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2 (Revised manuscript; Letter to Editor)

3 **Title: The Natural History of Peanut Sensitization and Allergy in a Birth Cohort.**

4

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25 **Capsule summary**

26 In this birth cohort, peanut allergy started in early childhood and persisted until young adult life. Allergic
27 sensitization to peanut rose gradually from early childhood, with a rapid increase during adolescence;
28 the latter being mostly asymptomatic.

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30 **Key Words:**

31 Peanut Allergy, peanut allergen sensitization, natural history, birth cohort

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35 To the editor,

36 Information on the natural history of peanut allergic sensitization (PAS) and clinical peanut
37 allergy (PA) remains limited. Most previous studies selected children who were diagnosed with PA,
38 which does not provide the population perspective and probably ignores those with low levels of
39 sensitization.^{1,2} There are no population based studies on the natural history of PAS or PA. To provide a
40 population perspective, we used the Isle of Wight (IoW) birth cohort (n=1,456) and determined the
41 natural history of PAS and PA, focusing on incidence, persistence and remission. At 1, 2, 4, 10 and 18
42 years, validated questionnaires were completed to obtain information on allergic symptoms, including
43 peanut allergic reactions. Skin prick test (SPT) were carried out to 14 aero- and food allergens, including
44 peanut at ages 4, 10 and 18 years in all consenting participants and at 1 and 2 years in those with allergic
45 symptoms.³ Allergic sensitization was defined as a mean weal diameter of 3 mm greater than the
46 negative control to an allergen on SPT. The diagnosis of PA was based on a convincing clinical history
47 (one or more recognized allergic symptoms developing within 2 hours of food ingestion) plus evidence
48 of sensitization to peanut on SPT. We used the term PAS, where SPT was positive to peanut irrespective
49 of clinical reactivity.

50 Details of experimental methods used and statistical analyses are provided in the online
51 supplement of this article. Briefly, prevalence and their 95% confidence intervals were calculated.
52 Means of SPT wheal sizes in those with persistent and remittent sensitization were compared using T
53 test. Figure E1 (see online repository) provides information on data at each assessment. Details of each
54 child sensitized to peanut at age 4, 10 and 18 years is provided in table E1, while table E2 provides a
55 complete picture with imputed data (see online repository).

56 PAS increased gradually in the first decade of life but showed a steeper rise from 10 to 18 years
57 (Fig 1a). At age 4 years, 13 of 976 children (1.3%, 95% confidence intervals (CI): 0.8%-2.3%) were

58 sensitized to peanut. This increased to 19 of 1034 (1.8%, 95% CI: 1.2%-2.9%) at age 10 years with a
59 further increase to 54 out of 851 (6.4%, 95% CI: 4.9-8.2%) at age 18 years. Previous studies have
60 reported a similar prevalence of PAS varying from 1.1% to 8.6%.^{4,5} We show that this is primarily age
61 dependent and varies from 1.3% in early childhood to 6.8% in adolescence (Fig 1b). At age 1 and 2, only
62 those children reporting allergic symptoms were skin prick tested and hence the prevalence could have
63 been overestimated. However, prevalence figures at age 1 and 2 are similar to those reported previously
64 in another unselected birth cohort on the IoW.⁶ All peanut sensitized children had positive reactions to
65 at least one aeroallergen with grass pollen sensitization being more common than tree pollen (Table E3).
66 Cross-reactivity of peanut and grass pollen has been reported previously.⁷ At 4 years, eczema was the
67 major co-morbidity, while at 10 and 18 years, rhinitis was present in the majority of peanut sensitized
68 children.

69 The most common pattern of peanut sensitization was its development for the first time at 18
70 years; in 42 of 66 children (63.6%, 95% CI: 51.6%-74.2%) in association with grass pollen sensitivity and
71 allergic rhinitis (Table 1 & E3). The other common pattern was persistent sensitization from age 4 (n=9)
72 or 10 (n=6) years (15 of 66 or 22.7%, 95% CI: 14.3%-34.2%). However, other patterns where sensitization
73 was transient or recurrent were observed in 9 of 66 (13.6%, 95% CI: 7.3%-23.9%) children. The mean
74 difference in wheal size of 1.1 mm between persistence (mean; 4.4, SD: 2.0) and transient group (mean;
75 3.3, SD: 0.4) failed to reach statistical significance (p=0.06).

76 There was minimal change in the overall prevalence of PA beyond early childhood and it
77 remained around 0.6% (Fig 1b). New onset of PA was uncommon at 10 years (1 of 6) but more common
78 at 18 years (3 of 6). Remission of PA was seen in 1 of 6 (17%) between ages 4 to 10 years and 1 of 4
79 (25%) from age 10 to 18 years (Table E4). The numbers with PA in our study were small and therefore,
80 these findings should be interpreted with caution. However, the development of natural tolerance in a

81 small proportion is consistent with previous reports.¹ We did not observe recurrence of PA, although
82 one patient had recurrence of PAS after initial loss of SPT reactivity (Table 1).

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

88 Sensitization to peanut in early childhood was more commonly associated with clinical reactivity
89 than during adolescence. Of those with sensitization at 4 year (n=10), 4 (40%) developed PA, while at
90 age 18, only 2 of 42 (4.76%) children with new-onset sensitization developed PA (P=0.009). Thus, the
91 increase in the number of subjects sensitized to peanut during adolescence was largely due to the onset
92 of asymptomatic sensitization.

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

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102

103 Contributors

104 SHA generated the original hypothesis and all authors contributed to study design. SHA, GR and RJK
105 were responsible for all allergy phenotype data collection. CV and TD advised on analysis and
106 interpretation of the data. SHA wrote the first draft of the manuscript, and all authors have seen and
107 approved the final version of the report. SHA will serve as guarantors for its contents.

108

109 Conflict of interest statement

110 None of the authors have any conflicts of interests to declare.

111

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119 **References**

- 120 1. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history
121 of peanut allergy. *J Allergy Clin Immunol* 2001; 107:367-74.
- 122 2. Savage JH, Limb SL, Brereton NH, Wood RA. The natural history of peanut allergy: Extending our
123 knowledge beyond childhood. *J Allergy Clin Immunol* 2007; 120:717-9.
- 124 3. Roberts G, Zhang H, Karmaus W, Raza A, Scott M, Matthews S, et al. Trends in cutaneous
125 sensitization in the first 18 years of life: results from the 1989 Isle of Wight birth cohort study. *Clin
126 Exp Allergy* 2012; 42:1501-9.
- 127 4. Arbes SJ, Jr., Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10
128 common allergens in the US population: results from the third National Health and Nutrition
129 Examination Survey. *J Allergy Clin Immunol* 2005; 116:377-83.
- 130 5. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food
131 allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; 120:638-46.
- 132 6. Dean T, Venter C, Pereira B, Arshad SH, Grundy J, Clayton CB, et al. Patterns of sensitization to food
133 and aeroallergens in the first 3 years of life. *J Allergy Clin Immunol* 2007; 120:1166-71.
- 134 7. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in
135 children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics.
136 *J Allergy Clin Immunol* 2010; 125:191-7 e1-13.
- 137 8. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis
138 and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert
139 Panel Report. *J Allergy Clin Immunol* 2010; 126:1105-18.

- 140 9. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate
141 prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol*
142 2011; 127:633-9.e1-3.
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145 **Figure Legend**

146 **Figure 1a: Sensitization to peanut on skin prick test from 1 to 18 years of age.**

147 Sensitization was defined as a positive SPT to peanut. Numbers above each point represent % of
148 participants with sensitization at each assessment point.

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150 **Figure 1b: Clinical allergy to peanut from 1 to 18 years**

151 Clinical allergy to peanut was defined as appearance of typical type I hypersensitivity symptoms within 2
152 hours of exposure to peanut in participants with sensitization on SPT. Numbers above each point
153 represent the % of participants with peanut allergy at each assessment.

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156 **Table 1: Natural history of sensitization to peanut during childhood.**

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	Sensitized subjects	SPT size at 4 year	SPT size at 10 year	SPT size at 18 year
Pattern of sensitization	N=66	Median (IQ range 25-75)	Median (IQ range 25-75)	Median (IQ range 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

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167 On-line Supplement

168 **METHODS:**

169 **Study setting:**

170 An unselected whole population birth cohort (n=1,536) was recruited in 1989 to prospectively study the
171 natural history of allergic diseases. After exclusion of adoptions, perinatal deaths and refusal for follow-
172 up, 1,456 children were enrolled with follow-up assessments conducted at 1, 2, 4, 10 and 18 years.^{E1-E5}

173 The study was approved by the local ethics committee before recruitment and for each assessments.

174 Informed consent was obtained from parents at age 1, 2, 4, 10 and from participants at age 18 years.

175 **Assessments:**

176 At each stage, validated questionnaires were completed to obtain information on allergic symptoms,
177 including peanut allergic reactions. Questions about eating nuts were asked at age 4, 10 and 18 years.

178 SPT were carried out to 14 aero- and food allergens, including peanut at ages 4, 10 and 18 years in all
179 consenting participants and at 1 and 2 years in those with allergic symptoms (ALK-Abello, Horsholm,
180 Denmark) as described before. Histamine (0.1 %) and physiological saline were used as positive and
181 negative controls. A mean weal diameter at least 3 mm larger than that seen with saline after 15
182 minutes was taken as a positive result.

183 **Definitions**

184 **Allergic Sensitization:** Allergic sensitization was defined as a mean weal diameter of 3 mm greater than
185 the negative control to an allergen on SPT. Results were discounted if the positive control was not at
186 least 3 mm in diameter.

187 **Peanut allergic sensitization (PAS):** SPT positive to peanut irrespective of clinical history of a reaction.

188 **Clinical peanut Allergy (PA):** The diagnosis of PA was based on a convincing clinical history verified by an
189 allergist (SHA, RK, GR) plus evidence of allergic sensitisation to peanut. We required all 3 of the following
190 criteria to be met;

- 191 1. The report of one or more recognized allergic symptoms such as:^{E6}
- 192 a) localized: itching, sting/ burning of the lips/ mouth or throat, urticaria/ hives,
- 193 angioedema
- 194 b) abdominal: nausea, vomiting, crampy/ colicky abdominal pain, diarrhea
- 195 c) respiratory: wheeze, stridor, watery rhinitis, redness of eyes/ nose
- 196 d) skin: urticaria, itching, flushed skin, worsening eczema
- 197 e) systemic reaction: anaphylaxis
- 198 2. Temporal relationship of a reaction with symptoms developing within 2 hours of food ingestion.
- 199 3. Positive SPT to peanut.

200 **Asymptomatic sensitization to peanut:** Where SPT was positive to peanut but there was no evidence of
201 a clinical reaction to peanut.

202 **Asthma:** At 4 year follow-ups, the medical investigator determined the presence of asthma based on
203 wheeze over the last 12 months and treatment given for asthma or asthma related symptoms. At the 10
204 and 18 year follow-ups, asthma was defined as having “physician diagnosed asthma” and either
205 “wheezing or whistling in the chest in the last 12 months” or “current treatment for asthma”, following
206 the International Study of Asthma and Allergies in Childhood (ISAAC) criteria.^{E6}

207 **Rhinitis** was defined by an affirmative answer to “have you ever had a problem with sneezing, runny or
208 blocked nose in the absence of cold or flu” plus “symptoms in the last 12 months”.^{E6}

209 **Eczema** was defined as chronic or chronically relapsing, itchy dermatitis lasting more than 6 weeks with
210 characteristic morphology and distribution, following Hanifin and Rajka criteria.^{E7}

211 **Statistical analysis**

212 Data were analysed using SPSS version 9. Means of SPT wheal sizes in those with persistent and
213 remittent sensitization were compared using T test. Children were regarded as having “any sensitization
214 to peanut” if SPT was positive to peanut at one or more assessment. When children developed PAS or

215 PA at 2 or 4 years, this was regarded as “Early childhood”. To provide a complete picture, data were
216 imputed, replicating adjacent sensitization data, as shown in Table E2. Thus, missing data at 4 and 18
217 years were imputed by that at 10 years (when most children were seen and had skin test.

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220 **Table E1: Natural history of sensitization to peanut during childhood (individual results).**

Subjects	4 year	10 year	18 year
	Skin prick test mean wheal diameter (in mm)		
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

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

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225 **Table E2: Natural history of sensitization to peanut during childhood (individual results; with**
 226 **imputation of missing data)**

Subjects	4 year	10 year	18 year	Pattern
	Skin prick test mean wheal diameter (in mm)			
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	--+

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

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

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

	4 year	10 year	18 year	236 237
Peanut sensitization	N=13	N=19	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%)	

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Table E4: Natural history of clinical peanut allergy

Subjects	4 year	10 year	18 year	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 one hour of peanut ingestion
5	PA	PA	No PA	Urticarial rash and throat tightness within an hour of peanut ingestion
6	PA	No PA	No PA	Urticaria within an hour of peanut ingestion
7	No PA	AS	PA	Immediate throat tightness, wheezing, generalized urticaria, 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 of acute asthma attack ^{E9}

243 PA= Peanut Allergy

244 No PA= No Peanut Allergy

245 AS= Asymptomatic sensitization

246 *Notes: Out of 6 cases of PA at age 4 years, 5 persisted to 10 years and one outgrew PA. Of these 5, 3 had*
247 *persistent allergy to 18 years (one was not seen at 18 years and one outgrew PA).*

248 *Allergic reaction to peanut caused typical symptoms including systemic manifestations or anaphylaxis.*

249 *One child at 4, 2 at 10 and 4 at 18 years had given a history of anaphylactic reactions to peanut.*

250 *All of these children had been given a diagnosis of asthma, eczema and rhinitis at some stage in their life*
251 *except one child (subject 7 in Table 4) who did not have eczema.*

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254 **References**

255

256 E1. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in
257 infancy. *J Allergy Clin Immunol* 1992; 90:235-41.

258

259 E2. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the
260 prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23:504-11.

261

262 E3. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk
263 factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;
264 101:587-93.

265

266 E4. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH.
267 Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003; 33:573-8.

268

269 E5. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaaratchy RJ, et al. Influence of atopy
270 and asthma on exhaled nitric oxide in an unselected birth cohort study. *Thorax* 2010; 65:258-62.

271

272 E6. Niggemann B. When is an oral food challenge positive? *Allergy* 2010; 65:2-6.

273

274 E7 Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood
275 (ISAAC): rationale and methods. *Eur Respir J.* 1995 Mar;8(3):483-91.

276

277 E8. Hanifin JM, Rajka G (1980) Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl
278 (Stockh) 92: 44-47.

279

280 E9. Kurukulaaratchy RJ, Matthews SM, Arshad SH. The natural history of fatal childhood asthma--a
281 case from the Isle of Wight Birth Cohort. J Asthma 2008; 45:944-7.

282