

Letter to the Editor

The natural history of peanut sensitization and allergy in a birth cohort

To the Editor:

Information on the natural history of peanut-induced allergic sensitization (PAS) and clinical peanut allergy (PA) remains limited. Most previous studies selected children who were given a diagnosis of PA, which does not provide the population perspective and probably ignores those with low levels of sensitization.^{1,2} There are no population-based studies on the natural history of PAS or PA. To provide a population perspective, we used the Isle of Wight birth cohort ($n = 1456$) and determined the natural history of PAS and PA, focusing on incidence, persistence, and remission. At 1, 2, 4, 10, and 18 years of age, validated questionnaires were completed to obtain information on allergic symptoms, including peanut-induced allergic reactions. Skin prick tests (SPTs) were carried out to 14 aeroallergens and food allergens, including peanut, at ages 4, 10, and 18 years in all consenting participants and at 1 and 2 years in those with allergic symptoms.³ Allergic sensitization was defined as a mean wheal diameter of 3 mm greater than that elicited by the negative control to an allergen on SPTs. The diagnosis of PA was based on a convincing clinical history (≥ 1 recognized allergic symptoms developing within 2 hours of food ingestion) plus evidence of sensitization to peanut on SPTs. We used the term PAS when SPT responses were positive to peanut, irrespective of clinical reactivity.

Details of the experimental methods used and statistical analysis are provided in the Methods section in this article's Online Repository at www.jacionline.org. Briefly, prevalences and their 95% CIs were calculated. Means of SPT wheal sizes in those with persistent and remittent sensitization were compared by using the t test. Fig E1 in this article's Online Repository at www.jacionline.org provides information on data at each assessment. Details of each child sensitized to peanut at age 4, 10, and 18 years is provided in Table E1 in this article's Online Repository at www.jacionline.org, whereas Table E2 in this article's Online Repository at www.jacionline.org provides a complete picture with imputed data.

PAS increased gradually in the first decade of life but showed a steeper increase from 10 to 18 years of age (Fig 1, A). At age 4 years, 13 (1.3%; 95% CI, 0.8% to 2.3%) of 976 children were sensitized to peanut. This increased to 19 (1.8%; 95% CI, 1.2% to 2.9%) of 1034 children at age 10 years, with a further increase to 54 (6.4%; 95% CI, 4.9% to 8.2%) of 851 children at age 18 years. Previous studies have reported a similar prevalence of PAS, varying from 1.1% to 8.6%.^{4,5} We show that this is primarily age dependent and varies from 1.3% in early childhood to 6.8% in adolescence (Fig 1, A). At age 1 and 2 years, only those children reporting allergic symptoms underwent SPTs, and hence the prevalence could have been overestimated. However, prevalence figures at age 1 and 2 years are similar to those reported previously in another unselected birth cohort on the Isle of Wight.⁶ All peanut-sensitized children had positive reactions to at least 1 aeroallergen, with grass pollen sensitization being more common than tree pollen sensitization (see Table E3 in this article's Online Repository at www.jacionline.org). Cross-reactivity of peanut and grass pollen has been reported

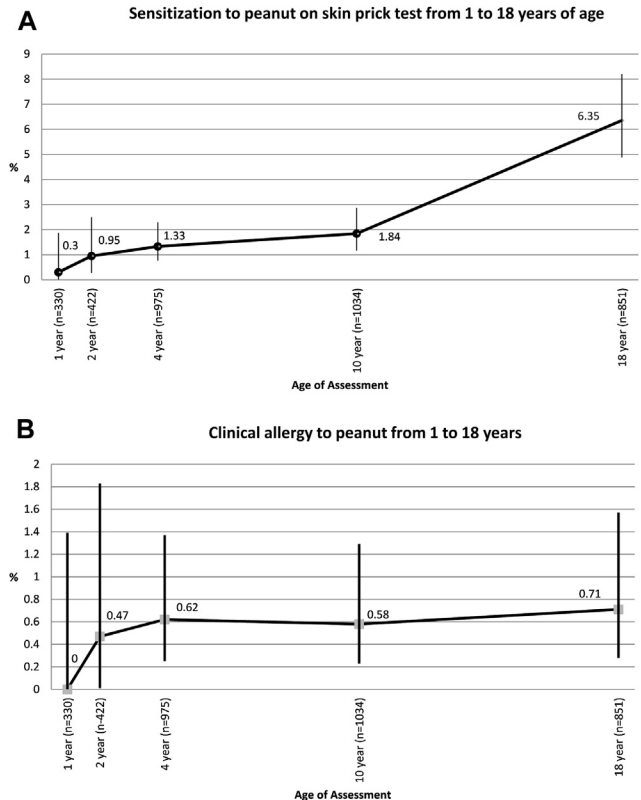


FIG 1. A, Sensitization to peanut on SPTs from 1 to 18 years of age. Sensitization was defined as a positive SPT response to peanut. Numbers above each point represent percentages of participants with sensitization at each assessment point. B, Clinical allergy to peanut from 1 to 18 years of age. Clinical allergy to peanut was defined as appearance of typical type I hypersensitivity symptoms within 2 hours of exposure to peanut in participants with sensitization on SPTs. Numbers above each point represent the percentage of participants with PA at each assessment.

previously.⁷ At 4 years of age, eczema was the major comorbidity, whereas at 10 and 18 years of age, rhinitis was present in the majority of peanut-sensitized children.

The most common pattern of peanut sensitization was its development for the first time at 18 years in 42 (63.6%; 95% CI, 51.6% to 74.2%) of 66 children in association with grass pollen sensitivity and allergic rhinitis (Table 1 and see Table E3). The other common pattern was persistent sensitization from age 4 ($n = 9$) or 10 ($n = 6$) years (15/66 [22.7%; 95% CI, 14.3% to 34.2%]). However, other patterns in which sensitization was transient or recurrent were observed in 9 (13.6%; 95% CI, 73.5% to 23.9%) of 66 children. The mean difference in wheal size of 1.1 mm between the persistent (mean, 4.4 mm; SD, 2.0 mm) and transient (mean, 3.3 mm; SD, 0.4 mm) groups did not reach statistical significance ($P = .06$).

There was minimal change in the overall prevalence of PA beyond early childhood, and it remained around 0.6% (Fig 1, B). New onset of PA was uncommon at 10 years of age (1/6) but more common at 18 years of age (3/6). Remission of PA was seen in 1 (17%) of 6 children between ages 4 and 10 years and 1 (25%) of 4 children from age 10 to 18 years (see Table E4 in this article's Online Repository at www.jacionline.org).

TABLE I. Natural history of sensitization to peanut during childhood

Pattern of sensitization	Sensitized subjects (n = 66)	SPT response size (mm) at 4 y, median (IQR 25-75)	SPT response size (mm) at 10 y, median (IQR 25-75)	SPT response size (mm) at 18 y, median (IQR 25-75)
+++	9 (13.6%)	3.5 (3.0-6.0)	4.5 (3.0-7.5)	5.50 (4.6-9.3)
+++	6 (9.1%)	0	3.5 (3.0-5.3)	3.50 (3.4-4.3)
--+	42 (63.6%)	0	0	4.0 (3.3-4.6)
++-	2 (3.0%)	3.3 (3.0-3.5)	4.50 (3.0-6.0)	0
+-+	4 (6.1%)	3.0 (3.0-3.8)	0	0
++-	1 (1.5%)	4.0	0	3.8
-+-	2 (3.0%)	0	3.0 (3.0-3.0)	0

IQR, Interquartile range.

org). The numbers with PA in our study were small, and therefore these findings should be interpreted with caution. However, the development of natural tolerance in a small proportion is consistent with previous reports.¹ We did not observe recurrence of PA, although 1 patient had recurrence of PAS after initial loss of SPT reactivity (Table I).

The diagnosis of PA can be questioned because an oral challenge was not performed. However, a history of acute clinical reaction and evidence of allergic sensitization are considered adequate for the diagnosis in most cases.⁸ Moreover, we have previously shown that even a 3-mm wheal has about 75% positive predictive value for PA if symptoms are present.⁹ Another limitation was missing information for SPTs, which is inevitable in a long-term study spanning more than 20 years.

Sensitization to peanut in early childhood was more commonly associated with clinical reactivity than during adolescence. Of those with sensitization at age 4 years (n = 10), 4 (40%) had PA, whereas at age 18 years, only 2 (4.76%) of 42 children with new-onset sensitization had PA ($P = .009$). Thus the increase in the number of subjects sensitized to peanut during adolescence was largely due to the onset of asymptomatic sensitization.

In summary, in this cohort PA started early in childhood and persisted in most children until adulthood. A few adolescents did have new-onset PA, compensating for those with remittance, and therefore, the overall prevalence remained around 0.6%. The natural history of PAS differed from that of PA in that it increased gradually from early childhood, with a significant peak incidence during adolescence. Most of this new-onset sensitization to peanut was asymptomatic and associated with pollen sensitization and allergic rhinitis. The numbers with PA were small, and thus generalizability of these findings is uncertain. Similar assessments in other longitudinally followed birth cohorts will clarify developmental patterns of PAS and PA during childhood.

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REFERENCES

- Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001;107:367-74.
- Savage JH, Limb SL, Brereton NH, Wood RA. The natural history of peanut allergy: extending our knowledge beyond childhood. *J Allergy Clin Immunol* 2007;120:717-9.
- Roberts G, Zhang H, Karmaus W, Raza A, Scott M, Matthews S, et al. Trends in cutaneous sensitization in the first 18 years of life: results from the 1989 Isle of Wight birth cohort study. *Clin Exp Allergy* 2012;42:1501-9.
- Arbes SJ Jr, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377-83.
- Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638-46.
- Dean T, Venter C, Pereira B, Arshad SH, Grundy J, Clayton CB, et al. Patterns of sensitization to food and aeroallergens in the first 3 years of life. *J Allergy Clin Immunol* 2007;120:1166-71.
- Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-7, e1-13.
- Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the united states: summary of the NIAID-sponsored Expert Panel Report. *J Allergy Clin Immunol* 2010;126:1105-18.
- DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol* 2011;127:633-9, e1-3.

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METHODS

Study setting

An unselected whole-population birth cohort ($n = 1536$) was recruited in 1989 to prospectively study the natural history of allergic diseases. After exclusion of adoptions, perinatal deaths, and refusal for follow-up, 1456 children were enrolled, with follow-up assessments conducted at 1, 2, 4, 10, and 18 years of age.^{E1-E5} The study was approved by the local ethics committee before recruitment and for each assessment. Informed consent was obtained from parents at age 1, 2, 4, and 10 years and from participants at age 18 years.

Assessments

At each stage, validated questionnaires were completed to obtain information on allergic symptoms, including peanut-induced allergic reactions. Questions about eating peanut and tree nuts were asked at age 4, 10, and 18 years. SPTs were carried out to 14 aeroallergens and food allergens, including peanut, at ages 4, 10, and 18 years in all consenting participants and at age 1 and 2 years in those with allergic symptoms (ALK-Abelló, Hørsholm, Denmark), as described previously. Histamine (0.1%) and physiologic saline were used as positive and negative controls. A mean wheal diameter at least 3 mm larger than that seen with saline after 15 minutes was taken as a positive result.

Definitions

Allergic sensitization. Allergic sensitization was defined as a mean wheal diameter of 3 mm greater than that elicited by the negative control to an allergen on SPTs. Results were discounted if the positive control was not at least 3 mm in diameter.

PAS

PAS was defined as a positive SPT response to peanut, irrespective of the clinical history of a reaction.

Clinical PA

The diagnosis of PA was based on a convincing clinical history verified by an allergist (S.H.A., R.K., and G.R.) plus evidence of allergic sensitization to peanut. We required all 3 of the following criteria to be met:

1. report of 2 or more recognized allergic symptoms, such as^{E6}:
 - A. *localized*: itching, sting/burning of the lips/mouth or throat, urticaria/hives, and angioedema;
 - B. *abdominal*: nausea, vomiting, crampy/colicky abdominal pain, and diarrhea;
 - C. *respiratory*: wheeze, stridor, watery rhinitis, and redness of the eyes/nose;
 - D. *skin*: urticaria, itching, flushed skin, and worsening eczema; and
 - E. *systemic reaction*: anaphylaxis;
2. temporal relationship of a reaction with symptoms developing within 2 hours of food ingestion; and
3. positive SPT response to peanut.

Asymptomatic sensitization to peanut. Asymptomatic sensitization was defined as a positive SPT response to peanut but without evidence of a clinical reaction to peanut.

Asthma. At the 4-year follow-up encounters, the medical investigator determined whether asthma was present based on wheeze over the last 12 months and treatment being given for asthma or asthma related symptoms. At the 10- and 18-year follow-up encounters, asthma was defined as having “physician-diagnosed asthma” and either “wheezing or whistling in the chest in the last 12 months” or “current treatment for asthma,” according to the International Study of Asthma and Allergies in Childhood criteria.^{E7}

Rhinitis. Rhinitis was defined by an affirmative answer to the following question: “Have you ever had a problem with sneezing, runny or blocked nose in the absence of cold or flu” plus “symptoms in the last 12 months.”^{E7}

Eczema. Eczema was defined as chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution, according to the Hanifin and Rajka criteria.^{E8}

Statistical analysis

Data were analyzed with SPSS version 9 software (SPSS, Chicago, Ill). Means of SPT wheal sizes in those with persistent and remittent sensitization were compared by using the t test. Children were regarded as having “any sensitization to peanut” if SPT responses were positive to peanut at 1 or more assessments. When children had PAS or PA at 2 or 4 years of age, this was regarded as “early childhood.” To provide a complete picture, data were imputed, replicating adjacent sensitization data, as shown in Table E2. Thus missing data at 4 and 18 years of age were imputed by those at 10 years of age (when most children were seen and had skin tests).

REFERENCES

- E1. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992;90:235-41.
- E2. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;23:504-11.
- E3. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587-93.
- E4. Kurukulaarachy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003;33:573-8.
- E5. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaarachy RJ, et al. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax* 2010;65:258-62.
- E6. Niggemann B. When is an oral food challenge positive? *Allergy* 2010;65:2-6.
- E7. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
- E8. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980;60:44-7.
- E9. Kurukulaarachy RJ, Matthews SM, Arshad SH. The natural history of fatal childhood asthma—a case from the Isle of Wight Birth Cohort. *J Asthma* 2008;45:944-7.

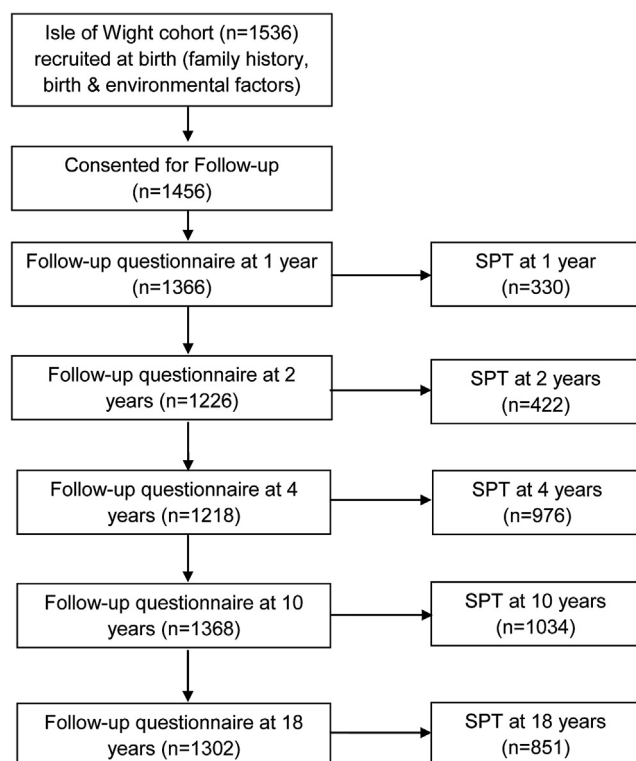


FIG E1. Flow chart of children seen at each follow-up: data available for peanut allergy and allergic sensitization to peanut at each follow-up.

TABLE E1. Natural history of sensitization to peanut during childhood (individual results)

Subject	SPT mean wheal diameter (mm)		
	4 y	10 y	18 y
1	6.0	4.5	4.75
2	3.5	3.0	5.0
3	6.0	6.0	9.0
4	3.0	4.5	5.5
5	4.0	7.0	10.5
6	3.0	8.0	Missing
7	10.0	9.5	Missing
8	Missing	3.0	4.5
9	Missing	3.0	3.25
10	0	6.0	3.5
11	0	3.0	6.0
12	0	5.0	3.5
13	0	3.5	3.75
14	0	3.0	Missing
15	0	3.5	Missing
16	3.5	6.0	0
17	Missing	3.0	0
18	4.0	0	0
19	3.0	0	0
20	3.0	0	0
21	3.0	0	Missing
22	4.0	0	3.75
23	0	3.0	0
24	0	3.0	0
n = 42*	13 Missing	7 Missing	3.0-7.5

*At age 18 years, 42 subjects had new-onset sensitization. However, 13 of these were not seen at age 4 years, and 7 were not seen at age 10 years.

TABLE E2. Natural history of sensitization to peanut during childhood (individual results, with imputation of missing data)

Subject	SPT mean wheal diameter (mm)			Pattern
	4 y	10 y	18 y	
1	6.0	4.5	4.8	+++
2	3.5	3.0	5.0	+++
3	6.0	6.0	9.0	+++
4	3.0	4.5	5.5	+++
5	4.0	7.0	10.5	+++
6	3.0	8.0	8.0	+++
7	10.0	9.5	9.5	+++
8	3.0	3.0	4.5	+++
9	3.0	3.0	3.3	+++
10	0	6.0	3.5	-++
11	0	3.0	6.0	-++
12	0	5.0	3.5	-++
13	0	3.5	3.8	-++
14	0	3.0	3.0	-++
15	0	3.5	3.5	-++
16	3.5	6.0	0	++-
17	3.0	3.0	0	++-
18	4.0	0	0	+--
19	3.0	0	0	+--
20	3.0	0	0	+--
21	3.0	0	0	+--
22	4.0	0	3.8	+ - +
23	0	3.0	0	- + -
24	0	3.0	0	- + -
n = 42*	0	0	3.0-7.5	- - +

Note: Imputation of missing data. For the first 24 subjects, missing data at 4 and 18 years of age were imputed by those obtained at age 10 years. For those with new-onset sensitization (n = 42) at age 18 years, missing SPT results at 4 and 10 years of age were presumed to be negative and regarded as zero.

*Those 42 subjects who had new-onset sensitization at the age of 18 years were grouped together.

TABLE E3. Associated allergic sensitization and clinical allergic conditions in those with peanut sensitization at each age

Peanut sensitization	4 y (n = 13)	10 y (n = 19)	18 y (n = 54)
Sensitization to any aeroallergen	11 (84.6%)	17 (89.5%)	52 (96.3%)
Sensitization to grass pollen mix	6 (46.2%)	12 (63.2%)	47 (87.0%)
Sensitization to tree pollen mix	Not done	3 (15.8%)	27 (50.0%)
Sensitization to any food allergen	3 (23.1%)	5 (26.3%)	48 (88.9%)
Sensitization to wheat	0	3 (15.8%)	47 (87.0%)
Sensitization to soya	1 (7.7%)	1 (5.3%)	4 (7.4%)
Asthma	6 (46.2%)	6 (31.6%)	23 (42.6%)
Eczema	8 (61.5%)	6 (31.6%)	7 (13.0%)
Rhinitis	3 (23.1%)	10 (52.6%)	47 (87.0%)

TABLE E4. Natural history of clinical PA

Subjects	4 y	10 y	18 y	Nature of worst allergic reaction
1	PA	PA	PA	Oral symptoms, vomiting, urticaria, and anaphylaxis
2	PA	PA	PA	Anaphylaxis within an hour of peanut ingestion
3	PA	PA	PA	Vomiting within an hour of peanut ingestion
4	PA	PA	Missing	Urticarial rash within 1 h of peanut ingestion
5	PA	PA	No PA	Urticarial rash and throat tightness within 1 h of peanut ingestion
6	PA	No PA	No PA	Urticaria within 1 h of peanut ingestion
7	No PA	AS	PA	Immediate throat tightness, wheezing, generalized urticaria, and anaphylaxis
8	No PA	No PA	PA	Urticaria and wheeze, progressing to anaphylaxis
9	No PA	No PA	PA	Anaphylaxis
10	AS	PA	Missing (died)	Immediate vomiting with peanut; died at age 11 y of acute asthma attack ^{E9}

Notes: Of 6 patients with PA at age 4 years, 5 persisted to 10 years, and 1 outgrew PA. Of these 5 patients, 3 had persistent allergy to age 18 years (1 was not seen at age 18 years and 1 outgrew PA). Allergic reactions to peanut caused typical symptoms, including systemic manifestations or anaphylaxis. One child at 4 years, 2 at 10 years, and 4 at 18 years of age provided a history of anaphylactic reactions to peanut. All of these children had been given a diagnosis of asthma, eczema, and rhinitis at some stage in their life except 1 child (subject 7) who did not have eczema.

AS, Asymptomatic sensitization.