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The sesame - peanut conundrum in Israel: Reevaluation of food allergy prevalence in young children

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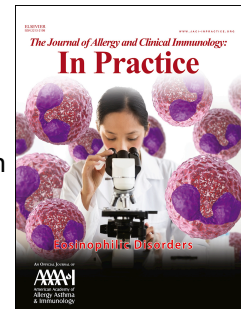
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Abstract	23
Background: Food allergies are on the rise worldwide. A previous cross-sectional study, from 2002 in Israel estimated the prevalence of IgE-mediated food allergy (FA) among young children at 0.85%. Although sesame was found to be a common allergen, peanuts were found to be a rare allergen.	24 25 26 27
Objective: To determine the prevalence and distributions of IgE-mediated food allergies among young children in Israel compared to previous data.	28 29
Patients and Methods: 1932 young children (56% males, 44% females) with a mean age of 22.4 months (range 18–30 months) were sequentially, recruited from 15 government family healthcare centers in north Israel. Parents completed a questionnaire with two screening questions for suspected FA. Subjects with suspected FA underwent further evaluation including telephone interview, skin prick tests and oral food challenge (OFC) as needed.	30 31 32 33 34 35
Results: After analyzing the questionnaires, 146 subjects were suspected to have FA. Seventy-nine subjects were excluded by telephone interview and thirteen were excluded based on negatives OFC .We identified 54/1932 (2.8%) young children with 75 IgE-mediated food allergies. Thirty-nine out of 54 (72.2%) had allergy to one food, nine (16.6%) to two foods. The most common food allergens were cow's milk 1%, eggs 0.88%, sesame 0.93%, tree nuts 0.57%, peanuts 0.2% and fish 0.2%.	36 37 38 39 40 41
Conclusions: The prevalence of IgE-mediated FA among young children in Israel has increased dramatically from 0.85% to 2.8%. The relative prevalence of the most common food allergens is similar to that identified in 2002, with a high prevalence of sesame and low prevalence of peanut FA.	42 43 44 45

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Clinical Implications statement: only 35 words	47
What is known already about the topic?	48
Food Allergies are on the rise worldwide. A previous, cross-sectional study, published	49
in 2002 estimated the prevalence of food allergy among Israeli young children (<2	50
years) at 0.85%, with high sesame and low peanut prevalence.	51
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What does this article add to our knowledge?	53
We revealed a substantial increase in the prevalence of FA among Israeli young	54
children in 18 years. The distribution and ranking of the main food allergens was	55
similar with high sesame and low peanut prevalence.	56
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How does this study impact current management guideline?	58
The increased prevalence of food allergy in Israeli young children constitutes an	59
important public health concern with tremendous implications for risk management.	60
Our findings strengthen the call for community-based allergy testing	61
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Key Words: food allergy; prevalence; young children; sesame; peanut	66
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Abbreviations:	77
FA- food allergy	78
AD- atopic dermatitis	79
FHC- family health care	80
OFC- oral food challenge	81
SPT- skin prick test	82
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Introduction	101
Food allergy (FA) is recognized as a worldwide medical problem in westernized	102
countries, and it appears to have increased alongside other atopic disorders, such as	103
atopic dermatitis (AD), allergic rhinitis and asthma. The true prevalence of food	104
allergy in the general population is uncertain, yet there are extensive data to suggest	105
that food allergies are common (up to 10% affected), and have been increasing in	106
prevalence over the last two to three decades (1). Gupta et al, used a self-report	107
electronic US household survey (n = 38,408) in 2015-2016 and estimated that 7.6% of	108
children have food allergy, with 39.9% of the children having multiple food allergies	109
(2). Nwaru et al. undertook a systematic review and meta-analysis (compiling 42	110
studies) of food allergy in Europe. They found an overall lifetime self-reported	111
prevalence up to 6% (3). An increase in the prevalence of food allergy may be	112
associated with an increase in reports of anaphylactic reactions to food. A	113
longitudinal study of children attending government schools in Australia (>550,000	114
students) found a 41% increase in students' risk of anaphylaxis from 2009 to 2014	115
(0.98% to 1.38%) (4). Similarly, in the United States, the prevalence of food allergies	116
among children increased from 3.4% in 1997 to 1999 to 5.1% between 2009 to 2011	117
(5). Although the data from Israel is limited, a cross-sectional study, which was	118
performed from May to October 2000 and published in 2002 estimated the overall	119
prevalence of clinically relevant IgE-mediated FA among young children (<2 years)	120
at 0.85% (78/9070) (6). Furthermore, sesame was found to be a major cause of IgE-	121
mediated food allergic reactions. In fact, sesame was second only to cow's milk as a	122
cause of anaphylaxis and third as an overall cause of IgE-mediated FA. In contrast,	123

Peanut, a major food allergen in Europe and North America, was found to be very rare 124
 allergen in Israel (6). Interestingly, Du Toit et al. in 2008 compared the prevalence of 125
 peanut allergy, between Jewish schoolchildren in United Kingdom and Israel, using a 126
 clinically validated questionnaire. They found a lower prevalence of peanut allergy in 127
 Israel, 0.17% vs.1.85% ($p<0.001$), which was assumed to be due to early introduction 128
 and higher consumption of peanuts in the Israeli group (7). This research led to the 129
 LEAP study and the recommendation of early introduction of peanuts in infants with 130
 severe atopic dermatitis (8). In a prospective study among 13,019 infants in Israel, the 131
 cumulative incidence of IgE-mediated cow's milk allergy was found to be 0.5% (9). In 132
 a recent study also done in Israel the prevalence of FA among Israeli young adults 133
 was 0.67%, lower than other western countries (10). 134
 However, because these studies are largely based on self-report accounts, rather than 135
 objective assessments of true IgE-mediated food allergy, oral food challenges, the 136
 potential for over-estimation bias should not be discounted. 137
 Accordingly, this study seeks to assess the current prevalence of IgE-mediated food 138
 allergic reactions among young children in Israel and to examine whether there was a 139
 change in the total prevalence and the order of frequency of food allergies compared 140
 to previously known data in Israel and other countries. 141

Material and methods 142

This cross-sectional study was conducted among ~~2-years~~ 2-year-old young children 144
 who were followed-up in 15 family health care (FHC) centers in the north of Israel. 145
 These government- operated centers offer national preventive health services to 146
 infants and children up to five years of age by providing immunizations and early 147
 detection of multitude of pediatric health problems. It is estimated that 95% of all 148
 children visit these centers. 149

Recruitment: In every FHC one of the nurses (the study nurse), recruited 150
consequently all the study infants on her shift, during their routine examinations. 151
The nurse, instructed and asked all the parents of these subjects, to fill out a short 152
questionnaire with two screening questions: (1) Do you think your child has food 153
allergy and if yes to which food (s); (2) Was your child diagnosed as having a food 154
allergy in allergy clinic? and if yes, to which food(s). Children whose parents 155
answered yes to at least one of these questions were considered eligible for inclusion 156
in the study. These parents were then contacted by phone and participated in a more 157
detailed interview. They were asked to provide further details regarding their child's 158
food allergies including the children's history of food allergy (description of the 159
symptoms, type and quantity of food required to evoke a reaction, whether the food is 160
raw or cooked, the time elapsed between ingestion and the onset of symptoms, the age 161
of onset, and the number of episodes of allergic reactions), and the child's history of 162
atopic diseases. Subjects with suspected IgE-mediated reactions were requested to 163
undergo, as needed, a skin prick test (SPT) or serum specific IgE at the Pediatric 164
Allergy/Immunology Unit at the Bnai Zion Medical Center. Additionally, for those 165
invited to the Allergy/Immunology Unit and whose diagnosis of food allergy was 166
questionable, an oral food challenge (OFC) was used to determine if indeed the child 167
had a food allergy. The study was approved by the Ethics Committee of the Bnai Zion 168
Medical Center, and informed consent was obtained from all the patients' caregivers. 169

Skin prick test 170

Skin prick tests were performed on the volar aspect of the forearm with single peak 171
lancets (Heinz Herenz, Hamburg, Germany) using commercial sesame extracts from 172
ALK Abello™ (Port Washington, NY) to cow's milk, egg, peanut, sesame, fish, and 173
any other food suspected by history. Additionally, in case of tree nuts we used also 174

fresh extracts (2mg protein/ml). The SPT included a positive control with histamine (1 mg/ml) and a negative control with saline (ALK Abello). Wheals with a mean diameter ≥ 3 mm greater than the negative control were considered positives reactions. All subjects avoided short-acting antihistamines for 72 hours prior to the SPT. Fresh extracts and commercial extracts were used.

Oral Food challenge

Oral food Challenge (OFC) was performed as open incremental oral challenges by using a standardized protocols developed on the basis of FA work group report and EAACI position paper (11, 12). They were conducted by a well-trained nurse and supervised by a pediatric allergist. The top dose administered was the normal daily intake of the food in question, adjusted for the age of the infant.

For example, An oral food challenge to sesame was performed using tahini paste (240 mg protein/ gram) or halva by introducing increasing doses from 20 mg protein through 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1.2 gram, 2 grams, every 20–30 min, with a 120-minute observation period following the final dose. The challenge was ended if a cutaneous, respiratory, gastrointestinal, or systemic response was observed. Patients who showed no reaction during the OFC were considered tolerant if no allergic symptoms appeared after a week of ingesting the tested food at home.

Definitions of food allergy

We utilized the following definitions for IgE-mediated food allergy.

1. Probably food allergy (p) - This includes all cases of self-reported food allergy, with clinical history of an IgE-mediated reaction but without presence of supporting confirmatory documents of tests.
2. Confirmed food allergy (c) - This includes infants who had positive food challenge or infants with convincing clinical history of an IgE-mediated reaction to the index food at the past 6 months and their physician provided

confirmation of a positive skin prick test (SPT) or a serum food-specific IgE >0.35 200
 kU/L. For this study, all infants diagnosed with probably - p or confirmed - c IgE- 201
 mediated food allergy, were defined as IgE-mediated food allergy - a. Thus $a = p + c$. 202
 Nevertheless, for clarity and precision, we always give also the prevalence of the 203
 confirmed IgE-mediated food allergy in brackets. Accordingly, the format that we will 204
 use, will be – a(c) 205

Sample size:

 206

Prior data indicate that the prevalence of patients with IgE-mediated food allergy 207
 reactions among a previous population of 9070 children was 0.85% (6). If the true 208
 prevalence among current population increase to 1.6%, and we study 1900 patients, 209
 we can be able to reject the null hypothesis that the prevalence of patients with IgE- 210
 mediated food allergy reactions, for present and previous population are equal with 211
 probability (power) of 0.8. The Type I error probability associated with this test of 212
 this null hypothesis is 0.05. We use an uncorrected chi-squared statistic to evaluate 213
 this null hypothesis. 214

Statistics

 215

To compare the prevalence of patients with IgE-mediated food allergy reactions, the 216
 number of overall and specific IgE-mediated positive reactions, between our present 217
 population and the historical population, we used an uncorrected chi-squared statistic 218
 or the exact fisher's test as appropriate, to evaluate the null hypothesis. 219

Results

 220

Between November 2017 and December 2018, a total of 1932 questionnaires were 221
 obtained from the 15 FHC survey sites. The group consisted of young children with a 222
 mean age of 22.4 months (range 18–30 months). After analyzing the results of the 223
 questionnaires, 146 of the young children, were suspected to have IgE-mediated food 224

allergy. Seventy-nine cases of the possible food allergies were excluded based on the
follow-up telephone interview. Of the remaining 67 patients, twenty-two (32.8%)
performed an open oral food challenge. Thirteen of these patients had a negative
outcome on the oral challenge, resulting in their exclusion as FA patients (see figure
1). Accordingly, we identified 54 patients (56% males) with 75 IgE-mediated food
allergic reactions.

In 47 out of 75 cases of food reactions (62.6%), the diagnosis of food allergy was
based on a convincing recent history of allergic reaction that appeared in the past 6
months with a positive SPT or specific IgE. In 19 cases, parents reported on diagnosis
of food allergy made by an allergist but declined additional follow-up. Therefore, as
planned in the method section, we provide both, the FA prevalence in which the lower
value in brackets (c), resemble confirmed FA and the higher value – a include the sum
of confirmed – c and the probably FA - p.

The most common food allergens were cow's milk 1% (0.57%), eggs 0.88% (0.77%),
sesame 0.93% (0.72%), tree nuts 0.57% (0.51%) (Walnut and cashew predominant),
peanuts 0.2% (0.2%) and fish 0.2% (0.1%) (Table 1). The nominal numbers are given
in table -2 compared to the historical data, published by one of this study author's
(reference 6 – Dalal I et al.), - 18 years ago. For comparison, we used the same
ranking of the previous data: Egg first, cow's milk second and so on. Indeed, the
prevalence of the IgE-mediated food allergy reactions increased significantly
altogether and specifically for every food examined, compared to previous data
measured 18 years ago. However, the distribution and ranking of the main FA
reactions in our study did not change significantly compared with the historical
ranking: $p=0.6$ for both - eggs versus cow's milk and versus sesame. Only the tree
nuts prevalence (0.57%) looked nominally higher than peanuts prevalence (0.2%)

contrary to historical data ranking but this did not reach statistically significant (p=0.12). Altogether, we identified 54 (44-confirmed FA) patients with 75 IgE-mediated food allergic reactions out of 1932 young children recruited, in comparison to 78 patients with 104 IgE-mediated food allergic reactions out of 9070 followed in the previous data (table 1-2). Thus, the patient prevalence with IgE-mediated FA increased in 18 years from 0.85% ($p < 0.001$) for both overall and confirmed prevalence (table 3). The allergic food reactions, reported by the 54 patients to the major food allergens, are listed in Table 2. Anaphylaxis was the presenting symptom in 2/54 (3.7%). Thirty-nine of the 54 patients (72.2%) had allergy to one food, nine (16.6%) to two foods, and six (11.1%) to three or more foods. A history of hyperactive airway was reported in 31% (7/22) and atopic dermatitis in 52% (11/21).

Discussion

Food allergy is a common problem among children; the prevalence appears to be increasing over the past decades (13). In this study, we assessed the prevalence of FA in the general population of young children in the north of Israel using a short questionnaire followed by telephone interview and OFC or recent allergic reaction documented by a physician with positive skin prick test. We found that the point prevalence of FA in Israeli Infants 2 years of age (range 18–30 months) is approximately 2.8% (confirmed FA -2.3%). The current data suggest that the overall prevalence of food allergy among young children increased from 0.85% to 2.8% over an 18-year period from 2000 to 2018. This finding of a robust, upward trend can be taken with confidence in that the methods used in the current study were similar to those used in the 2000 study conducted by Dalal et al.(6). Given the similarity in

methods, we can also estimate increased allergy prevalence with respect to certain 275
types of food. Specifically, based on the OFC performed in 32.8% of cases, we 276
estimate that from 2000 to 2018, cow's milk allergy increased from 0.3% to 1% 277
(0.57%), hen's egg allergy increased from 0.5% to 0.88% (0.77%), sesame allergy 278
increased from 0.18% to 0.93% (0.72%) and peanut allergy increased from 0.04% to 279
0.2% (0.2%). 280

Studies on the prevalence of food allergies are plagued by inconsistent methodologies 281
and variations in interpretation of results. Hence, it becomes difficult to compare the 282
prevalence of food allergies in different studies. Therefore, for more precision, we 283
gave both a and c as a(c). We believe that although it could be sometimes more 284
difficult to follow, this is one the strength in our study. Moreover, the type of food and 285
its importance as a common allergen varies among countries. With all the restrictions 286
we have mentioned, the overall 2.8% prevalence of diagnosed FA in this study is still 287
lower than the, 8.3%, 7.7% , 4.4% prevalence reported in prior studies in others 288
countries (2, 14, 15). The three most prevalent allergens in the study were; cow's milk 289
protein 1% (0.57%), sesame 0.93% (0.72%) and hen's egg 0.88% (0.77%). The 290
EuroPrevall birth cohort study which recruited infants in nine centers across different 291
European regions was designed to assess the cumulative incidence of food allergy 292
from birth to 2 years old. The IgE mediated cow's milk allergy at the age of 2 years 293
varied from 0% in Greece to 0.29% in Italy, 0.47% in Germany to higher incidence in 294
Spain 0.8% and 1.29% in Lithuania (16). The average of all the European centers was 295
0.59%, which is less than our total cow's milk allergy prevalence, but similar to our 296
confirmed cases. In contrast, Gupta et al. found a higher prevalence of 4.3% at the age 297
of 2 years in infants from USA and 1.6% in infants from the Isle of Wight (2, 15). 298
Regarding hen's egg allergy, data from the EuroPrevall birth cohort showed a mean 299

adjusted challenge-diagnosed incidence of hen's egg allergy of 1.23% in the first 2 years of life or 1.3% in infants from the Isle of Wight, which is higher than the prevalence in our study (15, 17). Sesame (0.93%, 0.72%) allergy is a common allergen in Israel higher than 0.2% that reported in infants in USA (2). In a longitudinal study of Australian recruited at the age of 1 year and then followed up until the age of 4 years, the prevalence of sesame allergy at the age of 1 years old 0.6% and 0.4% at the age of 4 years (18).

We found a low prevalence of peanut allergy (0.2%) which consistent with an earlier Israeli study, almost two decades prior. This is notable and interesting finding as peanuts are a major food allergen in Europe and North America and sesame is considerably less common (19, 20). In contrast, although Israeli infants are exposed early to both peanuts and sesame, the low prevalence of peanut allergy in juxtaposition to the high prevalence of sesame allergy may be viewed as the sesame peanut conundrum. There are several factors that may explain this phenomenon. First, the slightly later introduction of sesame, around 6-9 months, mostly in the form of tahini paste might pose a significant food allergy culprit. In 2003 Dalal et al. reported on the pattern of sesame sensitivity among infants and children in Israel (21). In this study the median age at allergic reaction was 9 months (interquartile range [IQR], 8-12 months). As of 2016, the Israeli health ministry recommends on early introduction of sesame, and in a study published by our group on the use sesame paste in the diagnosis of sesame allergy (22), we recruited patients from different parts of Israel and the median age of reaction to sesame was 6 months (IQR, 6-9 months) (unpublished data). Importantly however, the exact quantities of sesame consumed in young infants less than 1 year of age in Israel has not been investigated.

Second, earlier studies on food allergies, suggest that beyond any effect of age of 324
introduction, a sufficient quantity is also required to achieve food tolerance. In the 325
LEAP study, the intervention was with at least 6 grams of peanut protein per week. 326
Modelling in the EAT study demonstrated a protective requirement against allergy of 327
2 grams per week of egg white protein and peanut protein between 3-6 months of age. 328
The equivalent amount of sesame protein would be approximately 15 grams of tahini 329
(1 large tablespoon) which is a substantial amount and likely not achieved. Hence, in 330
contrast to peanut, the Israeli infants may not be consuming sufficient quantities of 331
sesame during infancy their early months. Additionally, bamba (peanut snack), an 332
extremely popular among young infants, is produced by a unique industrial process 333
which may affects the allergenicity of the peanut proteins as compared to tahini which 334
is a crash sesame. 335

Besides the timing and quantity of the introduced food allergens, other factors may 336
also be involved, Marenholz et al identified five food allergy susceptibility loci in a 337
large group of German children which emphasis the probable genetic factor that might 338
play a role in food allergy development (23). It seems that further studies are needed 339
to investigate if early introduction of food allergen will decrease food prevalence for 340
every allergen in different populations. The fact that peanut allergy in Israel remains 341
very low at 0.2%; whereas 2.8% of children have a food allergy, should encourage 342
countries and public health bodies who are debating whether or not peanuts can be 343
successfully introduced into the diet of a whole population, to recommend on early 344
introduction of peanuts such as the Israeli bamba snack which is palatable, nutritious 345
and safe. In Israel, it is given by most parents to their children at an early age (before 346
12 months of age). 347

In a recent Israeli study, the overall prevalence of FA in young adults was found to be 0.67%. This is lower than prevalence rate reported in previous studies in other parts of the world (10). This study was conducted during a similar time period to ours. Although the research methods were not identical, several conclusions can be drawn from their data. First in both studies, the prevalence of FA was low compare others parts of the world. The prevalence of FA in young adults is about one-fourth the prevalence in 2 years old children. Tree nut allergy was the most common in young adults and also a significant in our study (0.51%, 0.57%) compares to 0.03% in the study conducted in 2002 (6). This change is most likely attributable to a change in dietary habits, and in particular, the increased accessibility of tree nuts as paste given to infants. Cow's milk allergy is still a dominant food allergen at all ages and over time.

Our study has several limitations. First, we examined young children in only one geographic area in Israel. Although, the populations in the center and the north of Israel (distance of only ~ 60 miles) are inter-mixed and the demographic, cultural, medical services and for our purpose, food habits are not different. Second, we do not know the percentage of parents refuse to participate in this study. However, we believe that the way of recruiting consequently and unconditionally every young child coming for their routine examination during the shift of the study nurse, confirms that the 1932 patients recruited to fill screening questionnaires, do represent our population. Third, in 19 cases the parents reported on FA, and refuse to provide supporting confirmatory tests or to perform OFC, Fourth, the methodology of the study including the definition of food allergy, the study age group or the method of data collection were similar but not identical to the previous study that we compare the results.

In conclusion, when compared with prevalence data collected over 18 years earlier, 373
the current data suggest a substantial growing burden of FA in Israeli young children 374
from 0.85% to 2.8% in two decades. The increase of FA in young children constitutes 375
an important health issue due to its huge impact, with the most common food 376
allergens in young children are cow's milk, sesame and hen's egg. Moreover, we 377
confirmed previous findings of low peanuts and high sesame prevalence in Israel, in 378
two different studies two decades apart. 379

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Figure Legend 475

Figure 1- A Flowchart of food allergy assessment protocol. All questionnaire were 476
assessed, 146 of the subjects were suspected to have IgE-mediated food allergy. 477
Seventy-nine cases were excluded based on the detailed telephone interview. Of the 478
remaining 67 patients, thirteen of these patients had a negative outcome on the oral 479
challenge, resulting in their exclusion ~~from the study~~ as FA patients. Therefore, we 480
identified 54 patients with IgE-mediated FA. 481

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TABLE I. The prevalence of IgE mediated food allergy for each food allergen among the study population (n=54)

Type of food allergen	Sesame 0.72%-0.93% (n=18)	Peanut 0.2% (n=4)	Cow's milk 0.57%-1% (n=21)	Hen's egg 0.77%-0.88% (n=17)	Tree-nut 0.51%-0.57% (n=11)	Fish 0.1%-0.2% (n=4)
positive OFC	7			2		
recent allergic reaction and positive SPT/specific IgE	7	4	11	13	10	2
Parental self-report without further investigation	4		10	2	1	2
multi food allergy	11/18	2/4	5/21	9/17	7/11	2/4

Data present the prevalence of each food allergen; we identified 54/1932 (2.8%) young children with 75 IgE-mediated food allergies. the presented percentage (%) include a range from the low vale which is confirmed cases of FA to the high value, which include the confirmed and probable cases.

Table II. Prevalence of IgE-mediated food allergy reactions compared to previous data in Israel

Food allergen	Previous data* n = 9070 (%)	Current article n = 1932 (%)	<i>P value</i>
Egg	42 (0.5)	17 (0.88)	0.023
Cow's milk	28 (0.3)	21 (1)	< 0.001
Sesame	16 (0.18)	18 (0.93)	< 0.001
Peanut	4 (0.04)	4 (0.2)	0.036
Tree nuts	2 (0.02)	11 (0.57)	< 0.001
Fish	1 (0.01)	4 (0.2)	0.004
Total IgE-mediated food allergic reaction	104 (1.15)	75 (3.88)	< 0.001

*reference 6

TABLE III. Prevalence of young children with IgE-mediated food allergy reactions compared

Food Allergy	Previous data* n = 9070 (%)	Current article n = 1932 (%)	P value
Total young children with IgE-mediated food allergic reaction	78 (0.85)	54 (2.8)	< 0.001
Total young children with "confirmed" IgE-mediated food allergic reaction	78 (0.85)	44 (2.3)	<0.001

to previous data published in Israel

* reference 6.

