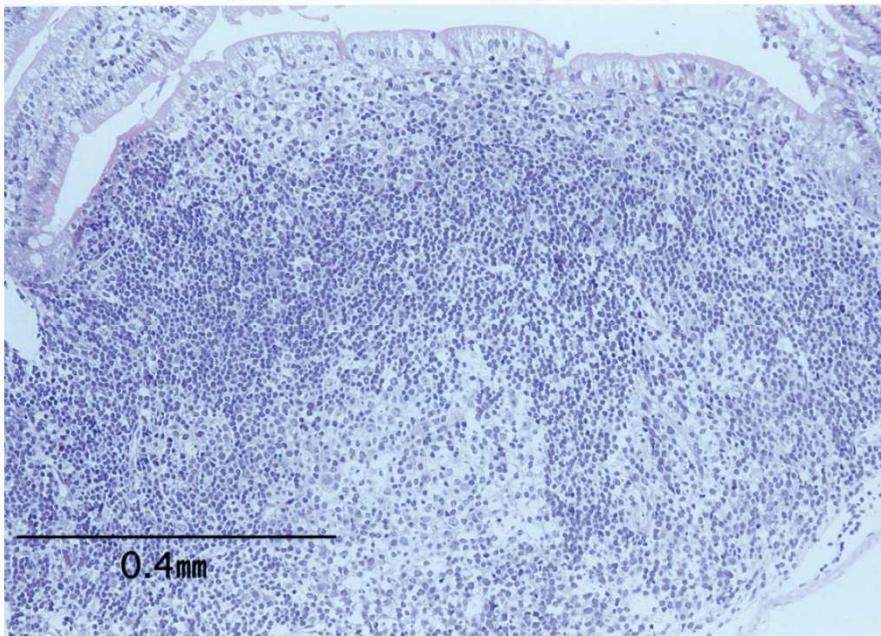


GF: Germ free
SPF: Specific pathogen free
BiG: *Bifidobacterium infantis* - associated gnotobiotic
EcG: *Escherichia coli* - associated gnotobiotic
CpG: *Clostridium perfringens* - associated gnotobiotic
SaG: *Staphylococcus aureus* - associated gnotobiotic

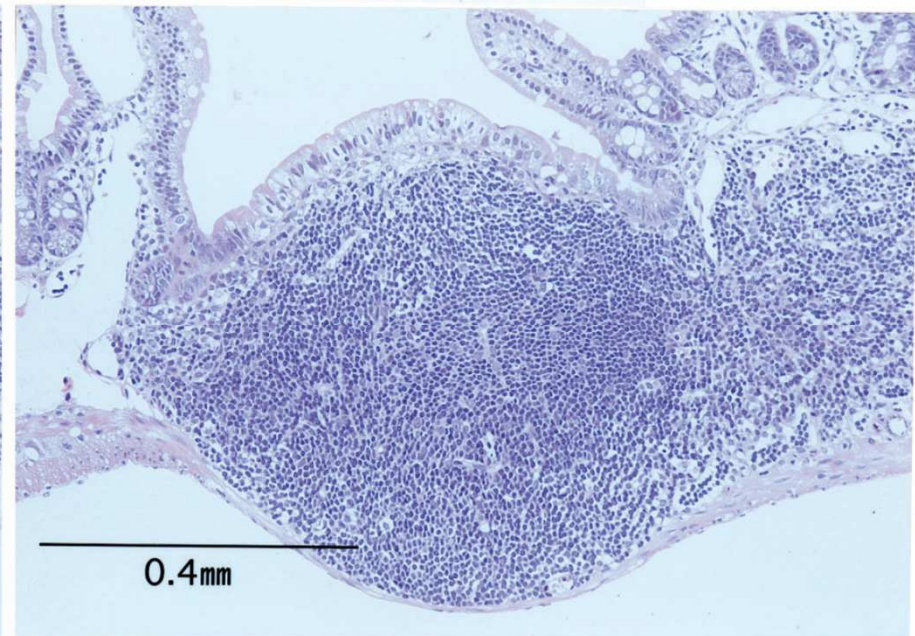
Histological analyses of Peyer's patches

HE staining

Specific pathogen free mice



Germ-free mice



Effect of Peyer's patch cell transfer on tolerance induction

Cell	Donor cells ^a	Number	Recipient mice ^b
			Ag-specific IgG1 (unit/ml)
-		4	719 ± 136 ^c
+	Whole PP cells	3	148 ± 112
+	T cell-depleted PP cells	6	576 ± 185

$p < 0.01$ ^d

}

}

NS

^a Donor cells were obtained from PPs of SPF mice, which had been fed 20 mg OVA in days -7 to day -4 and then sacrificed on day 0 to collect PP cells.

^b GF mice as recipients were given i.v. 3×10^6 of donor cells on day 0, and challenged i.p. three times with OVA in alum on day 0, day 14 and day 28.

^c Mean ± SD

^d Statistically significant based on Student's *t*-test.

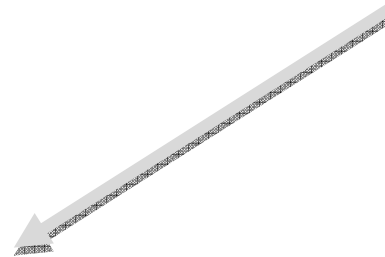
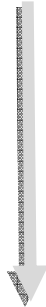
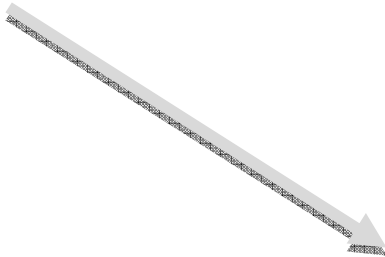
- Colostrum
- Cytokines



- Antigen



- Salivary factors
- Bacteria



**ORAL
TOLERANCE**

Cytokine concentrations in colostrum, mature breast milk and saliva

Cytokine	Saliva	Colostrum	Mature milk
IL-1 β	64.5 \pm 89.6 pg / mL	17 \pm 4 pg / mL	10 \pm 2 pg / mL
IL-2	7.3 \pm 3.0 pg / mL	90.1 (50.0–132.0) pg / mL	50.0 (50.0–50.0) pg / mL
IL-4	19.60 \pm 1.21 pg / mL	172 (53–261) pg / mL	83 (13–180) pg / mL
IFN- γ	35.10 \pm 17.94 pg / mL	708 (8–2228) pg/ml	175 (3–792) pg/ml
IL-6	27.6 \pm 26.3 pg / mL	978.80 \pm 86.80 pg/ml	86.92 \pm 2.47 pg/ml
IL-8	755.3 \pm 700.4 pg / mL	585.70 \pm 30.75 pg/ml	200.30 \pm 25.01 pg/ml
IL-10	8.97 \pm 1.91 pg / mL	43.95 \pm 5.26 pg/ml	35.82 \pm 2.98 pg/ml
IFN- γ	427.93 \pm 117.23 pg / mL	708 (8–2228) pg/ml	175 (3–792) pg/ml
TNF- α	11.2 \pm 8.5 pg / mL	402.80 \pm 29.65 pg/ml	178.30 \pm 14.41 pg/ml
TGF- β 1	24.96 \pm 2.38 pg / mL	140 (67 - 186) pg/ml	83 (17 - 114) pg/ml
IgA1	71.7 \pm 21.9 mg/mL	8.55 \pm 9.04 mg/mL	10.48 \pm 12.94 mg/mL
IgA2	103.2 \pm 42.9 mg/mL	0.36 \pm 0.23 mg/mL	0.27 \pm 0.19 mg/mL
IgG1	38.2 \pm 46.1 μ g/mL	195.0 \pm 83.2 μ g/mL	35.72 \pm 4.40 μ g/mL
IgG2	122.7 \pm 183.7 μ g/mL	12.3 \pm 0.4 μ g/mL	4.18 \pm 0.69 μ g/mL
IgG3	14.6 \pm 21.4 μ g/mL	14.7 \pm 2.5 μ g/mL	1.31 \pm 0.15 μ g/mL
IgG4	28.9 \pm 58.9 μ g/mL	2.4 \pm 0.4 μ g/mL	0.516 \pm 0.109 μ g/mL
IgM	2.1 \pm 1.7 μ g/mL	122.30 \pm 100.19 mg/dl	25.71 \pm 20.39 mg/dL
sCD14	190 x 10 ³ pg/mL	15 (12–20) pg/mL	8 (6–10) pg/mL

Current practice for feeding infants



Breastfeeding

Hypoallergenic formula
Baby rice, lamb, chicken

Eggs, peanut
Nuts, fish

0 – 6 months

6 – 12 months

12 months – 3
years

Conclusions

1. Avoidance studies to prevent allergy have failed.
2. Complete allergen avoidance is rarely possible.
3. Oral tolerance induction needs to be investigated in RCT's. Studies are currently in progress.
4. The choice of participants and clinical endpoints is critical.
5. Safety is paramount and studies should have independent data safety monitoring boards.

Conclusions

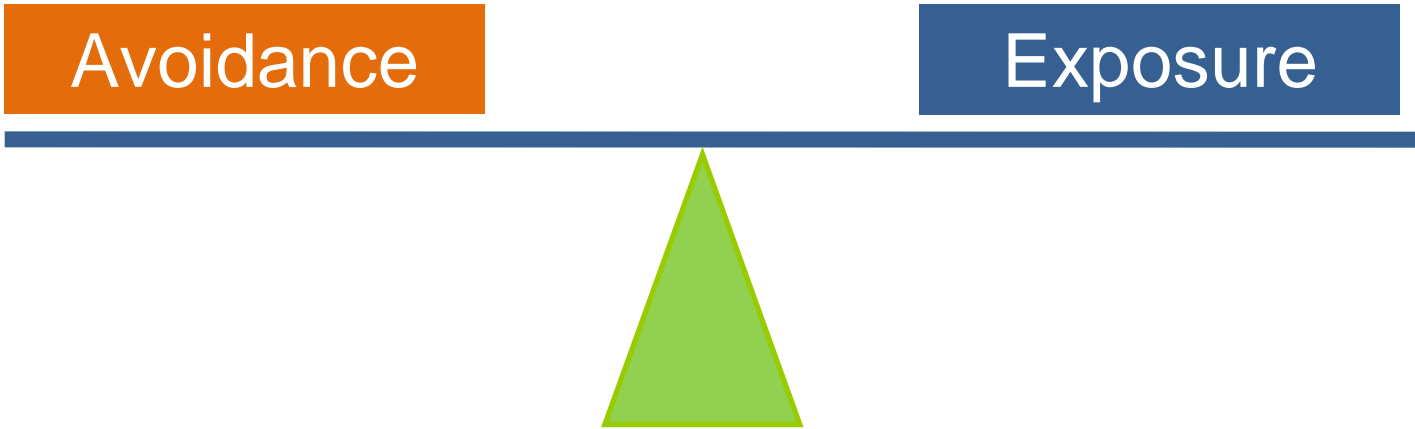
6. Oral tolerance induction through early antigen exposure is currently being tested in the EAT and the LEAP studies.
7. Oral consumption of allergen is a necessary condition but a sufficient condition for the development of oral tolerance induction.
8. Other facilitating factors may be necessary for OTI to occur – saliva, breast milk, bacteria, cytokines.

Equipoise

?

Avoidance

Exposure



Acknowledgements

- Jean Golding
- George Du Toit
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- Alick Stephens
- Graham Roberts
- Susana Radulovic
- Lori Nirenstein
- Martin Penagos
- National Peanut Board
- Immune Tolerance Network
- Food Standards Agency
- Medical Research Council
- FAAN
- Food Allergy Initiative