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Der p 23-specific IgE response throughout childhood and its association with allergic disease: A birth cohort study

Leandra Forchert[1] | Ekaterina Potapova[1] | Valentina Panetta[2] | Stephanie Dramburg[1] | Serena Perna[1] | Daniela Posa[1] | Yvonne Resch-Marat[3] | Christian Lupinek[3] | Alexander Rohrbach[1] | Linus Grabenhenrich[4] | Katja Icke[4] | Carl-Peter Bauer[5] | Ute Hoffman[5] | Johannes Forster[6] | Fred Zepp[7] | Antje Schuster[8] | Ulrich Wahn[1] | Thomas Keil[4,9,10] | Susanne Lau[1] | Susanne Vrtala[3] | Rudolf Valenta[3] | Paolo Maria Matricardi[1]

[1]The Department of Pediatrics, Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité—Universitätsmedizin Berlin, Berlin, Germany

[2]L'altrastatistica srl, Consultancy & Training, Biostatistics office, Rome, Italy

[3]The Division of Immunopathology, Department of Pathophysiology and Allergy Research, Centre of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Wien, Austria

[4]The Institute for Social Medicine, Epidemiology and Health Economics, Charité—Universitätsmedizin Berlin, Berlin, Germany

[5]The Department of Pediatrics, Technical University of Munich, Munich, Germany

[6]The Department of Pediatrics, Allergy Working Group, University Clinic Freiburg, Freiburg, Germany

[7]The Department of Pediatrics and Adolescent Medicine, University Medicine Mainz, Mainz, Germany

[8]The Department of Pediatrics, Heinrich-Heine-University, Düsseldorf, Germany

[9]The Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany

[10]The State Institute of Health, Bavarian Health and Food Safety Authority, Bad Kissingen, Germany

Correspondence
Paolo M. Matricardi, Department of Pediatrics, Division of Pulmonology, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, Augustenburgerplatz, 1, 13353 Berlin, Germany.
Email: paolo.matricardi@charite.de

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Abstract

Background: The *Dermatophagoides pteronyssinus* molecule Der p 23 is a major allergen whose clinical relevance has been shown in cross-sectional studies. We longitudinally analysed the trajectory of Der p 23-specific IgE antibody (sIgE) levels throughout childhood and youth, their early-life determinants and their clinical relevance for allergic rhinitis and asthma.

Methods: We obtained sera and clinical data of 191 participants of the German Multicentre Allergy Study, a prospective birth cohort. Serum samples from birth to 20 years of age with sIgE reactivity to Der p 23 in a customised semiquantitative microarray were newly analysed with a singleplex quantitative assay. Early mite exposure was assessed by measuring the average content of Der p 1 in house dust at 6 and 18 months.

Abbreviations: AD, Atopic dermatitis; AR, Allergic rhinitis; CRD, Component resolved diagnosis; *D.pt.*, *Dermatophagoides pteronyssinus*; GM, Geometric mean; HDM, House dust mites; MAS, German Multicentre Allergy Study; sIgE, specific immunoglobulin E; TFS, Thermofisher Scientific; tIgE, total immunoglobulin E.

Results: Der p 23-sIgE levels were detected at least once in 97/191 participants (51%). Prevalence of Der p 23 sensitisation and mean sIgE levels increased until age 10 years, plateaued until age 13 years and were lowest at age 20 years. Asthma, allergic rhinitis (AR) and atopic dermatitis (AD) were more prevalent in Der p 23-sensitised children, including those with monomolecular but persistent sensitisation (11/97, 11%). A higher exposure to mites in infancy and occurrence of AD before 5 years of age preceded the onset of Der p 23 sensitisation, which in turn preceded a higher incidence of asthma.
Conclusions: Der p 23 sensitisation peaks in late childhood and then decreases. It is preceded by early mite exposure and AD. Asthma and AR can occur in patients persistently sensitised to Der p 23 as the only mite allergen, suggesting the inclusion of molecular testing of Der p 23-sIgE for subjects with clinical suspicion of HDM allergy but without sIgE to other major *D.pt*. allergens.

KEYWORDS
asthma, birth cohort, childhood, Der p 23, *Dermatophagoides pteronyssinus*, house dust mite allergy, IgE

1 | INTRODUCTION

House dust mites (HDM) account for the majority of perennial allergies.[1] Several studies report that exposure to *Dermatophagoides pteronyssinus (D.pt)* and *Dermatophagoides farinae (D.fa)* facilitates sensitisation in later years.[2,3] Moreover, mite-related IgE responses increase over time, in both complexity of the molecular sensitisation profile and mean IgE concentrations,[4,5] following a phenomenon already described for grass-related IgE responses.[6] Additionally, a strong correlation between IgE sensitisation to mite allergens and asthma was demonstrated[2] and further defined on a molecular level.[4,5,7] Due to the development of component resolved diagnostics (CRD), over 30 different molecules of *D.pt*. have been identified and sequenced in the WHO/IUIS Allergen Nomenclature. These molecules have been further classified into major (Der p 1, Der f 1, Der p 2, Der f 2 and Der p 23) and minor allergen molecules if they induce IgE responses in more or less than 50% of mite-allergic patients, respectively.[4,7] A hierarchy of epidemiological and clinical relevance among these molecules has been proposed[8] and further confirmed by longitudinal studies disclosing regular sequence of IgE sensitisation.[4] Accordingly, three different molecular categories were defined: Group A (Der p 1, Der p 2 and Der p 23), that is, initiator molecules reaching a prevalence higher than 40%; Group B, (Der p 4, Der p 5, Der p 7 and Der p 21) including molecules inducing IgE sensitisation at later stage in 15%–30% of patients; and Group C (Der p 11, Der p 14, Der p 15, Clone 16/Der p 37 and Der p 18), consisting of molecules whose IgE sensitisation is the latest and the least frequent (prevalence <10%).[4]

While Der p 1, Der p 2 and homologous molecules in *D.fa*. have been characterised over 40 years ago,[9,10] Der p 23 was discovered in 2013.[11] Its biological, epidemiological and clinical roles have recently been further characterised in experimental and cross-sectional studies.[12-18] According to different studies, 40%–75% of HDM allergic patients in Europe are sensitised to Der p 23,[4,12,13,19] rendering it the third most frequently recognised mite allergen. Being a peritophin-like protein of 8 kD, it is located in the intestinal tract of mites.[11] There it is associated with the peritrophic matrix, a membrane synthesised by posterior midgut epithelial cells.[11,20] This membrane surrounds faecal pellets to protect the intestinal gut against mechanic or toxic damage. Consequently, Der p 23 is closely attached to faecal pellets. Despite its small amounts in mite extracts though, the allergenic activity of Der p 23 seems to be comparable to that of Der p 1 (cysteine protease) and Der p 2 (NPC2 protein)[14] and linked to asthma.[15,17] While mite-allergic patients with monomolecular IgE sensitisation to Der p 23 have been observed in cross-sectional studies,[14,16,20] the longitudinal evolution and clinical relevance of the IgE response to this molecule during childhood has not yet been examined in its details.

Therefore, the primary aim of the present study was to examine the trajectory of the sIgE antibody response to Der p 23 from birth to the age of 20 years and to investigate its early-life determinants as well as its clinical relevance, with a focus on allergic rhinitis and asthma. Secondarily, we aimed to thoroughly study those subjects that were monosensitised to Der p 23. To this end, we have resorted

Key Message

In this study, we investigated the sensitisation pattern to the major *Dermatophagoides pteronyssinus* molecule Der p 23 within the MAS birth cohort. The sensitisation was found to have a strong association with asthma and to be facilitated by early mite exposure and atopic dermatitis. Der p 23 is a major allergen molecule that should be considered in the algorithm of mite allergy testing.

to the German Multicentre Allergy Study (MAS), a prospective population-based allergy-risk enriched birth cohort that investigated over 20 years children born in five German cities in 1990[21] and whose sIgE responses to several *D.pt*. allergen molecules had been already examined with a customised, semiquantitative, allergen microarray.[4]

2 | METHODS

2.1 | Study design and population

The MAS cohort recruited 1314 of 7609 infants born in 1990 in six university hospitals in five German cities[22] with inclusion criteria and study design described elsewhere in detail.[22] Children were examined at 1, 3, 6, 12, 18 and 24 months and annually from age 3 to 13 years and at 15 and 20 years. The study was approved by local ethic committees. Each parent provided written informed consent. In the present work, we included participants with ≥1 serum sample positive for specific IgE (sIgE) to *D.pt*. extract (cut-off ≥0.35 kU/L; ImmunoCAP 100, TFS) and less than four missing follow-ups between 3 and 20 years.[4]

2.2 | IgE assays

Serum samples were obtained at 1, 2, 3, 5, 6, 7, 10, 13 and 20 years (Table S1 in e-repository). All sera with sIgE reactivity to Der p 23 (≥0.3 ISU/L) in a customised semiquantitative microarray (ImmunoCAP ISAC, TFS, Uppsala, Sweden) and with a residual volume of ≥100 µL were included. These sera and 40 negative controls (see e-repository for selection criteria) were again tested for sIgE to Der p 23 with a singleplex quantitative assay (ImmunoCAP 100, TFS). A result of ≥0.35 kU/L was considered positive.

2.3 | Statistical analysis

Normality of data was tested using the Shapiro–Wilk test. Chi-square test and Mann–Whitney U test were used for categorical and quantitative not normally distributed variables, respectively, to test differences between groups. Inter-quartile ranges (IQR) were calculated for median mite exposure, number of sensitised *D.pt*. molecules and median age of onset of allergic diseases. Univariable logistic regression was used to investigate the influence of exposure to Der p 1 in house dust and occurrence of AD before 5 years of age, respectively, on Der p 23 sensitisation. Geometric mean (GM) and geometric standard deviation (GSD) were calculated for mean IgE concentrations. Correlations between sIgE levels with the two different assays were analysed with two-sided Spearman rank correlation (Figure S2) and plotted in a Bland–Altman-Agreement plot after log 10 transformation (Figure S3). sIgE values from birth to the age of 20 were analysed by linear mixed models, considering patient ID as a random factor and age, Der p 23 sensitisation status, as well as their interaction as fixed factors with log 10 transformed sIgE concentrations as the outcome variable. sIgE concentrations (GM) and their 95%CI were estimated by the model. The clinical relevance of Der p 23 and the two other Group A molecules (Der p 1, Der p 2) was assessed by logistic mixed models, which considered patient ID as a random factor, and age and prevalence status as well as their interaction as fixed factors. The models were adjusted for sensitisation to the respective other Group A molecules. This was conducted for asthma, AR and AD separately. A *p*-value of <0.05 was considered statically significant. The statistical analysis was performed with SPSS (IBM®SPSS®STATISTICS, Version 27, 2020) and STATA software (STATA 16.1 Revision 06 April 2021 StataCorp LLC, College Station TC77845) for calculations based on mixed models.

3 | RESULTS

3.1 | IgE sensitisation to Der p 23

Overall, 191 of the initially recruited 1314 subjects in the MAS cohort met the inclusion criteria of this study.[4] Ninety-seven subjects (51%) had at least one sample with positive sIgE to Der p 23 in the microarray (thence referred to as '*Ever Der p 23 sensitised*'), of which 11 subjects presented sIgE exclusively to Der p 23 among the 12 tested *D.pt*. molecules at all times. Ninety-four subjects (49%) were never sensitised to Der p 23 in the microarray; thence named '*Never Der p 23 sensitised*' (Figure S1). In the singleplex assay (ImmunoCAP 100), 89/97 subjects also had ≥1serum with positive sIgE to Der p 23, while sIgE concentrations of eight subjects remained below the cut-off (*see OR for detailed information*).

3.2 | Risk factors for IgE sensitisation to Der p 23

We found no difference for potential risk factors such as sex, nationality, parental history of atopy, breastfeeding, maternal history of smoking during pregnancy and the presence of pets before the age of 7 years (Table 1) between the ever and never Der p 23-sensitised subjects. By contrast, average exposure to Der p 1 between 6 and 18 months was observed to be significantly higher ($p = .027$) in the Der p 23-sensitised group (Figure 1). Univariable logistic regression showed that early exposure to Der p 1 in domestic environment significantly influenced Der p 23 sensitisation (OR = 1.74; 95% CI = 1.11–2.73; *p-value* = .015).

3.3 | Molecular profiles of 'ever mite sensitised' subjects

Both prevalence and sIgE concentrations at 20 years to *D.pt*. extract were significantly higher in Der p 23-sensitised subjects than in the never Der p 23-sensitised subjects. The same observation

TABLE 1 Characteristics of the study population

	Never Der p 23-sensitised ($n = 94$)[a]		Ever Der p 23-sensitised ($n = 97$)[a]		p-Value[f]
Sex (male) (%)	62	*66.0*	62	*63.9*	.768
German nationality (%)	90	*96.8*	92	*96.8*	.649
Parental history of atopy (%)[b]	54	*58.7*	70	*72.2*	.051
Breastfeeding (>1 month) (%)	77	*81.9*	79	*81.4*	.933
Mother smoking in pregnancy (%)	16	*17.2*	22	*22.7*	.346
Pets in household (%)[c]	27	*31.8*	35	*37.6*	.412
Molecular associates					
tIgE [kU/L], mean (*SD*)[d]	144.5	*3.8*	174.5	*3.5*	.236
Prevalence of sIgE to *D.pt*. extract at 20 years (%)	50	*76.9*	70	*94.6*	.002
sIgE to *D.pt*. extract [kU/L], mean (*SD*)[d]	3.9	*5.6*	13.6	*4.3*	<.001
Prevalence of sIgE to Der p 1 at 20 years (%)	26	*40.0*	51	*70.0*	<.001
sIgE to Der p 1 [ISU/L], mean (*SD*)[d]	5.1	*3.7*	11.9	*3.6*	<.001
Prevalence of sIgE to Der p 2 at 20 years (%)	36	*55.4*	58	*79.5*	.002
sIgE to Der p 2 [ISU/L], mean (*SD*)[d]	4.3	*4.8*	16.1	*3.7*	<.001
N sensitised *D.pt*. molecules, median (IQR)[g]	1	*1–3*	4	*2–9*	<.001
Sensitisation profile[e]					
Monomolecular (%)	29	*30.9*	11	*11.3*	<.001
Oligomolecular (%)	33	*35.1*	35	*36.1*	
Polymolecular (%)	9	*9.6*	51	*52.6*	
NA (%)	23	*24.5*	-	-	

Note: Data were summarised as numbers (*n*) and frequencies (%) if they were categorical, or geometric mean and standard deviation (*SD*) and median and inter-quartile range (IQR), respectively, if quantitative.

[a]Numbers refer to sIgE positivity to Der p 23 measured with ImmunoCAP ISAC (ISU/L) with sIgE concentrations ≥0.3 ISU/L. Sporadic missing values have been considered and the respective percentages adapted to the denominator.

[b]One or both parents with history of atopic disease.

[c]Presence of any pet in household before the age of 7 years.

[d]IgE concentrations at 20 years.

[e]Sensitisation profiles refer to the maximum number of D.pt. molecules against which subjects were ever sensitised between 0–20 years. Monomolecular = sensitised to one D.pt. molecule; oligomolecular = sensitised to 2–4 D.pt. molecules; polymolecular = sensitised to ≥5 D.pt. molecules.

[f]Chi-square test was used to evaluate the association of categorical data between groups; Mann–Whitney *U* test was used to compare quantitative not normally distributed variables between groups (Shapiro–Wilk test was used to assess normality of data).

[g]Refers to the maximum number of D.pt. molecules against which subjects were ever sensitised between 0 and 20 years; Der p 23 excluded.

could be made for sIgE to Der p 1 and 2. Furthermore, the number of positive *D.pt*. molecules besides Der p 23 was significantly higher in ever Der p 23-sensitised subjects. Accordingly, the distribution of *D.pt*. sensitisation profiles differed significantly between the Der p 23-sensitised and non-sensitised subjects ($p < .001$) (Table 1).

3.4 | Prevalence, onset and evolution of the sIgE response to Der p 23

Both prevalence and concentrations of sIgE to Der p 23 strongly increased between 3 and 10 years, plateaued at 13 years with a decrease towards 20 years (*description in e-repository*). First detection of Der p 23-sIgE as well as maximum sIgE levels was mostly found at 10 years.

3.5 | sIgE to Der p 23 and to *D.pt*. extract: a quantitative correlation

Levels of sIgE to Der p 23 in oligo/polymolecularly sensitised children were at nearly all times significantly lower than those to the *D.pt*. allergen extract ($p < .001$). On average, sIgE to Der p 23 made up 16% of sIgE to the extract. Interestingly, while Der p 23-sIgE in monomolecularly sensitised children was generally as high as in the oligo/polymolecularly sensitised subjects, an opposite scenario

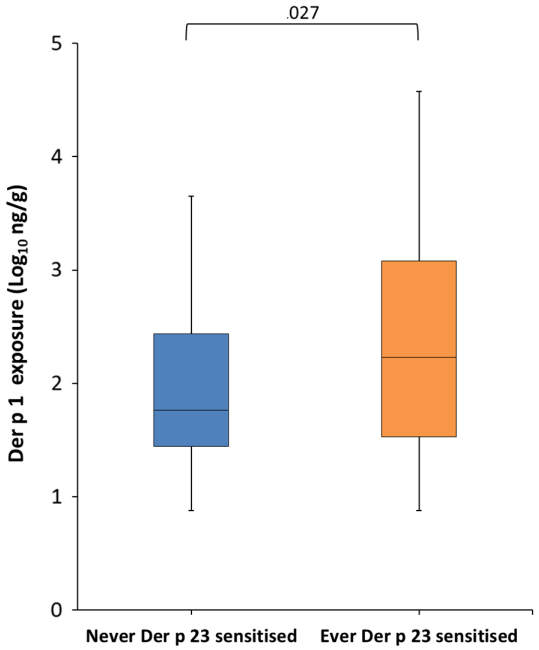

FIGURE 1 Exposure to Der p 1 between 6 and 18 months, by sIgE sensitisation to Der p 23. Average content of Der p 1 in carpet dust (ng/g) between 6 and 18 months, of all subjects with available data at both time points. Data were log 10 transformed for further analysis and given in box plots with median and the 25th and 75th percentile as boundaries of the box. Of the never Der p 23-sensitised subjects, Der p 1 exposure was calculated for 57 subjects (median = 1.76 ng/g; IQR = 1.45–2.44; data shown in blue), compared with 63 subjects within the ever Der p 23-sensitised subjects (median = 2.23 ng/g; IQR = 1.53–3.08; data shown in orange); $p = .027$

could be observed with significantly higher levels of sIgE to Der p 23 than to the extract ($p < .001$, (Figure 2)).

3.6 | Case series report: Der p 23 monomolecularly sensitised subjects

Within the 11 children exclusively sensitised to Der p 23 (among the tested *D.pt*. molecules), we found that eight subjects (73%, microarray) were exposed to mite dust during early childhood, while nine subjects (82%) had a positive history of parental atopy. In four/six cases with more than one positive serum, peak sIgE concentrations were directly achieved at first detection (Table 2). Regarding the individual molecular and clinical profiles of these children, all 11 were affected by AR, while four children also suffered from asthma. Subjects with high house dust mite exposure in early childhood appeared to have more sera positive for Der p 23-sIgE, but not forcefully greater manifestations of allergic diseases. In all 11 subjects, sIgE levels to Der p 23 were at all times higher than sIgE levels to the mite extract (Figure S5).

3.7 | Clinical outcome

The prevalence of asthma was significantly higher in ever Der p 23-sensitised subjects (42%) than in never Der p 23-sensitised subjects (26%; $p = .015$). A similar trend was observed for AR (91% vs. 80%; $p = .033$) and AD (53% vs. 36%; $p = .023$) (Table 3). Regarding the evolution of the different allergic diseases over time, prevalence of asthma and AR increased significantly with age both within the Der p23-sensitised and non-sensitised group (asthma: obs = 2172; groups = 191; $p < .001$. AR: obs = 2160; groups = 191; $p < .001$ (Figure 3a,b)). While we could not observe any influences of Der p 23 sensitisation to the prevalences of asthma and AR, the mixed models on the correlation of Der p 1, respectively, Der p 2 and the prevalences of allergic diseases showed no significant influence on one of these two diseases either (*data not shown*). Remarkably, the prevalence of asthma was significantly (two fold) higher after the first detection of Der p 23 sensitisation than before it ($p < .001$) (Figure 4). By contrast to asthma and AR, AD peaked at 1 years, decreased to a minimum at 4 years and plateaued thereafter both in Der p 23-sensitised and non-sensitised children. A significant higher prevalence of AD was observed at any time among children with Der p 23 sensitisation (obs = 1321; groups = 191; $p = .019$) (Figure 3c). Accordingly, univariable logistic regression showed that AD before age 5 years ($n = 73/85$ [86%]) significantly influenced the development of Der p 23 sensitisation after 5 years ($n = 92/97$ [95%]) (OR = 2.21; 95% CI = 1.22–4.01; $p = .009$).

4 | DISCUSSION

This birth cohort study is the first study focusing on onset, quantitative evolution, risk factors and clinical relevance of serum IgE responses to the major *D.pt*. allergen Der p 23. We found that IgE sensitisation to Der p 23: (A) often begins very early in the first decade of life, with a declining trend during adolescence; (B) is associated with high exposure to *D.pt*. allergens in infancy and history of AD during the first 4 years of life; (C) can be monomolecular, yet associated with symptoms of AR and/or asthma over many years; and (D) is—together with Der p 1 and Der p 2—related to a higher risk of current and future allergic asthma.

4.1 | Onset, prevalence and IgE levels over time

The overall prevalence of Der p 23 sensitisation in the MAS cohort was 51%, defining Der p 23 as a Group A molecule.[4] First detection of Der p 23-sIgE appeared averagely at 10 years, as previously hypothesised in a cross-sectional study among mite-allergic patients.[17] However, the youngest children showing an IgE response to Der p 23 were 2 years old, while sensitisation started at 20 years in other patients. Our study highlights that Der p 23 can be both, an initiator of the IgE response to *D.pt*. very early in childhood, or an allergen molecule accompanying the sensitisation process at later stages. We also observed a peak, in both prevalence and sIgE level at 10 years and decreased sensitisation rates and antibody levels towards adulthood, as suggested by cross-sectional studies.[13,15] This decline may reflect a general dampening after puberty of Th2-inflammation and

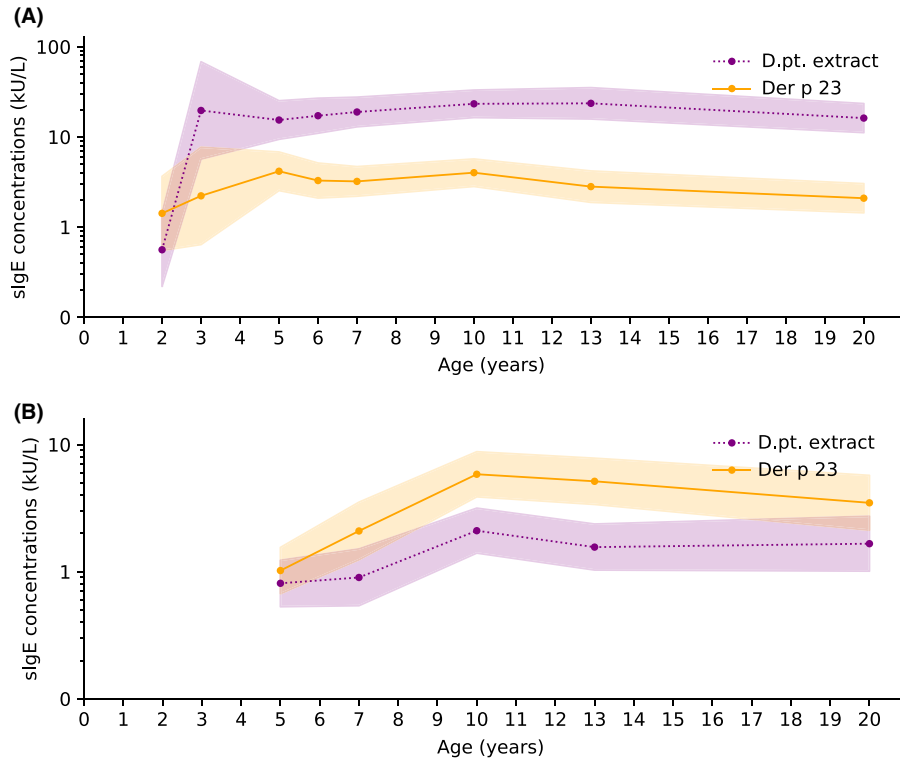

FIGURE 2 Evolution of sIgE to Der p 23 and the *D.pt*. extract among *D.pt*. oligo/polymolecularly sensitised subjects (A) and Der p 23 monomolecularly sensitised subjects (B), from birth to the age of 20 years. Mean sIgE concentrations to *D.pt*. extract and Der p 23 (GM; kU/L) estimated by mixed model on log 10 transformed data. Shaded areas represent 95% CI. A detailed definition of the different molecular profiles is given in the main text. (A) sIgE levels of *D.pt*. oligo/polymolecularly sensitised subjects ($n = 79$). In this population, we found significantly different sIgE levels to the extract vs. Der p 23 at each age ($p < .011$) as well as different evolution patterns ($p < .001$). (B) sIgE levels within the Der p 23 monomolecularly sensitised group, defined here as no sensitisation to any other *D.pt*. molecule ($n = 10$). Overall, sIgE levels were lower than in the *D.pt*. oligo/polymolecularly sensitised population and an inversion of sIgE concentrations could be observed. Here, sIgE to Der p 23 and the extract also differed significantly ($p < .001$) at all ages, with similar evolution patterns (trend for interaction; $p = .093$)

respiratory allergies starting in childhood.[23] The immunological basis of this evolution has been described and deeply investigated in the MAAS, BAMSE and the PIAMA cohort studies,[24-26] along with a reduction in IgE levels and increase in IgG levels against major allergenic proteins simultaneously to a decline in respiratory allergic reactivity in the second decade of life.

4.2 | Early risk factors of sIgE sensitisation to Der p 23

A higher exposure to house dust mites in infancy was associated with Der p 23 sensitisation. This outcome adds an important information to earlier observations of a synergy of early exposures and genetic predisposition to an increased overall sensitisation to mites.[3,27] Interestingly, we also observed that children with a history of AD in the first 4 years of life were also at greater risk of developing IgE sensitisation to Der p 23 later on. One could speculate that the disruption of the skin barrier and the underlying Th2-inflammation may generate the immunological conditions to develop IgE sensitisation to Der p 23.[28]

4.3 | Patients with monomolecular sensitisation: biological and clinical implications

We found many subjects with sIgE exclusively to Der p 23 among the tested *D.pt*. molecules. Our observation confirms that Der p 23 is a strong allergen whose triggering of IgE-mediated degranulation by basophiles and mastcells[11] is related to symptoms. From a diagnostic standpoint, our results show that a minority of mite-allergic children can suffer from AR and/or asthma even lacking sIgE to Der p 1 and/or Der p 2. Consequently, mite allergy could be overlooked by diagnostics using allergen extracts with no or small amounts of Der p 23.[12,15,29] Due to its close attachment to the peritrophic membrane of faecal pellets, Der p 23 is poorly released in hydrophilic solutions when compared to other mite allergens such as Der p 1 and Der p 2.[11] This underrepresentation of Der p 23 in some allergen extracts is also suggested by our own results. Indeed, Der p 23-sIgE in *D.pt*. oligo/polysensitised subjects was a fixed percentage (≈16%) of sIgE to the mite extract, while Der p 23-sIgE levels surpassed *D.pt*.-sIgE levels in monomolecularly sensitised children. Molecular testing of Der p 23-sIgE should be, therefore, included into the diagnostic algorithm for subjects with stringent clinical suspicion of HDM

TABLE 2 Characteristics of Der p 23 monomolecularly sensitised subjects[a]

Subject	Sex	ATP[b]	*D.pt.* exposure (ng/g)[c]	Pos. sera (*n*)[d]	First Der p 23-sIgE (y)	First Der p 23-sIgE (ISU/L)	Peak Der p 23-sIgE (y)	Peak Der p 23-sIgE (ISU/L)	AD (y)	AR (y)	Asthma (y)
1	f	1	255	2	13	5.01	20	5.27	-	8–20	-
2	m	1	-	1	20	5.8	-	-	-	6–20	-
3	m	1	345	1	5	0.9	-	-	1–7	6–20	7–13
4	m	1	18	2	13	33.23	13	33.23	-	3–20	-
5[e]	f	1	22	1	13	5.58	-	-	1	5–20	9–20
6	f	0	260	3	10	17.22	10	17.22	2–7	13–20	-
7	m	0	-	1	20	3.63	-	-	-	8–13	-
8	f	1	-	4	5	2.8	10	58.16	1–7	6–13	6–13
9	f	1	238	3	10	16.06	10	16.06	2–6	11–20	-
10	f	1	2790	3	5	4.55	5	4.55	2	11	-
11[e]	m	1	332	1	7	31.16	-	31.16	5–7	5–13	8–13

[a]Data based on test with microarray (ISU/L).
[b]ATP = Parental history of atopy.
[c]Mean D.pt. exposure between 6 and 18 months. Relative content of Der p 1 (ng) per extracted dust (g).
[d]Pos. Sera = sera per subject with sIgE positivity to Der p 23.
[e]Subject showed no sIgE positivity to Der p 23 when tested with ImmunoCAP 100 kU/L.
[f]Subject within second control group with sIgE at 20 years = 0.57 kU/L, but no positive sIgE to D.pt. extract.

TABLE 3 Prevalences of allergic diseases

	Never Der p 23-sensitised (*n* = 94)[a]		Ever Der p 23-sensitised (*n* = 97)[a]		*p*-Value[b]
AR					
Age at onset (year), median (IQR)	6	*4–11*	6	*4–11*	.415
Prevalence (%)	75	*79.8*	88	*90.7*	.033
Asthma					
Age at onset (year), median (IQR)	8.5	*7–11*	8	*7–11*	.706
Prevalence (%)	24	*25.5*	41	*42.3*	.015
AD					
Age at onset (year), median (IQR)	2	*1–4*	1	*1–2*	.135
Prevalence (%)	34	*36.2*	51	*52.6*	.023

Note: Data were summarised as numbers (*n*) and frequencies (%) if they were categorical, or median and inter-quartile range (IQR) if they were quantitative.
[a]Der p 23 positivity according to sIgE concentrations measured with microarray (ISU/L).
[b]Chi-square test was used to evaluate the association of categorical data between groups; Mann–Whitney *U* test was used to compare quantitative not normally distributed variables between groups (Shapiro–Wilk test was used to assess normality of data).

allergy but no IgE to Der p 1 and Der p 2 or even to *D.pt*. extract. Furthermore, high-quality mite extracts, used for allergen immunotherapy, should be checked for their content of sufficient amounts of Der p 23, as previously suggested.[30,31]

4.4 | Clinical relevance

In agreement with other cross-sectional[11,13,15,17] and longitudinal studies,[4] we found a remarkably higher prevalence of asthma in Der p 23-sensitised subjects than in non-sensitised subjects. Strikingly, the overall prevalence of asthma increased after the detection of Der p 23-sIgE, possibly in line with a hypothesis of causality in this sequential association. Prevalence of AR and AD differed to a lesser, but still significant extent between never and ever Der p 23-sensitised subjects. While we could not observe strong influences of Der p 23 sensitisation on the prevalences of asthma and AR, Der p 1 and Der p 2 showed no influence on the allergic diseases either. We thus presume that not sensitisation to one Group A molecule alone, but rather to Group A molecules in their entity (*see*

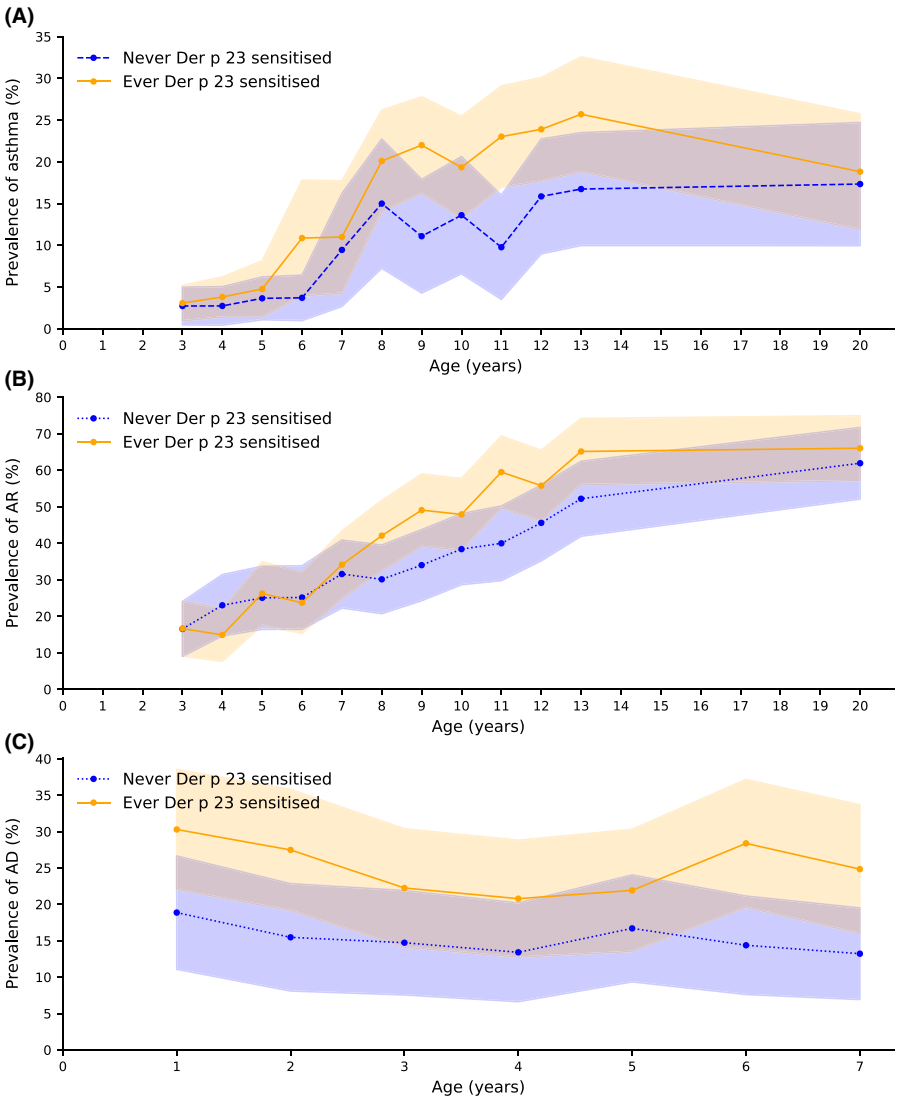

FIGURE 3 Prevalence rates of allergic diseases, by age and sIgE sensitisation to Der p 23. Prevalence rates were estimated by mixed model. 95% CI are represented in shaded areas. Der p 23 sensitisation refers to results obtained in the microarray. (A) Prevalence rates of asthma differed significantly for age ($p < .001$) and with a significance at limits between the groups of Der p 23-sensitised vs non-sensitised subjects ($p = .064$). In both groups, the prevalence of asthma evolved similarly (trend for interaction; $p = .366$). (B) Prevalence rates of AR significantly increased with age ($p < .001$). Whereas no significance for the prevalence between Der p 23-sensitised and non-sensitised subjects could be observed ($p = .194$), prevalence rates evolved significantly differently in the two groups ($p = .035$). (C) Prevalence of AD did not change significantly over time in both groups ($p = .148$). AD was found more often in Der p 23-sensitised subjects than in non-sensitised ones ($p = .017$), while the overall evolution was similar in both groups (trend for interaction; $p = .765$)

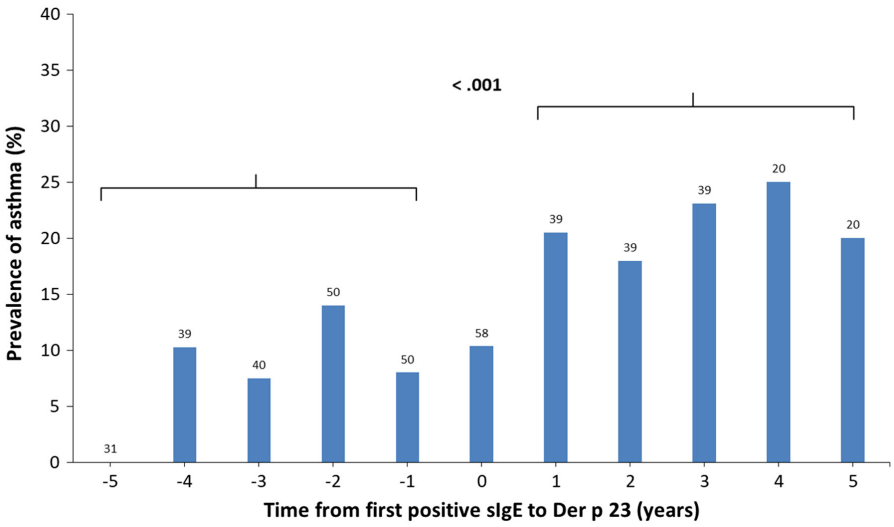

FIGURE 4 Prevalence of asthma by time from the detection of positive sIgE to Der p 23 (years). Numbers on the x-axis display the time in years from first detection of Der p 23-sIgE, calculated for each subject individually. Bars show the prevalence (%) of asthma in subjects who presented at follow-ups. The number of tested subjects is indicated above each bar. Only subjects with data at all time points were included for analysis ($n = 58$). Prevalences were calculated for a range of ±5 years from first positive sIgE to Der p 23. Chi-square test was used for comparison of the prevalence of asthma before and after the detection of first sIgE to Der p 23 ($p < .001$), as visualised by the parentheses

online repository: Molecular spreading within Group A) influence the onset of allergic diseases as described by Posa et al. Regarding AD, we assessed another trend: Given that, most frequently, detection of sIgE to Der p 23 happened from the age of 5 years onwards and that the first onset of AD rarely happened after 4 years, we speculated about the possibility of AD as a risk factor of Der p 23 sensitisation rather than the other way around.

5 | LIMITATIONS

Not all subjects were followed at each age and missing values of subjects, especially at the first follow-ups, limited our analyses. We used mixed models for statistical analysis to compensate missing values. Furthermore, in the Der p 23 monomolecularly sensitised subjects, allergic diseases evolved sometimes before the first detection of sIgE to Der p 23. Due to missing sera, we often could not tell if the subjects were already Der p 23-sensitised at the onset of the allergic disease. However, an undetected, earlier sensitisation would have reinforced rather than weakened our conclusions. Finally, the 11 subjects monomolecularly sensitised to Der p 23 presented positive sIgE to other allergen sources (i.e. food allergens) whose role in the patient's asthma, although unlikely, cannot be excluded.

6 | CONCLUSIONS

This study is the first to examine in detail the IgE evolution as well as molecular and clinical characteristics of Der p 23-sensitised subjects in a birth cohort. The results suggest clinical relevance of the sensitisation to the major mite allergen Der p 23 and strengthen the role of this molecule as a predictor for mite-related allergic rhinitis and asthma.

AUTHOR CONTRIBUTIONS

Leandra Forchert: Data curation (lead); investigation (lead); methodology (lead); visualization (lead); writing – original draft (lead). **Ekaterina Potapova:** Data curation (equal); investigation (supporting); methodology (supporting); supervision (equal); validation (equal); writing – review and editing (equal). **Valentina Panetta:** Formal analysis (supporting); methodology (supporting). **Stephanie Dramburg:** Project administration (equal). **Serena Perna:** Data curation (equal); formal analysis (equal). **Daniela Posa:** Investigation (equal). **Yvonne Resch-Marat:** Project administration (equal). **Christian Lupinek:** Project administration (equal). **Alexander Rohrbach:** Formal analysis (equal). **Linus Grabenhenrich:** Project administration (equal). **Katja Icke:** Project administration (supporting). **Carl-Peter Bauer:** Project administration (equal). **Ute Hoffmann:** Project administration (equal). **Johannes Forster:** Project administration (equal). **Fred Zepp:** Project administration (equal). **Antje Schuster:** Project administration (equal). **Ulrich Wahn:** Project administration (equal). **Thomas Keil:** Project administration (equal). **Susanne Lau:** Project administration (equal). **Susanne Vrtala:** Project administration (equal). **Rudolf Valenta:** Project administration (equal). **Paolo Maria Matricardi:** Investigation (equal); methodology (equal); project administration (equal); supervision (lead); visualization (equal); writing – review and editing (lead).

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CONFLICT OF INTEREST

All authors declared no conflicts of interest.

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ORCID

Linus Grabenhenrich https://orcid.org/0000-0002-9300-6625
Susanne Lau https://orcid.org/0000-0002-5189-4265
Rudolf Valenta https://orcid.org/0000-0001-5944-3365
Paolo Maria Matricardi https://orcid.org/0000-0001-5485-0324

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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