

1 **Prevalence and cumulative incidence of food hypersensitivity in the first ten**
2 **years of life**

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5 **Carina Venter^{1,2}, Veeresh Patil¹, Jane Grundy¹, Gillian Glasbey¹, Roger**
6 **Twiselton¹, Syed Hasan Arshad¹, Taraneh Dean^{1,2}**

7

8 1 The David Hide Asthma and Allergy Research Centre, St. Mary's Hospital,
9 Newport, Isle of Wight, PO30 5TG, UK

10 2 School of Health Sciences and Social Work, University of Portsmouth, James
11 Watson West, 2 King Richard 1st Road, Portsmouth, PO1 2FR, UK

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15 Correspondence to:

16 Dr Carina Venter

17 School of Health Sciences and Social Work

18 University of Portsmouth

19 James Watson West

20 2 King Richard 1st Road

21 Portsmouth

22 PO1 2FR

23 Tel: +44 (0)23 92 844405 (direct)

24 +44 (0)23 92 844440 (general)

25 Fax: +44 (0)23 92 844402

carina.venter@port.ac.uk

26

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37 **C. Venter, V. Patil, J. Grundy, G. Glasbey, R. Twiselton, S. H. Arshad, T. Dean**

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39 **Prevalence and cumulative incidence of food hypersensitivity in the first ten**
40 **years of life**

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43

44 **Abstract**

45

46 **Background**

47 Prevalence, incidence and natural history of food hypersensitivity (FHS) and its
48 trends in an unselected cohort of older children is unclear.

49

50 **Methods**

51 A birth cohort born on the Isle of Wight (UK) between 2001-2002 was followed up
52 prospectively. Children were clinically examined and skin prick tested at set times
53 and invited for food challenges when indicated. At 10 years of age, children were
54 also invited for a blood test.

55

56 **Results**

57 969 children were recruited at 12 weeks pregnancy and 92.9%, 88.5%, 91.6% and
58 85.3% were assessed at one, two, three and ten years.

59

60 Prevalence of sensitisation to any allergen over 10 years was 186/969 (19.2%; 95%
61 CI: 16.84-21.8) and 108/969 (11.2%; 95% CI: 9.31-13.29) children were sensitised to
62 at least one predefined food allergen. Excluding wheat (due to cross reactivity with
63 pollen), 40/969 (4.1%; 95% CI: 3.19 - 5.32) children were sensitised to a predefined
64 food allergen. Using food challenges and/or a good clinical history, the cumulative
65 incidence of food hypersensitivity (FHS) in the first decade of life was 64/947 (6.8%,
66 95% CI: 5.2-8.4), while the prevalence of FHS at 10 years was 30/827 (3.6%, 95%
67 CI: 2.54-5.15). The vast majority, 25/827 (3.0%, 95% CI: 1.8 – 4.2) suffered from IgE
68 mediated food allergy, while 5/827 (0.6%, 95% CI: 0.07 – 1.3) had non-IgE mediate
69 food allergy/food intolerance.

70

71 **Conclusions**

72 By the age of ten years 6.8% of children suffered from FHS based on food
73 challenges and a good clinical history. There was a large discrepancy between
74 reported and diagnosed FHS.

75

76 **Keywords:** Food allergy, Food hypersensitivity, Food intolerance, Incidence,
77 Prevalence

78

79 Correspondence to:

80 Dr Carina Venter

81 School of Health Sciences and Social Work

82 University of Portsmouth

83 James Watson West

84 2 King Richard 1st Road

85 Portsmouth

86 PO1 2FR

87 Tel: +44 (0)23 92 844405 (direct)

88 +44 (0)23 92 844440 (general)

89 Fax: +44 (0)23 92 844402

carina.venter@port.ac.uk

90

91 **Introduction**

92 Food Hypersensitivity (FHS) is the umbrella term for food allergies (FA) [IgE and non-
93 IgE mediated] and non-allergic food hypersensitivity as currently defined by the
94 European Academy of Allergy and Clinical Immunology (EAACI) and the World
95 Allergy Organization.⁽¹⁾

96

97 Very few studies are available with the majority of these focusing on IgE mediated
98 food allergies only. An EAACI systematic review reported food allergy rates based on
99 a clinical history/food challenge of 1.1 – 1.2% in 6 year olds and 1.4 – 2.3% in 11 –
100 17 year olds. Based on food challenge only, these figures were 0.4 - 4.2% in 6-10
101 year olds and 0.1 – 5.7% in 11 – 17 year olds.⁽²⁾

102

103 We have previously reported FHS in 6, 11 and 15 year old cohorts on the Isle of
104 Wight (IOW). At six years of age,⁽³⁾ the prevalence of FHS based mainly on open
105 food challenge (OFC) outcomes and positive skin prick test (SPT) responses plus a
106 history of adverse reactions was 20/798 (2.5%) (95% CI 1.5 to 3.8). In the older
107 children we found that the prevalence of FHS was 18/775 (2.3%) in the 11-year-old
108 cohort and 17/757 (2.3%) in the 15-year-old cohort⁽⁴⁾.

109

110 The aim of the present study is to address key knowledge gaps with respect to FHS
111 in older children, namely: the prevalence, cumulative incidence and natural history of
112 FHS in the first ten years of life (including both FA and non-allergic FHS), and how
113 clinically defined FHS relates to reported symptoms of FHS. In this paper we will
114 continue to use the term FHS in order to compare our data with previous studies from
115 the IOW, using the same methodology. However, our focus is primarily on IgE
116 mediated food allergies.

117

118

119 **Methods**

120

121 A whole population birth cohort was established on the Isle of Wight to study the
122 prevalence and cumulative incidence of FHS.⁽⁵⁾ At one, two and three years, cohort
123 children were invited to attend the clinic for a medical examination guided by a
124 detailed questionnaire. At 10 years, visits to the schools were performed for SPT
125 upon consent. Information regarding any adverse reactions to food was obtained
126 using a standardised questionnaire.^(3,4) SPT was performed using ALK Abello
127 diagnostic extracts.⁽⁶⁾ Lupin flour (only performed at 10 years) and sesame allergens
128 were obtained from Stallergens. SPT reactions with a mean wheal diameter of 3 mm
129 or greater than the negative control were regarded as positive.

130 Based on their history and SPT results at ten years of age the following children were
131 invited for food challenges.

- 132 - Those with a positive SPT to a food that they had not knowingly eaten previously.
- 133 - Those who indicated a previous adverse reaction to foods (regardless of their skin
134 prick test data).
- 135 - Those with a previous diagnosis of a food allergy, without any recent exposure with
136 a clear reaction.

137 The following children were excluded:

- 138 - Those with a previous diagnosis of food allergy based on a food challenge
139 where the SPT size increased significantly
- 140 - Those with a previous diagnosis of a food allergy, where consultation with the
141 allergist indicated that a food challenge would be too risky
- 142 - Those with a SPT size above the 95% predictive values with a history of a
143 clinical reaction.⁽⁶⁾

144

145 Food challenges were performed using the PRACTALL⁽⁷⁾ guidelines for IgE mediated
146 food allergy. To diagnose non-IgE mediated food allergy, a normal daily amount was
147 given to the individual, based on the information of the National Diet and Nutrition
148 Survey (UK) until the child showed a reaction or a maximum period of 7 days.⁽⁸⁾ In
149 order to minimise any bias, food challenges were performed blinded where possible,
150 but always when looking for delayed/subjective symptoms.

151

152 Symptoms for IgE and non-IgE mediated FHS was classified according to the NICE
153 guidelines⁽⁹⁾ i.e. we diagnosed immediate type symptoms based on the symptoms
154 listed by the NICE guidelines occurring within 2 hours of ingestion of the foods.

155 Delayed symptoms were diagnosed based on the symptoms listed by the NICE
156 guidelines occurring 2 hours up to 7 days after ingestion of the food.

157

158 **Ethics permission**

159 Ethical approval for the study was obtained from the NRES South Central -
160 Southampton B Research Ethics Committee (REF 10/H0504/11).

161

162 **Analysis of data**

163 Data were double entered by different operators on SPSS versions 20 and 21 and
164 were compared and verified (SPSS Inc, Chicago, USA). Frequency tables were
165 produced at each time point from which prevalence rates were computed for each
166 allergen together with 95% confidence intervals. Numbers indicating loss of follow-up
167 were clearly stated. Missing data were handled by showing the relevant denominator
168 in each instance. Reasons for loss of follow-up or missing data were: family declined
169 any further involvement in the study, children declined to provide a blood sample or
170 undergo skin prick tests, families/children declined food challenges due to previous
171 reactions (defined as assessment by a paediatric allergist and symptoms in
172 agreement with the UK NICE guidelines)⁽⁹⁾ or positive oral challenges, and families
173 moved out of area. Confidence intervals were calculated using the Clopper-Pearson
174 test. In order to rule out selection bias at 10 years we used the following
175 methodology: A family history of allergic disease was defined as a first degree
176 relative (mother, father or sibling) with a “yes” answer to any of the validated ISAAC
177 questions⁽¹⁰⁾.

178 We compared (using a 2x2 table and Fisher’s exact test) those who completed the
179 FAIR recruitment questionnaire with a positive answer to a family history of allergic
180 disease vs. those who completed the 10 year questionnaire with a positive answer to
181 a family history of allergic disease. We then compared those who consented to SPT
182 at one year who reported a family history of allergy to those who consented to SPT
183 at ten years with a reported family history of allergy. We measured education level by
184 comparing the mothers in the consenting families at one and 10 years with higher
185 (college/university) and high school/less.

186

187

188 **Results**

189 The study population consisted of 969 (91% of the target population of 1063)
190 children. 827/969 (85%) children were seen at 10 years. Over the course of the 10
191 years, 725/969 (74.8%) children were seen at one, two, three and 10/11 years of
192 age and 947/969 (97.7%) children were seen at any time point. We have therefore
193 used 947 as our denominator for FHS over 10 years.

194

195 To rule out selection bias at 10 years, we compared reported family history of allergy
196 at recruitment vs those seen at 1 year 752/900 (83.6%) and those seen at 10 years
197 (691/827 (83.4%) and there was no difference between the two groups (p=0.99). The
198 same applied to those consenting to SPT at one year (637/736 [86.5%]) and ten
199 years (490/588 [83.6%]); p=0.64). We also compared maternal education between
200 those seen at 1 year (558/900 [62%]) and 10 years (527/827 [63.6%]); p=0.75 with
201 no difference.

202

203 **Sensitisation rates**

204 Sensitisation rates at three and ten years are summarised in table 1. Cumulatively
205 over the period of 10 years, 40/969 (4.1%; 95% CI: 3.19 - 5.32) children were
206 sensitised to a predefined food allergen.

207

208 Where history indicated, children were skin prick tested to other allergens. At the age
209 of ten years, five children who were not sensitised to any of the predefined food
210 allergens were sensitised to hazel nut (3), brazil nut (4), cashew nut (3), pistachio (3),
211 walnut (1), almond (1) and tomato (1).

212

213 **Reported symptoms of allergic disease in the first ten years of life**

214

215 Over the 10 year period, 203/947 (21.4%) children or parents reported a food related
216 problem. 77/827 (9.3%) children reported a food related problem to 107 foods, to the
217 question "do you have any food related problems". On further questioning of the
218 77/827 (9.3%) participants, it was noted that a number of children/parents interpreted
219 this question as food related aversion/dislike and 23 children were excluded for these
220 reasons. Of the 54 remaining participants followed with further phone-calls and
221 history taking by the study clinical and specialist allergy dietitian:

- 222 • 1 child showed no improvement on the elimination diet (wheat) and was
223 therefore not indicated to undergo a food challenge;

- 224 • 2 further children declined the intervention (reported GI symptoms but did not
225 want to trial an elimination diet);
226 • 8 children reported that the problem resolved naturally on further questioning
227 • in 3 children the physician advised no challenges as they were diagnosed
228 with coeliac disease;
229 • 2 children outgrew their egg allergy;

230

231 Of the 38 children eligible for food challenges

- 232 • 23 underwent food challenges;
233 • 5 children moved to the mainland and did not come for further follow-up but
234 were included in prevalence data if they were considered to be still allergic
235 based on skin/serum testing and recent history
236 • 10 children declined food challenges but were included in prevalence data if
237 they were considered to be still allergic based on skin/serum testing and
238 recent history

239

240 162 children who were avoiding a food for reasons such as aversion, fear of allergic
241 reaction or avoidance without giving any reason, a further 15 children were invited to
242 be further investigated based on reported symptoms suggestive of FHS: 9 underwent
243 food challenges, 2 children declined intervention/challenges, another 2 children
244 reported that the problem resolved naturally and 2 children showed no improvement
245 on an exclusion diet (figure 1).

246

247 **Diagnosis of Food Hypersensitivity based on food challenges at 10 years**

248 Overall, 37 food challenges were performed in 32 children (23 in those reporting food
249 allergy and 9 in those reporting food avoidance). These challenges were: 11 one day
250 OFC, 10 one day DBPCFC, 5 one week OFC and 11 one week DBPCFC. Of these,
251 6 one day OFC, 3 one week OFC and 2 one week DBPCFC were positive.

252

253 We invited all children for food challenges, but some declined. We have therefore
254 concluded that the following children were suffering from a FHS at 10 years of age,
255 based on the following criteria:

- 256 • 6 positive OFC 1 day: 2 peanut, 2 brazil nut, 1 sesame and 1 egg
257 • 3 positive OFC 1 week: 2 wheat and 1 milk
258 • 2 positive DBPCFC 1 week: 1 wheat and 1 egg
259 • 6 positive SPT plus clear history: 3 peanut (SPT 5 mm, 6 mm and 8 mm), 2

- 260 sesame (SPT 5 mm and 6 mm) and 1 hazelnut (SPT 6 mm)
- 261 • 6 SPT above the 95% predicted values (> 8 mm): 5 peanut and 1 brazil nut
- 262 • 2 still avoiding the food and report reactions on recent accidental ingestion: 2
- 263 egg (refused SPT but 5 mm and 5 mm at last follow-up)
- 264 • 2 positive food challenges for delayed type symptoms in the past who refused
- 265 further food challenges: 2 milk
- 266 • 3 children diagnosed with coeliac disease
- 267

268 (two of these children, one with a peanut allergy and one with an egg allergy did

269 not initially report a problem but were picked up from further questioning and

270 challenges and were diagnosed with a food allergy)

271

272 Of these 30 children, 9 had more than one food allergy, leading to 30 children

273 allergic to 50 foods.

274

275 Based on those with a positive food challenge and/or clear history (i.e. objective

276 symptoms on consumption of the allergen), the prevalence of FHS at ten years is

277 30/827 (3.6%, 95% CI: 2.54 to 5.15). Of the 77/827 (9.3%) children who initially

278 reported adverse reactions to foods, only 23/77 (29.9%) could be verified by means

279 of a food challenge and/or a clear history.

280 Dividing the children into those with IgE mediated and non-IgE mediated food allergy:

281 25 children suffered from IgE mediated food allergy: 25/827 (3.0%, 95% CI: 1.8 –

282 4.2) and 5 children suffered from non-IgE mediated food allergy: 5/827 (0.6%, 95%

283 CI: 0.07 – 1.3). We did not rule out that these children might have suffered from food

284 intolerances.

285

286 **The cumulative incidence of FHS by ten years of age**

287 The cumulative incidence of food hypersensitivity over 10 years was 64/947 (6.7%,

288 95% CI: 5.2 to 8.4). Between 3 and 10 years of age, 9/947 children (0.95%, 95% CI:

289 0.3 to 1.6) outgrew their food hypersensitivity (egg 4, milk 3, sesame 1, peanut 1)

290 and 12/947 (1.3%, 95% CI: 0.60 to 2.0) children developed new food

291 hypersensitivities (peanut 2, egg 1, wheat 2, sesame 2, gluten 2, milk 1, tree nuts 2).

292 (table 2)

293

294 **Foods implicated in FHS**

295 Milk and egg were the most common food hypersensitivities encountered in the first
296 ten years of life, although peanut was the most prevalent allergen at 10 years. (table
297 2)

298

299 **Discussion**

300 To our knowledge, this is currently the only cohort in the world providing this kind of
301 information. The prevalence of FHS at ten years was 30/827 (3.6%, 95% CI: 2.54 to
302 5.15), while the cumulative incidence of food hypersensitivity over a 10 year period
303 was 64/947 (6.7%, 95% CI: 5.20 to 8.4). 25/827 (3.0%, 95% CI: 1.8 – 4.2%) suffered
304 from IgE mediated food allergy, 5/827 (0.6%, 95% CI: 0.07 – 1.3%) from non-IgE
305 mediated food allergy/food intolerance.

306

307 *Sensitisation to food allergens*

308 Sensitisation rates to milk were relatively low. No child was sensitised to milk using
309 the SPT solution, but one child showed a positive prick-prick to milk and was
310 clinically milk allergic. Mustafayev et al.⁽¹¹⁾ reported a sensitisation rate of 1.1% in 10-
311 11 year olds in Turkey and Ronchetti et al.⁽¹²⁾ reported sensitisation rates of 0.5% in 9
312 year olds and 2% in 13 year olds in Italy.

313

314 In this cohort, sensitisation to egg was 2/588 (0.34%). Ronchetti et al.⁽¹²⁾ reported egg
315 sensitisation of 0% in 6-9 year olds in Italy and 1% in 13 year olds.

316

317 In our cohort, 14/588 (2.4%) children were sensitised to peanut at 10 years of age.
318 Sensitisation rates to peanuts in the previous two cohorts were 3.7% (11 year) and
319 2.7% (15 year).⁽⁴⁾ Mustafayev et al.⁽¹¹⁾ reported a 0.7% prevalence of SPT positive
320 peanut sensitisation in 10-11 year old Turkish children, while Nicolau et al.⁽¹³⁾
321 reported 5.1% sensitisation in 8 year olds from the UK.

322

323 *Clinical Allergy*

324 We have diagnosed 3/827 (0.36%) children with a clinical reaction to cow's milk but
325 only one child was sensitised and showed signs of IgE mediated CMA (0.12%).
326 Other studies in this age group have reported IgE mediated CMA varying from 0.1%
327 (Mustafayev et al.⁽¹¹⁾ and Orhan et al.⁽¹⁴⁾) up to 13.3% (Wan et al.⁽¹⁵⁾).

328

329 At 10 years of age 6/827 (0.73%) were egg allergic; all IgE mediated. Based on OFC
330 and a good clinical history, Mustafayev et al.⁽¹¹⁾ reported 0.1% egg allergy in 10-11
331 year olds and Orhan et al.⁽¹⁴⁾ reported 0.9% egg allergy in Turkish children.

332

333 Over the course of the 10 years, 13/947 (1.4%) children were diagnosed with peanut
334 allergy, and 12/827 (1.5%) children were allergic at 10 years, similar to Nicolau et
335 al.⁽¹³⁾ who diagnosed 1.9% of 8 year olds in the UK with a peanut allergy. In our
336 earlier cohorts, we have found that 7/775 (0.9%) at 11 years and 6/757 (0.8%) at 15
337 years were peanut allergic.

338

339 In our ten year old follow up, 6/827 (0.73%) children were clinically allergic to
340 sesame. In our other cohorts we have found that 0/775 11 year olds and 1/757
341 (0.013%) 15 year olds was sesame allergic.

342

343 We have found 4/827 (0.48%) children with wheat allergy at the age of 10 years. We
344 could not find any other studies reporting wheat allergy at 10 years of age.

345

346 *Reported vs Diagnosed food allergy*

347 It is well known that there is a discrepancy between reported and diagnosed FHS. At
348 ten years 77/827 (9.3%) parents reported a food related problem and of these, 23/77
349 29.9% were diagnosed with FHS. The EAACI systematic review reported self-
350 reported rates of food allergy at 6-17 years of age of 1.6 – 24.2%.⁽²⁾ Brugman et al.⁽¹⁶⁾
351 reported self-reported food allergy in children in the Netherlands aged 4-15 years of
352 7.2%.

353

354 *Foods implicated*

355 In a German study by Roehr et al.⁽¹⁷⁾ the authors identified that the children mainly
356 reacted to apple, kiwi, soy, hazelnut, and wheat. The foods identified in our study
357 were cows' milk, hens' eggs, wheat, peanut, sesame, and tree nuts.

358

359 One possible limitation of the study is the low uptake of food challenges. We do
360 however feel that all those children considered to be food allergic at ten years of age
361 were questioned by an experienced allergy dietitian/allergist, have been seen over
362 the years at the David Hide Asthma and Allergy Centre and have clear histories of
363 reactions plus positive SPT results in the case of IgE mediated food allergies. The
364 findings of our study do not represent food allergy data across the world, but
365 according to the UK census data, is representative of the South of England and our

366 data confirms with the recently published cow's milk allergy data from
367 Southampton/Winchester.⁽¹⁸⁾

368

369 To conclude, in this study we have found that 64/947 (6.8%) of children suffer from
370 FHS over the first decade of life. There was a large discrepancy between reported
371 and diagnosed FHS. The main foods implicated were cows' milk, hens' eggs and
372 peanut. A large number of children seem to outgrow their allergies to milk and egg by
373 10 years, with smaller numbers for peanut and sesame. New onset food allergies at
374 10 years of age were found for most foods studied.

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388

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469 **Table 1: Sensitisation rates in the first ten years of life**

470

Sensitisation	3 years (n=642)	10 years (n=588)	Positive at 3 and 10 years (persistent allergy)	Positive at 10 years but negative at 3 years (new onset)	Positive at 3 years but not at 10 years (outgrown)
	n (%) (95% CI)	n (%)	These figures include only those that were SPT at 3 and 10 years		
Any of the predefined allergens	76 (11.8) (9.3- 14.3)	145 (24.7) (21.2 - 28.1)	51/60 (85.0)	76/424 (17.9)	9/60 (15.0)
Any of the predefined food allergens	29** (4.5) (2.9 - 6.1) 23 (3.6) (2.2 - 5.0)	87** (14.6) (11.9 - 17.7) 16 (2.7%) (1.4 - 4.0)	15/21 (71.4) 9/18 (50.0)	64/463 (13.8) 6/466 (1.3)	6/21 (28.6) 9/18 (50.0)
Any of the predefined aero- allergens	70 (10.9) (8.5 - 13.3)	141 (24.1) (20.5 - 27.4)	47/55 (85.5)	77/429 (18.0)	8/55 (14.5)
Milk	3 (0.5) (-0.1 - 1.1)	0	0	0	3/3 (100)
Egg	9 (1.4)	2 (0.34)	2/7 (28.6)	0	5/7 (71.4)

	(0.5 - 2.3)	(0 - 0.8)			
Wheat	8 (1.3)* (0.4 - 2.2)	79 (13.4) (10.7 - 16.2)	4/5 (80.0)	66/478 (13.8)	1/5 (20.0)
Fish (Cod)	3 (0.5) (-0.1 - 1.1)	1 (0.17) (0 - 0.5)	1/3 (33.3)	0	2/3 (66.7)
Peanut	13 (2.0) (0.9- 3.1)	14(2.4) (0.1 - 0.4)	7/10 (70.0)	6/476 (1.3)	3/10 (30.0)
Sesame	9 (1.4) (0.5-2.3)	1 (0.17) (0 - 0.5)	1/5 (20.0)	0	4/5 (50.0)
Lupin (10 years only)		4 (0.68) (0 - 1.3)	NA	NA	NA
House dust mite	43 (6.7) (4.8 - 8.6)	80 (13.6) (11.1 - 16.6)	25/34 (73.5)	46/451 (10.2)	9/34 (26.5)
Grass	21(3.3) (1.9 - 4.7)	96 (16.7) (13.6 -19.6)	15/17 (88.2)	70/465 (15.1)	2/17 (11.8)
Cat	26 (4.1) (2.6 - 5.6)	45 (7.7) (5.8-10.1)	13/21 (61.9)	24/463 (5.2)	8/21 (38.1)

471 * All children with a positive SPT to wheat also had a positive SPT to grass and

472 consumed wheat without any problems.

473 ** including those sensitised to wheat

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475

476 **Table 2: FHS to single foods**

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	Number of children with FHS over 10 years (<i>no of IgE mediated cases</i>)	FHS at three years (n)	FHS at ten years (n) IgE vs.non-IgE
Milk	26 (2)	4	3 (0.36%) (1 outgrew) 1*:2 (both with diarrhoea and bloatedness; also to cheese) * had negative SPT using solution but positive SPT using pasteurised milk
Egg	19 (13)	9	6** (0.73%) (4 outgrew and 1 newly diagnosed) ** only two children consented to SPT at 10 years had positive results. Three children had positive SPTs during the first 10 years of life but refused SPT on the day. One child became sensitised after egg avoidance.
Wheat	6 (1)	2	4 (0.48%) (2 newly diagnosed) 1:3 (main symptoms included constipation/diarrhoea; coeliac disease ruled out)
Gluten	3 (0)	1	3 (0.36%) (2 newly diagnosed) 0:3
Peanut	13 (13)	11	12 (1.5%) (1 outgrew peanut allergy and 2 new onset) 12:0
Sesame	7 (7)	5	6 (0.73%) (1 outgrew sesame allergy and 2 new onset)* 6:0
Brazil nut	4 (4)	2	4 (0.48%) (2 new onset) 4:0

Corn	1 (1)	1	0
Fish	1 (1)	0	0
Tomato	1 (0)	0	0
Salicylate	1 (0)	1	0
Pineapple	1 (0)	1	0
Almond	2 (1)	2	2
Hazelnut	3 (3)	1	3 (0.36%) (2 new onset) 3:0
Cashew nut	3 (3)	1	3 (0.36%) (2 new onset) 3:0
Pistachio	3 (3)		3 (0.36%) 3:0
Walnut	1 (1)		1 (0.12%) 3:0

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479 * In table 1 only one child showed a positive SPT to sesame. The six children with sesame allergy had SPT of 4.5 mm, 2.5 mm, 1.5 mm and 3
480 refused SPT at 10 years of age, but were still clinically allergic.

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