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Staphylococcus aureus enterotoxin-specific IgE is associated with asthma in the general population: a GA²LEN study

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Abstract

Background: Specific IgE to *Staphylococcus aureus* enterotoxins (SE-IgE) has been associated with asthma. In the general population, we aimed to determine the prevalence of and risk factors for serum SE-IgE and to examine the association with asthma.

Methods: A postal questionnaire was sent to a random sample of adults in 19 centers across Europe. A random sample of respondents was invited for clinical examination upon which they answered a questionnaire, underwent skin prick tests (SPTs) for common aeroallergens, and provided blood for measurement of total IgE and SE-IgE. Risks were analyzed within centers using weighted logistic regression, and overall estimates calculated using fixed-effects meta-analysis.

Results: 2908 subjects were included in this analysis. Prevalence of positive SE-IgE was 29.3%; no significant geographic variation was observed. In contrast to positive skin prick tests, SE-IgE was more common in smokers (<15 pack-year: OR 1.11, $P = 0.079$, ≥15 pack-year: OR 1.70, $P < 0.001$), and prevalence did not decrease in older age-groups or in those with many siblings. Total IgE concentrations were higher in those with positive SE-IgE than in those with positive SPT. SE-IgE was associated with asthma (OR 2.10, 95% confidence interval [1.60–2.76], $P = 0.001$) in a concentration-dependent manner. This effect was independent of SPT result and homogeneous across all centers.

Abbreviations
CI, confidence interval; CRS, chronic rhinosinusitis; IQR, interquartile range; SE-IgE, specific IgE for *S. aureus* enterotoxin mix (SEA, SEC, TSST1); SPT-ANY, skin prick test to any of the tested allergens; SPT-HDM, skin prick test for house dust mite; SPT, skin prick test.

Conclusions: We report for the first time that SE-IgE is common in the general population throughout Europe and that its risk factors differ from those of IgE against aeroallergens. This is the first study to show that SE-IgE is significantly and independently associated with asthma in the general population.

In the general population, asthma or bronchial hyper-responsiveness is strongly associated with positive skin prick tests to common environmental perennial allergens (such as house dust mite and cat dander) (1) and with elevated levels of serum IgE to these allergens (2, 3). High total IgE concentrations have also been associated with asthma, even in the absence of detectable specific IgE (4). More recently, specific IgE antibodies directed against bacterial products such as Staphylococcal enterotoxins have been described locally in the upper airways (5). Enterotoxins are proteins secreted by most strains of *Staphylococcus aureus* and have classically been associated with food poisoning and toxic shock syndrome. Specific IgE to *S. aureus* enterotoxins (SE-IgE) has been found in the serum of patients with atopic dermatitis (6) and in nasal polyp tissue (5) and in the latter has been associated with more severe eosinophilic inflammation and the presence of comorbid asthma (7, 8). Small clinical studies have shown that SE-IgE is present in the peripheral blood from adults (9) and teenagers (10) with asthma and in those with severe asthma (11, 12).

The prevalence of *S. aureus* enterotoxin IgE and its association with asthma and sensitization to common allergens in the general population is unknown. The Global Allergy and Asthma Research Network (GA²LEN) conducted an international multicenter population-based study to determine the prevalence of and risk factors for asthma, allergy, and sinusitis in the European adult population and included measures of SE-IgE. In this report, we describe the prevalence of and risk factors for this *S. aureus* enterotoxin IgE and examine its association with asthma and total IgE concentration. We also compare the epidemiology of SE-IgE with that of sensitization to other allergens.

Methods

Study design

A postal questionnaire about symptoms of asthma, rhinitis, and chronic rhinosinusitis (CRS) was sent to a random sample of participants aged 15–75 years, identified from a population-based sampling frame in 19 centers (as described previously (13, 14)—see Fig. 1). Except for Montpellier, all centers conducted a clinical examination of a sample of responders (n = 3505), which was selected randomly from four groups—those with asthma, with CRS, with asthma and CRS, and with neither asthma nor CRS, according to the initial questionnaire.

The same protocol was used in all centers, with centralized fieldworker training. The postal survey was conducted between September 2007 and December 2008, and the clinical examinations were held between August 2008 and August 2010. In each center, the study was approved by local ethical review boards.

Variables

At the clinical interview, participants underwent interviewer-administered questionnaires, skin prick tests (SPTs) (grass mix, timothy grass, birch, *Blattella*, olive, *Artemisia*, *Parietaria*, *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria*, cat, dog) using allergens as described previously (15), and venepuncture for measurement of serum total IgE and specific IgE to a mixture (9) of *S. aureus* enterotoxin A, *S. aureus* enterotoxin C, and toxic shock syndrome toxin 1 (further referred to as SE-IgE). Assays were conducted in a single laboratory (Academic Medical Center, Amsterdam) using ImmunoCAP® (Phadia, Uppsala, Sweden).

Definitions

Asthma was considered present if participants reported they 'ever' had asthma and they had experienced at least one of the following in the preceding 12 months: wheezing, waking up with chest tightness, waking up with shortness of breath, or waking up with cough (13). SPT was considered positive if the mean wheal diameter at 15 min was greater than 0 mm (16). SPT to house dust mite was considered positive if there was a wheal for either *D. pteronyssinus* or *D. farinae*.

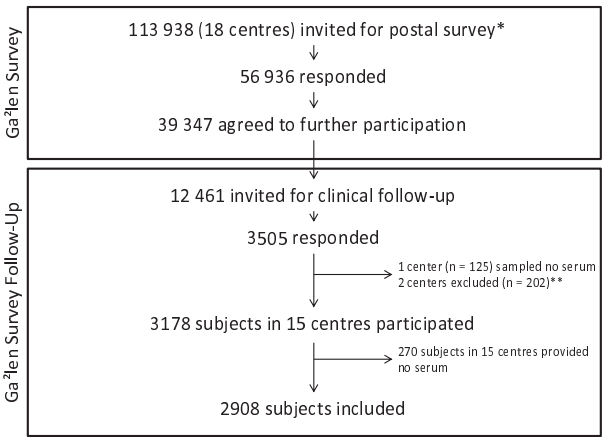

Figure 1 Study flowchart. Results from the first phase of the study (GA²LEN Survey, upper part) have been published before (13, 14). *This number only includes centers that participated in both the postal and clinical study. ** One center excluded for overall low rate of response and low rate of blood sampling (n = 50), one center excluded for low rate of sampling of controls (n = 152)

As per manufacturers' recommendations, a serum SE-IgE concentration above 0.10 kUA/L was considered positive (9, 11). Total IgE concentrations greater than 100 kUA/L were categorized as high.

Statistical methods

As responders to the postal survey were selected for clinical interview using a case–control design, inverse sampling-probability weights (17) were applied to standardize the joint distribution of baseline asthma and CRS status and study center to that of the postal survey. This means the prevalence and effect estimates presented in this report reflect those we would see whether all postal survey responders in the centers sampled had been seen in the clinical examination. As CRS was not considered an outcome variable in this study, analyses were weighted based on the sampling status of CRS, but no further analyses were performed.

Unadjusted prevalences and unadjusted and confounder-adjusted odds ratios for SE-IgE, house dust mite-positive SPT, any positive SPT, and asthma were estimated using logistic regression with sampling-probability weights and Huber variances. For ordinal predictor variables (age, pack-year, sibship size, specific IgE concentration tertiles), linear trend in effect was tested by applying logistic regression on the category rank value of the predictor. Unadjusted geometric means and adjusted geometric mean ratios for SE-IgE and total IgE were estimated using linear regression on the logged values. Tests for interaction of two predictor variables were performed by including the product of the predictors in the model.

Estimates were mutually adjusted for confounders, which included gender, age-group, smoking pack-years, sibship size, and parental history of allergy. Only subjects with serum sampled were included in the analyses. Other missing data were deleted pairwise.

All analyses were carried out within centers. Because of small sample sizes ($n < 5$) in some case groups in the two UK and three Polish centers, data were pooled to country level. Within-center estimates were combined using fixed-effects meta-analysis, and heterogeneity was assessed with the chi-square and I^2 statistic (18). Analyses were conducted using STATA v11.1 (StataCorp, College Station, TX, USA). Confidence intervals are 95% wide and indicated by square brackets.

Results

The overall response to the postal survey in the 18 centers that also took part in the clinical survey was 56936/113938. Of these, 12461 were invited for further tests, and 3505 (28.1%) responded (Fig. 1). Three centers were excluded from analysis (one collected no serum samples, one had too few serum samples, one had too few subjects sampled in the control group). No serum measure was available from 268 subjects, leaving a final sample of 2908 subjects in 15 centers. The median age was 48.9 years (IQR 36.0–60.3 year), and 56.7% of subjects were female.

Prevalence and risk factors of SE-IgE and sensitization to aeroallergen

Table 1 shows the weighted population prevalence of specific IgE to *S. aureus* enterotoxins (SE-IgE), positive skin prick tests to house dust mite (SPT-HDM), and positive SPT to

Table 1 Overall weighted prevalences of outcome parameters, as assessed in the follow-up phase. In each area, prevalence estimates were weighted for sampling by case status (control, asthma, CRS, or asthma + CRS) in survey phase

			SE-IgE		HDM-positive SPT		Any positive SPT		Asthma	
Area		Total *N*	Prevalence (%)	95% CI	Prevalence (%)	95% CI	Prevalence (%)	95% CI	Prevalence (%)	95% CI
Belgium	Ghent	148	28.3	[20.5–37.6]	28.18	[20.2–37.9]	45.7	[35.9–55.9]	9.1	[5.7–14.1]
Denmark	Odense	363	28.1	[21.8–35.5]	9.55	[6.0–14.8]	34.2	[27.3–41.9]	8.3	[6.1–11.2]
Finland	Helsinki	162	34.5	[26.0–44.2]	10.47	[5.8–18.1]	47.4	[37.9–57.2]	8.6	[5.9–12.3]
Germany	Brandenburg	177	27.7	[19.5–37.8]	10.54	[5.8–18.6]	51.1	[40.8–61.3]	4.6	[3.3–6.5]
Germany	Duisburg	191	27.2	[20.9–34.4]	19.82	[14.4–26.7]	54.0	[46.2–61.7]	9.3	[6.7–12.9]
The Netherlands	Amsterdam	215	30.6	[22.9–39.6]	22.83	[16.1–31.3]	49.3	[40.0–58.6]	8.5	[5.3–13.3]
Poland	*	242	35.2	[28.0–43.2]	16.54	[11.2–23.7]	37.9	[30.1–46.4]	6.4	[4.4–9.3]
Portugal	Coimbra	258	36.1	[29.2–43.7]	26.6	[20.5–33.8]	48.9	[41.0–56.9]	14.4	[10.9–18.7]
Sweden	Stockholm	337	35.7	[28.8–43.2]	8.61	[5.3–13.8]	41.4	[34.1–49.0]	9.9	[7.3–13.2]
Sweden	Umea	276	21.5	[14.3–30.9]	8.97	[4.6–16.8]	45.2	[35.1–55.6]	15.4	[10.6–21.9]
Sweden	Uppsala	378	22.0	[16.1–29.1]	14.38	[9.5–21.1]	50.3	[42.2–58.3]	10.9	[8.3–14.2]
United Kingdom	*	161	29.9	[20.8–40.9]	22.58	[14.6–33.2]	39.1	[28.6–50.8]	17.9	[12.0–26.0]
Overall		2908	29.3	[26.8–31.8]	14.92	[13.1–17.0]	44.4	[41.5–47.2]	10.6	[9.4–11.9]

Total *N*: total number of participants who provided blood samples. SE-IgE: detectable serum immunoglobulin E (>0.10 kUA/l) against mixture of SEA, SEC, and TSST-1. HDM: house dust mite. SPT: skin prick test. CI: confidence interval.

*Estimates pooled on country level because of low within-center sample sizes in Poland (Katowice, Lodz, Krakow) and UK (Southampton, London).

any of the tested allergens (SPT-ANY) in each center. The overall prevalence of SE-IgE was 29.3%, ranging from 21.5% (Umea) to 36.1% (Coimbra). Confidence intervals around estimates were wide but there was little evidence of geographic variation—only one center (Uppsala) had a confidence interval that was lower than the overall estimate. In contrast, there was considerable geographic variation in the prevalence of SPT-HDM (14.9%, ranging from 8.6% in Stockholm to 28.2% in Ghent) and SPT-ANY (44.4%, ranging from 37.9% in Poland to 54.0% in Duisburg).

Risk factors for SE-IgE, SPT-ANY, and SPT-HDM were identified and compared using a common logistic regression model (Fig. 2 and Table 2). SPT-ANY was more common in those with a familial history of allergy and less common in older age-groups (p_{trend} = 0.001), in smokers with >15 pack-year, and in those from larger families (>1 sibling). SPT to HDM was less common in older subjects (p_{trend} < 0.001), more common in those with a familial history of allergy, and was not associated with smoking (p_{trend} in pack-year = 0.570) or with family size (OR per extrasibling = 1.01, p_{trend} = 0.872). Sensitization to SE was more common in those with a familial history of allergy, but unlike SPT-ANY or SPT-HDM, it was more common in smokers, particularly in current smokers (OR current smokers = 2.02 [1.42–2.88], OR ex-smokers = 1.41 [1.06–1.89]). There was a dose-dependent relationship with the number of pack-years (p_{trend} < 0.001). Furthermore, there was some evidence that SE-IgE was more common in those with more siblings (although no overall significance was reached, there was between-center variation in the association: I^2 = 46–62%). The prevalence of SE-IgE was similar in all age-groups and less common in women. Analyses in which SE-IgE was considered as continuous outcome showed similar associations, and the associations were unaltered if adjustment for SPT-ANY or SPT-HDM was made. There was no evidence (P > 0.05) that SE-IgE was associated with parental smoking during pregnancy or childhood, birth order, history of severe childhood respiratory infections, day care attendance, bedroom sharing with siblings, and rural *vs* urban living during childhood (data not shown).

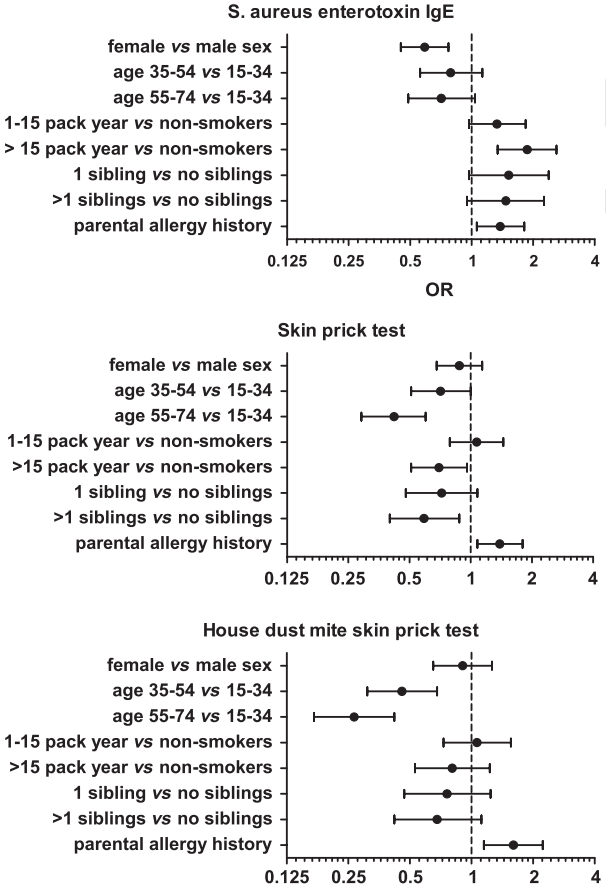

Figure 2 Risk factors for *Staphylococcus aureus* enterotoxin IgE, for positive skin prick tests to any allergen, and to house dust mite. Odds ratios and 95% confidence intervals are obtained from logistic regression model as shown in Table 2. Estimates were mutually adjusted for all predictor variables. Estimates were weighted for case sampling and were done within center after which they were meta-analyzed.

Association of SE-IgE with sensitization to aeroallergens and total IgE

SE-IgE-positive subjects were more likely than SE-IgE-negative subjects to have SPT-HDM or SPT-ANY (age-/sex-adjusted OR: 1.97 [1.47–2.65] and 2.95 [2.23–3.90], respectively). In those sensitized to SE, 22.4% [18.6–26.7%] was also sensitized to house dust mite. However, 42.2% [37.3–47.4] of those positive to SE-IgE had negative SPT to all tested aeroallergens, suggesting that under this testing regime, 16.9% [14.9–19.1%] of the overall population could be considered monosensitized to SE-IgE.

Increased total IgE levels were associated with the presence of SE-IgE and SPT-HDM. This was particularly marked for SE-IgE (adjusted ratio of geometric mean total IgE in those with SE-IgE compared with those without SE-IgE 4.26 [3.77–4.81]) in contrast to SPT-HDM (ratio 2.01 [1.74–2.32]).

SE-IgE, atopy, and asthma

Asthma was present in 10.6% of the general population. Without mutual adjustment, there was a significant association of asthma with SE-IgE, with total IgE, and with positive skin prick tests (SPT-ANY and SPT-HDM) (Table 3A). The prevalence of SE-IgE was higher in asthmatics than in non-asthmatics (40.7% *vs* 28.0%, OR 2.10 [1.60–2.76], P = 0.001).

To assess dose dependency in the association of specific IgE with asthma, IgE values were grouped in tertiles (Fig. 3). Increasing SE-IgE level was associated with increasing risk of asthma (OR 1.20, 1.74, 2.57 for respectively first, second, and third tertile above 0.10 kUA/L; p_{trend} = 0.010). Intervals of the tertiles were 0.10–0.18, 0.18–0.42, and ≥0.42 kUA/L. Total IgE showed a concentration-dependent association with asthma (OR per naturally logged unit increase 1.69 [1.52–1.87]).

Table 2 Multiple logistic regression analysis for the presence of (A) *Staphylococcus aureus* enterotoxin-specific IgE, (B) positive skin prick tests (SPTs), and (C) house dust mite-positive SPT

	Unadjusted estimates		Adjusted estimates			Heterogeneity	
	Prevalence (%)	OR	OR	95% CI	*P*	I^2	*P* (I^2)
(A) *S. aureus* enterotoxin IgE							
Male sex	34.7	(1)	(1)	[0.45–0.77]	<0.001	0%	0.599
Female sex	24.7	0.65	0.59				
Age 15–34	27.8	(1)	(1)				
Age 35–54	28.2	0.94	0.79	[0.56–1.13]	0.193	0%	0.657
Age 55–74	31.0	0.92	0.71	[0.49–1.04]	0.076	34%	0.122
Nonsmoker	25.2	(1)	(1)				
1–15 pack-year	27.6	1.11	1.33	[0.97–1.84]	0.079	0%	0.455
>15 pack-year	38.3	1.70	1.87	[1.34–2.60]	<0.001	7%	0.381
No sibling	22.2	(1)	(1)				
1 sibling	30.3	1.75	1.52	[0.97–2.38]	0.070	46%	0.041
>1 siblings	29.5	1.63	1.47	[0.95–2.26]	0.081	62%	0.003
Negative parental history of allergy	26.9	(1)	(1)				
Positive parental history of allergy	30.5	1.27	1.38	[1.06–1.81]	0.018	0%	0.445
(B) Positive skin prick tests							
Male sex	44.7	(1)	(1)				
Female sex	44.1	0.98	0.88	[0.68–1.14]	0.338	19%	0.258
Age 15–34	55.6	(1)	(1)				
Age 35–55	47.9	0.74	0.71	[0.51–1.00]	0.050	58%	0.007
Age 55–74	35.0	0.38	0.42	[0.29–0.60]	<0.001	52%	0.019
Nonsmoker	46.4	(1)	(1)				
1–15 pack-year	49.2	1.13	1.07	[0.79–1.45]	0.664	27%	0.183
>15 pack-year	36.4	0.60	0.70	[0.51–0.96]	0.027	38%	0.085
No siblings	48.6	(1)	(1)				
1 sibling	47.0	1.08	0.72	[0.48–1.08]	0.116	33%	0.125
>1 siblings	41.6	0.75	0.59	[0.40–0.88]	0.010	54%	0.013
Negative parental history of allergy	41.6	(1)	(1)				
Positive parental history of allergy	50.1	1.37	1.39	[1.08–1.8]	0.011	0%	0.666
C. House dust mite-positive SPT							
Male sex	15.3	(1)	(1)				
Female sex	14.6	0.95	0.91	[0.65–1.26]	0.553	0%	0.953
Age 15–34	21.0	(1)	(1)				
Age 35–55	14.8	0.55	0.46	[0.31–0.68]	<0.001	47%	0.035
Age 55–74	11.9	0.33	0.27	[0.17–0.42]	<0.001	59%	0.005
Nonsmoker	15.3	(1)	(1)				
1–15 pack-year	16.9	1.06	1.06	[0.73–1.56]	0.749	19%	0.254
>15 pack-year	12.3	0.67	0.81	[0.53–1.23]	0.314	0%	0.502
No siblings*	18.9	(1)	(1)				
1 sibling*	16.9	1.00	0.76	[0.47–1.24]	0.269	55%	0.013
>1 siblings*	13.8	0.75	0.68	[0.42–1.12]	0.131	61%	0.004
Negative parental history of allergy	13.3	(1)	(1)				
Positive parental history of allergy	18.5	1.63	1.61	[1.15–2.23]	0.005	0%	0.911

All estimates were weighted for case sampling. Adjusted odds ratios were mutually adjusted for all predictor variables, were estimated within each center, and meta-analyzed.

*One center (Umea, $n = 374$) excluded due to empty groups.

To assess possible confounding or interaction, the association of SE-IgE with asthma was adjusted for SPT sensitization and for total IgE (Table 3B). The association of SE-IgE remained unchanged after adjustment for SPT-ANY or HDM-positive SPT. However, the association of SE-IgE with asthma was attenuated by controlling for total IgE concentration (OR 0.93, [0.67–1.30], $P = 0.662$). This latter adjustment had little effect on the association of total IgE with asthma (OR for total IgE >100 = 1.69, [1.48–1.91], $P < 0.001$). Similarly, the association of total IgE with asthma was little altered after controlling for SPT-ANY (OR 1.47, [1.32–1.64], $P < 0.001$) or SPT-HDM (OR 1.57, [1.41–1.76], $P < 0.001$).

Table 3 (A) Prevalence of asthma and unadjusted and adjusted odds for asthma, for different sensitization states, obtained from logistic regression. (B) Association of SE-IgE with asthma, adjusted for different markers of atopy

	Unadjusted estimates		Adjusted estimates			Heterogeneity	
A	Prevalence	OR	OR	95% CI	*P*	I^2	*P*
SE-IgE negative	8.9	(1)	(1)	[1.6–2.76]	<0.001	4.2%	0.403
SE-IgE positive	14.7	1.76	2.10				
HDM SPT negative	8.9	(1)	(1)	[1.91–3.62]	<0.001	48.0%	0.032
HDM SPT positive	20.7	2.43	2.63				
All SPT negative	5.5	(1)	(1)	[3.12–5.43]	<0.001	0.5%	0.438
Any SPT positive	17.0	3.42	4.12				
Total IgE <100 kUA/l	8.3	(1)	(1)	[2.57–4.49]	<0.001	48.3%	0.031
Total IgE >100 kUA/l	19.3	2.89	3.40				

	Adjusted estimates			Heterogeneity	
B. OR for asthma of SE-IgE, adjusted for	OR	95% CI	*P*	I^2	*P*
Any positive SPT	1.75	[1.31–2.32]	<0.001	0.0%	0.449
HDM-positive SPT	2.01	[1.51–2.67]	<0.001	9.2%	0.355
Total IgE (log)	0.93	[0.66–1.3]	0.662	0.0%	0.528

A: All estimates were adjusted for age, sex, smoking, family history of atopy, sibship size, and history of severe childhood respiratory infections and weighted for case–control status. OR: odds ratio.
B: All estimates were weighted and adjusted as in Table 3A. The natural logarithm of total IgE concentration was used.

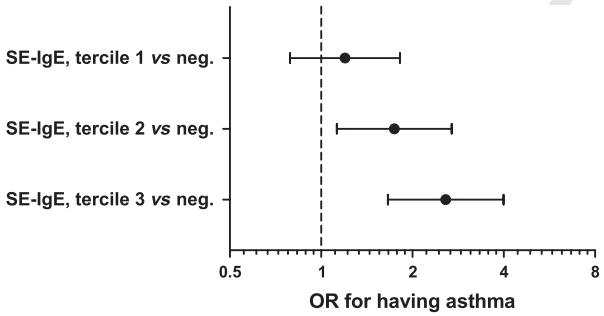

Figure 3 Odds ratios for asthma presence, for each of the tertiles of SE-IgE. The same logistic regression models were used as illustrated in Fig. 2. Estimates were mutually adjusted. Intervals of the tertiles were 0.10–0.18, 0.18–0.42, and ≥0.42 kUA/l.

Discussion

To our knowledge, this is the first large-scale population-based epidemiological study to demonstrate that sensitization to *S. aureus* enterotoxins is common in European adults, occurs independently of sensitization to other common aeroallergens, and is associated with high total IgE concentrations and asthma. In contrast to sensitization to other aeroallergens, SE-IgE is more common in smokers and is as common, if not more common, in those without siblings as it is in those with many siblings.

Participants in this multicenter international population-based epidemiological study were initially identified by random sampling from relevant local population-based sampling frames and can be considered representative of the general population (14). Although they were recruited into the clinical part of the study on the basis of symptoms reported in a postal survey, we have used appropriate statistical techniques to derive estimates that reflect the epidemiological pattern of sensitization and disease in the population. Response to the postal survey varied between centers, but we have previously shown that response was not related to disease status (14).

There is accumulating evidence that *S. aureus* enterotoxins might play a role in pathophysiology of chronic airway disease (19, 20). Enterotoxins act as superantigens, which, unlike allergens, provoke an intense polyclonal immune response by nonspecifically binding the major histocompatibility complex (MHC) class II molecules with the T-cell receptor. This interaction is independent of specific antigen recognition, resulting in a polyclonal T- and B-cell activation (21).

We have shown that almost one of the three adults has serum IgE antibodies to a mixture of enterotoxins secreted by *Staphylococcus aureus*, and this proportion does not vary across European countries to the same extent as do other common aeroallergen sensitizations such as house dust mite. Sensitization to house dust mite and other common aeroallergens showed considerable geographic variation, consistent with previous epidemiological observations (15, 22, 23). The relatively high prevalence of SE-IgE might indicate that exposure to *S. aureus* is common, even though some studies on colonization of the nasal vestibulum with *S. aureus* in healthy subjects reported that only 12–30% (24) carry the bacterium. Little is known about the relationship of sensitization with enterotoxins and colonization by *S. aureus* in the airways, although it is commonly held that colonization is more frequent than SE-IgE and that colonization alone is insufficient to generate an IgE response.

Some groups of the population (men, smokers, and those with a history of allergic disease in the family) are

particularly at risk of SE sensitization. Of particular note is the observation that SE-IgE was more common in smokers, did not show a sharp decline in elderly, and was not decreased in those with many siblings. A lower risk of sensitization to aeroallergens in smokers (as seen in our study) has been reported previously (25), and although this could have been related to a *healthy smoker bias*, the same study showed that house dust mite-specific IgE was more common in smokers, an observation we could not confirm with skin prick test. Cigarette smoke has a disruptive effect on the epithelial barrier of both nasal and bronchial respiratory mucosa, and sensitization, particularly to SE, may be enhanced by loss of this epithelial barrier. Disease-related loss of epithelial barrier integrity is thought to explain the association of SE sensitization with atopic dermatitis (26).

The protective effect of larger family size on allergic sensitization and allergic airway disease is well documented (27, 28) and has been attributed to increased microbial exposure from siblings. We found that family size had little effect on sensitization to SE. We speculate this may be because large families may be a risk factor for an increased risk of colonization early in life with SE, outweighing any other immunologic benefit.

Subjects sensitized to SE were more likely to be sensitized to other aeroallergens, but even so, about one in six adults was considered to be only sensitized to SE-IgE after skin prick test to ten of the most common aeroallergens in Europe. Total IgE levels were high in those who were SE sensitized, much higher than seen in those sensitized to aeroallergens, and this probably reflects superantigen-induced polyclonal IgE formation due to polyclonal B-cell proliferation and antigen-unspecific activation of V-beta subsets of T cells (21).

In line with previous small clinical studies, we have shown that SE-IgE is a risk factor for asthma in the general population (9, 10, 29, 30). Unlike these earlier studies, the asthmatics in this study represent the full spectrum of disease, which may explain why the strength of our associations is smaller than previously reported. The presence of asthma was ascertained by questionnaire, based on the self-reporting of a set of symptoms, as used previously (13), but similar associations were found when self-reported physician-diagnosed asthma was considered (data not shown). Our symptom-based definition has been validated as described previously (31, 32). Sensitization to SE-IgE has also been associated with CRS with nasal polyps and atopic dermatitis. Although no symptom-based definition of nasal polyposis is available, adjustment of the association with asthma, for either CRS (OR 2.06 [1.57–2.71]), allergic rhinitis (OR 1.76, [1.31–2.36]), or atopic dermatitis (OR 2.09 [1.58–2.77]) did not significantly alter the estimates, indicating an independent relationship.

Our study is the first to show that SE-IgE is associated with asthma in a concentration-dependent manner, independent of the increased tendency of those with SE-IgE to also be sensitized to aeroallergens. The relationship with asthma was attenuated by adjustment for total IgE. As SE-IgE and total IgE are considered to be very closely related on the same causal pathway (12), this effect of adjustment cannot be interpreted as evidence of confounding (33). In contrast, it suggests that the pathophysiologic effect of SE-IgE in asthma is predominantly mediated through high total IgE. Supporting this, treatment with omalizumab, a monoclonal antibody against IgE, has been shown to be effective in nasal polyposis, a disease characterized by *S. aureus* enterotoxins (34).

Conclusion

This is the first population-based study to describe the epidemiology of specific IgE to *Staphylococcus aureus* enterotoxins. Of relevance to public health, we here show that IgE sensitization to SE is common in Europe, may occur in the absence of sensitization to other allergens, and follows an epidemiological pattern different to that seen for aero allergen such as house dust mite sensitization, probably reflecting a different pathophysiologic basis. Of great clinical relevance is that IgE to SE is associated with the presence of asthma, independent of sensitization to other allergens. This effect may be mediated through its association with strongly increased total IgE concentrations via the polyclonal superantigen action of enterotoxins.

Authors' contributions

PB, DJ, and CB designed the study and the instruments that were used. PT, RN, and DJ analyzed the data. PT, CB, DJ, and PB interpreted the results. PT and DJ wrote the manuscript to which they equally contributed. All authors took part in data collection and reviewed the manuscript.

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Conflict of interest

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Appendix A

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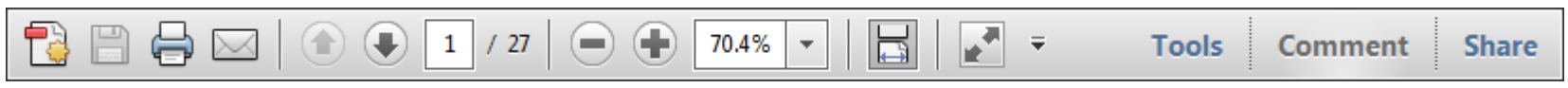

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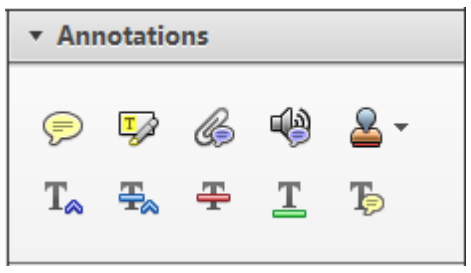

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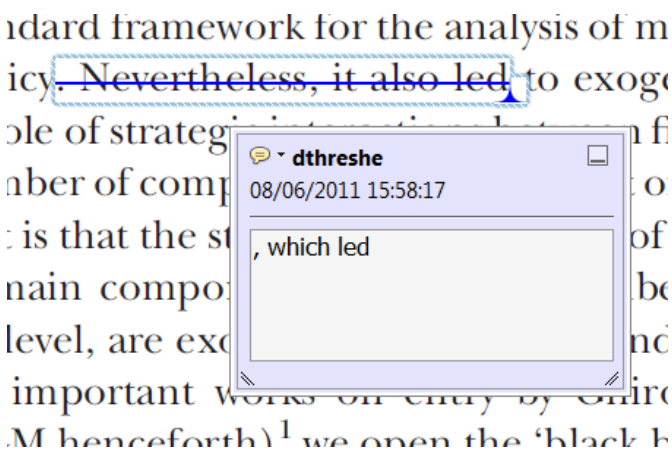

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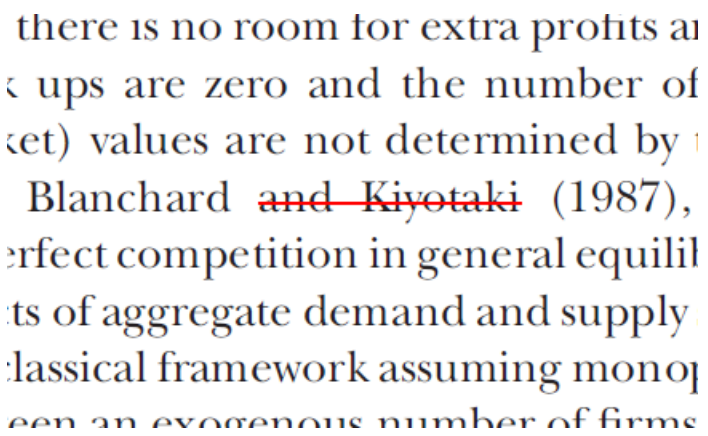

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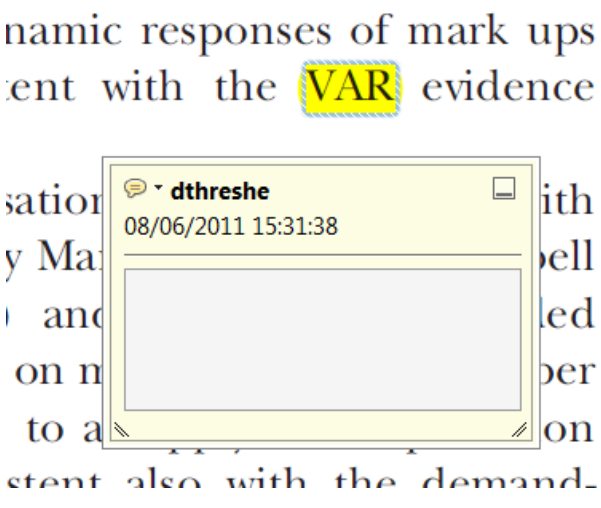

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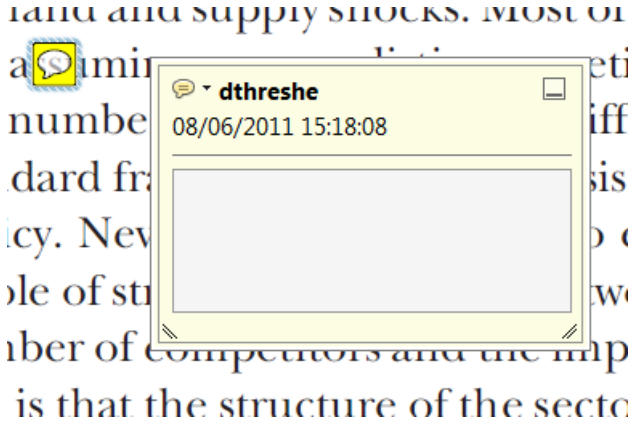

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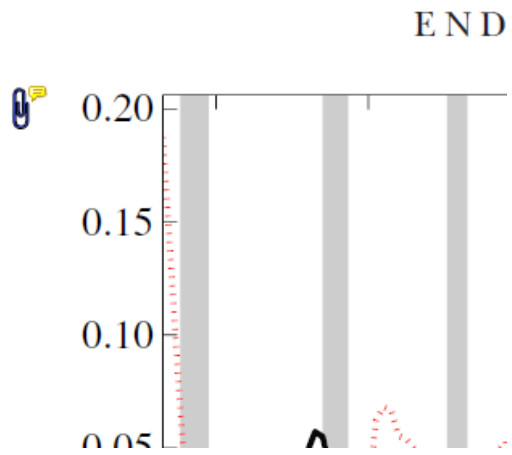

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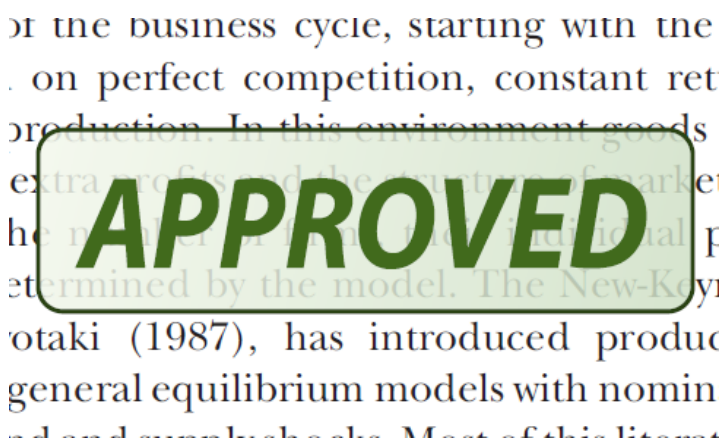

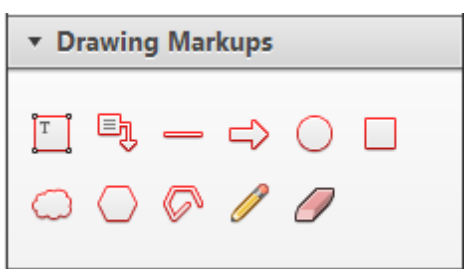

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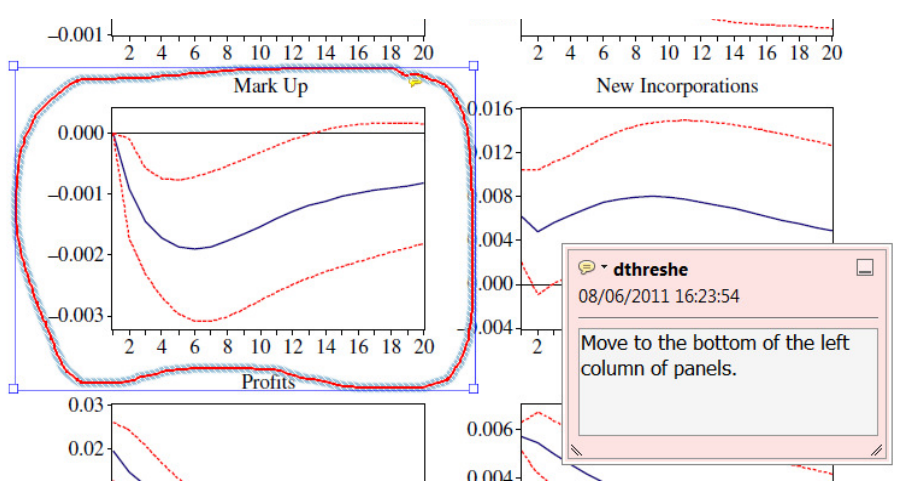

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