

help to better understand how urticaria and cancer are linked. This could enhance the guidance given on when and how to look for cancer in CSU patients, to not overwhelm all CSU patients with tests, but to not miss any cancer diagnosis either.

CONFLICTS OF INTEREST

The authors have no conflict of interests to disclose.

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Reply to: "Allergen-specific IgG responses preceding allergic sensitization"

In their comments to Huang et al,¹ Aalberse and Platts-Mills argue that a strong and persistent IgG response is generated by a mature GC, that is the same structure in secondary lymphoid organs that may lead to deletion, rather than to proliferation of IgE+ B cells.² The pre- or coexistence of such an IgG response with IgE to the same allergenic molecule would therefore disagree with their model of a "modified" Th2 response.² Hence, the authors ask for the following information: (i) our definition of a "strong" IgG response and whether a "pre-atopic" IgG response is already "strong" before the appearance of IgE; (ii) our definition of a "persistent" IgG response; (iii) whether there is a "non-allergen-specific" effect of atopic predisposition on the "(pre-)atopic" IgG response. To answer these interesting questions, we will highlight information available in our original papers and present further statistical analyses of our data sets.

In the last years, we have examined the evolution of serum antibodies with a microarray assay (ISAC, ThermoFisher, Uppsala) in the sera of children participating in the Multicenter Allergy Study (MAS),

a German birth cohort born in 1990 and followed until 20 years of age. Three of these papers^{1,3,4} focused on IgG antibodies in their relationship with IgE responses. The results of these can briefly be summarized as follows:

- IgG antibodies against most allergenic molecules are *normally* found in the serum of children already at 2 years of age ("default" IgG response). Prevalence and average concentration of these IgG antibodies are dependent on the extent and route of allergen exposure, being maximal for animal foods, intermediate for vegetable foods and minimal for airborne allergenic molecules.⁴ Moreover, we showed that this default IgG response is characterized by slightly higher prevalence and levels in atopic children⁴ as previously suggested by Aalberse's group.⁵
- The appearance of serum IgE to airborne PR.10 molecules is invariably anticipated or accompanied by an IgG response towards the same molecule.³ Observing the trajectory of its natural evolution at population level, this "(pre-)atopic" IgG response to PR.10

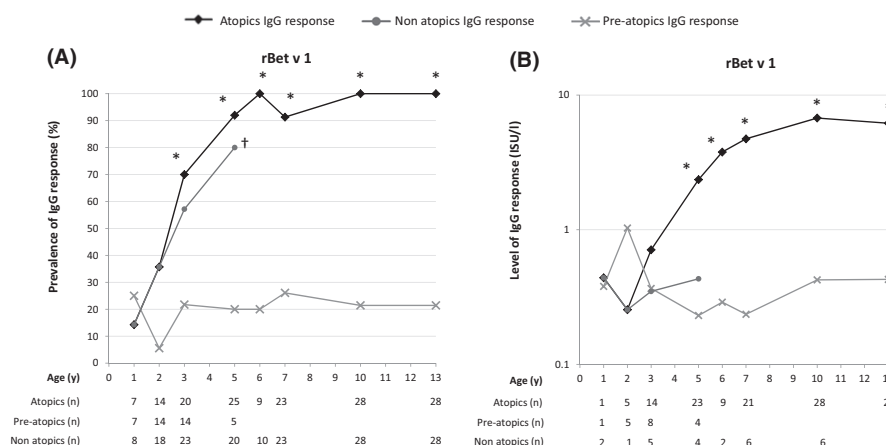


FIGURE 1 A,B, Prevalence (A) and levels (ISU/L) (B) of allergen-specific IgG responses to rBet v 1 in the sera of atopic (rhomb), pre-atopic (circle) and nonatopic (cross) children. Pre-atopic sera refer to the sera of patients sensitized to Bet v 1 which have been collected before the onset of IgE to Bet v 1. IgG levels were calculated as geometric mean of IgG-positive response (cut-off ≥ 0.1). *P* values refer to the comparisons of the IgG prevalence and IgG levels by age between atopic subjects and nonatopic subjects and were calculated with Fisher's exact test and Mann-Whitney *U* test, respectively. Statistically significant differences were highlighted (**P* < .05 for atopics vs nonatopics; †*P* < .05 for pre-atopics vs nonatopics)

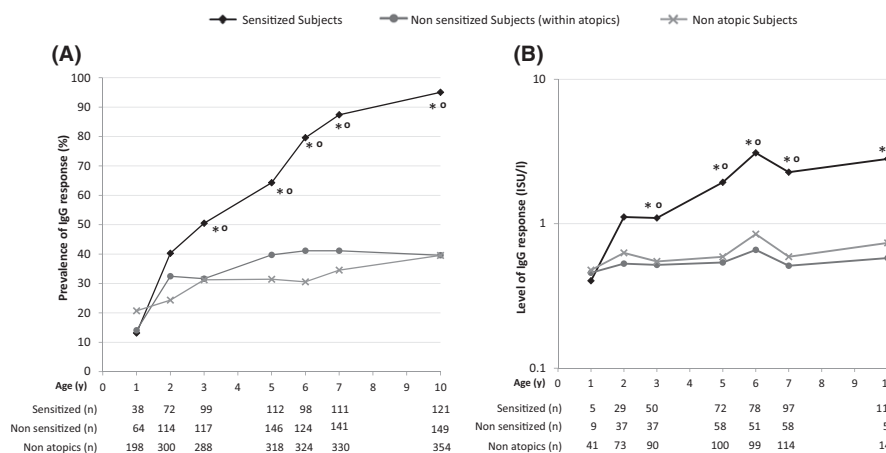


FIGURE 2 A,B, Cumulative prevalence (A) and levels (ISU/L) (B) of allergen-specific IgG responses to Der p 1, Der p 2, Bet v 1, Feld d 1, Phl p 1 and Phl p 5 and in atopic vs nonatopic subjects. Atopic subjects are divided into those sensitized to the included allergens and those atopic, but with no sensitization to the respective allergens. IgG levels were calculated as geometric mean of IgG-positive response (cut-off ≥ 0.1). *P* values refer to the comparisons of IgG prevalence and IgG levels by age. Taking into account multiple data from the same subjects, *P* values were calculated applying multilevel logistic regression and multilevel linear regression, respectively. Statistically significant differences were highlighted (**P* < .05 for sensitized vs nonatopics; **P* < .05 for sensitized vs non-sensitized; *P* = NS for non-sensitized vs nonatopics)

molecules can be distinguished from the normal or "default" IgG response to the same molecules in terms of prevalence (higher) (Figure 1A), concentration (higher) (Figure 1B)³ and persistence (Table 3 in Ref. 3). A new analysis of the same data set showed that samples collected from atopic subjects *before* the onset of an IgE response more frequently contain IgG to Bet v 1 when compared to never atopic controls (Figure 1A). On the contrary, levels of Bet v 1-specific IgG antibodies in IgE-negative sera are *similar* to those observed in the "default" response, that is in the never atopic controls (Figure 1B).³

- Finally, new and old analyses of the data set produced by Huang et al¹ show again that the serum IgG responses to inhaled molecules recognized by IgE in the same subject can be distinguished from the "default" IgG response (both, in atopic and in never

atopic children) in terms of prevalence (Figure 2A), concentration (Figure 2B, Table S1) and persistence (Figure 4B in Ref. 1). Analyses divided per allergenic molecule are reported in the electronic repository (Figure S1). In all analyses of the data set produced by Huang et al, the evolution of average prevalence and levels of the "default" IgG response were similar in children with no IgE response to the respective allergenic molecule, irrespective of their atopic status (Figures 2 and S1).

Given the above reported results, we would now like to answer the questions posed by Aalberse and Platts-Mills:

- Using the term "strong"^{1,3} we referred to the whole trajectory of IgG responses and not to their stage preceding the IgE response

to the same molecule. In this pre-IgE stage, the specific IgG response is still very weak (so we observed no “strong” IgG responses before an IgE response). However, those IgG responses rapidly grow over time and become soon stronger. In other words, we have used the word “strong” in a narrative—not statistical—way, and we applied it in the discussion of longitudinal results collected at population level. A cut-off value for a strong response, if needed, should be searched by ROC analysis, could be chosen as the upper 95% CI level molecule by molecule, or arbitrarily established, looking at Figure 2, at 1.0 ISU/L. We would like to refrain from giving a precise solution, as this answer would require specifically designed studies, and cut-off levels are population and context-dependent. Our observation that IgE responses to individual allergenic molecules are associated with a strong IgG response to the same molecule³ has been preceded 30 years by Platts-Mills’ group⁶ and further confirmed by other recent studies,^{7,8} making it a well-established fact.

2. As reported in the statistical methods of our paper,¹ “the persistence of an IgG response to each allergen molecule was computed as the percentage of positive IgG responses to the molecule, within the sera collected and examined after the onset of the IgE response.” To give an example, the persistence of an IgG response towards Bet v 1 observed at 2 years of age is 40% if IgG-Ab to Bet v 1 is detected in samples collected at age 3 and 5 years, but not in those collected at age 6, 7 and 10 (2/5 = 40%).¹
3. The new analyses given here (Figures 2 and S1, Table S1) clearly show that the default response in atopic children is not significantly contributing to the (pre-)atopic IgG response in its late, post-IgE onset stage. However, we agree with Aalberse and Platts-Mills that a default response may confound at individual level, due to its non-allergen-specific atopy component, the earliest, pre-IgE onset stage of the allergen-specific (pre-)atopic IgG response.

Studies and scientific debates on the evolution of the antibody response to allergens are essential to reason on the plausibility of old and new theories on the ontogeny of IgE+ B cells, a fascinating but still elusive scientific “enigma”.⁹

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

Keywords

allergen molecules, birth cohort, childhood, IgE, IgG

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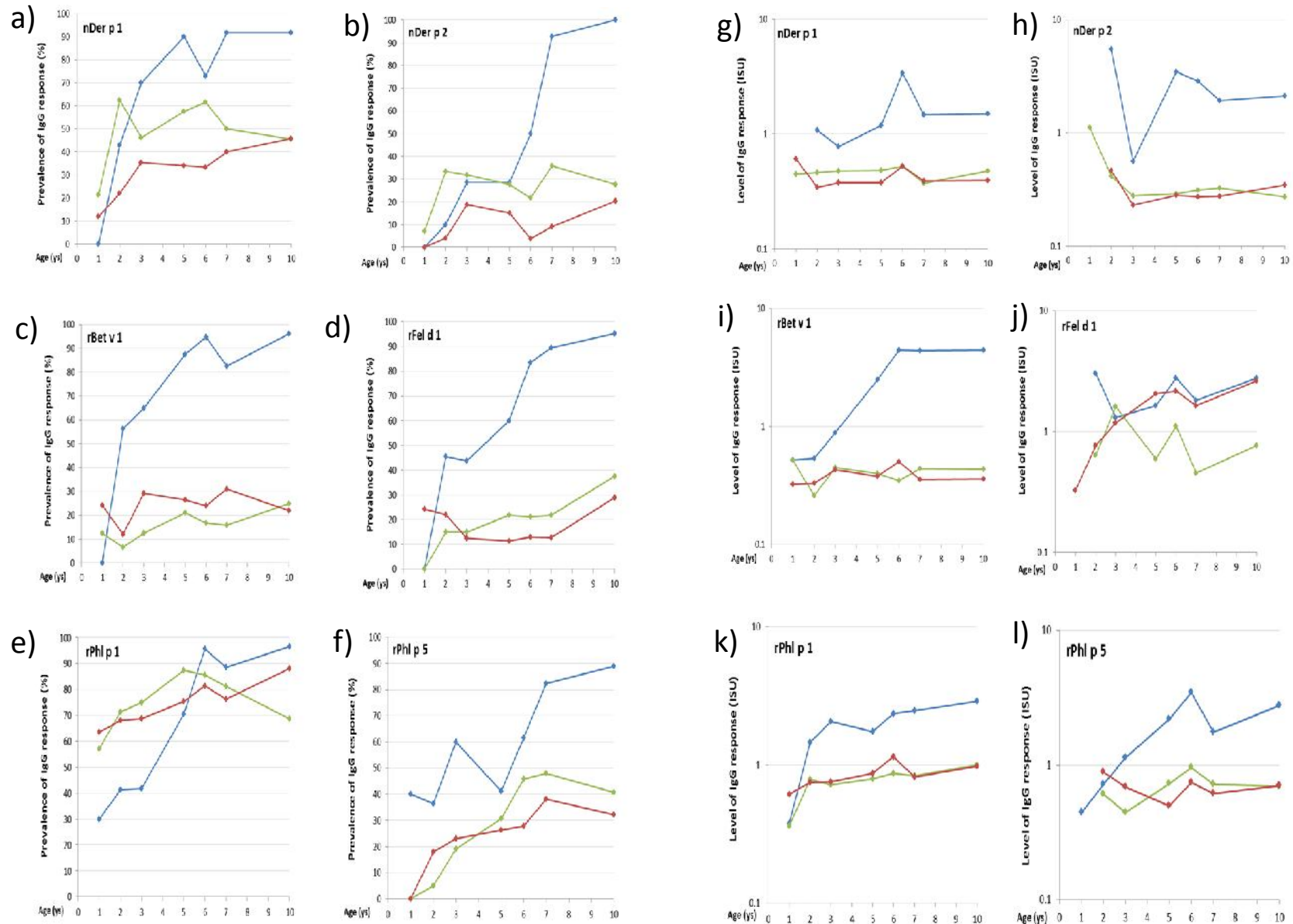
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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure E1

—●— Sensitized subjects to a specific molecule
 —●— Non-sensitized subjects to a specific molecule
 —●— Non-atopic subjects (within the atopic subjects)



ELECTRONIC REPOSITORY

Reply to

“Allergen-Specific IgG Responses Preceding Allergic Sensitization”

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Table: 1

Figure: 1

27 **Figure E1**

28 Prevalence **(a-f)** and levels (ISU/l) **(g-l)** of allergen-specific IgG responses to Der p 1 **(a,g)**, Der p 2 **(b,h)**, Bet v
29 1 **(c,i)**, Feld d 1 **(d,j)**, Phl p 1 **(e,k)**, Phl p 5 **(f,l)** and in atopic vs. non-atopic subjects. Atopic subjects are
30 divided into those sensitized to the included allergens and those atopic, but with no sensitization to the
31 respective allergens.

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Table E1 - Allergen-specific IgG levels (ISU/I) in IgE positive and IgE negative sera in atopic vs. non-atopic subjects.

Molecule	IgG levels in atopic subjects (n=45)					IgG levels in non-atopic subjects (n=59)			
	IgE positive sera*		IgE negative sera*		p‡	IgE negative sera*			p‡
	IgG level†	95% CI	IgG level†	95% CI		IgG level†	95% CI	p‡ξ	
rPhl p 1	2,65	(2.29-3.07)	0,87	(0.75-1.01)	<0.001	0,86	(0.78-0.94)	<0.001	0,844
rBet v 1	4,86	(3.70-6.38)	0,54	(0.41-0.72)	<0.001	0,39	(0.34-0.44)	<0.001	0,118
rFel d 1	2,75	(2.09-3.61)	0,73	(0.52-1.02)	<0.001	1,31	(0.84-2.05)	0,031	0,251
rPhl p 5	2,41	(1.76-3.30)	0,73	(0.53-1.01)	<0.001	0,67	(0.55-0.8)	<0.001	0,659
rAlt a 1	0,83	(0.57-1.20)	0,52	(0.4-0.69)	0,014	0,50	(0.42-0.59)	0,021	0,800
nDer p 2	2,34	(1.83-3.01)	0,35	(0.29-0.42)	<0.001	0,30	(0.24-0.36)	<0.001	0,206
nDer p 1	2,24	(1.69-2.95)	0,44	(0.39-0.5)	<0.001	0,40	(0.36-0.45)	<0.001	0,617

*Cut-off for positivity: IgE ≥0.3 (ISU)

† Geometric mean of IgE levels (ISU)

‡ Multilevel linear regression on logistic distribution taking into account multiple data from the same subject

ξ Comparison between IgG levels in IgE-positive atopic subjects and IgG levels in non-atopic subjects.

Comparison between IgG levels in IgE-negative atopic subjects and IgG levels in non-atopic subjects.

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