

IgG4 an enigma for understanding the effects of high exposure , Eosinophilic Esophagitis and Asthma.

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Learning Objectives

At the conclusion of this Activity, learners should be able to:

- Describe the physiologic characteristics of IgE antibodies vs. IgG isotypes
- Explain how IgG4 may modulate tolerance to allergens
- Discuss the association of IgG4 with EoE

IgG4 Fab Arm Exchange

Fig. 1a

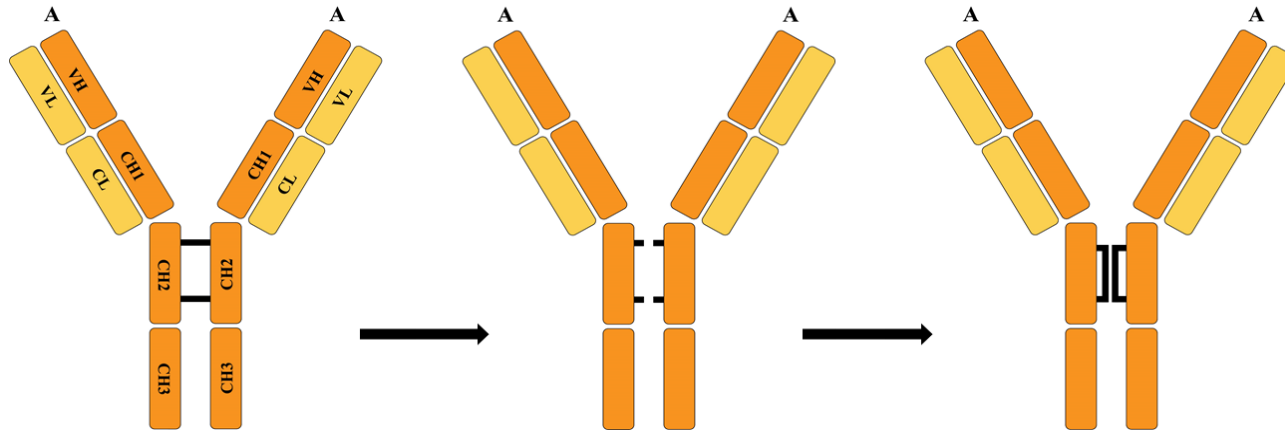
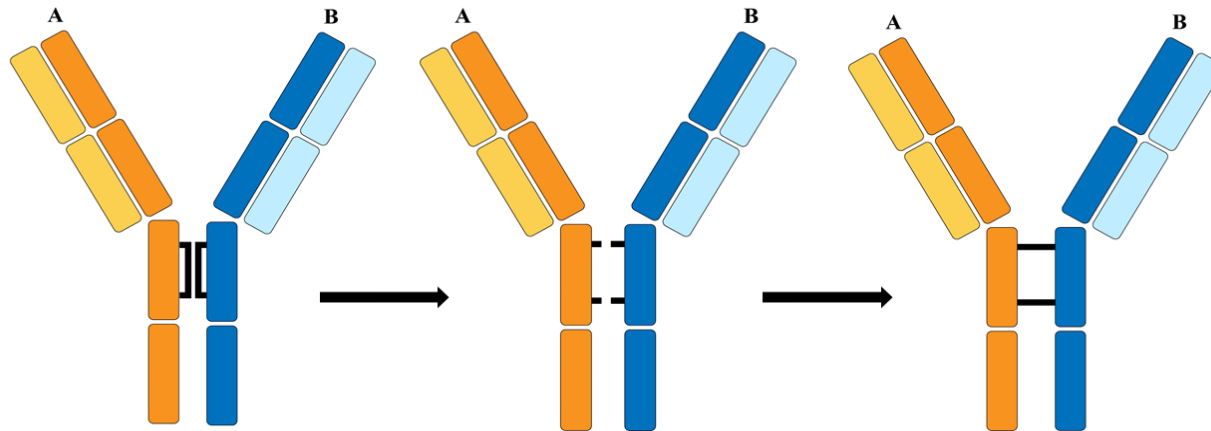


Fig. 1b



A + B

No precipitation

A1 + A2

Possible cross-linking between
two molecules from the same source

B or A + Unknown

No precipitation

PREVALENCE OF SENSITIZATION TO NINE ALLERGENS AMONG 616 EARLY TEENS (AGE 13) IN THE VIVA COHORT and STRENGTH of ASSOCIATION with ASTHMA.

	slgE \geq 0-35 IU/ml	slgE \geq 3.5 IU/ml	slgE \geq 50 IU/ml
Mite	244***	162**	48***
Cat dander	177***	87***	22***
Dog dander	162***	49***	3 n.s.
Rye grass	133 p=0.07	60 p =0.16	16 p= 0.18
Aspergillus	30***	3 n.s	-ns
Alternaria	43*	19 p=0.12	2 n.s.
Silver Birch	180***	100***	14***
Oak	183***	97***	17***
Ragweed	109**	30 p=0.05	3 n.s.

*** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$

n.s.= nonsignificant or numbers too low

- Characteristics of IgE and the Isotypes (subclasses) of IgG

	IgG1	IgG3	IgG4	IgE
Interleukins relevant to switch	-	-	IL-4-IL13, IL-10	IL4-IL-13
Hinge Region Length	15	62	12	15
Fab Arm Exchange	No	No	Yes	No
Fc Binding	Multiple ++	Multiple +++	FcγR1b +/-	FcεR1 +++
Complement Activation ^{\$}	++	+++	No	No
Half Life ^{# or ##}	~20 days	<7 days	~20 days	<2 days +++

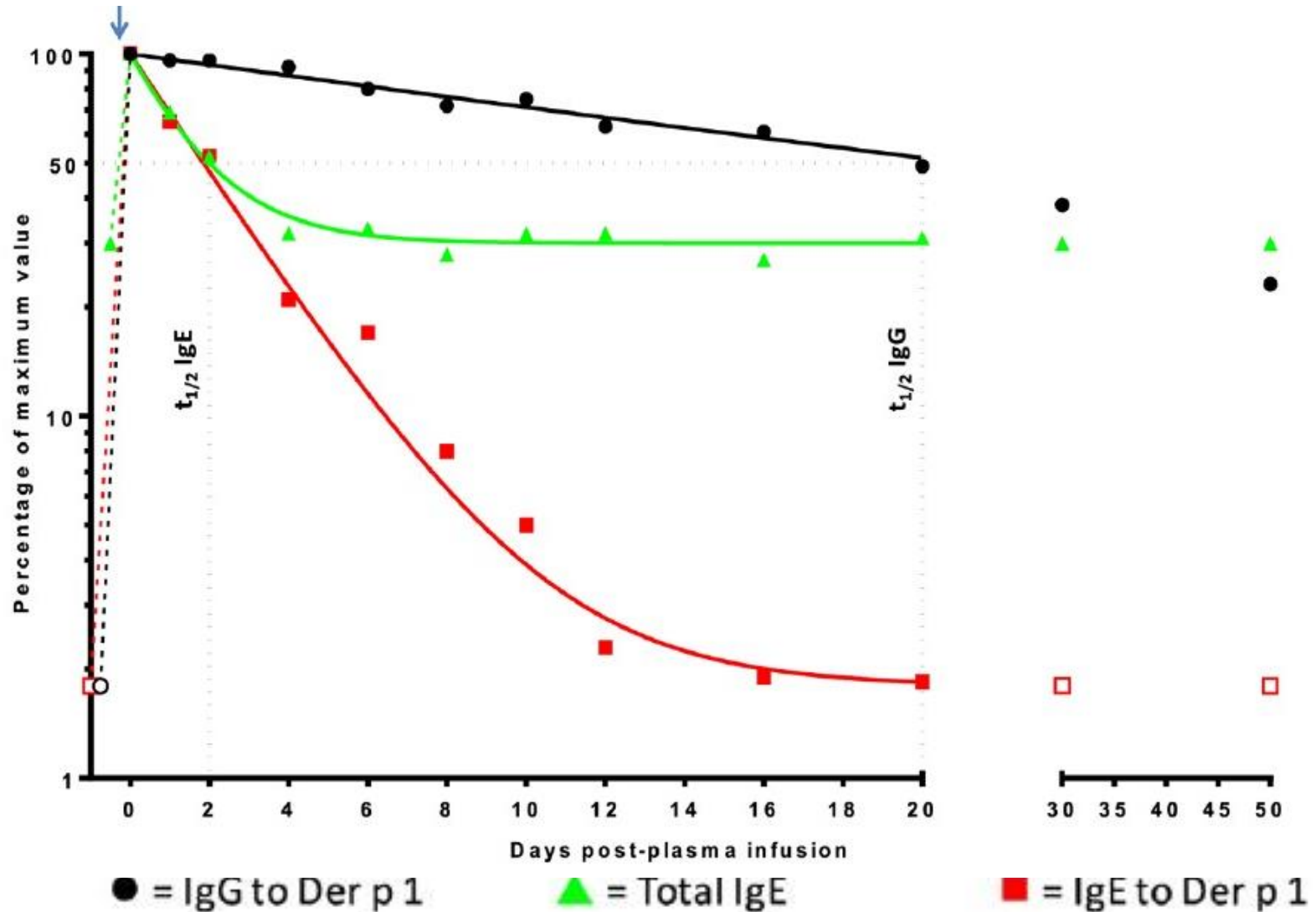
[#]Decreased half-life reflects poor binding to FcγRn of both IgE and IgG3.

^{\$}Complement activation by IgG1 and IgG3 is classical pathway.

^{##} IgG3 binding to FcγRn is decreased because it has Arginine at 435, but can be increased by a change to Histidine 435; R-435-H.

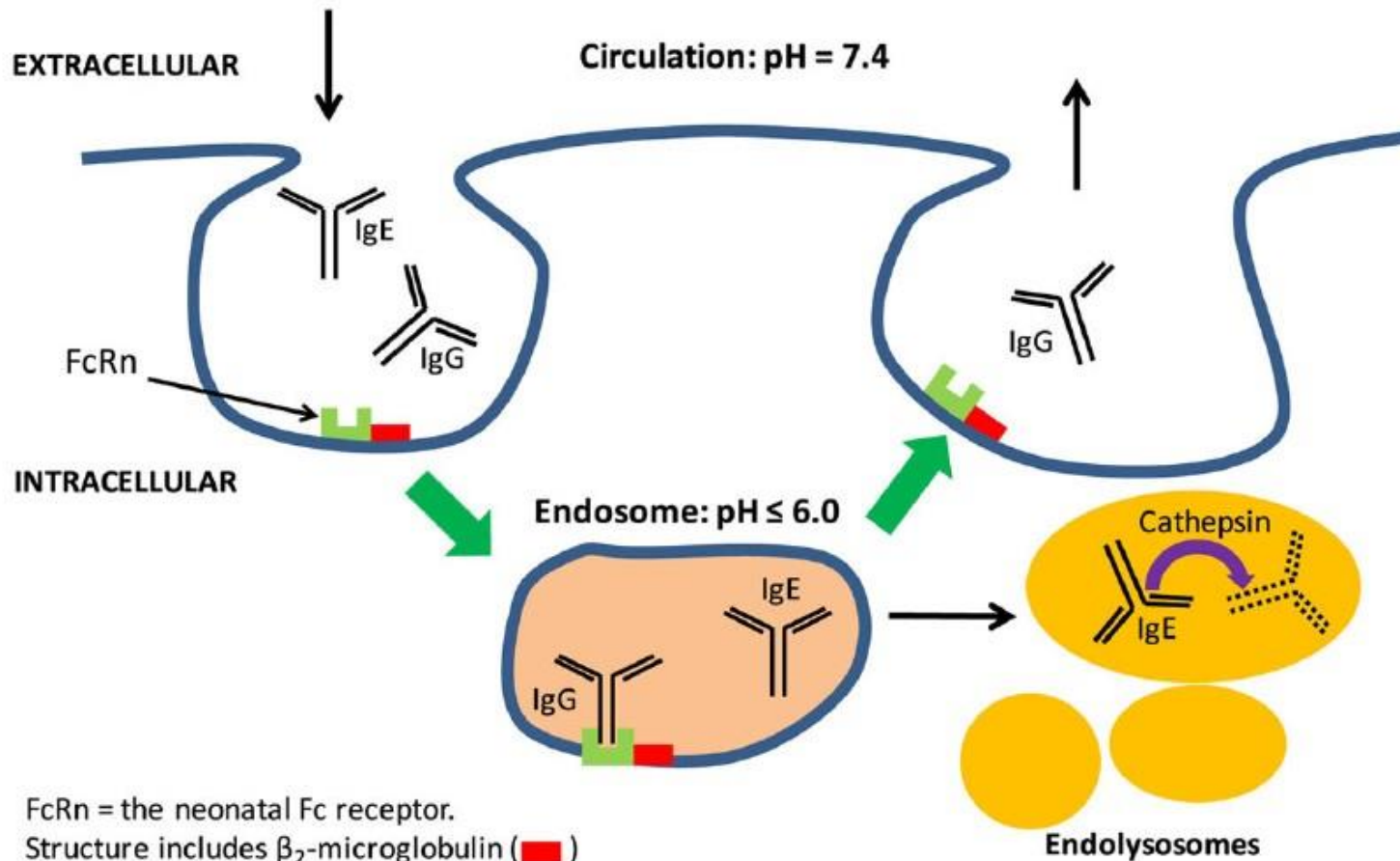
Decay of IgE & IgG Ab to Der p 1 following a transfusion of two Units a plasma from a highly allergic but Otherwise normal control.

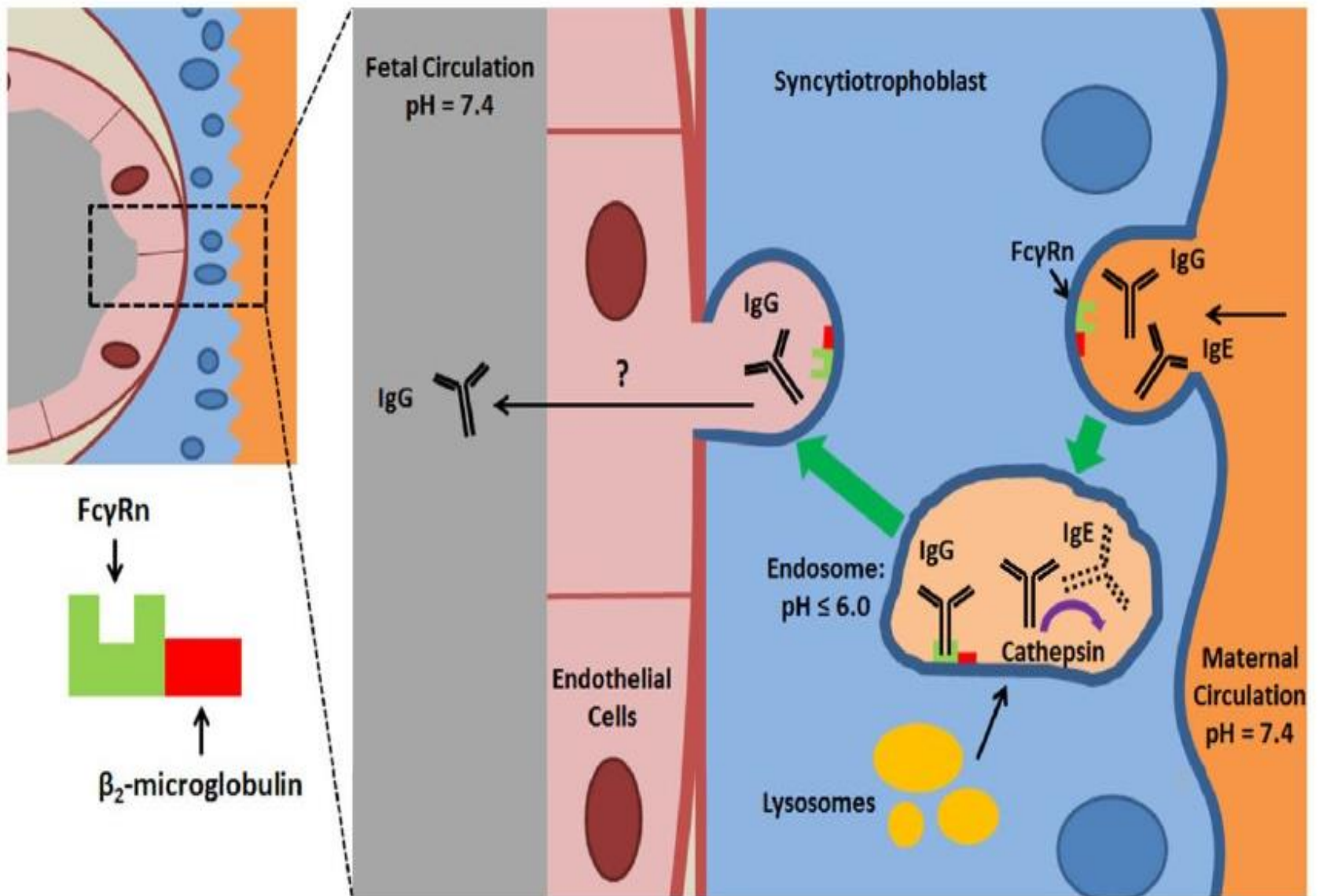
Lawrence M,Platts-Mills T A. JACI 2017.



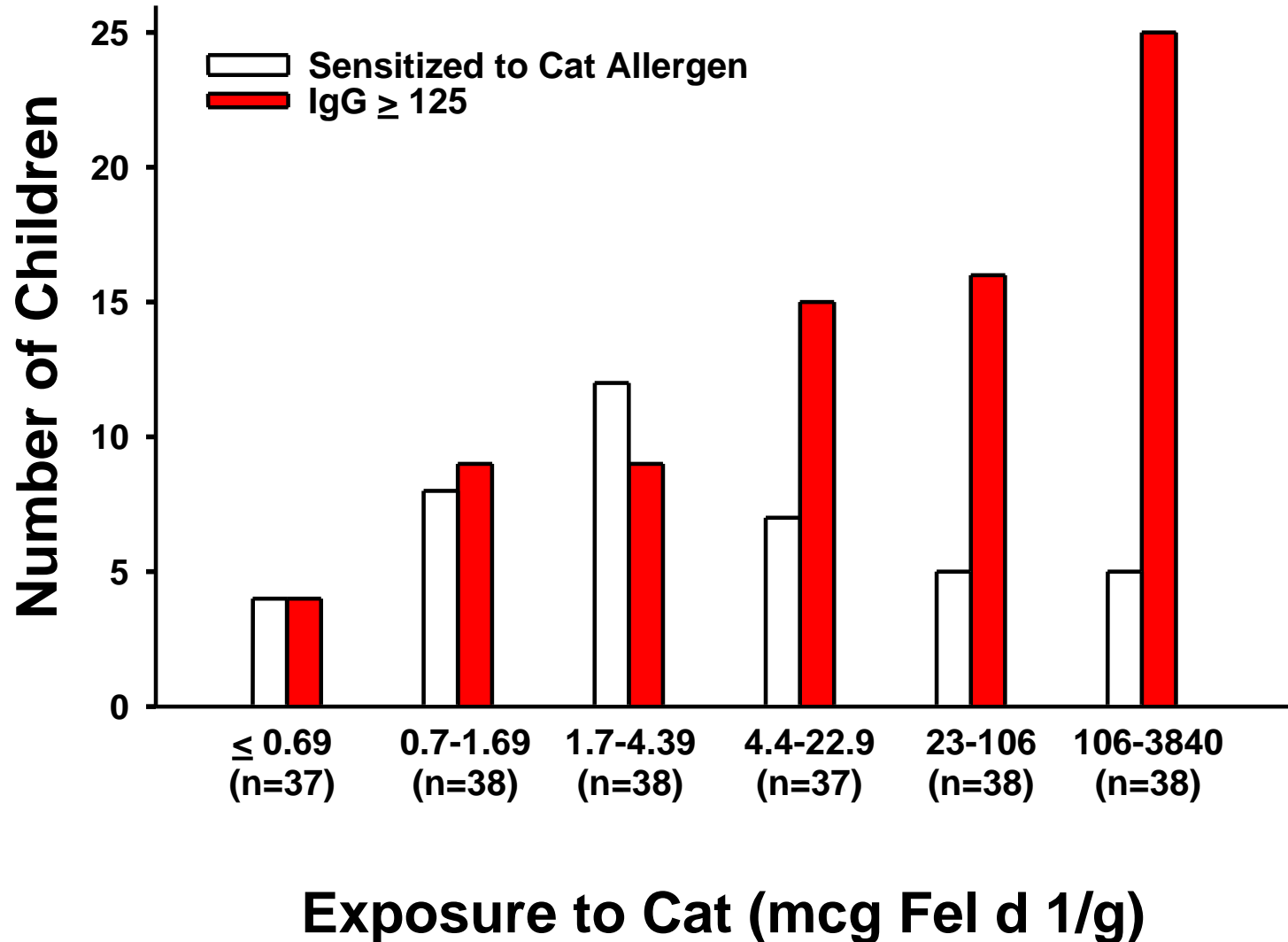
A

Endocytosis and the processing of IgG and IgE within endothelial cells

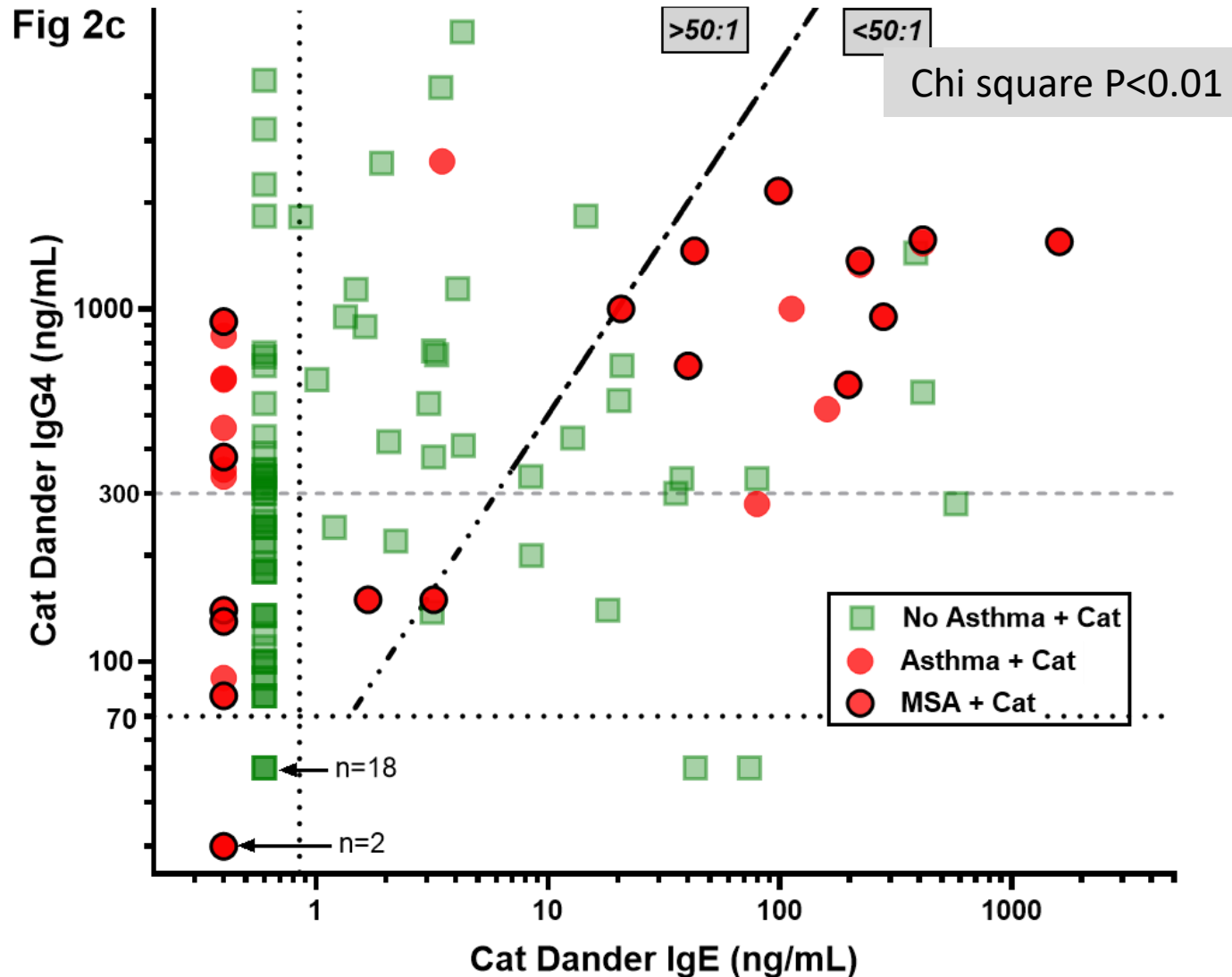


B

Exposure and Immune Response to Cat Allergen in 226 Middle School Children



IgG4 and IgE antibodies to cat extract in sera from 135 subjects in Viva age 13 living in a house with a cat & analysed according to current asthma (n=30) and moderate severe asthma (MSA) (n=17).

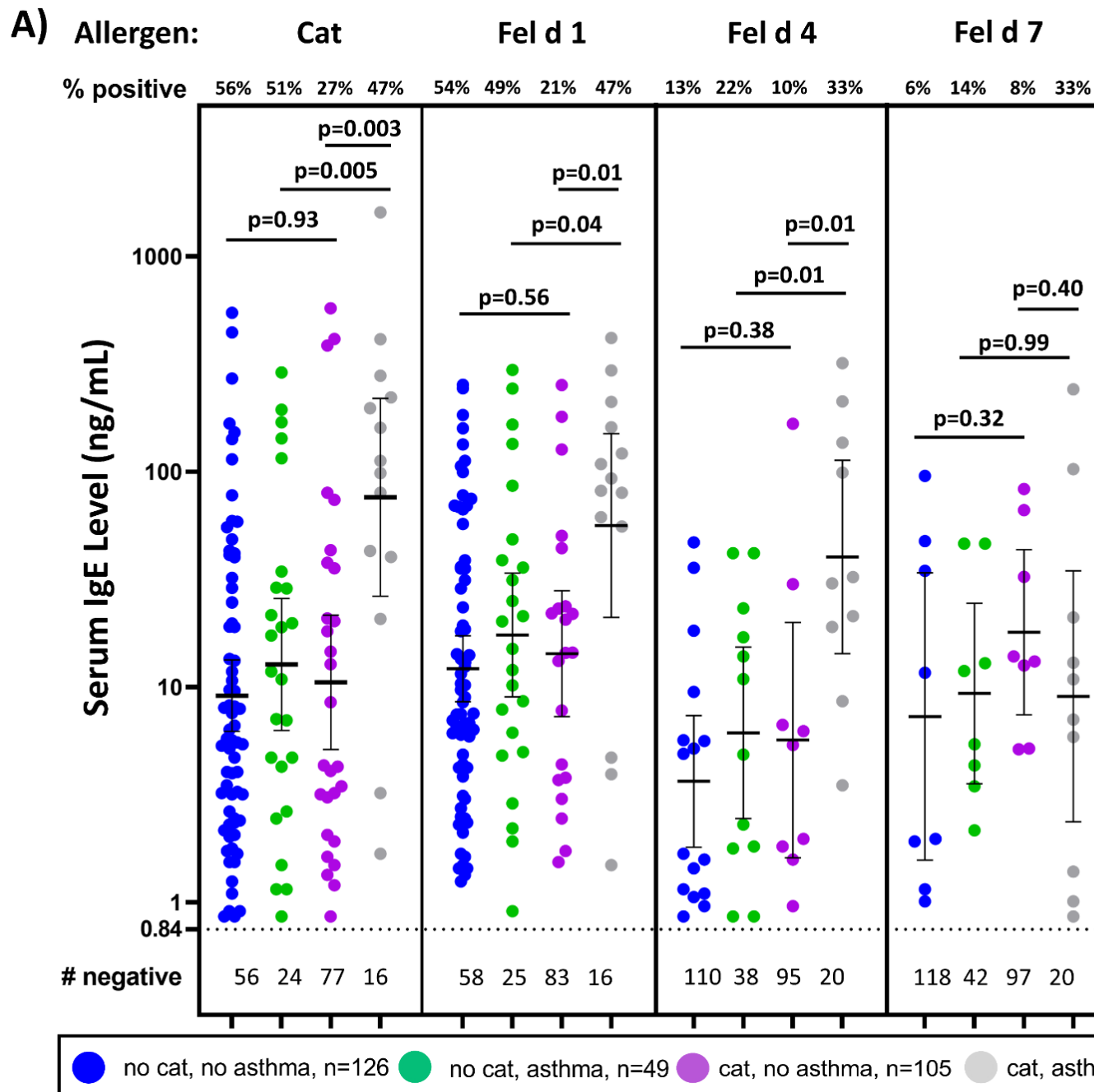


**RELATIONSHIP OF SIGE TO CAT COMPONENTS AMONG CHILDREN
WITH CURRENT ASTHMA (ASTHMA), MODERATE TO SEVERE
ASTHMA (MSA), AND NO ASTHMA**

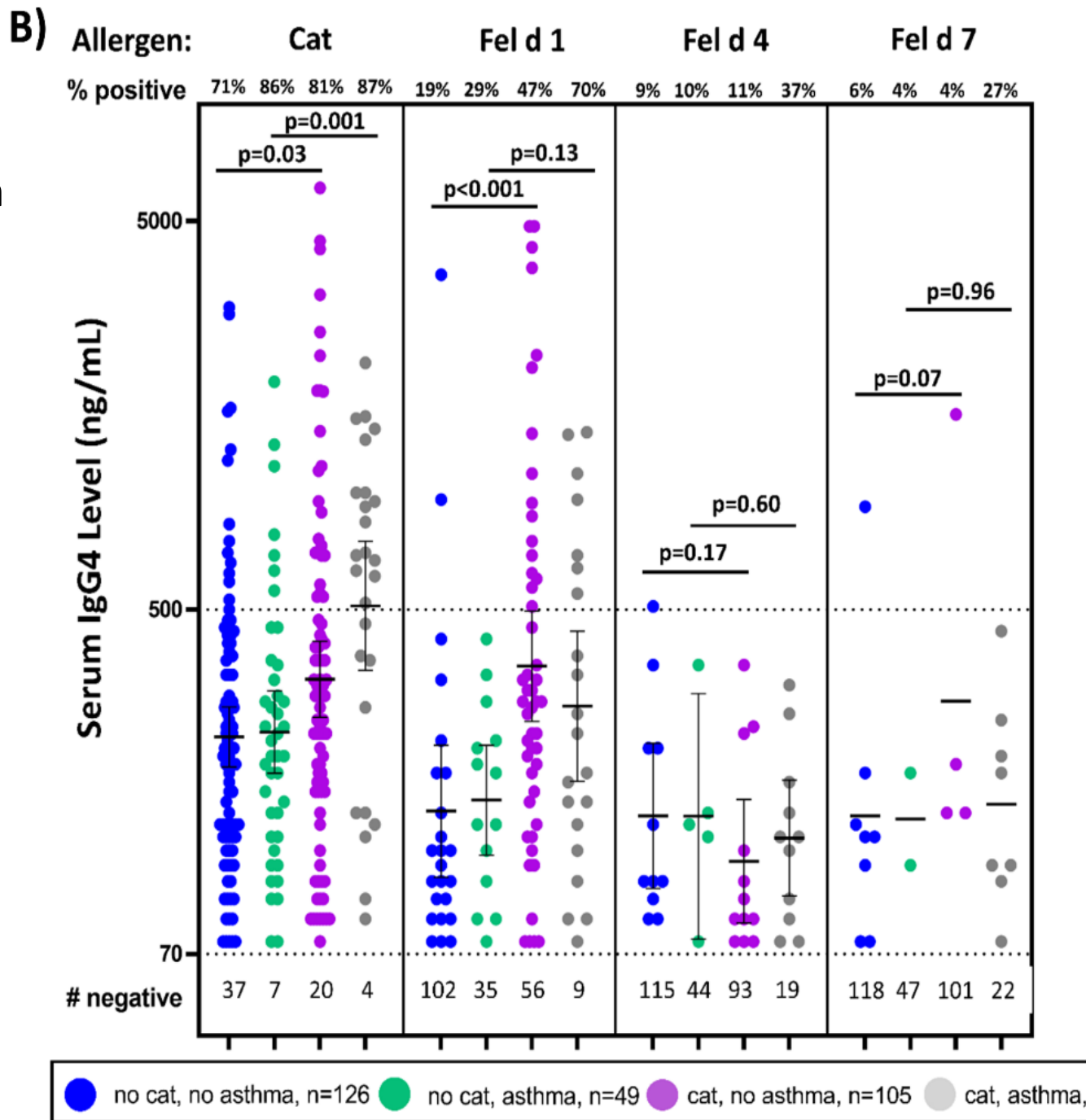
IgE IU/ml >0.35	No asthma (n=516)	Asthma (n=86)	Adjusted OR [+ or - C.I.]	MSA (n=45)	Adjusted OR [+ or - C.I.]
Fel d 1	110 (21%)	43 (50%)	4.3 (2.5, 7.4)	28 (62%)	7.1 (3.4, 14.7)
Fel d 4	30 (5%)	22 (25%)	6.7 (3.2, 14.3)	14 (31%)	10.5 (4.1, 26.5)
>3.5					
Fel d 1	60 (11%)	31 (36%)	4.6 (2.5, 8.4)	19 (42%)	6.2 (2.9, 13.2)
Fel d 4	7 (1%)	14 (16%)	17.5 (4.9, 62.8)	10 (22%)	29.4 (7.1, 121.2)
>50					
Fel d 1	11 (2%)	9 (10%)	6.0 (2.1, 17.2)	7 (15%)	8.2 (2.6, 25.9)
Fel d 4	1 (0.2%)	3 (3%)	11.3 (0.6, 208.8)	3 (6%)	28.7 (1.6, 528.0)

OR adjusted odds ratio and 95% confidence interval

Data is shown for the two components where we have data on the abundance of the protein in house dust.



sIgG4 to cat dander in 310 early teens,.Including 135 living in a house with a cat,and 79 with asthma.

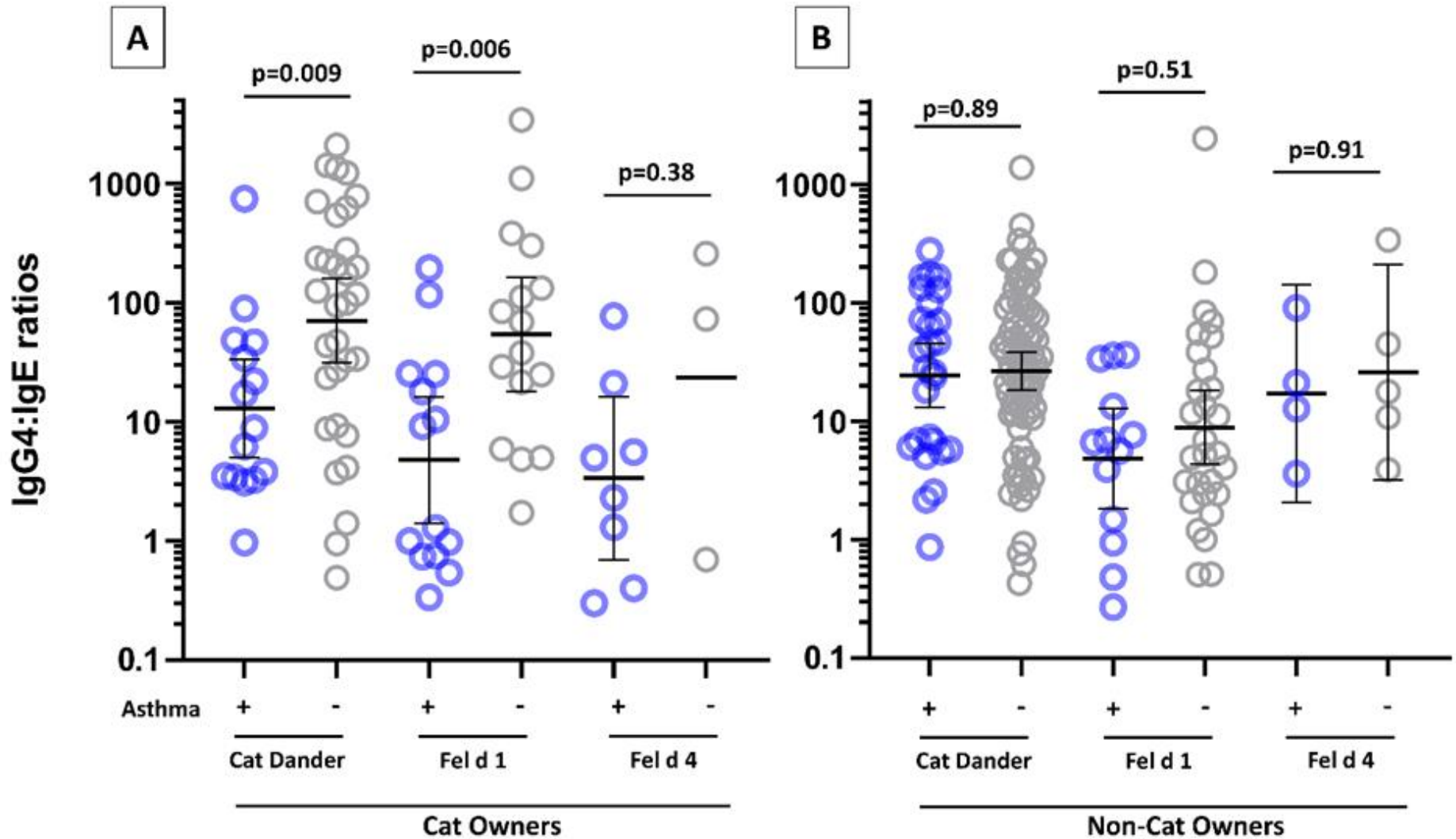


Available values for exposure to Cat and mite allergens.
Fel d 4 and Der p 23 results from Indoor Biotechnologies

Box 1: Estimates of Exposure to Allergens from Cat or Dust Mite: Airborne and Floor Dust

	Component	Airborne	Floor Dust / gram of dust
Cat	Fel d 1	2 $\mu\text{g}/\text{m}^3$	Up to 300 $\mu\text{g}/\text{g}$
	Fel d 4	No Measurements	$\sim 4 \mu\text{g}/\text{g}$
Mite	Der p 1	$\leq 0.068 \mu\text{g}/\text{m}^3$	0.3 – 30 $\mu\text{g}/\text{g}$
	Der p 2	$\leq 0.026 \mu\text{g}/\text{m}^3$	0.2 – 5 $\mu\text{g}/\text{g}$
	Der p 23	Too Low to Measure	$\leq 1 \mu\text{g}/\text{g}$

Ratios of IgG4: IgE antibodies to Cat Dander, Fel d 1 and Fel d 4 in ng/ml among individuals with a cat at home or not; and with or without asthma.



Intra- and Inter- Molecular Epitope Spreading

There is extensive evidence that clinically relevant IgE responses include IgE to multiple epitopes on “major” allergens: involving **Intra-molecular epitope spreading: certainly true for Fel d 1 and Der p 1.**

Epitope spreading from one protein to others from the same source may be equally important; that is **Inter-molecular epitope spreading**

What we appear to be looking at here is a major difference in **inter-molecular epitope spreading** between IgE and IgG4 antibodies to cat or mite components.

Hypothesis: The low or absent IgG4 response to some protein allergens (eg. Der p 2, Der p 23, and Fel d 4) could be the reason why some of these allergens have a greater role on symptoms including asthma.

Specific IgG4 to Dust Mite Components in 248 Mid-Teens With or Without Positive IgE or Current Asthma

		Total Group	Specific IgE Positive	Specific IgE Negative
Dust Mite	Overall	212/248 (85%)	126/141 (89%)	86/107 (80%)
	Asthma	74/84 (88%)	49/52 (90%)	25/32 (78%)
	No Asthma	138/164 (84%)	77/89 (89%)	61/75 (81%)
Der p 1	Overall	167/248 (67%)	67/88 (76%)	100/160 (62)
	Asthma	66/84 (78%)	28/31 (90%)	38/53 (58%)
	No Asthma	101/164 (61%)	39/57 (68%)	62/107 (58%)
Der p 2	Overall	50/248 (20%)	44/94 (46%)	6/154 (4%)
	Asthma	20/84 (24%)	19/27 (50%)	1/47 (2%)
	No Asthma	30/164 (18%)	25/57 (50%)	5/107 (5%)
Der p 23	Overall	13/248 (5.2%)	6/68 (9%)	7/180 (3.8%)
	Asthma	1/84 (1.2%)	1/26 (4%)	0/58 (0%)
	No Asthma	12/164 (7.3%)	5/42 (12%)	7/122 (6%)

KEY MESSAGES RELATED TO SPECIFIC IgG4 FOR MITE AND CAT ALLERGENS and ASTHMA

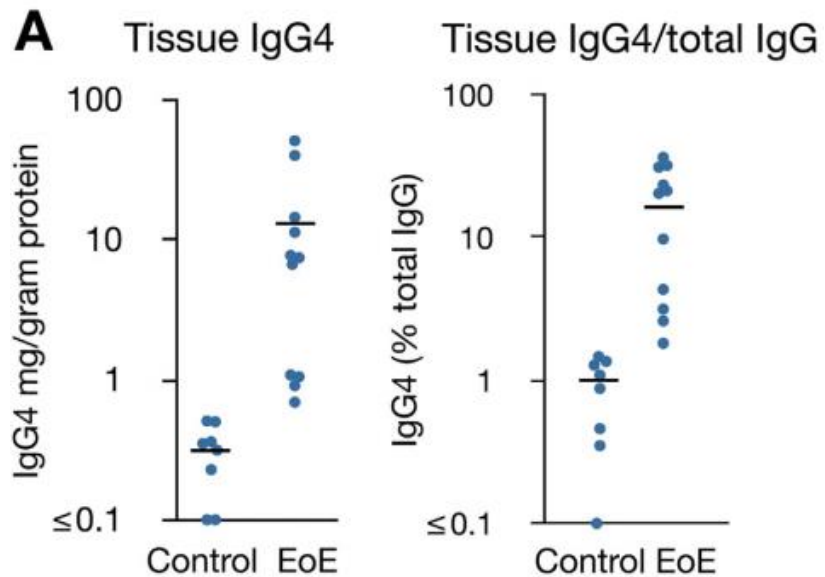
- The clinical tolerance to cats that can occur in children who are exposed to high levels of cat allergen is associated with high specific IgG4 antibodies to cat allergen. However, the high levels for IgG4 are specific for Fel d 1, but not Fel d 4 or Fel d 7.
- Our results show that a high prevalence of sIgG4 to mite allergens is seen with Der p 1 but is less to Der p 2 and absent for Der p 23.
- The implication is that the less abundant allergens, particularly Fel d 4, Der p 2, and Der p 23, have stronger associations with asthma because they induce less IgG4 relative to IgE.

Platts-Mills , Keshavarz, Wilson,et al eBioMedicine –Lancet discovery science. Vol 112: 105556. Feb 2025

CLINICAL—ALIMENTARY TRACT

Eosinophilic Esophagitis in Adults Is Associated With IgG4 and Not Mediated by IgE

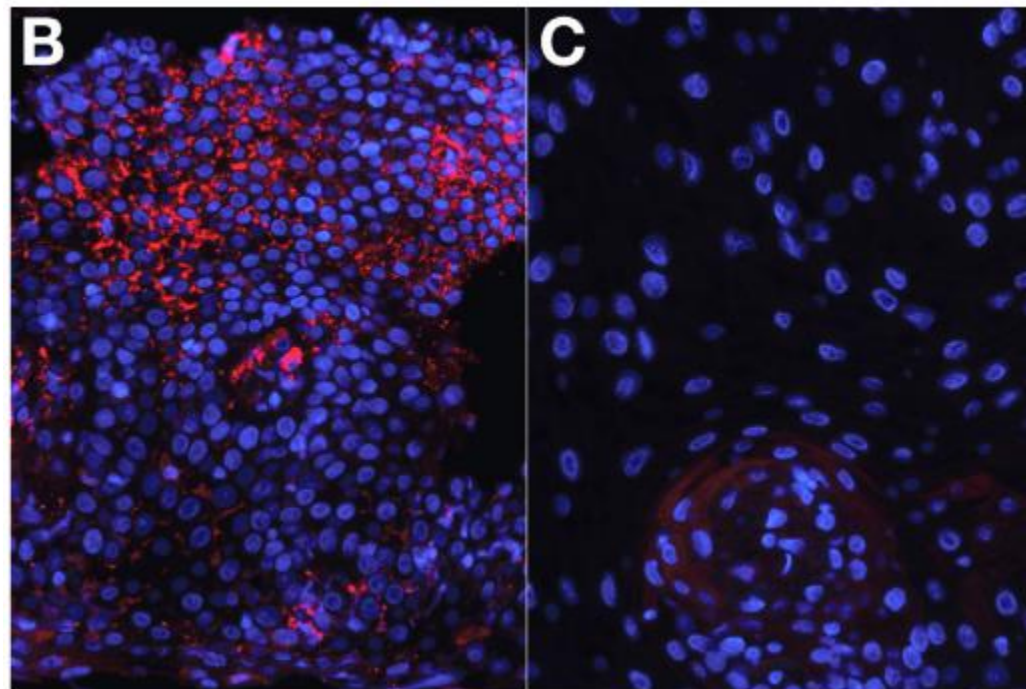
Frederic Clayton...Gerald J. Gleich...Kathryn A. Peterson :Gastroenterology 2014



IgG4 content of esophageal tissue homogenate in adults with EoE compared with control subjects

Adult with EoE

Control

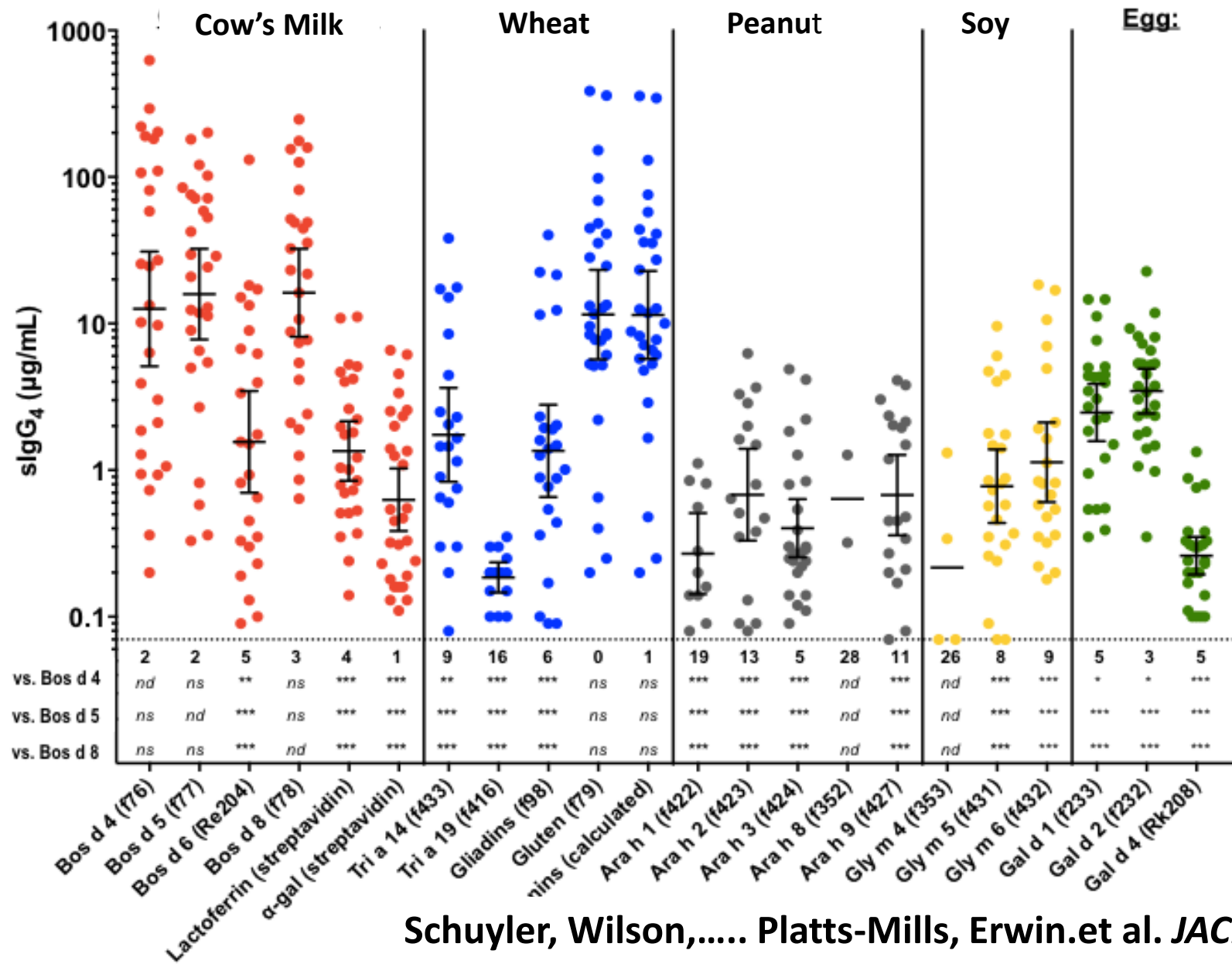


Red = granular intercellular IgG4

Blue = DAPI nuclear counterstain

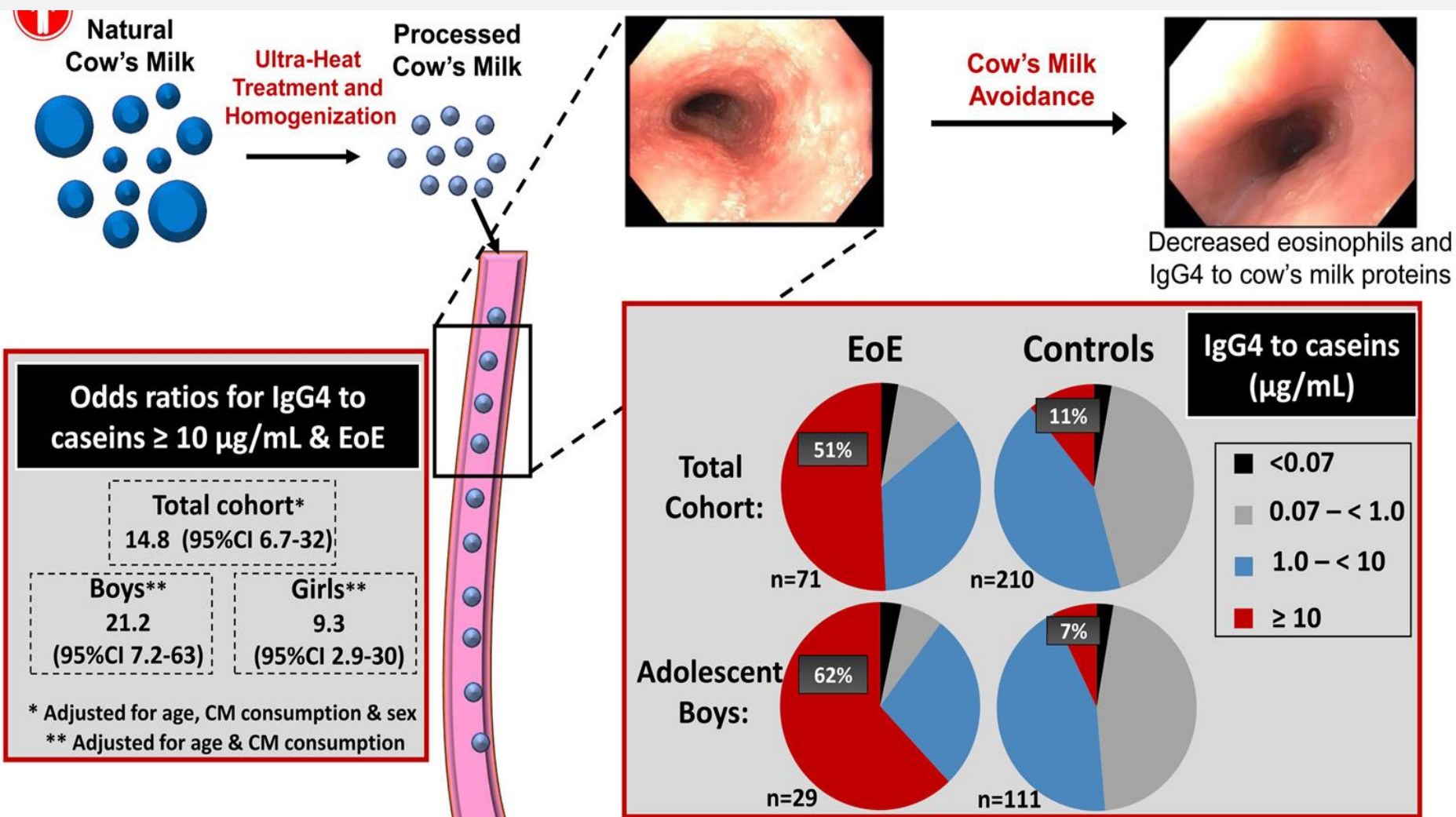
Co-staining for complement 9 (**Green**) is negative

Cow's milk proteins and gluten produce the highest levels of specific IgG₄ in 30 cases of pediatric EoE



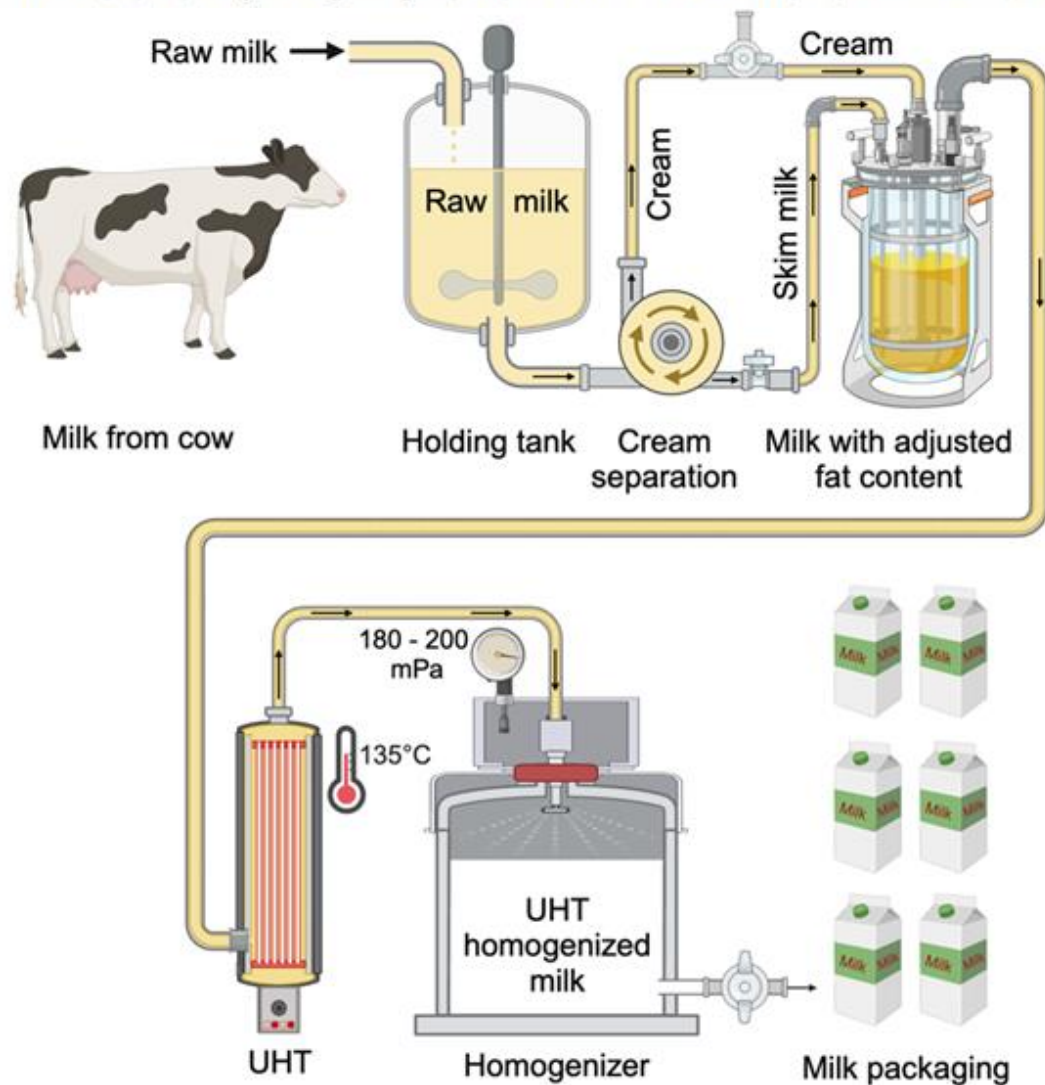
Schuyler, Wilson,..... Platts-Mills, Erwin.et al. *JACI* 2018

High titers of IgG4 to Cow's milk proteins are strongly associated with EoE in children age 13-18: controls from a birth cohort.

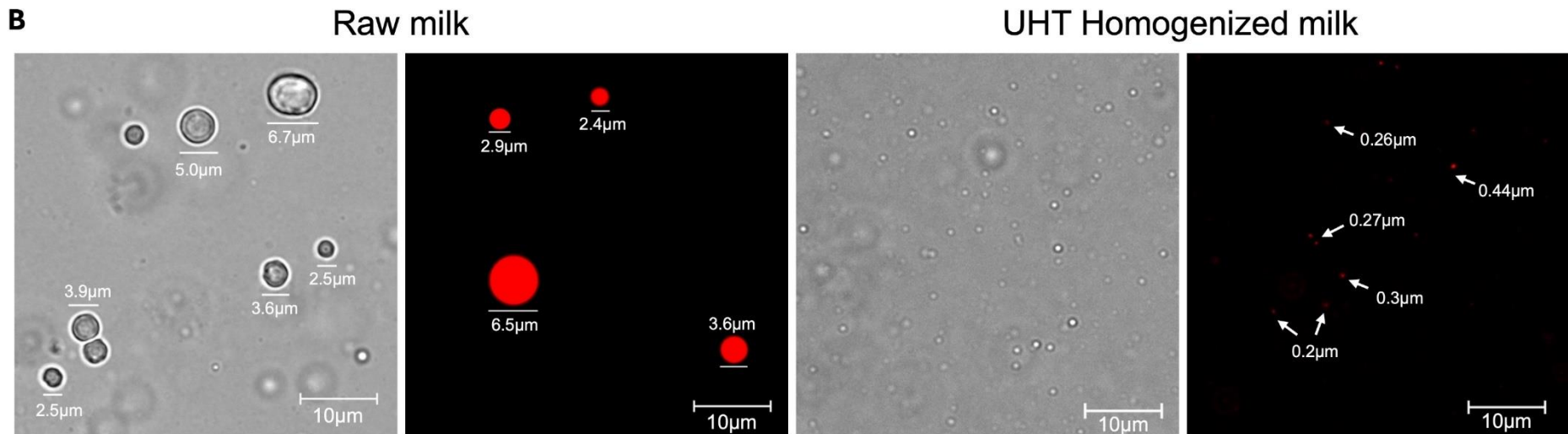
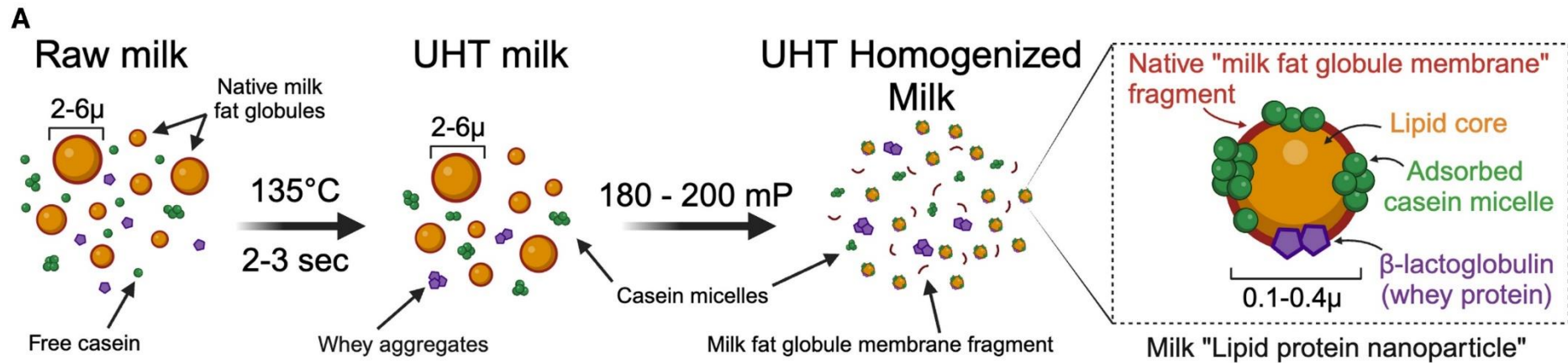


The processed milk hypothesis: A major factor in the development of eosinophilic esophagitis (EoE)?

James R. Baker, Jr, MD,^a Roopesh Singh Gangwar, PhD,^b and Thomas A. Platts-Mills, MD, PhD^c *Ann Arbor, Mich, and*

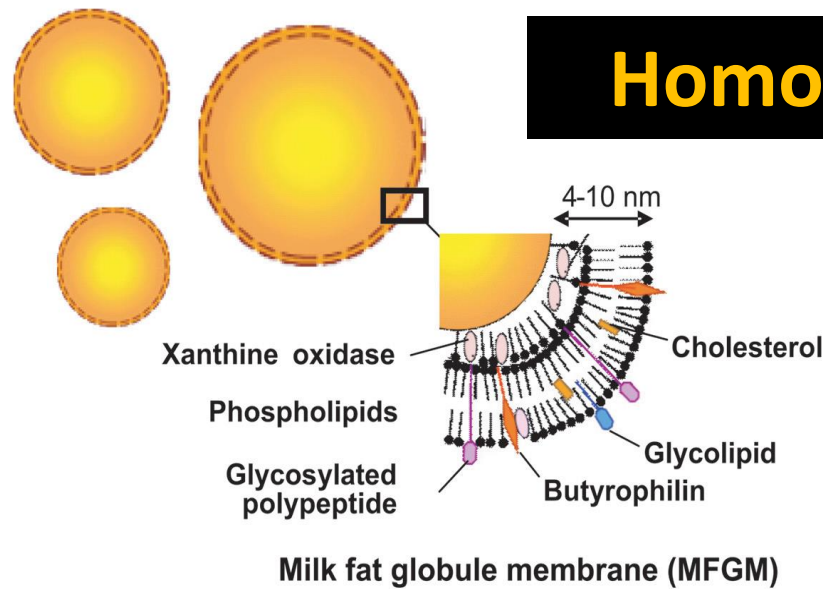


The processing of milk “Effectively weaponizes the fat droplets to immunize the esophagus”.

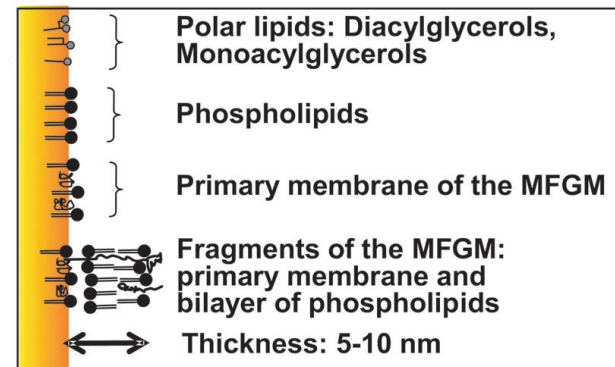
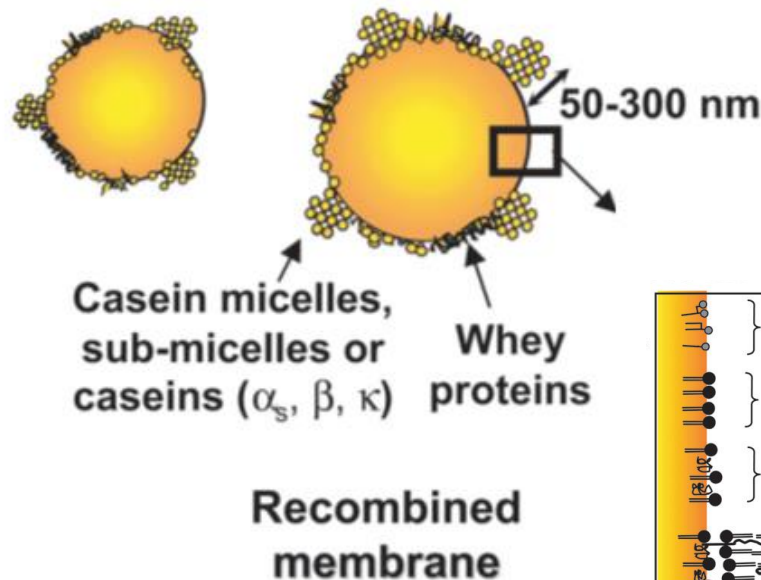


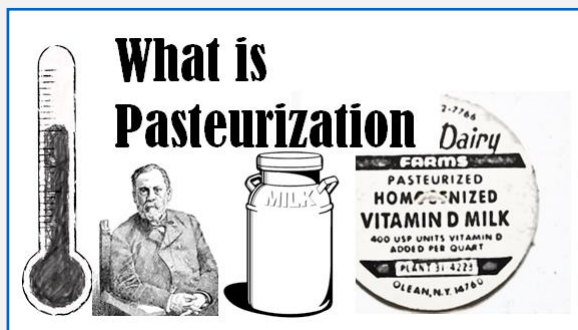
The Processed Milk Hypothesis; On Line JACI August 2024

(A) Natural milk fat globules
(mean diameter: 0.2-10 μm)

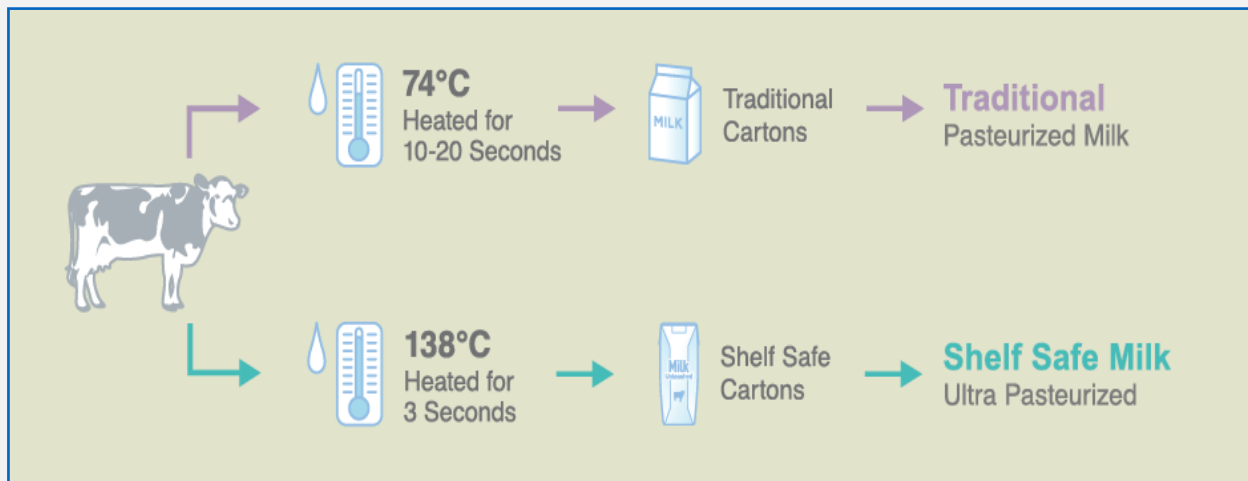


(B) Homogenized fat globules
(mean diameter: 0.2-2 μm)





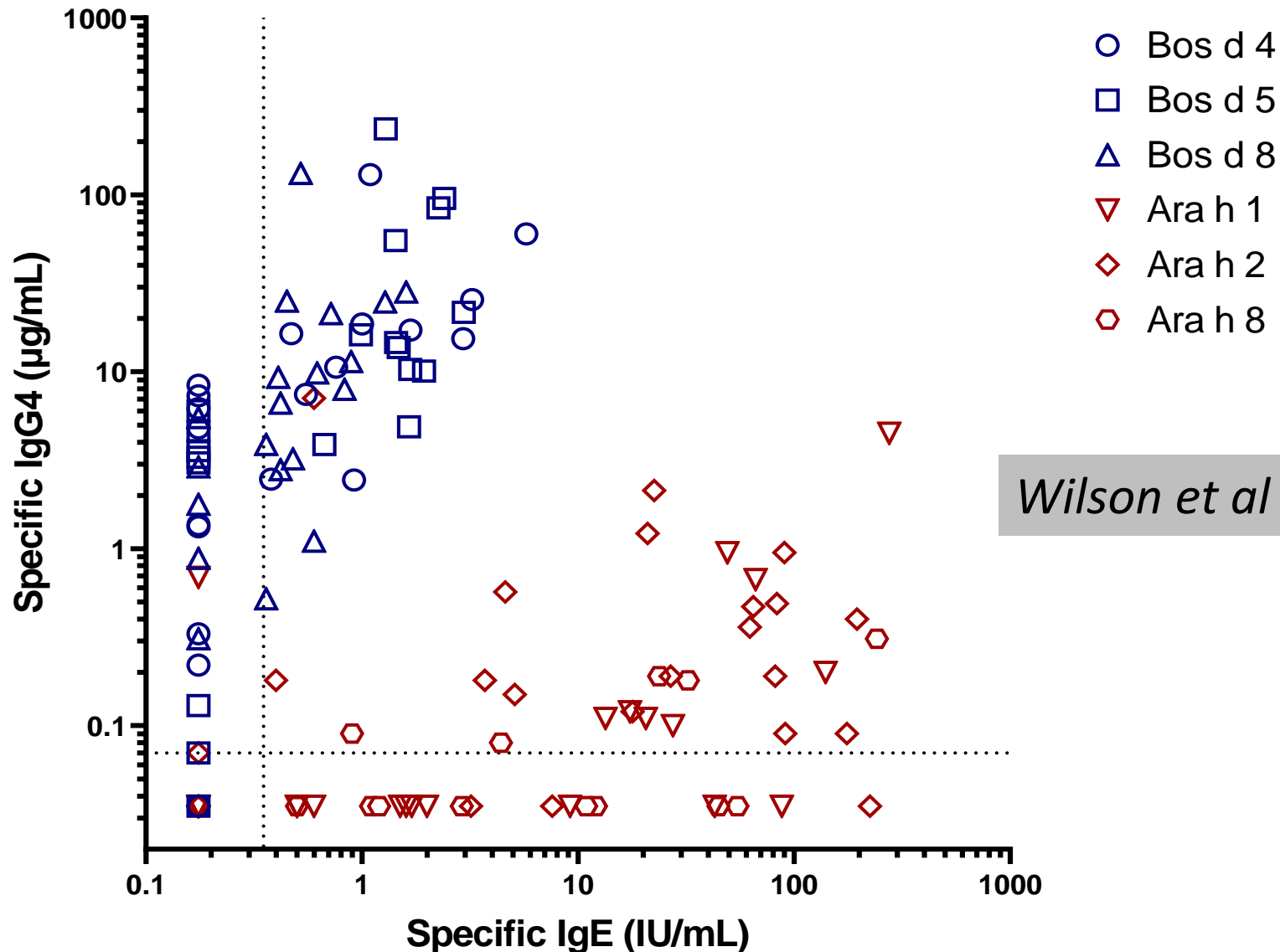
Pasteurization Methods vary by Temp and Time



Ultra pasteurized milk is more accurately described as DEAD

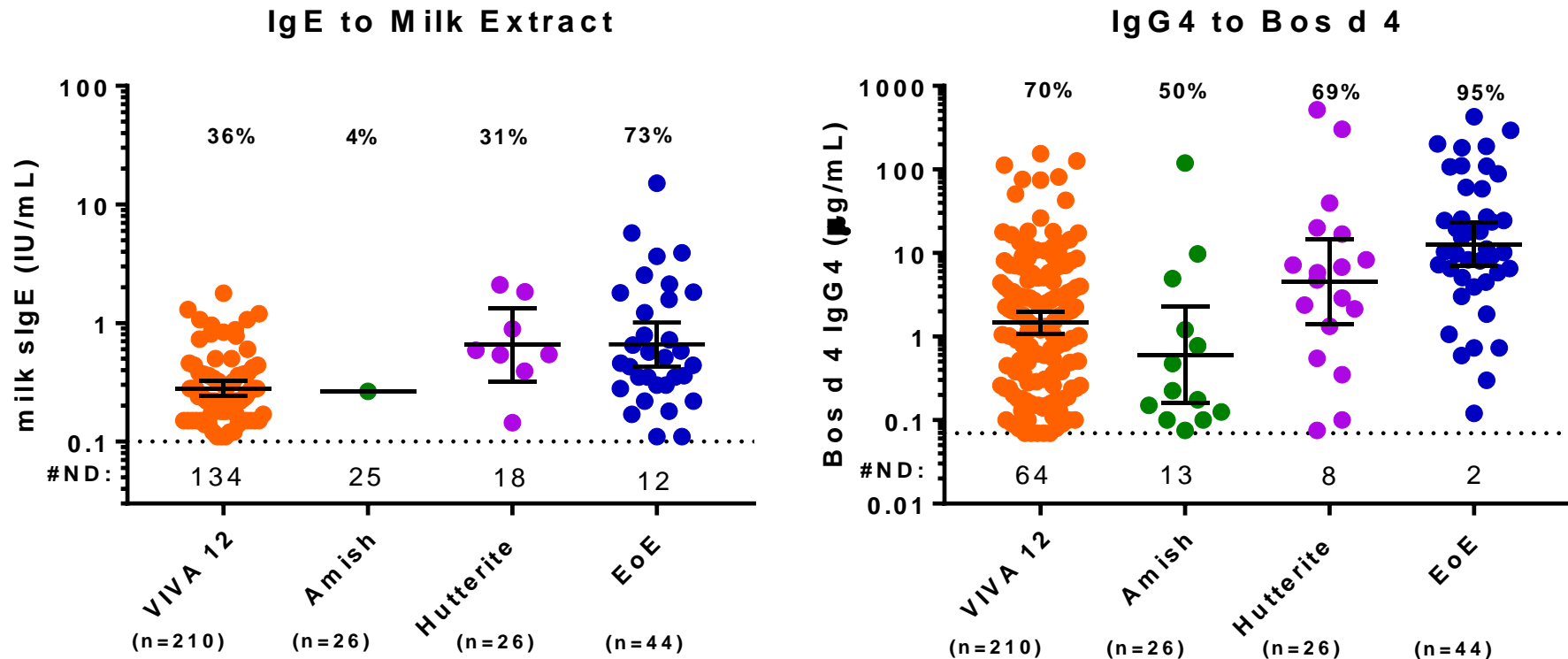
Country	percent
Austria	20.3
Belgium	96.7
Croatia	73 ^[12]
Czech Republic	71.4
Denmark	0.0
Finland	2.4
France	95.5
Brazil	88.1
Germany	66.1
Greece	0.9
Hungary	35.1
Ireland	10.9
Italy	49.8
Netherlands	20.2 ^[citation needed]
Norway	5.3
Poland	48.6
Portugal	92.9
Slovakia	35.5
Spain	95.7
Sweden	5.5
Switzerland	62.8
Turkey	53.1
United Kingdom	8.4

Milk proteins have a different IgG4/IgE 'signature' than peanut proteins: IgE+ve sera from Viva birth cohort age 7



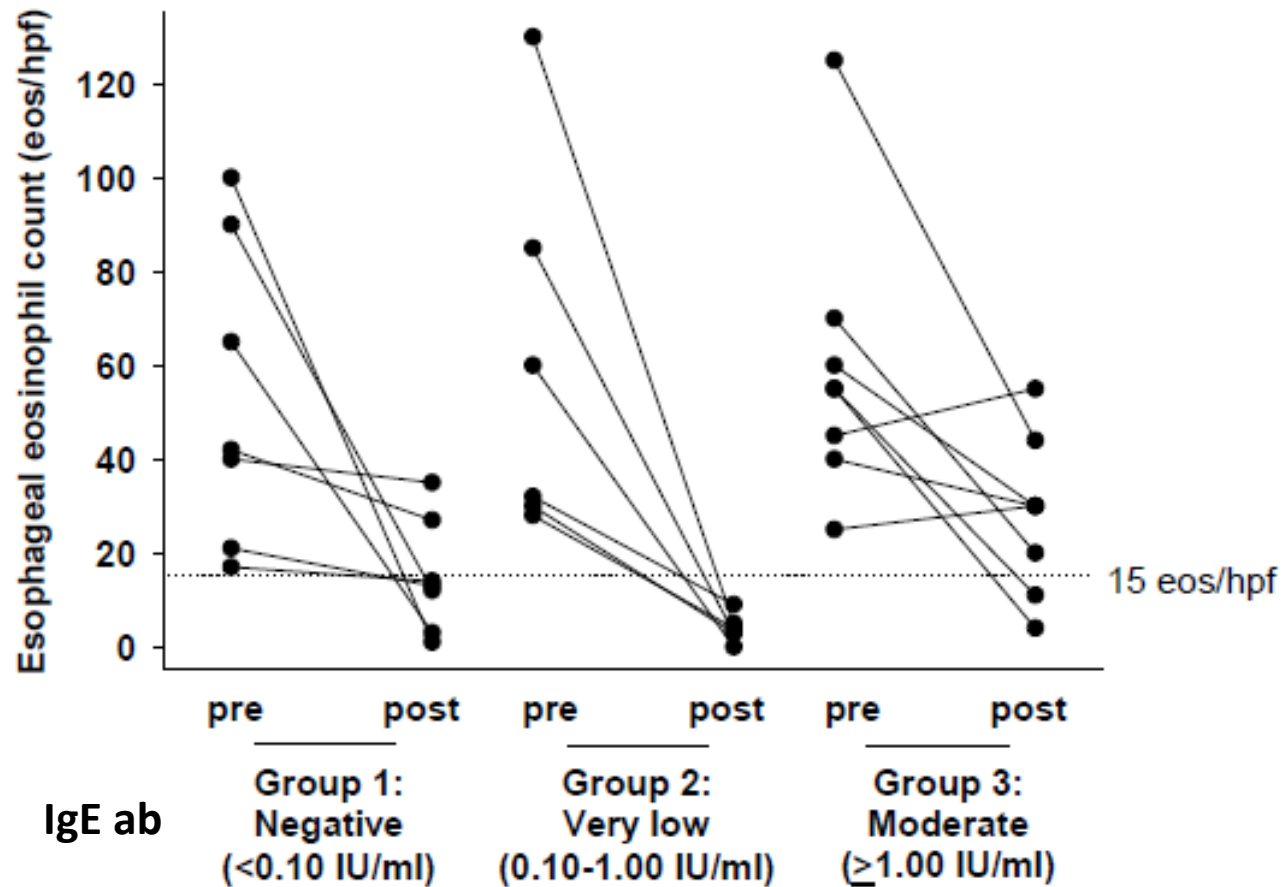
Wilson et al JACI 2017

IgE and IgG4 antibodies to Cow's Milk and the Cow's Milk protein Bos d 4 in sera from children with EoE age 10-15 compared to age similar controls and children from two Anabaptist communities in the USA



Sera curtesy Carol Ober from children studied in *Stein et al New England J Med 2016*

Histological response to six weeks Cow's milk avoidance in Children with Eosinophilic Esophagitis: responses are best in subjects with low titer IgE ab to milk...



Erwin et al : IgE to milk and response to milk free diet....JACI 2016

Erwin et al : IgE to food components in EoE... JACI in practice 2015

Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis

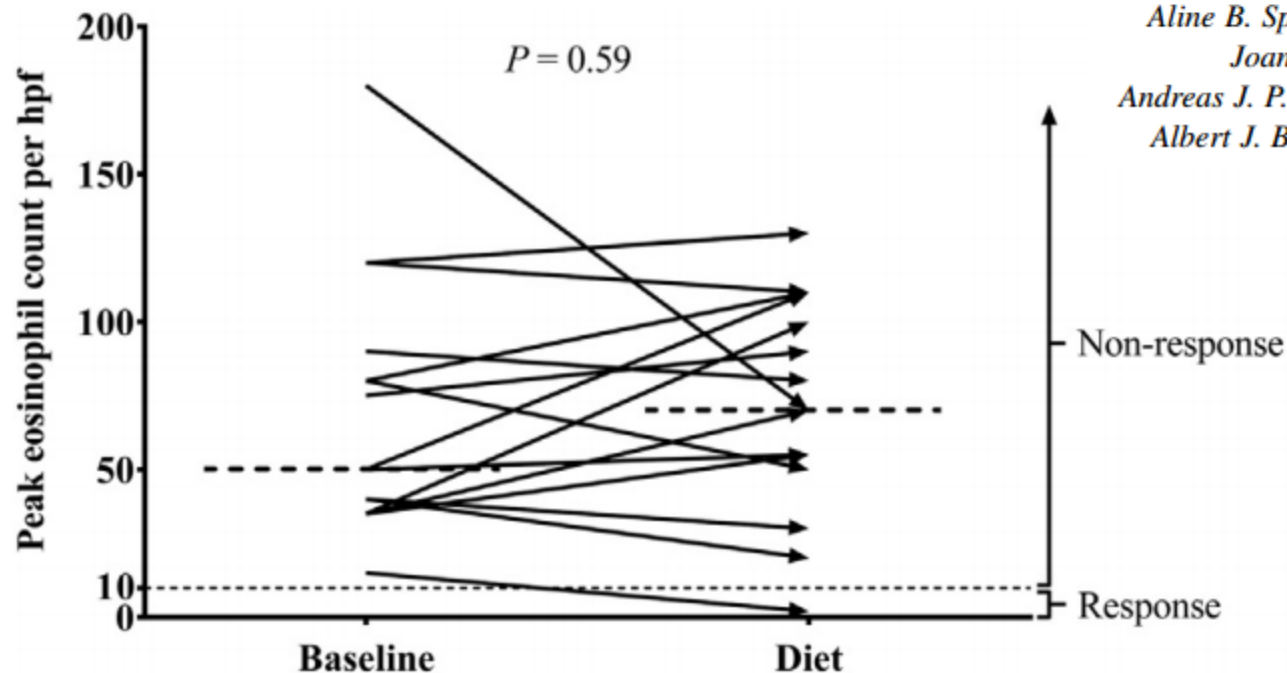
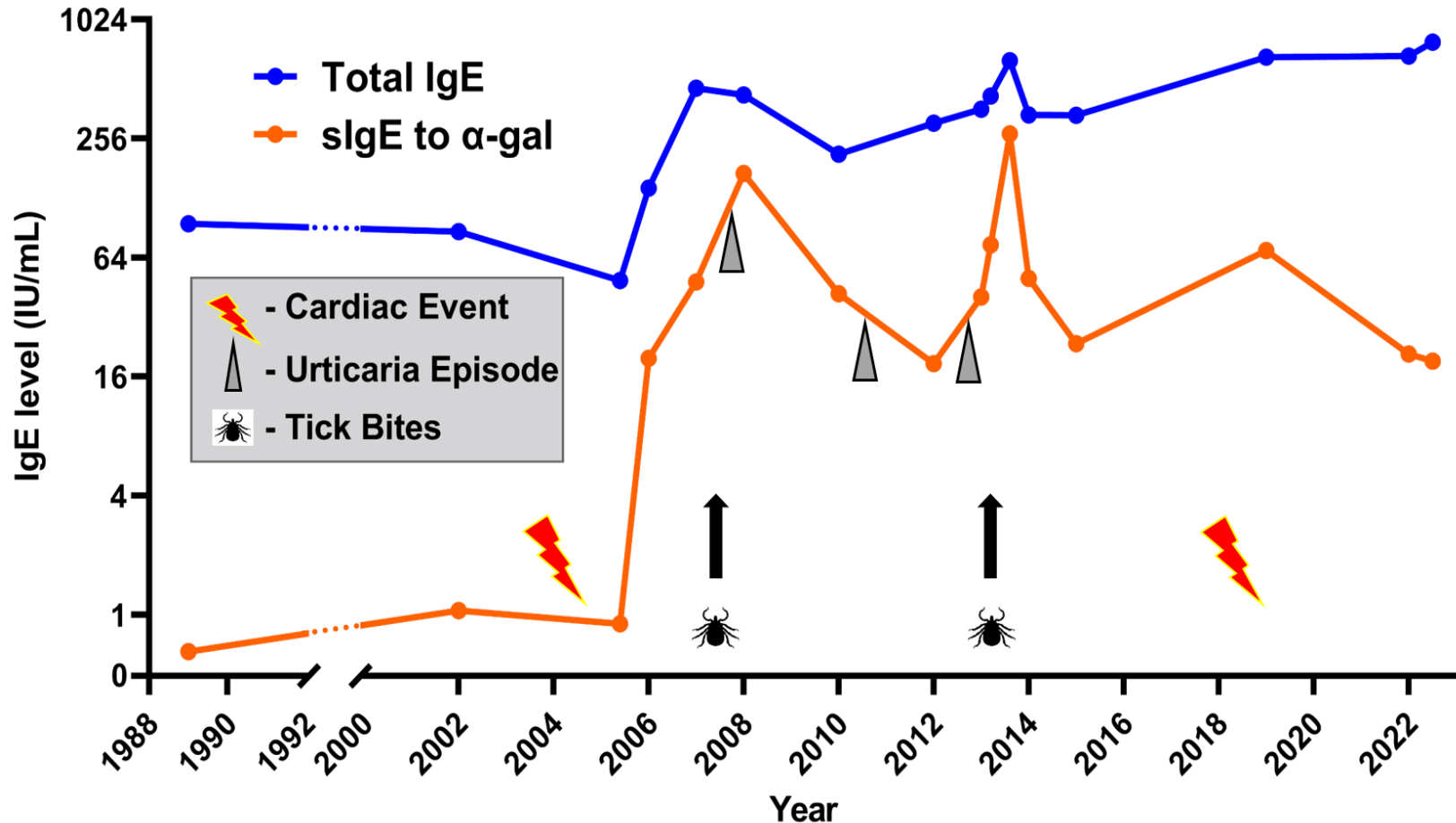
Bram D. van Rhijn, MD, PhD^aBerber J. Vlieg-Boerstra, PhD, RD^bSerge A. Versteeg, BSc^cJaap H. Akkerdaas, PhD^cRonald van Ree, PhD^{c,d}Ingrid Terreehorst, MD, PhD^dAline B. Sprickelman, MD, PhD^bJoanne Verheij, MD, PhD^eAndreas J. P. M. Smout, MD, PhD^aAlbert J. Bredenoord, MD, PhD^a

FIG 1. Esophageal peak eosinophil counts in patients with EoE before and after the CRD-guided food elimination diet. One patient histologically responded to the diet. *Black dotted bars* indicate medians.

IgE to cow's milk proteins were undetectable using ISAC in 14/15 adults and diet that did not exclude cows milk failed completely.

A thirty four year case report with tick bites, two cardiac events, delayed episodes of Urticaria, and major rises in both total and specific IgE.



Occasional tick bites have occurred in most years since 2010 with variable persistence of pruritis.

Longitudinal ImmunoCAP Results for Total IgE vs specific IgE, panIgG, IgG4 and IgG3 to galactose alpha-1,3-galactose

-----alpha-gal Specific Results* -----

sample ID/event	date of draw	total IgE kU/L	IgE kUA/L	pan IgG ug/ml	IgG4 ug/ml	IgG3 ng/ml
TPM 1989	1989	94.9	0.04	1.29	nd	287
TPM 2002	4/20/2002	49	0.51	0.71	nd	<100
1st cardiac event, 3/1/05						
Sugar Hollow tick bomb, 8/7/07						
E036a	5/21/2007	144	19.80	3.05	nd	210
E036o	4/2/2012	286	27.70	1.58	0.09	<100
Pasture Fence tick bomb, 8/25/13						
E036u	8/29/2013	334	40.50	nd	nd	nd
E036w	9/20/2013	633	89.30	7.59	0.09	243
2nd cardiac event, 8/19/18						
E036au	2/10/2021	575	26.40	6.03	nd	1303
E036bm	5/31/2023	781	14.50	5.88	0.33	1196
E036bp	9/21/2023	1350	116.00	19.6	4.76	9160
E036bs	3/20/2024	1171	60.50	6.11	nd	2322

nd = not determined

IgG4 LoD = <100ng/ml

*assayed using o215 CAP