Alimentary Myths

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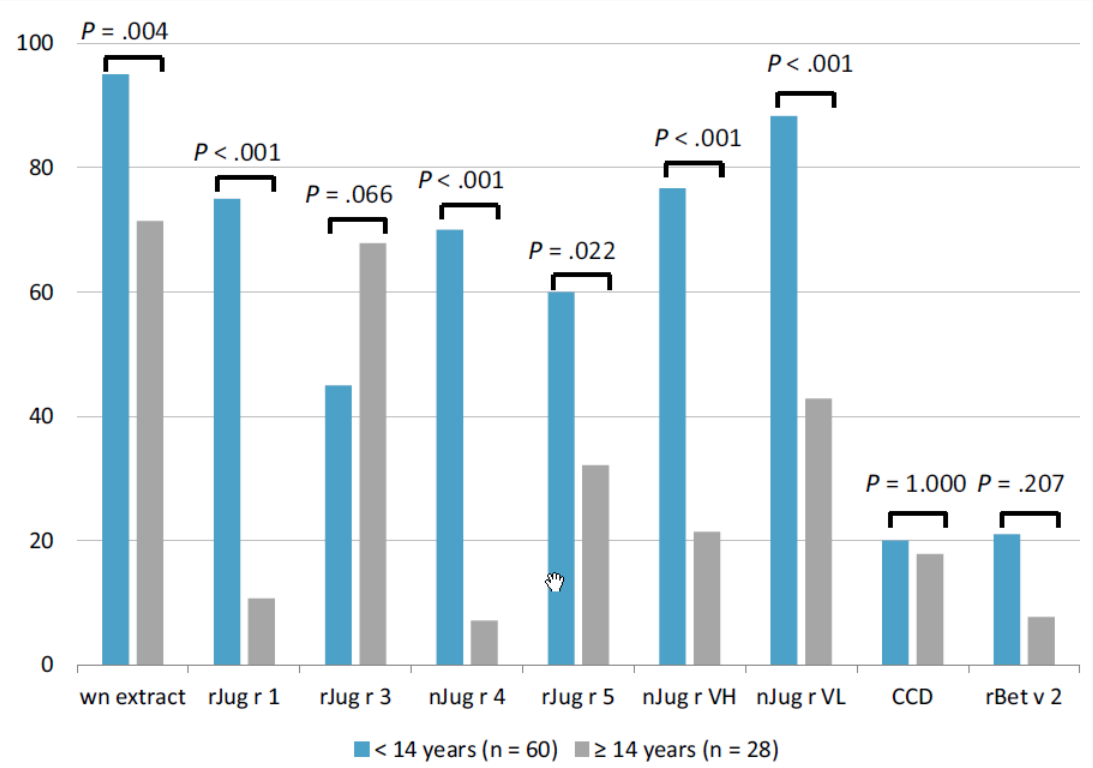
- **Primary food allergy is acquired in early childhood**
  Food allergy in adults is mediated by primary sensitisation to inhalant allergens

- **High sensitivity and high negative predictive value of extract based diagnostic tests in primary food allergy and a low sensitivity of extract based diagnostic tests particularly in birch pollen related food allergy**

Allergen Recognition Patterns in Walnut Allergy Are Age Dependent and Correlate with the Severity of Allergic Reactions

Barbara K. Ballmer-Weber, MD[a,b,c], Jonas Lidholm, PhD[d], Lars Lange, MD[e], Mariona Pascal, PhD[f], Claudia Lang, MD[a,b], Sunhild Gernert, MD[e], Jaime Lozano-Blasco, MD[g], Nora Gräni, MD[a,b], Caroline Guillod, MD[a,b], Andrea Wangorsch, PhD[h], Kay-Martin Hanschmann, MSc[h], Bo Pontoppidan, PhD[d], Linda Tjäder, MSc[d], Joan Bartra, MD[i], and Stefan Vieths, PhD[h]

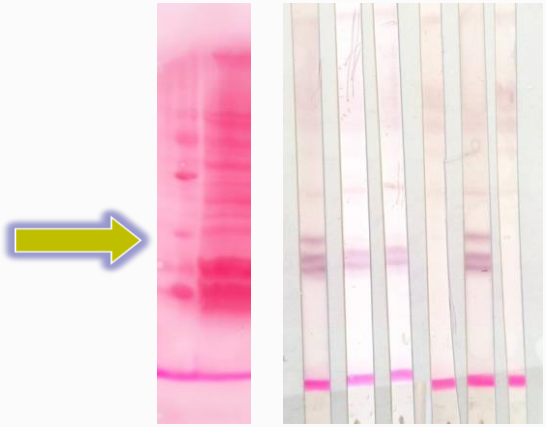
JACI in pract 2019



Identification and implication of an allergenic PR-10 protein from walnut in birch pollen associated walnut allergy

Andrea Wangorsch[1], Annette Jamin[1], Jonas Lidholm[2], Nora Gräni[3], Claudia Lang[3], Barbara Ballmer-Weber[3,4], Stefan Vieths[1] and Stephan Scheurer[1]

Mol Nutr Food Res 2017



- Walnut Tris-HCl-Extract
- 1. BB 11 without inhibitor
- 2. BB 11 + 10µg/ml rJug s PR10
- 3. BB 11 + 50µg/ml rJug s PR10
- 4. BB 11 + 1mg/ml walnut extract (25mM Tris-HCl, 150mM NaCl)
- 5. BB 11 + 50µg/ml BSA
- 6. 2.Ab control

15 CH patients with positive OFC with walnut
sensitisation to walnut extract: 40%
sensitisation to rJug r 5: 93%

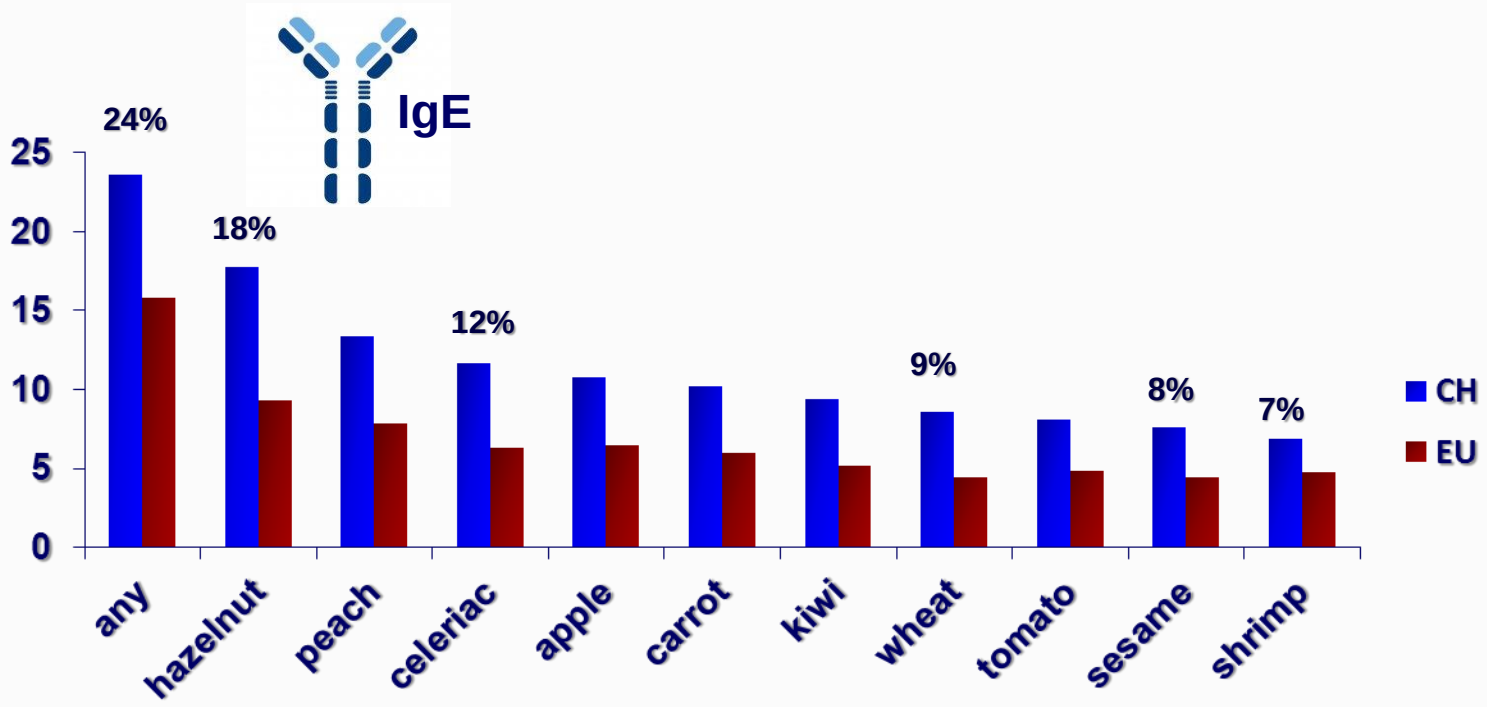
AA sequence identity: 67% with Bet v 1.01
74% with Mal d 1

Directive 2003/89/EC and Directive 2006/142/EC
14 allergenic ingredients must be declared

- Cereals	- Nuts
- Crustaceans	- Celeriac
- Fish	- Mustard
- Egg	- Sesame seed
- Peanut	- Sulphur dioxide/sulphites
- Soybean	- Lupin
- Milk	- Molluscs

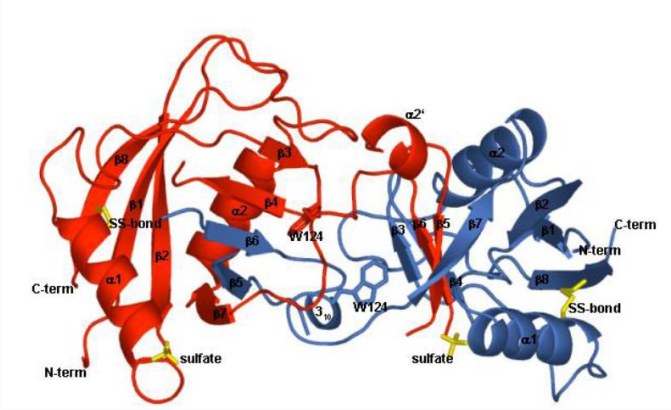
*and products thereof

Prevalence of sensitization to foods in Europa (adults)



Burney et al Allergy 2014

Cyclophilin – a novel cross-reactive determinant in PN



Asp f 11

Analysis of 15 sera with IgE to peanut but not to Ara h 1,2,3,6,8,9, CCD, profilin

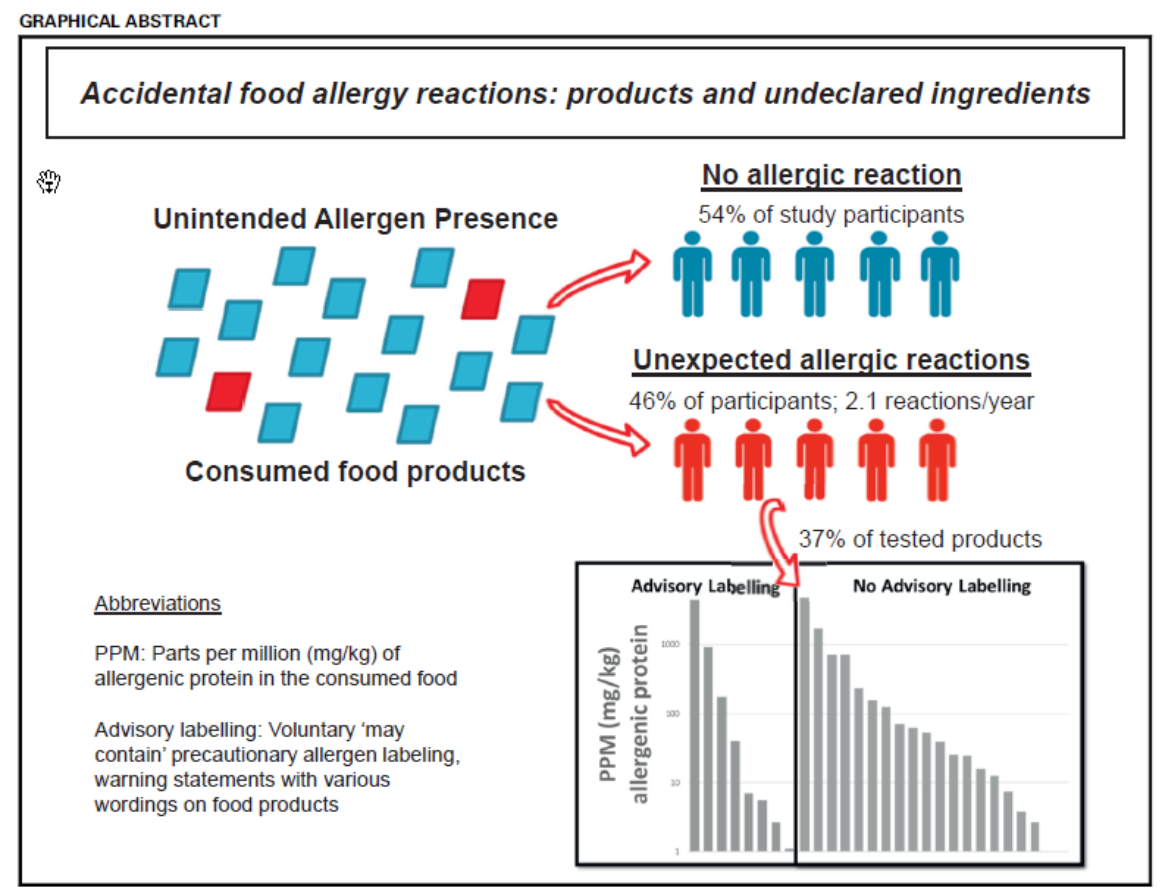
IgE to PN extract inhibited by grass pollen

→ **identification and characterisation:**
peanut cyclophilin
new pollen-related peanut allergen

Birch pollen (Bet v 7), olive pollen (Ole e 15)
molds (Asp f 11,27, Mala s 6), mites (Der f 29)
carrot, tomato (Sola a 11),……

Mattsson , Lidholm et al , abstract EAACI 2018
Molecular allergy guide, PAI 2016

Accidental food allergy reactions: Products and undeclared ingredients

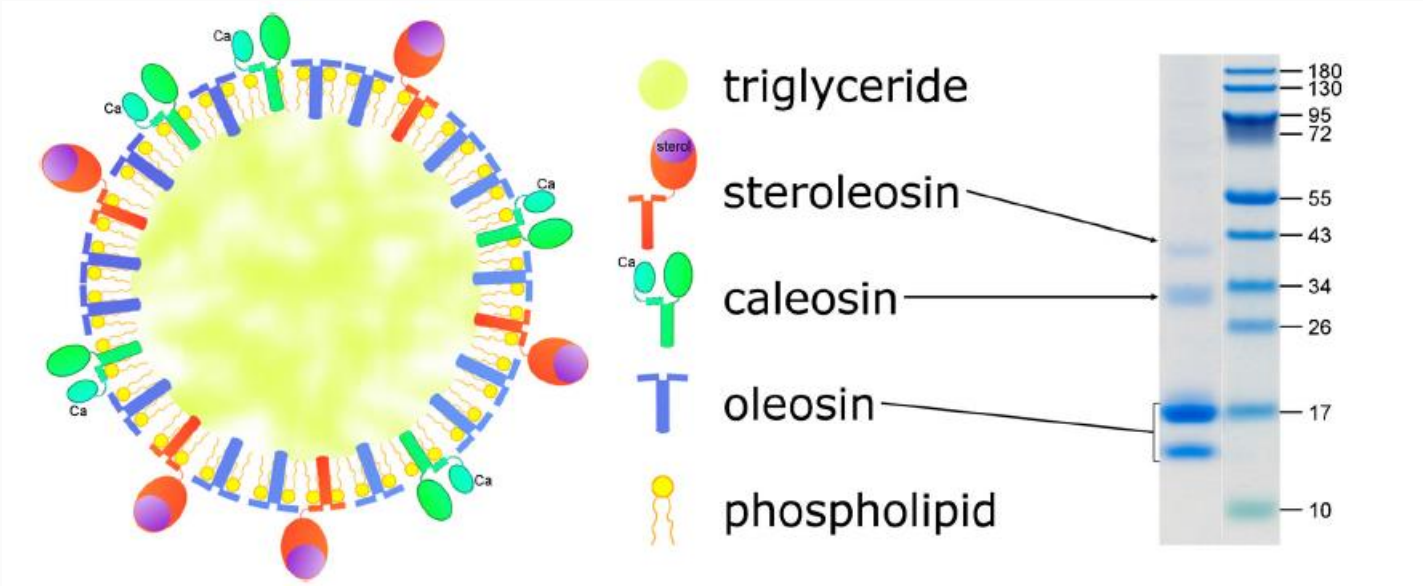


157 food allergics
n=73 patients with 151 accidental reactions/y
51 food samples analysed

- **Milk**
- **Peanut**
- **Sesame**
- **Hazelnut**
- **Pecan nut**
- **Walnut**
- **Hen's egg**
- **Celeriac**

Blom et al JACI 2018

Relevance of Oleosins?

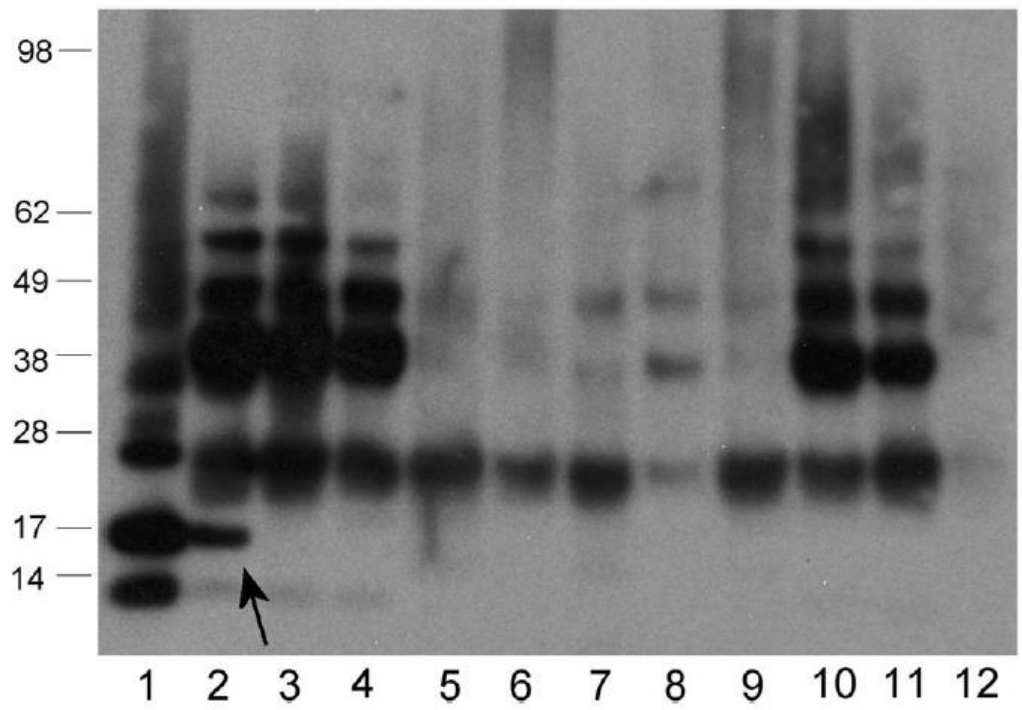


Schematic model of an oil body

peanut: Ara h 10/11/14/15
sesame: Ses i 4/5
hazelnut: Cor a 12/13

Uta Jappe et al. Curr Allergy Asthma Rep 2017

Oleosins are lipophilic proteins and may not be well represented in aqueous extracts



Immunoblot with rabbit-anti-OAP

1: natural HN-OAP-Fraktion
2: HN-extract, not defatted
4-12: commercial HN-extract

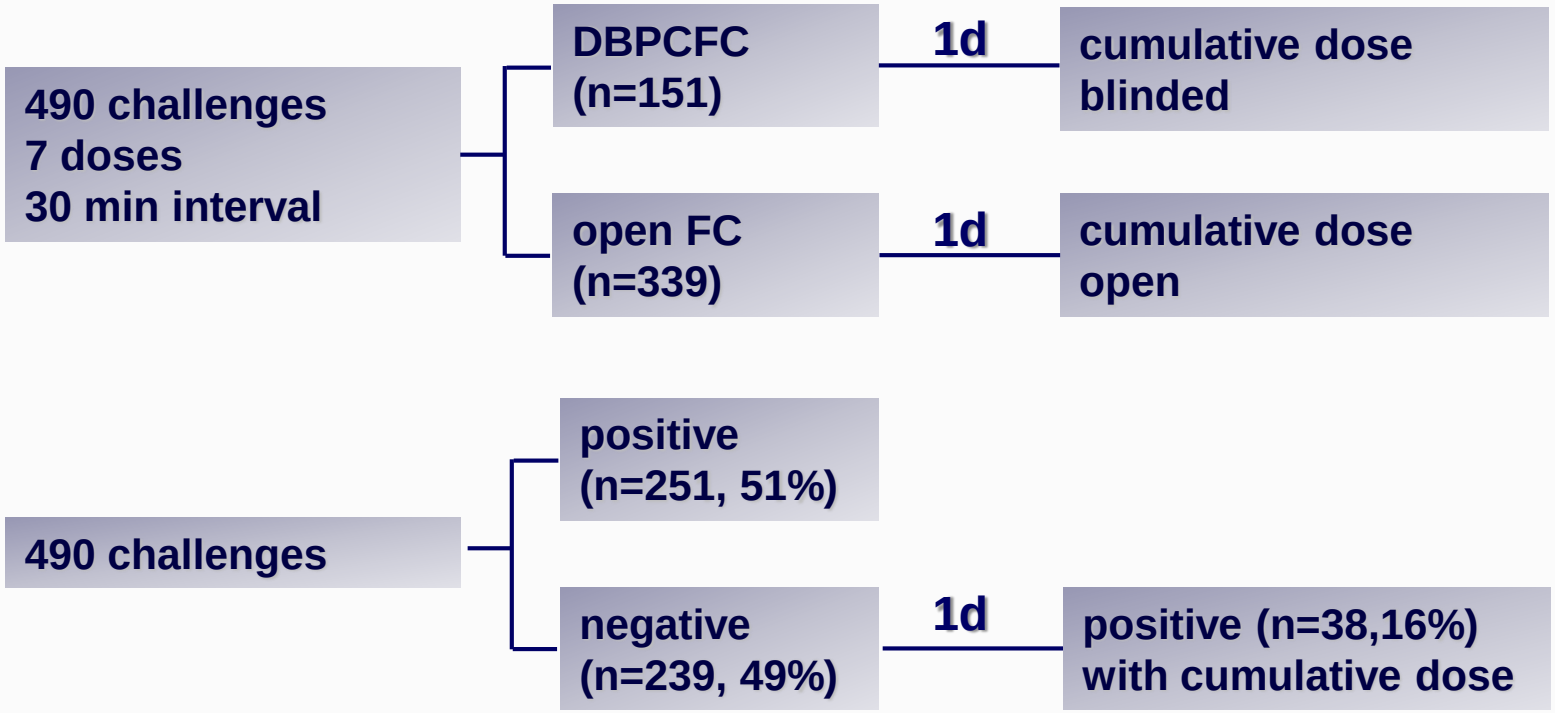
Cor a 12: 17kDa
Cor a 13: 14 kDa

Zuidmeer et al. Clinical and translational Allergy 2014

- **Double blind placebo controlled food challenge is the gold standard of food allergy diagnosis**

Accurate oral FC requires a cumulative dose on a subsequent day

Niggemann et al. JACI 2012

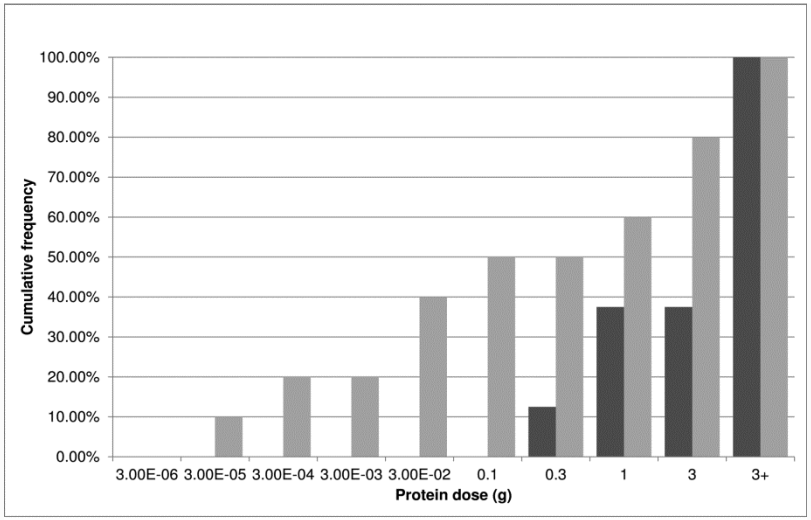


Mol Nutr Food Res. 2012 Sep 19. doi: 10.1002/mnfr.201200330. [Epub ahead of print]

High fat food increases gastric residence and thus thresholds for objective symptoms in allergic patients.

Mackie A, Knulst A, Le TM, Bures P, Salt L, Mills EN, Malcolm P, Andreou A, Ballmer-Weber BK.

Cumulatived threshold for objective symptoms in 6 allergics with hazelnut or peanut allergy



dessert matrix

chocolate bars

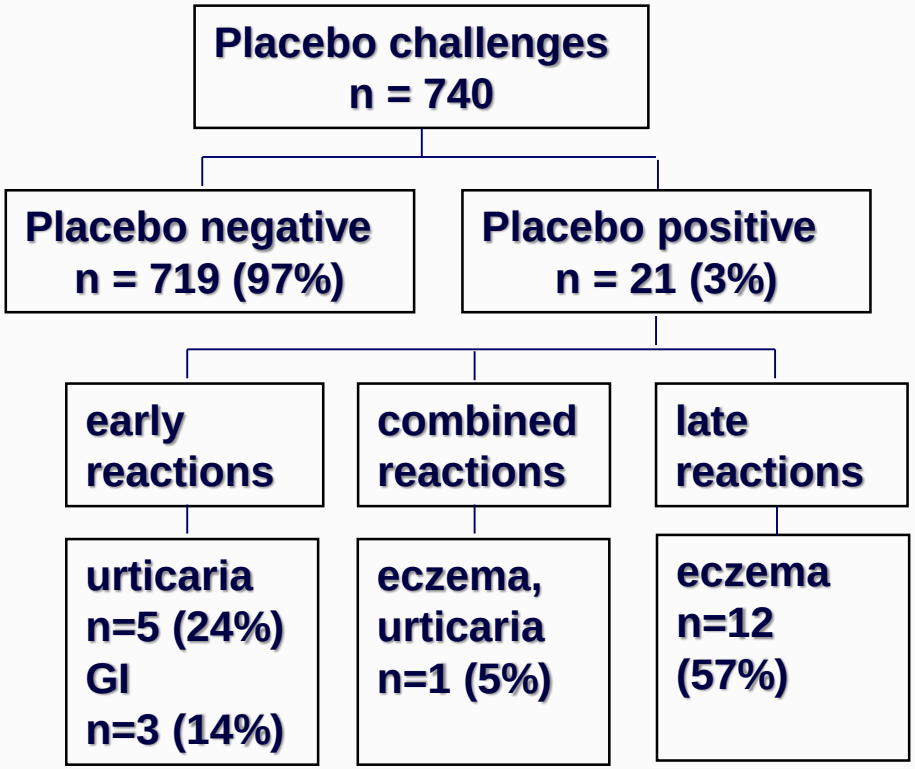
Higher threshold with chocolate bars than dessert matrix

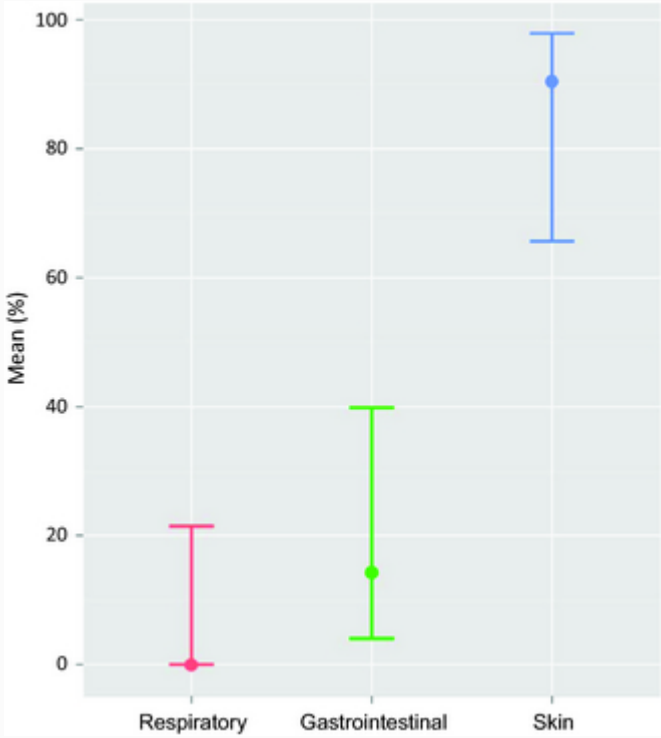
Lower gastric emptying with chocolate bars (MRI)

EuroPrevall

Positive reaction to placebo in children

Ahrens et al. Clin Exp Allergy 2014



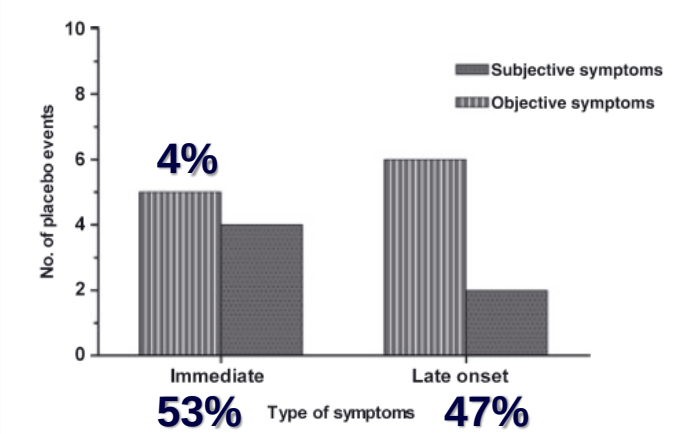


Positive reaction to placebo

Placebo challenges in children (n = 132)

- **Placebo negative n = 115 (87.1%)**
- **Placebo positive n = 17 (12.9%)**

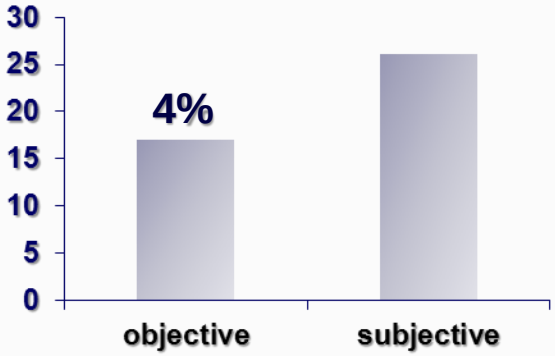
Vlieg-Boerstra et al Allergy 2007



Placebo challenges (n = 436)

- **Placebo negative n = 393 (90%)**
- **Placebo positive n = 43 (10%)**

Ballmer-Weber et al. JACI 2015



EuroPrevall

Anxiety and Depression Effects During Drug Provocation Test

JACI in pract 2018

Laura Michelina Losappio, MD, PhD[a], Alessandra Cappai, MD[b], Alessandra Arcolaci, MD[c], Iuliana Badiu, MD[d], Patrizia Bonadonna, MD, PhD[e], Elisa Boni, MD[f], Claudia Bussolino, MD[g], Marco Caminati, MD[e], Pietro Galati, MD[h], Enrico Heffler, MD, PhD[i], Rossella Intravaia, MD[j], Marina Mauro, MD[k], Ilaria Massaro, MD[l], Antonino Romano, MD[m], Gabriele Rumi, MD[m], Anna Parolo, MD[n], Stefano Pizzimenti, MD[o], Michele Nichelatti, PhD[p], and Elide Anna Pastorello, MD[a] *London, UK; and Milano, Cagliari, Cuneo, Verona, Casale Monferrato, Torino, Bologna, Catania,*

196 patients, investigating for drug allergy
Hospital anxiety and depression sale (questionnaire with 2x7 questions)
Drug provocation: placebo-4doses of drugs

60 patients abnormal HADS score (90% females)
54 patients (28%) placebo reaction (pruritus, asthenia, dyspnea)

Placebo reaction correlated significantly with
- history of severe reaction ($p<0.001$)
- abnormal HADS score ($p<0.001$): OR 117.

Is food challenge, in paticular DBPCFC the gold standard of food allergy diagnosis?

False negative food challenges:

- drugs
- missing cofactors
- blinding/matrix
- induction of short term non-reactivity

False positive food challenges:

- reaction to a matrix component
- placebo reactions

- **Bet v 1 mediated food allergy is always mild**

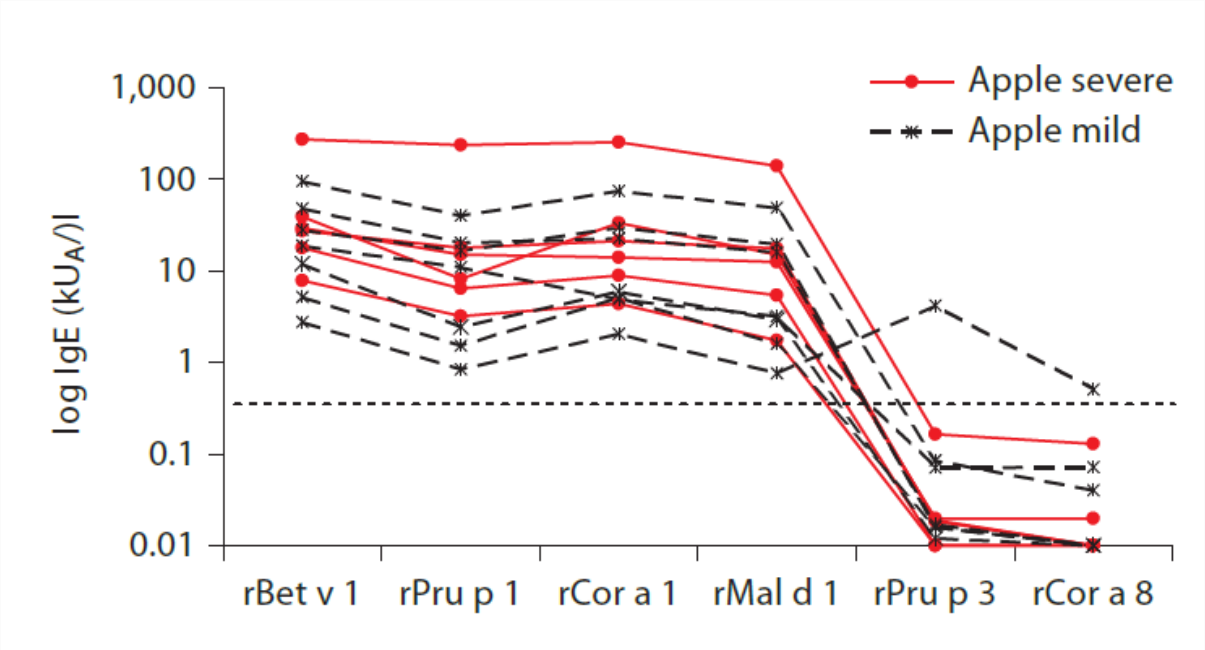
DBPCFC with rMal d 1

Bolhaar et al. Clin Exp Allergy 2005

rMal d 1 dose (mg)	patient 1	patient 2
0.01	neg	OAS 10
0.10	OAS 10	OAS 25
1.00	OAS 60	OAS 60 Pf↓ 50% hoarsness,cough

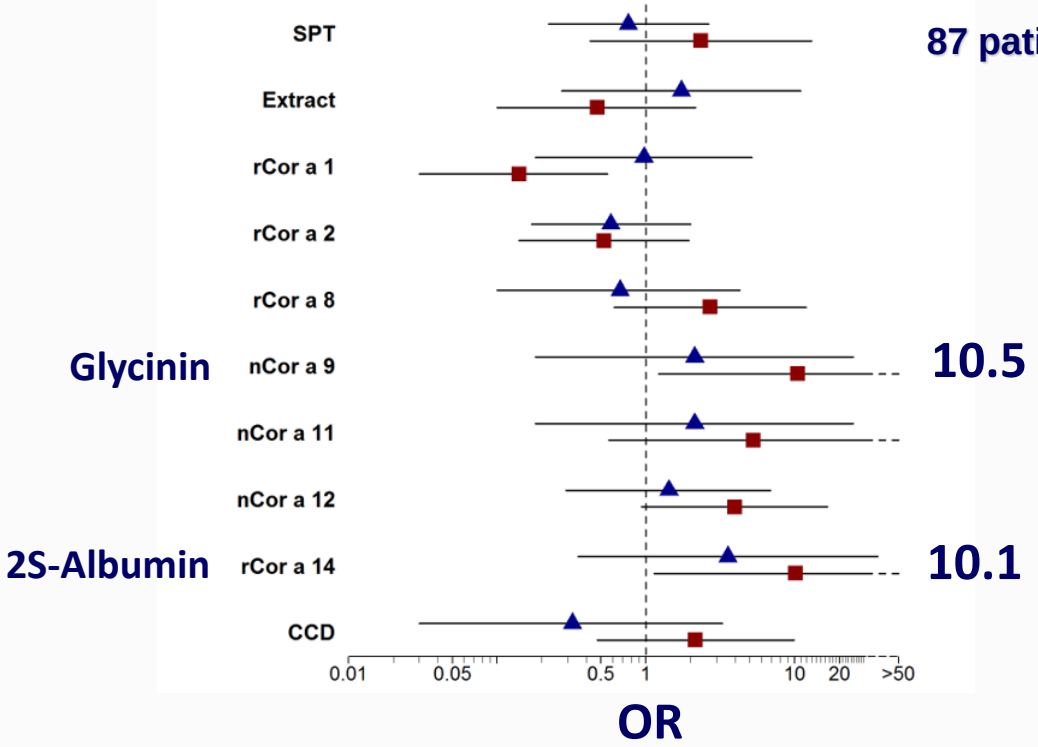
Anaphylactic reactions to apple in a birch-endemic area

Le et al. Int Arch Allergy Immunol 2013



Europrevall: CRD hazelnut allergy

87 patients DBPCFC+ve & 22 anaphylaxis cases

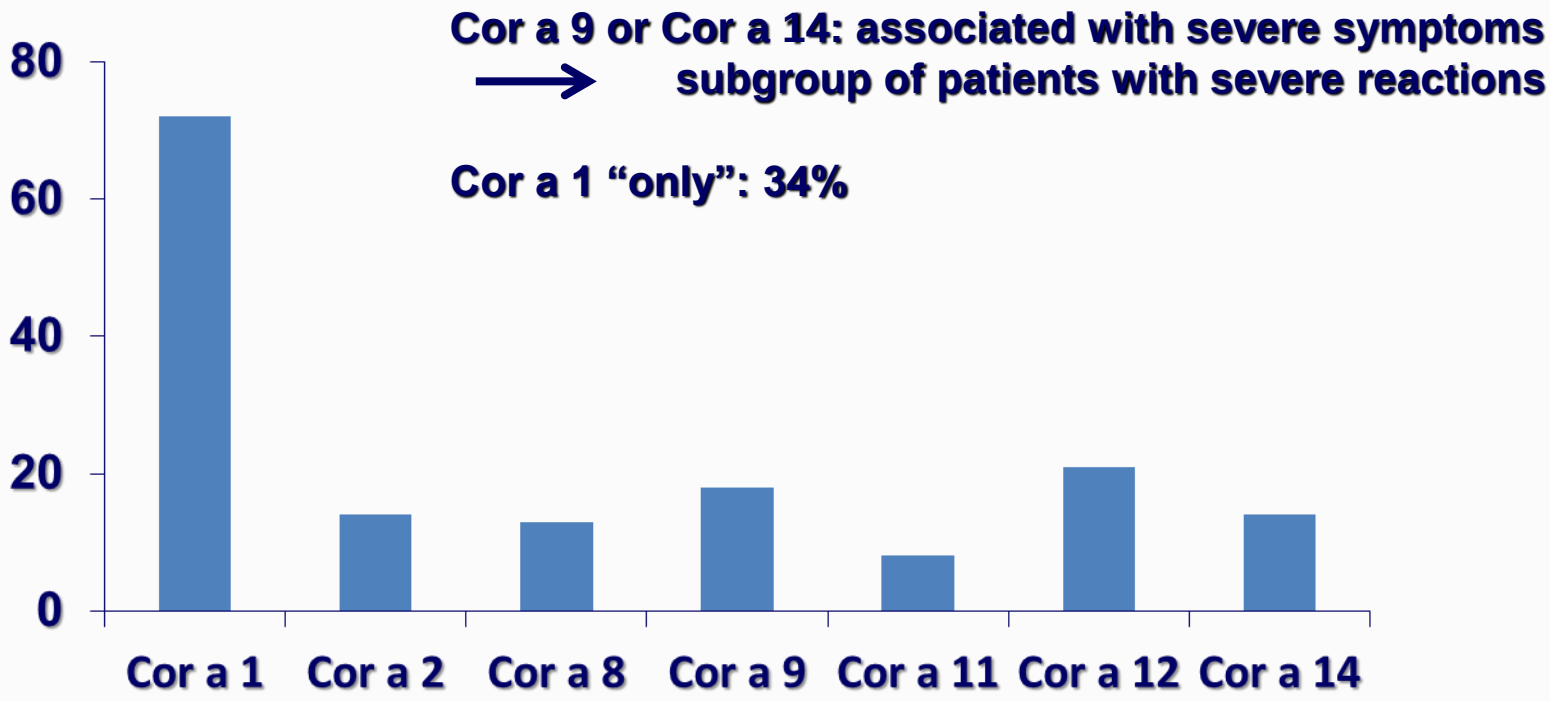


▲ «moderate»

■ «severe»

Datema et al. Allergy 2017

Sensitisation pattern in severe reaction

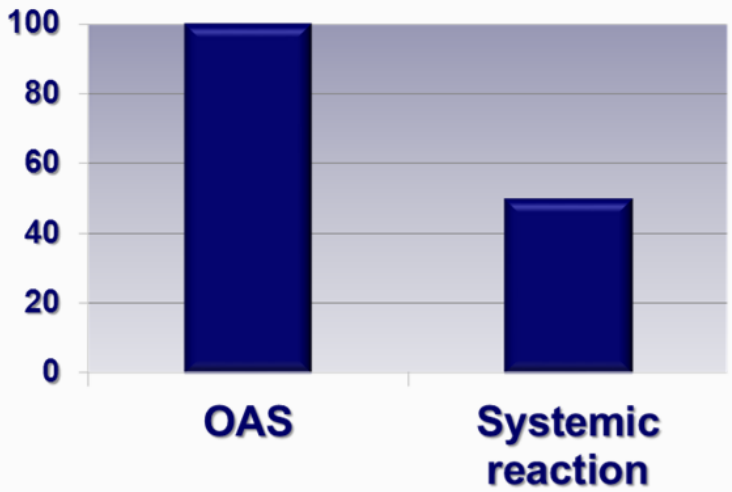


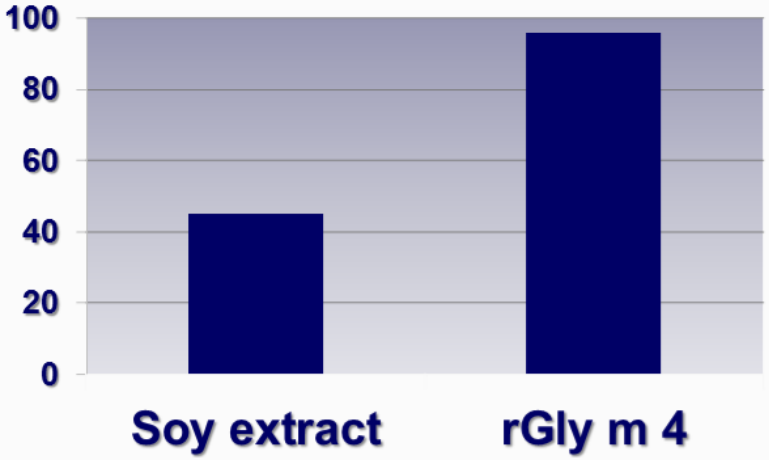
Datema et al. Allergy 2017

Soybean allergy in patients allergic to birch pollen: Clinical investigation and molecular characterization of allergens

Diana Mittag, MS,[a] Stefan Vieths, PhD,[b] Lothar Vogel, PhD,[b] Wolf-Meinhard Becker, PhD,[c] Hans-Peter Rihs, PhD,[d] Arthur Helbling, MD,[e] Brunello Wüthrich, MD,[a] and Barbara K. Ballmer-Weber, MD[a] *Zurich and Bern, Switzerland, and Langen, Borstel, and Bochum, Germany*

JACI 2004





«Bio-Bar»-Syndrom

Schulten et al. Mol Nutr Food Res 2011

Empty stomach with rapid rise of gastric pH and low protein content in food (apple 0.3%) → absorption of large amounts of IgE-reactive Bet v 1 related food allergens

Schulten et al Mol Nutr Food Research 2011

Bet v 1 related food allergy always mild?

Sensitisation to Bet v 1 homologous food proteins often silent or associated with symptoms localised to the oral mucosa

But more severe reactions observed in Bet v 1 related food allergy

empty stomach
high amount
particularly observed: Gly m 4, Api g 1, Cor a 1