Allergy

WILEY | EAACI

ORIGINAL ARTICLE OPEN ACCESS

Food Allergy and Gastrointestinal Disease

The Evolution of Sesame Seed Allergy Over Time

Ru-Xin Foong[1,2,3] | George Du Toit[1,3] | Henry T. Bahnson[1,4] | Ronald van Ree[5] | Suzana Radulovic[1,3] | Serge A. Versteeg[5] | Joanna Craven[1] | Matthew Kwok[1,2] | Zainab Jama[1,2] | Helen A. Brough[1,3] | Kirsty Logan[6] | Michael R. Perkin[7] | Carsten Flohr[8] | Alexandra F. Santos[1,2,3] | Gideon Lack[1,2,3]

[1]Department of Women and Children's Health (Paediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK | [2]Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, UK | [3]Children's Allergy Service, Evelina London Children's Hospital, Guy's and St Thomas' Hospital, London, UK | [4]Bahnson Analytics, LLC, Seattle, Washington, USA | [5]Department of Experimental Immunology, Amsterdam University Medical Centers, location AMC, Amsterdam, the Netherlands | [6]Department of Women and Children's Health, School of Life Course and Population Sciences, King's College London, London, UK | [7]Population Health Research Institute, St George's, University of London, London, UK | [8]St John's Institute of Dermatology, King's College London and Guy's & St Thomas' NHS Foundation Trust, London, UK

Correspondence: Ru-Xin Foong (ruxinfoong@gmail.com) | Alexandra F. Santos (alexandra.santos@kcl.ac.uk) | Gideon Lack (gideon.lack@kcl.ac.uk)

Received: 20 August 2025 | **Revised:** 20 January 2026 | **Accepted:** 9 February 2026

Keywords: biomarkers | food allergy | IgE | mast cell activation test | resolution | Ses i 1-sIgE | sesame allergy

ABSTRACT

Background: The prevalence of sesame allergy (SA) is increasing but little is known about how it changes over time. Our aims were to observe the natural history of sesame over time and the changes in biomarkers between sesame allergic and sesame sensitised but tolerant (SS) children.

Methods: Participants were recruited from the EAT and EAT-On studies in the UK who were exclusively breastfed babies seen at 3-months (m) old and followed up until 7–12 years (y) old. Clinical characteristics, skin prick test (SPT), sesame-specific IgE (sIgE), Ses i 1-sIgE and mast cell activation test (MAT) to sesame were assessed at 12 m, 36 m and 7–12 y. SA status was determined at 7–12 y.

Results: The period prevalence of SA increased from 0.5% (6/1170) between 12 and 36 m to 1.5% (14/947) between 7 and 12 y, with 71.4% of cases developing after 36 m. Longitudinal biomarker analyses were performed on SA and SS children ($n = 301$): 4 had persistent SA, 10 had new SA, 1 outgrew SA and 286 were SS. Children with SA at 7–12 y had larger SPT at 36 m and at 7–12 y, higher sesame-sIgE and Ses i 1-sIgE levels from 12 m onwards compared to SS children ($p < 0.001$). There were small but significant differences in MAT. A larger increase of sesame-sIgE and Ses i 1-sIgE from 12 to 36 m was predictive of new SA at 7–12 y.

Conclusion: The period prevalence of SA increased from 0.5% between 12 and 36 m to 1.5% between 7 and 12 y in a general population. Sesame-sIgE and Ses i 1-sIgE are informative biomarkers in terms of SA development, persistence and resolution.

1 | Background

Food allergies are becoming increasingly prevalent in children around the world with sesame seed allergy (SA) emerging as a more recent but common food allergy [1]. The prevalence of SA ranges from 0.1% to 0.9% based on self-report, skin prick test (SPT) or oral food challenge (OFC) [2]. Severe anaphylactic reactions can occur in children with varying rates depending on the geographical region (e.g., higher rates reported in the Middle East compared to North America) [3]. In fact, sesame is the second most common food to cause anaphylaxis in Israeli children [4]. A US study reported that 62% of children

Abbreviations: OFC, oral food challenge; SA, sesame seed allergy; sIgE, specific Immunoglobulin-E; SPT, skin prick test; SS, sesame sensitised but not allergic.

Alexandra F. Santos and Gideon Lack should be considered joint senior authors.

with SA present with anaphylaxis and for those with established SA, the annual rate of accidental exposure is 15.9% [5]. SA is usually persistent, with limited data in the literature indicating that natural tolerance develops in only 20%–30% of children [2, 6]. There is an association between sesame, peanut and tree-nut allergies with SA occurring in 15%–54% of patients with peanut allergy, 8%–14.8% of patients with tree-nut allergy and 50%–54% of children who have peanut and tree-nut allergies [2].

With its rising prevalence, accurate diagnosis and appropriate management of SA become even more important. A recent systematic review of the diagnostic accuracy for food allergy, including SA [7], reported optimal cut-offs for IgE-mediated SA of 8 mm for SPT (sensitivity 0.70, specificity 0.89), 7.5 kUA/L for sesame-sIgE (sensitivity 0.70, specificity 0.83), 2.0 kUA/L for Ses i 1-sIgE (sensitivity 0.77, specificity 0.87) and 10.9% CD63+ basophils for BAT to sesame (sensitivity 0.89, specificity 0.93) [7]. However, there is still a degree of variability between studies in terms of diagnostic cut offs. The discrepancies in SPT cut-offs across studies could be attributed to the type of material used for testing as allergens present in the various forms of sesame and with different extract preparation methods. For instance, SPT commercial extracts are poor in terms of lipophilic allergen content, such as oleosins, which are important in SA and present in oily forms of sesame such as tahini, which can be used for prick-to-prick testing [8]. Variation in reported diagnostic cut-offs has also been observed for sesame-sIgE [9]. The use of component testing, specifically Ses i 1-sIgE, has been shown to have high specificity for SA [10, 11]. Maruyama et al. reported that a recombinant form of Ses i 1-sIgE had better diagnostic performance compared to sesame-sIgE in terms of specificity (85.7% vs. 48.2%, respectively) [11] The use of novel diagnostic tests such as the basophil activation test (BAT) for sesame is being studied. The mast cell activation test (MAT) has, to our knowledge, yet to be studied for SA diagnosis.

We aimed to determine the prevalence of SA in a general population and its natural resolution across a decade, and to identify biomarkers of persistence and resolution of SA over time.

2 | Methods

2.1 | Study Population

The EAT study was a randomised controlled trial that recruited exclusively breastfed infants at 3-months who were randomised to a standard introduction group (i.e., exclusively breastfed for 6-months and then parents introduced solid as per national guidelines) or an early introduction group (i.e., introduced 6 allergenic foods including sesame from 3 to 4 months of life alongside breastfeeding). They were seen at 3-months (3 m), 12-months (12 m) and 36-months (36 m), with the primary outcome being the diagnosis of IgE-mediated food allergy between 12 and 36-months old [12]. The EAT-On study was the follow-on study conducted to establish whether the effects seen at the end of the EAT study represented a delay in food allergy onset or sustained tolerance. The study was approved by the Health Research Authority London—Chelsea Research Ethics Committee (Ref: 17/LO/1687). The EAT-On cohort was seen between ages 7–12 years (7–12 y) old. Participants were selected from this cohort and informed consent was obtained.

SA status was confirmed at 7–12 y by either a positive OFC or a clinician-taken history of an allergic reaction to sesame and SPT to tahini ≥ 5 mm, if an OFC was not conducted. Tolerance was determined by a negative OFC and/or consumption of sesame regularly in the child's diet defined by at least 3 g of sesame protein 3 times in the last 6 m. If the child was not consuming sesame and OFC was indeterminate or not available, a study-specific algorithm was used to determine the allergic status to sesame (Figure S1). Sesame sensitisation (SS) was defined as having a sesame SPT ≥ 1 mm and/or sesame-sIgE ≥ 0.1 kUA/L, based on previous literature cut-offs for peanut [13–15].

2.2 | Skin Prick Testing

SPT to sesame were performed on the forearm or back, using a standardised lancet (ALK-Abello), sesame extract (ALK-Abello), fresh whole unhulled tahini (26 g/100 g protein Sunita Bedford, UK), histamine 10 mg/mL or 50% glycerol, 50% buffered saline. Skin test sites were measured after 15 min as the average of the widest diameter of the wheal and its perpendicular.

2.3 | Immunoglobulin Levels

Serum sIgE and $sIgG_4$ to sesame and Ses i 1-sIgE were measured by ImmunoCAP (Thermofisher, Uppsala, Sweden). Ses i 1-sIgE was only assayed for participants with a sesame-sIgE ≥ 0.1 kUA/L. Therefore, for subjects with sesame-sIgE levels < 0.1KU/L, the median ratio of Ses i 1-sIgE to sesame-sIgE was used to impute the value for Ses i 1-sIgE. The ratio of sesame $sIgG_4$/IgE was calculated after sesame-$sIgG_4$ levels were converted from μg/L to ng/mL and sesame-sIgE levels were converted from kU/L to ng/mL using the formula ($IgG_4 \div (IgE \times 2.4)$) [16].

2.4 | Sesame Oral Food Challenge

An OFC was offered to any participant who had any of the following:

- SPT > 0 mm to sesame
- Previous history of SA
- Participants who were infrequent consumers of sesame (i.e., who consumed < 3 g of sesame protein at least 3 times in the last 6-months).

All OFCs were open challenges unless there was an investigator's concern about subjective symptoms, in which case a double-blinded placebo-controlled food challenge to sesame was performed using tahini. The open challenges involved a single-dose cumulative challenge or an incremental challenge, if deemed to be at a higher risk of reacting.

2.5 | Mast Cell Activation Test

LAD2 cells (Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases) were primed with IL-4 and incubated for 5 days before being sensitised with patient's plasma. The cells were stimulated with sesame extract (ALK Abello) diluted in RPMI medium (GIBCO, Paisley, UK) at three concentrations (1000, 10,000, 100,000 ng/mL), anti-IgE (1 μg/mL, Sigma-Aldrich, Poole, UK) or ionomycin (1 μg/mL, Millipore). Cells were stained with CD63-APC (Biolegend, San Diego, Calif) and, separately, with surface markers IgE-PE (Biolegend), CD32-APC, FceRI-FITC (eBioscience, San Diego, Calif). Viability dye eFluor 450 (eBioscience) was added to all tubes to exclude dead cells. Flow cytometry (CytoFLEX flow cytometer) was performed with FACSDiva software (BD Biosciences, San Jose, Calif) and data were analysed using FlowJo v10.8 Software (BD Life Sciences, Ashland OR). Dose finding experiments were performed to determine the optimum concentration for sesame extract, and subsequently the optimal concentration was used. MATs were performed for sesame allergic, and sesame sensitised but not allergic children (SS) with sesame-sIgE ≥ 1.0 kUA/L at 36 m, based on previous minimum allergen-specific IgE levels needed to induce mast cell activation to peanut in peanut allergic patients [17] MAT was done using samples collected at the three time points (12 m, 36 m, 7–12 y) if available. Imputed MAT results were performed for participants if they had a sesame-sIgE < 1.0 kUA/L based on previous work with peanut allergy that has shown MAT to be dependent on sIgE levels (i.e., if sIgE is undetectable or very low, MAT will be negative).

2.6 | Statistical Analysis

Data analysis was performed using Stata Statistical Software Release 17 College Stations, TX. StataCorp LLC and JMP, Version 18. SAS Institute Inc., Cary, NC, 2023. Mann Whitney and Kruskall-Wallis tests were performed to compare clinical characteristics and biomarkers between SA and SS children and for sub-group analysis. Logistic regression models were used to identify covariates that predicted SA status at 7–12 y. Univariate analyses were first conducted to assess the impact of individual covariates on SA at 7–12 y, followed by multivariable regression models to compare all biomarkers at each time point (i.e., SPT, sesame-sIgE, Ses i 1-sIgE and MAT). Additionally, a separate model was used to examine the longitudinal impact of single biomarkers across all 3 time points (i.e., 12 m, 36 m, 7–12 y) in predicting SA status at 7–12 y. Finally, a logistic regression model was fit to predict the development of new SA at 7–12 y, using the change in biomarkers from 12 to 36 m.

3 | Results

3.1 | Study Population

A total of 947 participants were enrolled in the EAT-On study. SA status was determined as shown in Figure S2. Out of the cohort, only participants who were SA and SS participants ($n = 301$) were included in the current analysis with 14 having SA and 287 being SS at 7–12 y. Four participants had persistent SA, 10 participants developed new SA, 1 patient outgrew their SA and 286 were sensitised to sesame but never allergic.

The prevalence rate of SA at 7–12 y was 1.5% (14/947, 95% CI 0.8%, 2.5%), which increased from the 0.5% (6/1170, 95% CI 0.2%, 1.1%) prevalence rate reported at the end of the EAT study. We also compared sesame sensitisation rates (defined as either IgE ≥ 0.1 kUA/L and/or SPT ≥ 1 mm) across time, which showed a progressive increase in all 3 biomarkers (Figure 1). Of the children with SA at 7–12 y, 71.4% (10/14) developed SA after 36 m of which 64.3% (9/14) were confirmed by OFC and 35.7% (5/14) were confirmed by clinical history of reaction and SPT ≥ 5 mm (see Figure S2 and Table S1). For the children who had clinical assessments during EAT and EAT-On studies, the rate of SA resolution was 20% (1/5). If we assumed that the 1 child who was diagnosed with SA from the EAT study but did not return for the EAT-On study remained allergic, the resolution rate would be 16.7% (1/6).

Children with SA were younger at the time they were seen in the EAT On study, have a history of eczema and have eczema or asthma at 7–12 y compared to the SS children and the children with no other food allergies and not sensitised to sesame (Table S2). When comparing all 3 groups, non-Caucasian children were more likely to be sesame allergic than Caucasian (5.4% (5/92) vs. 1.4% (9/646) ($p < 0.01$)) (Table S2).

3.2 | Comparison of Biomarkers Between Sesame Allergic and Sesame Sensitised but Not Allergic Groups

The SA group had higher serological and SPT biomarkers compared to the SS groups (Table 1). SPT to tahini was significantly higher in the SA group compared to the SS group at 7–12 y. SPT was also significantly different at 36 m despite both median SPT being 0 mm. Sesame-sIgE was significantly higher in the SA group compared to the SS group from 12 m onwards, as was Ses i 1-sIgE. The percentage of sesame-activated CD63+ LAD2 cells was also significantly higher in the SA group from 12 m onwards compared to the SS group, although actual mast cell activation was low. Overall, at 3 m there was no distinction in biomarkers between the SA and SS groups; however, from 12 m onwards, IgE markers and MAT were higher in the SA group and sIgG4 were higher in the SS group.

3.3 | Comparison of Biomarkers Between Sub-Groups of SA Status at 7–12 Years

Children with persistent SA and the child who had SA at 36 m and outgrew it had larger SPT (median of 3.8 and 3 mm, respectively) compared to SS who had SPT 0 mm ($p < 0.01$) (Table 2). At 7–12 y, children with new SA had significantly higher SPT compared to the other groups ($p < 0.001$). Interestingly, SPT of children with persistent SA stayed approximately the same from 36 m to 7–12 y at lower levels compared to those who developed new SA.

Sesame-sIgE was significantly higher in the children with SA from 12 m onwards (i.e., persistent or new SA) although the rise

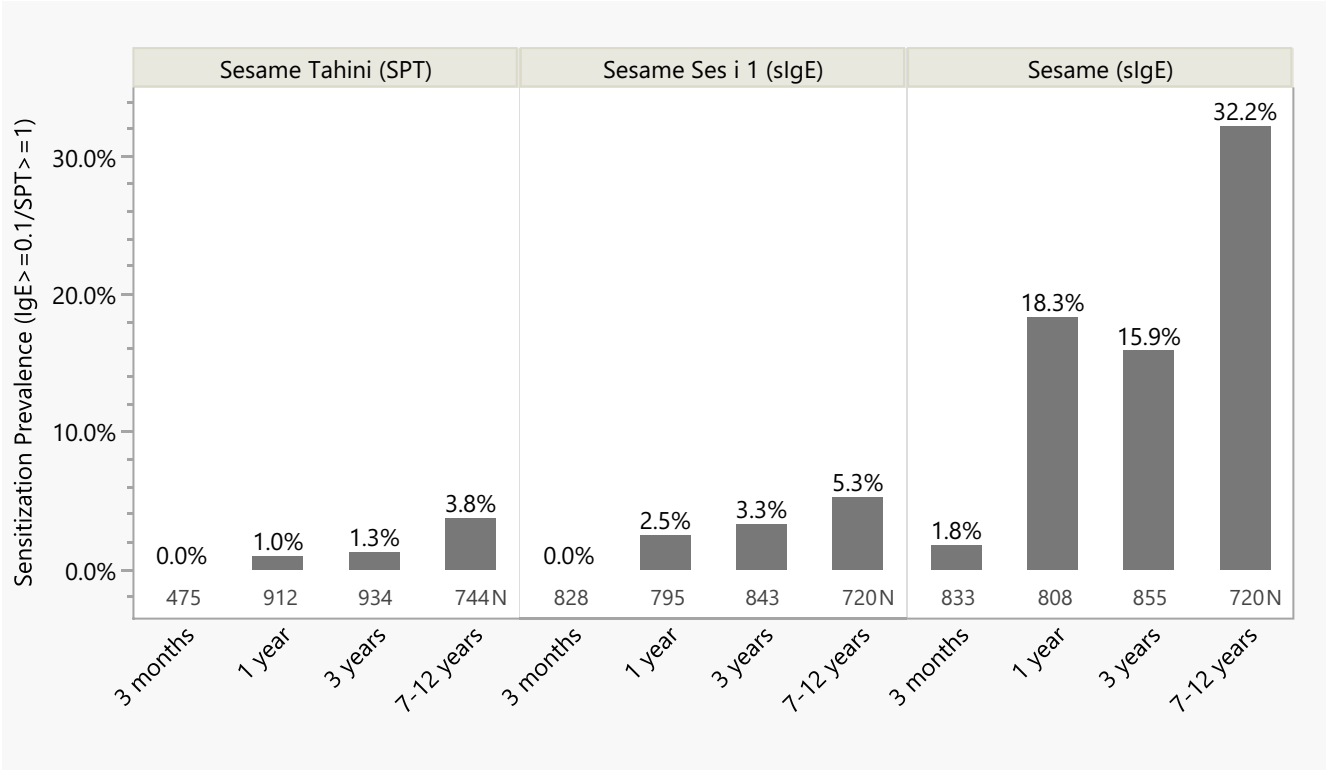

FIGURE 1 | This figure shows the sesame sensitisation prevalence at the different time points the children were seen during childhood.

in sesame-sIgE was only evident in the new SA group at 36 m. Ses i 1-sIgE component was significantly different from 12 m onwards as well and continued to increase in the groups that were SA at 7–12 y. At 12 m, the children with persistent SA had higher Ses i 1-sIgE component levels compared to the child who subsequently outgrew her SA and the new SA group (who at 12 m were not SA). By 7–12 y, those with SA (whether that was persistent or new) had significantly higher Ses i 1-sIgE levels compared to the outgrown SA and SS groups (Table 2). Table 2 also shows changes in MAT over time at the optimal concentration of 10,000 ng/mL. MAT results were higher in children with persistent and new SA compared with SS and the child whose SA resolved. The %CD63+ LAD2+ cells were, however, low across groups.

A comparison between the biomarkers from the children who had SA at 12–36 m, those who had new SA at 7–12 y old and the children sesame sensitised but not allergic is compared in Figure 2. The graph depicts how children with SA at 7–12 y, regardless of when they developed it, had increasing sesame-sIgE and Ses i 1-sIgE levels from 12 m.

Further analysis focussing on the children who developed new SA and SS groups showed similar sesame consumption in the two groups at 12 m but by 36 m the SS group was consuming significantly higher amounts of sesame in terms of weekly consumption (Table S3). Among the 10 children who developed new SA at 7–12 y, 60% were either consuming no sesame or only eating it once a month at 36 m. The remaining 40% who reported consumption of sesame more frequently at 36 m (i.e., anywhere from daily to four times a week) were found to be allergic during their EAT-On study. By 7–12 y, none of those who had new SA at the EAT-On study were consuming any sesame.

3.4 | Biomarkers Associated With SA Diagnosed at 7–12 Years

Logistic regression analyses were performed to see which covariates were associated with having SA at 7–12 y. Univariate analyses for individual covariates showed that history of eczema or asthma at 7–12 y, sesame SPT at 36 m or 7–12 y and sesame-sIgE, Ses i 1-sIgE and MAT to sesame at 12 m, 36 m or 7–12 y were all significantly associated with SA at 7–12 y (Table S4). In the multivariate logistic regression models, sesame SPT at 36 m and 7–12 y and Ses i 1-sIgE at 12 m, 36 m and 7–12 y remained associated with SA at 7–12 years (Table S5). These analyses show that Ses i 1-sIgE was the best biomarker at all time points when comparing it to the other biomarkers at each time point, which suggests that Ses i 1-sIgE might have a causal role in driving SA. The ROC analyses of the logistic regression models for SA at the three different time points all yielded AUC ≥ 0.9, which suggests that the models have excellent discriminatory power in determining SA versus SS cases.

Figure 3 and Figure S3 (real data) demonstrate the change in sesame-sIgE and Ses i 1-sIgE from 12 and 36 m in the children who developed new SA at 7–12 y and the SS children.

We then created a model to predict the likelihood of developing new SA by 7–12 y based on changes in sesame-sIgE and Ses i 1-sIgE between 12 and 36 m. This model showed that children with a greater increase in Ses i 1-sIgE levels or sesame-sIgE from 12 to 36 m had increased odds of having SA at 7–12 y (OR 7.6, 95% CI 2.3, 25, $p < 0.001$ and OR 9.5, 95% CI 2.4, 37.3, $p = 0.001$, respectively) (Figure 4; also see Tables S6 and S7). We were unable to perform this regression analysis for SPT due to the fact that many of the children who went on to develop new SA at

TABLE 1 | Comparison of biomarkers between sesame allergic and sesame sensitised but not allergic participants across time (allergic status determined at 7–12 years old).

	Sesame allergic ($n=14$)	Sesame sensitised but not allergic[a] ($n=287$)	
	Median (IQR)	Median (IQR)	*p*
Sesame (tahini) SPT mm			
3 months[b]	0 (0, 0) ($n=9$)	0 (0, 0) ($n=154$)	—
12 months	0 (0, 0)	0 (0, 0) ($n=282$)	0.29
36 months	0 (0, 3)	0 (0, 0) ($n=284$)	<0.001
7–12 years	7 (3, 16.5)	0 (0, 0) ($n=285$)	<0.001
Sesame-sIgE kUA/L			
3 months	0.06 (0.06, 0.07) ($n=9$)	0.06 (0.05, 0.07) ($n=252$)	0.24
12 months	1.7 (0.4, 6.6) ($n=12$)	0.08 (0.05, 0.2) ($n=255$)	<0.001
36 months	5.2 (1.1, 11.3) ($n=12$)	0.07 (0.05, 0.2) ($n=263$)	<0.001
7–12 years	6.3 (1.6, 19.4)	0.16 (0.1, 0.4) ($n=278$)	<0.001
Ses i 1-sIgE (kUA/L)			
3 months	0.01 (0.01, 0.01)	0.01 (0.01, 0.01) ($n=247$)	0.85
12 months	0.3 (0.1, 0.9) ($n=12$)	0.01 (0.01, 0.01) ($n=245$)	<0.001
36 months	4.0 (0.5, 6.0)	0.01 (0.01, 0.01) ($n=286$)	<0.001
7–12 years	3.3 (0.4, 7.9)	0.01 (0.01, 0.03) ($n=278$)	<0.001
Sesame IgG4 (μg/L)			
3 months	50.3 (35.9, 78.8) ($n=9$)	54.2 (42.6, 67.0) ($n=243$)	0.93
12 months	520.3 (89.4, 2022.1) ($n=12$)	97.7 (58.5, 352.9) ($n=250$)	0.02
36 months	767.1 (308.6, 2863.7) ($n=12$)	216.9 (91.3, 743.7) ($n=255$)	0.07
7–12 years	620.9 (324.3, 1398.9)	156.8 (60.3, 458.4) ($n=278$)	<0.001
Sesame IgG4/IgE ratio			
3 months	385.1 (249.3, 547.5)	398.9 (290.2, 518.2) ($n=241$)	0.72
12 months	162.9 (26.2, 556.3)	510.1 (273,1, 1140.3) ($n=250$)	<0.01
36 months	94.3 (51.3, 280.7)	1109.1 (510.6, 2548.0) ($n=255$)	<0.001
7–12 years	56.5 (38.6, 118.2)	375.3 (111.5, 1268.8) ($n=278$)	<0.001
Mast cell activation (%CD63+ LAD2 cells)			
12 months	0.8 (0.4, 2.5) ($n=13$)	0.01 (0.01, 0.01) ($n=253$)	<0.001
36 months	0.3 (0.01, 32.9) ($n=12$)	0.01 (0.01, 0.01) ($n=262$)	<0.001
7–12 years	0.4 (0.01, 1.4)	0.01 (0.01, 0.01) ($n=251$)	<0.001

[a]The total *n* is denoted in parenthesis next to each individual biomarker value if it differs from the total *n* of the whole group.
[b]At the 3-month time point, only children in the early introduction group had SPT performed.

7–12 y had no change in their SPT results from 12 and 36 m because they were not sesame allergic at those time points.

4 | Discussion

SA is considered one of the top 14 major food allergies in the UK and US and has recently been considered the 9th most common food allergy [18]. In this cohort recruited from the general population, the prevalence rate of SA increased from 0.5% at 12–36 m to 1.5% at 7–12 y, which is higher than the 0.1%–0.9% rates reported in the literature [2]. This represents a three-fold increase in the prevalence of SA during childhood demonstrating that the kinetics of SA differs from other food allergens. For example, most egg and milk allergies develop during the first year of life with a 50%–60% resolution rate by 6-years old [19–21]. With

TABLE 2 | Comparison of biomarkers for children grouped according to their sesame allergy status determined at 7–12 years.

	Sesame allergic status at the 7–12 year time point				
	Persistent sesame allergy (*n* = 4)	**New sesame allergy (*n* = 10)**	**Outgrown sesame allergy (*n* = 1)**	**Sesame sensitised, not allergic[a] (*n* = 286)**	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	***p* value**
SPT to tahini (mm)					
3 months[b]	0 (0, 0)	0 (0, 0)	—	0 (0, 0) (*n* = 154)	1.00
12 months	0 (0, 1.8)	0 (0, 0)	0	0 (0, 0) (*n* = 281)	0.88
36 months	3.8 (3, 5)	0 (0, 0)	3	0 (0, 0) (*n* = 283)	< 0.01
7–12 years	8.3 (3.5, 11)	6.8 (3, 17.5)	4	0 (0, 0) (*n* = 284)	< 0.001
Sesame-sIgE (kUA/L)					
3 months	0.06 (0.05, 0.07)	0.06 (0.06, 0.07)	0.06	0.06 (0.05, 0.07) (*n* = 251)	0.68
12 months	1.4 (0.43, 51.6)	1.8 (0.4, 3.2)	0.31	0.08 (0.05, 0.2) (*n* = 254)	< 0.001
36 months	1.2 (0.78, 38.6)	6.1 (2.9, 11.3)	0.39	0.07 (0.05, 0.2) (*n* = 262)	< 0.001
7–12 years	12.2 (2.8, 20.4)	6.3 (1.6, 18.4)	0.25	0.2 (0.1, 0.4) (*n* = 277)	< 0.001
Ses i 1-sIgE (kUA/L)					
3 months	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01	0.01 (0.01, 0.01) (*n* = 246)	1.00
12 months	0.7 (0.3, 18.9)	0.3 (0.01, 0.6)	0.33	0.01 (0.01, 0.01) (*n* = 244)	< 0.001
36 months	0.6 (0.2, 10.0)	4.1 (0.9, 5.1)	0.52	0.01 (0.01, 0.01) (*n* = 285)	< 0.001
7–12 years	2.7 (1.3, 4.7)	4.0 (0.4, 9.6)	0.14	0.01 (0.01, 0.03) (*n* = 277)	< 0.001
Sesame-IgG4 (μg/L)					
3 months	39.4 (32.6, 46.2)	75.3 (35.9, 92.2)	41.3	54.4 (42.6, 67.0) (*n* = 242)	0.31
12 months	106.4 (92.5, 1587.6)	703.5 (86.3, 2456.6)	50.0	97.7 (58.8, 352.9) (*n* = 249)	0.07
36 months	454.0 (183.7, 1383.6)	1013.9 (465.3, 3719.6)	85.3	219.8 (91.5, 743.7) (*n* = 254)	0.17
7–12 years	346.7 (257.6, 1668.9)	833.5 (350.2, 1398.9)	107.5	159.7 (60.3, 458.4) (*n* = 277)	< 0.01
Sesame IgG4/IgE ratio					
3 months	289.5 (193.8, 385.1)	448.4 (249.3, 640.5)	286.6	400.0 (290.9, 519.1) (*n* = 240)	0.51
12 months	32.6 (12.8, 89.6)	316.9 (50.9, 610.8)	67.3	511.1 (273,4, 1140.3) (*n* = 249)	< 0.01
36 months	86.6 (35.9, 200.6)	108.8 (57.3, 423.4)	91.1	1116.0 (533.5, 2548.0) (*n* = 254)	< 0.001

(Continues)

TABLE 2 | (Continued)

	Sesame allergic status at the 7–12 year time point				
	Persistent sesame allergy ($n=4$)	**New sesame allergy ($n=10$)**	**Outgrown sesame allergy ($n=1$)**	**Sesame sensitised, not allergic[a] ($n=286$)**	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	***p* value**
7–12 years	44.1 (18.8, 90.4)	57.2 (43.5, 118.2)	178.6	379.5 (111.5, 1268.8) ($n=277$)	<0.001
MAT to sesame (%CD63+ LAD2 cells)					
12 months	0.8 (0.4, 24.5)	0.8 (0.4, 2.5)	0.01	0.01 (0.01, 0.01) ($n=252$)	<0.001
36 months	0.3 (0.07, 1.9)	0.2 (0.02, 3.8)	0.01	0.01 (0.01, 0.01) ($n=261$)	0.02
7–12 years	0.1 (0.01, 3.7)	0.7 (0.01, 1.4)	0.01	0.01 (0.01, 0.01) ($n=250$)	0.01

[a]The total *n* is denoted in parenthesis next to each individual biomarker value if it differs from the total *n* of the whole group.
[b]At the 3-month time point, only children in the early introduction group had SPT performed.

peanut allergy, children develop this allergy by 3–5-years of life although a significant proportion are already allergic by 1-year old [21–23]. The fact that 10 children developed new onset SA at 7–12 y of age having previously been tolerant at 36 m of age is of interest. It is unclear whether they developed late onset SA because they had stopped eating sesame which is a possibility. In the LEAP study, immunological changes continued to occur between 2.5 and 5 years of age in the peanut consumption group and the inhibition of linear IgE epitope spreading to peanut occurred between 2.5 and 5 years of age. The other possibility to consider in the EAT study is that the children who stopped eating sesame did so because they were developing SA manifesting as an aversion to sesame.

SA was found significantly more often in non-Caucasian than Caucasian children (5.4% vs. 1.4%, respectively). This is similar to findings for peanut allergy, where non-White ethnicity was associated with greater development of peanut allergy in the first year of life [24] highlighting that these children are at greater risk of developing food allergies and are important target populations for prevention strategies.

Children with SA at 7–12 y had larger SPT, higher sesame-sIgE and Ses i 1-sIgE levels, and stronger sesame-induced mast cell activation at the different time points compared to SS children. Sesame-sIgE was significantly higher in the SA group at 36 m and 7–12 y compared to the SS group. Although the differences were statistically significant, the median sIgE levels were low in comparison to diagnostic cut-offs for sesame-sIgE in the literature [7, 25]. It is interesting that sesame-sIgE levels in children with persistent SA or new SA increased over time. Perhaps monitoring changes in sesame-sIgE could provide more insight into the development of SA rather than diagnostic cut-offs especially as other studies looking at peanut have reported that decreasing peanut sIgE levels and Ara h 2 are associated with natural resolution of peanut allergy [26, 27] MAT to sesame has not been studied before and, although the sesame allergic children had significantly higher mast cell activation to sesame in comparison to the SS group, the actual percentage of cell activation was low. The low MAT results could be related to the low allergen-sIgE levels and low allergen/total IgE ratios or to the fact that the sesame extract used in the MAT is similar to the sesame allergen extracts used for SPT and that are known for their poorer diagnostic performance compared to modified SPT using tahini [28]. The literature has shown BAT to sesame to be an effective diagnostic tool with high sensitivity and specificity [7]; however, it was not possible for this study due to historical samples being used to test for samples across various time points.

As expected, sesame-sIgG$_4$/IgE ratio was higher from 12 m onwards in the SS group compared to the SA group, as has been previously reported in peanut sensitised but tolerant children compared to children with peanut allergy [15].

The biomarker that best reflected SA at 7–12 y and predicted its development after 36 m was Ses i 1-sIgE, and for most of our children, it was already high from 12 m onwards. Maruyama et al. looked at IgE to different sesame components in the diagnosis of SA and showed that Ses i 1-sIgE had the best diagnostic performance [11]. Another study found that Ses i 1-sIgE was the most indicative parameter in predicting a positive OFC [10]. Children who developed new onset SA after 36 m had Ses i 1-sIgE levels increasing over time from 12 m despite not being allergic at 36 m. 60% (6/10) already had detectable Ses i 1-sIgE levels >0.1 kUA/L at 36 m. There was 1 child who developed new SA, diagnosed by positive OFC at 7–12 y who had consistently low sesame IgE and ses i 1-sIgE even at 7–12 y of age (0.79 and 0.01 kUA/L respectively). There are other sesame proteins that may be useful in diagnosing SA including ses i 2-sIgE or oleosins [29, 30] that were not tested for in our cohort; however, from the evidence available so far, ses i 1-sIgE is still the better diagnostic marker [11].

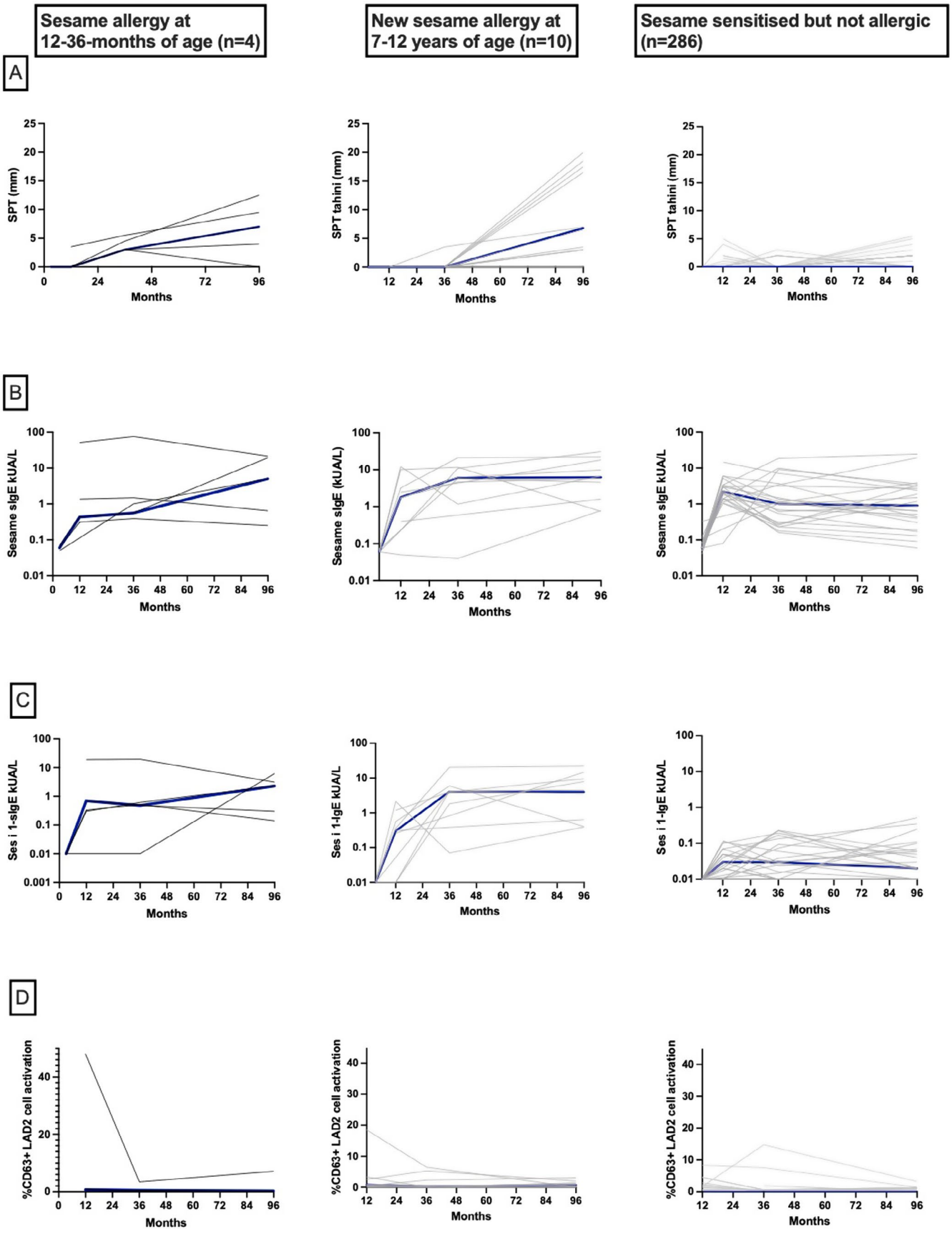

FIGURE 2 | A comparison of sesame biomarkers (A) SPT (tahini), (B) Sesame sIgE, (C) Ses i 1-sIgE, (D) MAT %CD63 activation between those who develop sesame allergy early by 12–36 m, those who developed sesame allergy later in childhood (7–12 years) and those who are sensitised but never allergic. The dark blue lines represent the median value for the biomarkers within each graph and light grey lines represent each individuals changing biomarkers over time.

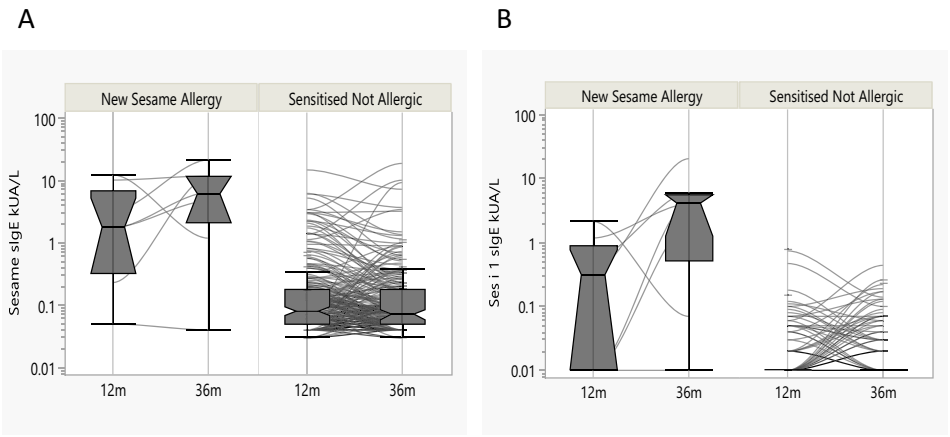

FIGURE 3 | This figure demonstrates the change in (A) sesame-sIgE and (B) Ses i 1-sIgE from 12- to 36-months in the children who went on to develop new sesame allergy compared to those who were sensitised to sesame but never allergic.

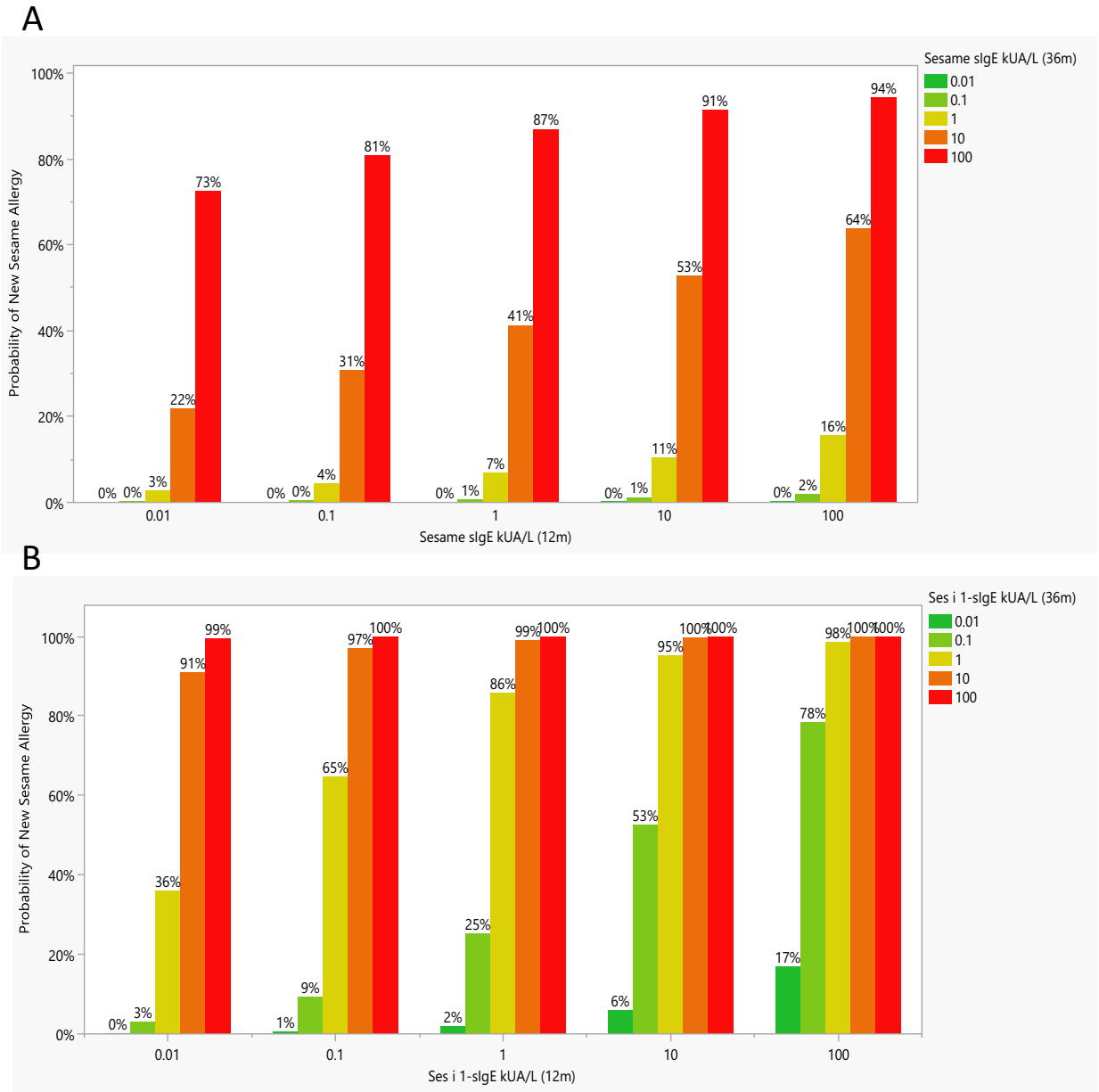

FIGURE 4 | This figure demonstrates the probability of developing new sesame allergy by 7–12-years old based on changes in (A) sesame-sIgE from 12- to 36-months and (B) Ses i 1-sIgE from 12- to 36-months.

Interestingly, 40% of the children who developed new SA at 7–12 y were consuming at least weekly quantities of sesame at 36 m but by 7–12 y all of them were no longer consuming any sesame. It is possible that, by stopping consumption of sesame after 36 m, they lost their tolerance which resulted in the development of SA in later childhood. Alternatively, these children could have developed subclinical symptoms and aversion to sesame that led to cessation of consumption. The predictive model we developed could be used as an early biomarker to help identify children at risk of developing SA later in childhood by monitoring changes in Ses i 1-sIgE and/or sesame-sIgE levels between 12 and 36 m. It is possible that by identifying children with detectable Ses i 1-sIgE early in childhood, greater emphasis on regular sesame consumption could prevent future development of SA.

There are several limitations in this study including the small number of children who were either sensitised and/or allergic to sesame, especially for the subgroup analysis where only 1 child outgrew SA and 4 had persistent SA. There were biomarker data missing (e.g., baseline SPT at 3 m was only performed in children randomised to the early introduction group of the EAT study; Ses i 1-sIgE data and MAT to sesame were performed in a selected group of sensitised children). Imputations were performed for Ses i 1-sIgE and MAT based on sIgE levels where available but there was missing data.

The study has many strengths. It is one of few large studies assessing the natural history and biomarker changes of SA across childhood with rigorous diagnostic criteria including OFC, especially with the threshold for offering an OFC in terms of history of consumption being relatively low. It is a striking observation that 10 new cases of SA developed after 36 m. SA is a food that deserves further studies on allergen characterisation, immune mechanisms of allergy and tolerance acquisition and longitudinal cohorts to better understand its natural history.

5 | Conclusions

The prevalence of SA in this cohort increased three-fold from 0.5% by 3 years to 1.5% at 7–12 years which is higher than previously reported. Most cases of new SA occurred in later childhood, and the rate of SA resolution was 20%. Ses i 1-sIgE levels were significantly higher in SA children compared to SS, and this seems to be the most informative biomarker in terms of SA development, persistence and resolution.

Author Contributions

R.-X.F. designed and led this study including the design, data collection including performance of the mast cell activation tests, data analysis and wrote the first draft of the manuscript. H.A.B., A.F.S. and G.L. were involved in the study design of this work and provided regular input during the analysis phase. G.D.T., S.R., J.C., K.L., H.T.B. and G.L. were members of both the EAT and EAT-On study team who had key roles in the main study protocol design, data collection and analysis but also this work. R.v.R., S.A.V., M.K. and Z.J. helped with the laboratory analysis of biomarkers including support with the MAT work. M.R.P. and C.F. were original authors of the EAT study of which their data was used in this work. All authors critically reviewed the manuscript and approved its final version.

Acknowledgements

The authors would like to thank the parents and children for taking part in this trial; the entire EAT and EAT-On Study Teams including Dr. Marta Krawiec, Dr. Irene Bartha, Dr. Andreina Marques-Mejias, Professor Graham Roberts, Dr. Tom Marrs, Dr. Rosan Meyer; the EAT-On nursing team including Lydia McMunn, Helen Willis, Dr. Helen Fisher; the EAT-On dietitians including Nicola Fox, Daphna Kesary, Faye Harrison, Karen Wright, Charlotte Stedman; Ewa Pietraszewicz, Latifa Rahman, Monica Basting, Michelle Stewart for their support with data management and patient recruitment; Alick Stephens and Asha Sudra for their help with processing blood samples; Allison Baumgartner for data management, statistical analyses and feedback on the manuscript. The EAT and EAT-On studies were also supported by grants from the Food Standards Agency (T07051), the Medical Research Council (MC_G1001205), Action Medical Research (GN2551) and the Food Allergy Research and Education (RE14333).

Funding

This work was supported by the Food Allergy Research and Education (Grant RE14333), the Action Medical Research (Grant GN2551), the Medical Research Council (Grant MC_G1001205) and the Food Standards Agency (Grant T07051).

Conflicts of Interest

G.D.T. reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, Action Medical Research and National Peanut Board. Scientific Advisory Board member Aimmune. Investigator on pharma-sponsored allergy studies (Aimmune and DBV Technologies). Scientific advisor to Aimmune, DBV and Novartis. R.v.R. consults for HAL Allergy BV, Citeq BV, Angany Inc., Reacta Healthcare Ltd., Mission MightyMe, The Protein Brewery, and AB Enzymes and has equity in Angany Inc. S.R. reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH) to cover parts of a research salary. H.T.B. reports consulting fees from King's College London and stock options from DBV Technologies, where he is currently employed. H.A.B. reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), and speaker fees from DBV Technologies, Viatris, Stallegenes and Parexel outside of the submitted work. C.F. is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principle Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium and directs the Global Atopic Dermatitis Atlas (www.atopicdermatitisatlas.org). His department has received funding from Sanofi-Genzyme and Pfizer for skin microbiome work. He has also received compensation from the British Journal of Dermatology (reviewer and Section Editor) and EuroGuiDerm (guidelines lead). A.F.S. reports grants from Medical Research Council (MR/M008517/1; MC/PC/18052; MR/T032081/1), Food Allergy Research and Education (FARE), the Immune Tolerance Network/National Institute of Allergy and Infectious Diseases (NIAID, NIH), Asthma UK (AUK-BC-2015-01), BBSRC, Rosetrees Trust and the NIHR through the Biomedical Research Centre (BRC) award to Guy's and St Thomas' NHS Foundation Trust during the conduct of the study; personal fees from Thermo Scientific, Nutricia, Infomed, Novartis, Allergy Therapeutics, Buhlmann, as well as research support from Buhlmann and Thermo Fisher Scientific through a collaboration agreement with King's College London. A.F.S. is Chair of the EAACI Food Allergy Guidelines. G.L. reports grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), other from Food Allergy & Research Education (FARE), other from MRC & Asthma UK Centre, other from UK Dept of Health through NIHR, other from National Peanut Board (NPB), other from The Davis Foundation, during the conduct of the study; shareholder in DBV Technologies and Mighty Mission

Me, personal fees from Novartis, personal fees from Sanofi-Genyzme, personal fees from Regeneron, personal fees from ALK-Abello, personal fees from Lurie Children's Hospital, outside the submitted work. All the other authors have nothing to disclose.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. C. M. Warren, A. S. Chadha, S. H. Sicherer, J. Jiang, and R. S. Gupta, "Prevalence and Severity of Sesame Allergy in the United States," *JAMA Network Open* 2, no. 8 (2019): e199144.

2. K. T. Tuano, K. H. Dillard, D. Guffey, and C. M. Davis, "Development of Sesame Tolerance and Cosensitization of Sesame Allergy With Peanut and Tree Nut Allergy in Children," *Annals of Allergy, Asthma & Immunology* 117, no. 6 (2016): 708–710.

3. A. Adatia, A. E. Clarke, Y. Yanishevsky, and M. Ben-Shoshan, "Sesame Allergy: Current Perspectives," *Journal of Asthma and Allergy* 10 (2017): 141–151.

4. I. Dalal, I. Binson, R. Reifen, et al., "Food Allergy Is a Matter of Geography After All: Sesame as a Major Cause of Severe IgE-Mediated Food Allergic Reactions Among Infants and Young Children in Israel," *Allergy* 57, no. 4 (2002): 362–365.

5. L. Segal, M. Ben-Shoshan, R. Alizadehfar, et al., "Initial and Accidental Reactions Are Managed Inadequately in Children With Sesame Allergy," *Journal of Allergy and Clinical Immunology. In Practice* 5, no. 2 (2017): 482–485.

6. K. Sokol, M. Rasooly, C. Dempsey, et al., "Prevalence and Diagnosis of Sesame Allergy in Children With IgE-Mediated Food Allergy," *Pediatric Allergy and Immunology* 31, no. 2 (2020): 214–218.

7. C. Riggioni, C. Ricci, B. Moya, et al., "Systematic Review and Meta-Analyses on the Accuracy of Diagnostic Tests for IgE-Mediated Food Allergy," *Allergy* 79 (2023): 324–352.

8. P. Permaul, L. M. Stutius, W. J. Sheehan, et al., "Sesame Allergy: Role of Specific IgE and Skin-Prick Testing in Predicting Food Challenge Results," *Allergy and Asthma Proceedings* 30, no. 6 (2009): 643–648.

9. R. L. Peters, K. J. Allen, S. C. Dharmage, et al., "Skin Prick Test Responses and Allergen-Specific IgE Levels as Predictors of Peanut, Egg, and Sesame Allergy in Infants," *Journal of Allergy and Clinical Immunology* 132, no. 4 (2013): 874–880.

10. N. Yanagida, Y. Ejiri, D. Takeishi, et al., "Ses i 1-Specific IgE and Sesame Oral Food Challenge Results," *Journal of Allergy and Clinical Immunology. In Practice* 7, no. 6 (2019): 2084–2086.e4.

11. N. Maruyama, T. Nakagawa, K. Ito, et al., "Measurement of Specific IgE Antibodies to Ses i 1 Improves the Diagnosis of Sesame Allergy," *Clinical and Experimental Allergy* 46, no. 1 (2016): 163–171.

12. M. R. Perkin, K. Logan, A. Tseng, et al., "Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants," *New England Journal of Medicine* 374 (2016): 1733–1743.

13. J. J. Koplin, R. L. Peters, S. C. Dharmage, et al., "Understanding the Feasibility and Implications of Implementing Early Peanut Introduction for Prevention of Peanut Allergy," *Journal of Allergy and Clinical Immunology* 138, no. 4 (2016): 1131–1141.e2.

14. A. F. Santos, A. Douiri, N. Becares, et al., "Basophil Activation Test Discriminates Between Allergy and Tolerance in Peanut-Sensitized Children," *Journal of Allergy and Clinical Immunology* 134, no. 3 (2014): 645–652.

15. A. F. Santos, L. K. James, H. T. Bahnson, et al., "IgG4 Inhibits Peanut-Induced Basophil and Mast Cell Activation in Peanut-Tolerant Children Sensitized to Peanut Major Allergens," *Journal of Allergy and Clinical Immunology* 135, no. 5 (2015): 1249–1256.

16. G. Du Toit, G. Roberts, P. H. Sayre, et al., "Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy," *New England Journal of Medicine* 372, no. 9 (2015): 803–813.

17. A. F. Santos, N. Couto-Francisco, N. Becares, M. Kwok, H. T. Bahnson, and G. Lack, "A Novel Human Mast Cell Activation Test for Peanut Allergy," *Journal of Allergy and Clinical Immunology* 142 (2018): 689–691.e9.

18. L. Nachshon, J. Westerhout, W. M. Blom, et al., "Sesame Eliciting and Safe Doses in a Large Sesame Allergic Population," *Allergy* 78, no. 12 (2023): 3212–3220.

19. A. A. Schoemaker, A. B. Sprikkelman, K. E. Grimshaw, et al., "Incidence and Natural History of Challenge-Proven Cow's Milk Allergy in European Children—EuroPrevall Birth Cohort," *Allergy* 70, no. 8 (2015): 963–972.

20. R. L. Peters, J. J. Koplin, L. C. Gurrin, et al., "The Prevalence of Food Allergy and Other Allergic Diseases in Early Childhood in a Population-Based Study: HealthNuts Age 4-Year Follow-Up," *Journal of Allergy and Clinical Immunology* 140, no. 1 (2017): 145–153.e8.

21. R. L. Peters, I. Guarnieri, M. L. K. Tang, et al., "The Natural History of Peanut and Egg Allergy in Children up to Age 6 Years in the HealthNuts Population-Based Longitudinal Study," *Journal of Allergy and Clinical Immunology* 150, no. 3 (2022): 657–665.e13.

22. R. L. Peters, K. J. Allen, S. C. Dharmage, et al., "Natural History of Peanut Allergy and Predictors of Resolution in the First 4 Years of Life: A Population-Based Assessment," *Journal of Allergy and Clinical Immunology* 135, no. 5 (2015): 1257–1266.e1-2.

23. H. S. Skolnick, M. K. Conover-Walker, C. B. Koerner, H. A. Sampson, W. Burks, and R. A. Wood, "The Natural History of Peanut Allergy," *Journal of Allergy and Clinical Immunology* 107, no. 2 (2001): 367–374.

24. G. Roberts, H. T. Bahnson, G. Du Toit, et al., "Defining the Window of Opportunity and Target Populations to Prevent Peanut Allergy," *Journal of Allergy and Clinical Immunology* 151, no. 5 (2023): 1329–1336.

25. R. X. Foong, J. A. Dantzer, R. A. Wood, and A. F. Santos, "Improving Diagnostic Accuracy in Food Allergy," *Journal of Allergy and Clinical Immunology. In Practice* 9, no. 1 (2021): 71–80.

26. K. M. Parker, T. D. Dang, R. Wijesuriya, et al., "Longitudinal Peanut and Ara h 2 Specific-IgE, -IgG(4), and -IgG(4)/-IgE Ratios Are Associated With the Natural Resolution of Peanut Allergy in Childhood," *Allergy* 79, no. 7 (2024): 1868–1880.

27. R. X. Foong, G. Du Toit, R. van Ree, et al., "Biomarkers of Peanut Allergy in Children Over Time," *Allergy* 79, no. 10 (2024): 2775–2786.

28. R. Bahri, A. Custovic, P. Korosec, et al., "Mast Cell Activation Test in the Diagnosis of Allergic Disease and Anaphylaxis," *Journal of Allergy and Clinical Immunology* 142 (2018): 485–496.e16.

29. H. Zhang, B. F. Griswold, L. Sloper, et al., "High Prevalence of Food Allergies in Patients With Ehlers-Danlos Syndromes," in *ASHG Annual Meeting* (2007), Abstract Number 21352.

30. V. Leduc, D. A. Moneret-Vautrin, J. T. Tzen, M. Morisset, L. Guerin, and G. Kanny, "Identification of Oleosins as Major Allergens in Sesame Seed Allergic Patients," *Allergy* 61, no. 3 (2006): 349–356.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** EAT-On algorithm to determine food allergic status at the end of the study. This diagram details how food allergic status was determined based on oral food challenges, consumption and allergy test results in a hierarchical way. This was used for all 6 food allergens studied originally as a part of the EAT study including sesame seed. **Figure S2:** Determining sesame seed allergy status for the entire EAT-On cohort. This flow diagram details how

sesame seed allergic status was determined based on patient encounters during the EAT-On study. Patients had a clinical and/or telephone visit and were found to be sesame seed allergic or tolerant based on OFC and/or consumption (regular consumption was defined as eating 3 g of sesame seed protein at least 3 times in the last 6 months). If neither OFC nor consumption data were available, SPT < 5 mm was used to determine tolerance. The red box indicates sesame allergic children who were included in the biomarker analysis. [1] Represents where the patients who were sesame seed sensitised and not allergic were selected from for the biomarker analysis. **Figure S3:** Scatter plot showing the sesame sIgE values at 12 and 36 months in relation to the sesame allergy outcome at 7–12 years for (A) sesame sIgE and (B) ses i 1-sIgE. **Table S1:** Biomarkers of the sesame allergic children at 7–12 years who did not have an OFC. **Table S2:** Baseline clinical characteristics between sesame allergic, sesame sensitised not allergic and not food allergic or sensitised to sesame children. **Table S3:** Comparison of consumption at different time points between the children who developed new sesame allergy at 7–12 years old and the sesame sensitised not allergic children. **Table S4:** Univariate analysis looking at the covariates affecting sesame allergy at 7–12 years. **Table S5:** Multivariable logistic regression analyses looking at the covariates that correlate with sesame allergy determined at 7–12 years of age by time point over time. **Table S6:** Baseline and change from 1 to 3-years of age of Ses i 1-sIgE in predicting sesame allergy at 7–12-years of age. **Table S7:** Baseline and change from 1 to 3-years of age of sesame-sIgE in predicting sesame allergy at 7–12-years of age.