

# A Comprehensive Review of Sensitization and Allergy to Soy-Based Products

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**Abstract** Since 1943, cases of sensitization or allergy to soy-based formulas (SBFs) have been described without any consensus on their real prevalence. We identified the adjusted prevalence of IgE-mediated soy allergies in children and performed a secondary analysis of the impact of age (less than and more than 6 months). We performed a systematic review with meta-analysis of studies published from 1909 to 2013 in PubMed, Embase, LILACS, ARTEMISA, Cochrane, Bandler, DARE and the GRADE system for grading quality. Results are presented in tables and graphs using a forest plot. The 40 studies identified established weighted prevalence of soy allergies of 0 to 0.5 % (0.27) for the general population, 0.4 to 3.1 % (1.9) for the referred population, and 0 to 12.9 %

(2.7) for allergic children. Prevalence of sensitization after the use of SBFs is 8.7 and 8.8 %, depending on the method used. The prevalence of allergies to soy and IgE sensitization to the use of SBFs is less than reported. Not enough evidence exists to show a higher risk of allergy in infants younger than 6 months. The concern about soy allergy is no reason to postpone the use of SBFs in IgE-mediated cow's milk allergy infants until the age of 6 months.

**Keywords** Soy · Infant formula · Allergy · Cow's milk allergy · Soy allergy · IgE

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## Introduction

The availability of effective and safe infant formulas is a very recent phenomenon. Even in the eighteenth century, a significant proportion of infants that could not be breastfed by their mothers or wet nurses died in the first year of life [1–3]. Later discoveries in the field of medicine and biology laid the foundations for the development of alimentation sources other than maternal milk. Von Liebig patented the first infant formula [4], followed by other companies, some of which still exist today [5].

Although a description of soy formulas being used as a substitute for cow's milk (CM) appeared for the first time in 1909 [6], the use of soy in infant alimentation actually dates back to Asian civilizations as early as 82 BC [7]. In 1929, soy protein formulas (SPFs) began to be used as substitutes for cow's milk in children with cow's milk protein allergies (CMPAs) [8].

Originally, fat-free soy flour was used as a source of protein for SPFs; however, the presence of some nondigestible carbohydrates, like stachyose and raffinose, caused infants to present with semi-liquid odorous evacuations. Therefore, these products were substituted with proteins derived from water-soluble

soy isolates, giving rise to formulas with protein derived from soy, like those we know today, which have an improved type of carbohydrates and mixture of vegetable oils and are fortified with methionine, taurine, carnitine, and iron [9–18].

The antigenicity of soy (capacity of the soy to promote synthesis of IgG, IgA, or IgM) has been described and frequently overestimated in the medical literature for more than 30 years, based on the studies of Eastham and collaborators, who reported that soy protein could be considered as antigenic as cow's milk [19, 20]. Later analysis demonstrated that what the authors measured was soy hemagglutinins, which are predominantly IgG and are frequently produced by healthy individuals and at higher rates during infancy and are often associated with tolerance induction of food [15].

From 1943 to 1996 (53 years), around 30 articles have been published related to soy allergies, especially in children with CMPAs [21–52]; however, many of these are “apparently” based on the concept of allergenicity. However, when a detailed analysis is performed on these studies, the allergy diagnosis in the majority of cases was based solely on clinical suspicion, parents'

reports or, in some cases, skin-prick tests (SPTs), without performing an oral challenge test, which is currently considered the standard of reference. Moreover, most studies included heterogeneous cohorts of children in different age groups and clinical presentations, which included cases with true IgE-CMPA and others with non-IgE allergy but many with mixed populations. Some had gastrointestinal manifestations, such as immediate vomiting, which could in fact represent true IgE-mediated reactions; others included abdominal pain or diarrhea, which could be unrelated or questionable; and the majority had cutaneous manifestations. There were at least two kinds of skin manifestations—immediate urticarial and/or angioedema—suggestive of IgE-CMPA, and “worsening of eczema,” which is an issue of debate. Some studies also relied on small sample sizes, which could lead to a type II error.

The first study on soy allergy was published by Hill in 1942. He described 13 cases of presumed milk allergy that were successfully treated with soy. Seven of the 13 were subsequently sensitized to soy, with positive SPTs, but without clinical consequences [52]. In 1997, Cantani found a

**Table 1** Prevalence of OFC-proven soy allergy in children

| Author, year (reference)   | Country | Ages                | Type of population  | n/total  | Prevalence (%) | Design          | Quality of evidence   |
|----------------------------|---------|---------------------|---------------------|----------|----------------|-----------------|-----------------------|
| <b>General population</b>  |         |                     |                     |          |                |                 |                       |
| Roehr, 2004 [62]           | Germany | 1 month–14 years    | Unselected          | 4/739    | 0.5            | Cross-sectional | Low <sup>a</sup>      |
| Osterballe, 2005a [63]     | Denmark | 1 month–2 years     | Unselected          | 0/111    | 0.0            | Cohort          | Moderate              |
| Osterballe, 2005b [63]     | Denmark | 3–17 years          | Unselected          | 0/787    | 0.0            | Transversal     | Low                   |
|                            |         |                     | Prevalence          | 4/1,946  | 0.27           |                 |                       |
| <b>Referred population</b> |         |                     |                     |          |                |                 |                       |
| Bock, 1990 [59]            | USA     | 3 months–19 years   | Suspected FA        | 15/480   | 3.1            | Cross-sectional | Low <sup>b</sup>      |
| Giampietro, 1992 [24]      | Italy   | 1 months–10 years   | 78 AD               | 5/317    | 1.6            | Cross-sectional | Low <sup>c</sup>      |
| Bruno, 1997 [60]           | Italy   | 6–168 months        | Atopic parents      | 1/243    | 0.4            | Cross-sectional | Low                   |
| Bruno, 1997 [60]           | Italy   | 6–168 months        | Suspected FA and AD | 6/505    | 1.2            | Cross-sectional | Low                   |
| Magnolfi, 1996 [46]        | Italy   | 1 months–18 years   | Suspected FA and AD | 8/262    | 3.1            | Cross-sectional | Low <sup>d</sup>      |
|                            |         |                     | Prevalence          | 35/1,807 | 1.9            |                 |                       |
| <b>Atopic children</b>     |         |                     |                     |          |                |                 |                       |
| Zeiger, 1999 [61]          | USA     | 3 months–4 years    | CMA                 | 12/93    | 12.9           | Cohort          | Moderate <sup>e</sup> |
| Crespo, 1995 [42]          | Spain   | 5.4 years           | FA                  | 0/355    | 0.0            | Transversal     | Low                   |
| Niggeman, 1999 [66]        | Germany | 5 m–12 years (21 m) | AD                  | 7/107    | 6.5            | Transversal     | Low                   |
| Caminiti, 2009 [64]        | Italy   | 5–10 years          | CMA                 | 0/13     | 0.0            | Transversal     | Low <sup>f</sup>      |
| Klemola, 2005 [65]         | Finland |                     | CMA                 | 0/140    | 0              | Cross-sectional | Low <sup>g</sup>      |
|                            |         |                     | Prevalence          | 19/708   | 2.7            |                 |                       |

FA food allergy, CMA cow's milk allergy, AD atopic dermatitis

<sup>a</sup> Only one out the four had cutaneous symptoms

<sup>b</sup> Positive sensitization was not required. Could include non-IgE

<sup>c</sup> Ten had “positive” challenge, but only five had sIgE to soy

<sup>d</sup> Two had reaction after >48 h—IgE mediated

<sup>e</sup> A multicenter study (four centers), but all positive were from a single tertiary center—clinic for multiple food allergies

<sup>f</sup> All 13 in the study had negative history and SPT to soy

<sup>g</sup> Cases 4, 6, and 8 had late reactions, no cutaneous signs, and reacted to large doses. Unlikely IgE mediated

**Table 2** SPT-proven sensitization to soy in children

| Author, year (reference)   | Country   | Ages                                    | Type of population | n/total   | Prevalence (%) | Design         | Quality of evidence |
|----------------------------|-----------|-----------------------------------------|--------------------|-----------|----------------|----------------|---------------------|
| <b>General population</b>  |           |                                         |                    |           |                |                |                     |
| Arshad, 2001 [89]          | England   | 4 years                                 | Unselected         | 2/981     | 0.2            | Cohort         | Moderate            |
| Dalal, 2002 [79]           | Israel    | 1 month–2 years                         | Unselected         | 3/9,070   | 0.0            | Transversal    | Low                 |
| Rance, 2005 [90]           | France    | 2–5 years                               | Unselected         | 1/2,716   | 0.0            | Transversal    | Low                 |
| Roberts, 2005 [91]         | England   | 7 years                                 | Unselected         | 2/1,173   | 0.2            | Cohort         | Moderate            |
|                            |           |                                         | Prevalence         | 8/13,940  | 0.1            |                |                     |
| <b>Referred population</b> |           |                                         |                    |           |                |                |                     |
| Magnolfi, 1996 [46]        | Italy     | 1 month–18 years (7 years and 8 months) | CMA                | 148/704   | 21             | Transversal    | Low                 |
| Bruno, 1997 [60]           | Italy     | 6–168 months (69 months)                | Suspected FA       | 31/505    | 6.1            | Transversal    | Low                 |
| Chiang, 2007 [92]          | Singapore | 0.2–15.4 years (5.2 years)              | Other              | 8/227     | 3.5            | Transversal    | Low                 |
| Agostoni, 2007 [76]        | Italy     | 5–6 months                              | CMA                | 15/160    | 9.4            | Clinical trial | Moderate            |
|                            |           |                                         | Prevalence         | 202/1,596 | 12.7           |                |                     |
| <b>Atopic children</b>     |           |                                         |                    |           |                |                |                     |
| Zeiger, 1999 [61]          | USA       | 3 months–4 years                        | CMA                | 12/93     | 12.9           | Cohort         | Moderate            |
|                            |           |                                         | Prevalence         | 12/93     | 12.9           |                |                     |

history-based soy allergy incidence of 27 % after analyzing 17 studies in children [53]. Upon analyzing only six of those studies ( $n=2,496$ ), in which the soy allergy diagnosis was confirmed by a challenge test, the average prevalence was found to be 4.2 % [24–26, 41, 46, 54].

Considering the discrepancies in the reported prevalence rates, the objective of this study was to carry out a systematic review of the evidence, with the goal of identifying the adjusted prevalence of IgE-mediated soy allergies in individuals younger than 19 years old and performing a secondary analysis on the prevalence of soy allergy among infants younger than 6 months of age.

## Materials and Methods

### Studies Included and Their Characteristics

The present review includes all the analytical transversal studies, studies of cases and controls, cohort studies, and clinical trials that have evaluated the prevalence of sensitization or allergy to soy performed on infants and children up to 19 years old, including newborns. Studies are performed independent of country of origin, language or clinical condition that led to the search for allergy or sensitization to soy.

**Table 3** sIgE-proven sensitization to soy in children

| Author, year (reference)   | Country     | Ages                          | Type of population | n/total  | Prevalence (%) | Design         | sIgE level=positive | Quality of evidence |
|----------------------------|-------------|-------------------------------|--------------------|----------|----------------|----------------|---------------------|---------------------|
| <b>General population</b>  |             |                               |                    |          |                |                |                     |                     |
| Baatenburg, 2011 [93]      | Netherlands | 0–18 years                    | Unselected         | 63/9,044 | 0.7            | Transversal    | >0.35 kU/L          | Low                 |
|                            |             |                               | Prevalence         | 63/9,044 | 0.7            |                |                     |                     |
| <b>Referred population</b> |             |                               |                    |          |                |                |                     |                     |
| Giampietro, 1992 [24]      | Italy       | 1 month–10 years (5 months)   | Suspected FA       | 69/317   | 21.8           | Transversal    | 0.35 PRU/mL         | Low                 |
| Matricardi, 2007 [94]      | Germany     | 7 years                       | Other              | 12/273   | 4.4            |                | >1 kU/L             | Moderate            |
| Ferrari, 2011 [95]         | Switzerland | 0–16 years (1.9 months)       | FA                 | 6/151    | 4              | Transversal    | 0.7 kU/L            | Low                 |
|                            |             |                               | Prevalence         | 87/741   | 11.7           |                |                     |                     |
| <b>Atopic population</b>   |             |                               |                    |          |                |                |                     |                     |
| Zeiger, 1999 [61]          | USA         | 3 months–4 years              | CMA                | 11/93    | 11.8           | Cohort         | NA                  | Moderate            |
| Niggeman, 1999 [66]        | Germany     | 5 months–12 years (21 months) | AD                 | 45/107   | 42.1           | Transversal    | >0.35 kU/L          | Low                 |
| Klemola, 2005 [65]         | Finland     | 2–11 months                   | CMA                | 36/140   | 25.7           | Clinical trial | >0.35 kU/L          | Moderate            |
|                            |             |                               | Prevalence         | 92/340   | 27.1           |                |                     |                     |

**Table 4** Prevalence of self-reported soy allergy in children

| Author, year (reference) | Country     | Ages             | Type of population  | n/total   | Prevalence (%) | Design      | Quality of evidence |
|--------------------------|-------------|------------------|---------------------|-----------|----------------|-------------|---------------------|
| Brugman, 1998 [80]       | Netherlands | 4–15 years       | Unselected          | 27/4,450  | 0.6            | Transversal | Low                 |
| Van Bockel, 1992 [81]    | Netherlands | 5–6 years        | Unselected          | 1/1,039   | 0.1            | Transversal | Low                 |
| Eggesbo, 1999 [82]       | Norway      | 2 years          | 11.6 % CMA          | 4/3,623   | 0.1            | Transversal | Low                 |
| Kristjansson, 1999 [96]  | Sweden      | 1–5 years        | 52 CMA <sup>c</sup> | 1/652     | 0.3            | Transversal | Low                 |
| Dalal, 2002 [79]         | Israel      | 0–2 years        | Unselected          | 3/9,070   | 0.0            | Transversal | Low                 |
| Osterballe, 2005a [63]   | Denmark     | 1 months–2 years | Unselected          | 2/111     | 1.8            | Cohort      | Low <sup>a</sup>    |
| Osterballe, 2005b [63]   | Denmark     | 3–17 years       | Unselected          | 1/787     | 0.1            | Cohort      | Low <sup>b</sup>    |
|                          |             |                  | Prevalence          | 39/19,732 | 0.2            |             |                     |

<sup>a, b</sup> None of these was confirmed in OFC

<sup>c</sup> We did not identify if they were cases or percentages of cases

The identification of the prevalence of sensitization was performed as a result of clinical manifestations, parent reports, serum concentrations of specific immunoglobulin E (sIgE), an SPT or an oral challenge test [55].

### Search Strategies

Highly sensitive search strategies were employed as described by Robinson for clinical trials and by Wilczynski for the identification of observational studies [56, 57], adding to said strategy the key words “(soy or (soy and infant and formula)) and (sensitization or allergy or tolerance or allergenicity),” limiting the search strategy to studies in human beings and not limiting publication language. The search was carried out electronically and manually in the databases PubMed (1909 to March 2013), Embase (1988 to March 2013), LILACS (1990 to May

2009), ARTEMISA (review of the 13th edition up to December 2012), Cochrane-controlled trials register, Bandolier, and DARE.

### Evidence Quality Evaluation

We used the standardized methods described by the Ibero-American Cochrane Collaboration to prepare the protocol, apply criteria of inclusion, evaluate the quality of publications and extract information. The quality of publications was determined using the GRADE system [58]. Two authors used a double-blind, independent manner to extract and evaluate the quality of relevant information in formats designed a priori for this objective. Disagreements were resolved by discussion and analysis of the information.

**Table 5** Prevalence of soy allergy, after use of formula with soy bases protein in infants and children up to 19 years old

| Author, year (reference) | Country  | Ages             | Type of population | n/total | Prevalence (%) | Design         | Quality of evidence   |
|--------------------------|----------|------------------|--------------------|---------|----------------|----------------|-----------------------|
| Cantani, 1990 [15]       | Italy    | 5–15 months      | AD                 | 1/20    | 5              | Cohort         | Moderate              |
| Bruno, 1997 [60]         | Italy    | 43–71 months     | Atopic parents     | 1/243   | 0.4            | Cohort         | Low                   |
| Klemola, 2002 [74]       | Finland  | 2–11 months      | CMA                | 2/80    | 2.5            | Clinical trial | Moderate <sup>a</sup> |
| Dias, 2010 [67]          | Spain    | 3 months–2 years | CMA                | 1/52    | 1.9            | Cohort         | Moderate              |
| Terracciano, 2010 [75]   | Italy    | 2–37 months      | CMA                | 0/29    | 0              | Clinical trial | Moderate              |
| Antunes, 2009 [68]       | Portugal | 4–6 months       | CMA                | 0/4     | 0              | Case series    | Low                   |
| Buts, 1993 [69]          | Belgium  | 6 months–3 years | CMA                | 1/17    | 5.9            | Cohort         | Low <sup>b</sup>      |
| Katz, 2010 [78]          | Israel   | 3–12 months      | CMA                | 0/64    | 0              | Transversal    | Low                   |
| Klemola, 2005 [65]       | Finland  | 4 years          | CMA                | 0/70    | 0              | Clinical trial | Moderate              |
| Agostoni, 2007 [76]      | Italy    | 5–6 months       | CMA                | 0/32    | 0              | Clinical trial | Moderate              |
| Zeiger, 1999 [61]        | USA      | 8–38 months      | CMA                | 12/93   | 12.9           | Clinical trial | Moderate              |
| Arato, 1995 [77]         | Hungary  | 2 months–2 years | CMA                | 0/16    | 0              | Clinical trial | Moderate              |
|                          |          |                  | Prevalence         | 18/720  | 2.5            |                |                       |

<sup>a</sup> Only cases 2 and 5 had evidence of soy sensitization (sIgE)

<sup>b</sup> Diarrhea in 72 h. Resumed soy later, suggesting not allergy

**Table 6** Sensitization to soy in infants and children up to 19 years old after use of soy bases formula

| Author, year (reference)       | Country | Ages                      | Type of population | n/total   | Prevalence (%) | Design         | Quality of evidence and cut-off level of sIgE |
|--------------------------------|---------|---------------------------|--------------------|-----------|----------------|----------------|-----------------------------------------------|
| Sensitization measured by SPT  |         |                           |                    |           |                |                |                                               |
| Bruno, 1997 [60]               | Italy   | 43–71 months              | Atopic parents     | 14/243    | 5.8            | Transversal    | Low                                           |
| Klemola, 2002 [74]             | Finland | 2–11 months               | CMA                | 0/76      | 0              | Clinical trial | Moderate                                      |
| Agostoni, 2007 [76]            | Italy   | 5–6 months                | CMA                | 3/32      | 9.4            | Clinical trial | Moderate                                      |
| Katz, 2008 [97]                | Israel  | 0–48 months               | CMA                | 4/23      | 17.4           | Transversal    | Low                                           |
| Dias, 2010 [67]                | Spain   | 3 months–2 years          | CMA                | 8/58      | 13.8           | Cohort         | Moderate                                      |
| Terracciano, 2010 [75]         | Italy   | 2–37 months               | CMA                | 11/29     | 37.9           | Clinical trial | Moderate                                      |
|                                |         |                           | Prevalence         | 40/461    | 8.7            |                |                                               |
| Sensitization measured by sIgE |         |                           |                    |           |                |                |                                               |
| Klemola, 2002 [74]             | Finland | 2 years                   | CMA                | 15/76     | 19.7           | Clinical trial | Moderate, >0.35 kU/L                          |
| Klemola, 2005 [65]             | Finland | 4 years                   | CMA                | 22/70     | 31.4           | Clinical trial | Moderate, >0.35 kU/L                          |
| Cantani, 1990 [15]             | Italy   | 5–15 months               | AD                 | 2/20      | 10.0           | Cohort         | Moderate, NA                                  |
| Ahn, 2003 [98]                 | Korea   | 3–141 months (2.5 years)  | CMA                | 41/224    | 18.3           | Transversal    | Low, >0.7 kU/L                                |
| Ahn, 2003 [98]                 | Korea   | 2–35 months (12.8 months) | Suspected CMA      | 74/1,363  | 5.4            | Transversal    | Low, >0.7 kU/L                                |
|                                |         |                           | Prevalence         | 154/1,753 | 8.8            |                |                                               |

### Synthesis and Analysis of Information

The evidence obtained is presented in tables, calculating the weighted prevalence and stratifying the results based on the type of method used to establish the suspicion/diagnosis of allergy or sensitization to soy. The results of the evidence concerning the prevalence of soy allergy are presented graphically, as are the results associated with sensitization to soy after the use of formulas with soy-based protein. Finally, we calculated the influence of age (older and younger than 6 months) on the relative risk of developing sensitization to soy using a Mantel–Haenszel fixed-effects model. For all estimates, a confidence interval of 95 % (CI<sub>95</sub> %) was calculated. A heterogeneity test was performed in all cases using the  $I^2$  test, with a  $p < 0.05$  significance level. Additionally, the risk analysis is presented in graphic form using a forest plot and, in the case of suspected bias of publication, a funnel plot

was prepared. In some cases, a sensitivity analysis was necessary.

### Results

#### Description and Quality of Studies

The initial search strategy yielded a total of 357 potential studies to be included in this review. Upon careful review of the summaries of each article, 306 were eliminated. These covered topics not related to our review questions or examined a population of individuals older than 19 years. Of the remaining 51 studies, upon complete review, an additional 11 studies were eliminated because they were narrative reviews of the evidence or lacked sufficient congruence and/or yield between what was described in the objectives and what was reported in

**Table 7** Prevalence of self-reported soy allergy in infants and children up to 19 years old after use of soy protein based formula

| Author, year (reference)  | Country   | Ages                    | Type of population  | n/total   | Prevalence (%) | Design         | Quality of evidence   |
|---------------------------|-----------|-------------------------|---------------------|-----------|----------------|----------------|-----------------------|
| Berger-Achituv, 2005 [70] | Israel    | 2–4 months              | General population  | 1/144     | 0.7            | Cohort         | Moderate              |
| Berger-Achituv, 2005 [70] | Israel    | 6–14 months             | General population  | 0/234     | 0              | Cohort         | Moderate              |
| Jirapinyo, 2007 [84]      | Thailand  | 2–24 months             | CMA                 | 12/18     |                | Clinical trial | Low <sup>a</sup>      |
| Agostoni, 2007 [76]       | Italy     | 3–6 months (5.5 months) | CMA                 | 5/32      |                | Clinical trial | Moderate              |
| Mehr, 2008 [71]           | Australia | 9.5 months (mean)       | CMA                 | 0/29      | 0              | Cohort         | Moderate              |
| Nachmias, 2010 [72]       | Israel    | 1–6 months              | Parental preference | 0/982     | 0              | Cohort         | Moderate              |
| Sladkevicius, 2010 [73]   | England   | 1–12 months             | CMA                 | 90/1,000  | 9              | Cohort         | Moderate <sup>b</sup> |
|                           |           |                         | Prevalence          | 108/2,439 | 4.4            |                |                       |

<sup>a</sup> No. of persons who could not tolerate chicken soup, 4/20

<sup>b</sup> Symptomatic on extensively hydrolyzed formula, 29%

**Table 8** Rate of allergy to soy among infants and children sensitized to soy

| Author, year (reference) | Country | Ages              | Type of population | Sensitized |      |       | OFC proven allergy | Allergy/sensitization (%) |
|--------------------------|---------|-------------------|--------------------|------------|------|-------|--------------------|---------------------------|
|                          |         |                   |                    | SPT        | sIgE | Total |                    |                           |
| Giampietro, 1992 [24]    | Italy   | 1 months–10 years | Most AD            |            | 69   | 69    | 5                  | 7.2                       |
| Magnolfi, 1996 [46]      | Italy   | 1 months–18 years | Suspected allergy  | 131        |      | 131   | 8                  | 6.1                       |
| Bruno, 1997 [60]         | Italy   | 6–168 months      | Suspected FA       | 31         |      | 31    | 6                  | 19.3                      |
| Bruno, 1997 [60]         | Italy   | 6–168 months      | Atopic parents     | 14         |      | 14    | 1                  | 7.1                       |
| Dias, 2010 [67]          | Spain   | 3 months–2 years  | CMA                | 8          |      | 8     | 1                  | 12.5                      |
| Katz, 2008 [97]          | Israel  | 0–48 months       | CMA                | 4          |      | 4     | 0                  | 0.0                       |
| Terracciano, 2010 [75]   | Italy   | 2–37 months       | CMA                | 11         |      | 11    | 0                  | 0.0                       |
| Klemola, 2002 [74]       | Finland | 2–11 months       | CMA                |            | 20   | 20    | 2                  | 10.0                      |
| Klemola, 2005 [65]       | Finland | 4 years           | CMA                |            | 36   | 36    | 0                  | 0.0                       |
| Niggemann, 1999 [66]     | Germany | 5 months–12 years | AD                 |            | 45   | 45    | 7                  | 15.5                      |
| Cantani, 1990 [15]       | Italy   | 5–15 months       | CMA                |            | 2    | 2     | 1                  | 50.0                      |
| Roehr, 2004 [62]         | Germany | 1 months–14 years | General population | 10         |      | 10    | 4                  | 40.0                      |
|                          |         |                   |                    | 209        | 103  | 312   | 35                 | 11.2                      |

the analysis, or they did not contain sufficient extractable information to contribute to reaching the goals of our review, leaving a total of 40 articles for further analysis (Tables 1, 2, 3, 4, 5, 6, 7, 8, and 9).

### Quantitative Synthesis of Results

The 40 articles we considered for further analysis were related to the topic of soy allergy prevalence or sensitization. Most of them were transversal or cohort studies with moderate- to low-quality methodological design and with evident biases related to sample size, age of inclusion, patient's country of origin and length of time followed in the case of longitudinal studies. The weighted prevalence of oral food challenge (OFC)-proven soy protein allergy for the general population, referred population and atopic children was 0.27 (CI<sub>95</sub> %, 0.1–0.44), 1.9 (1.1–2.7), and 2.7 (1.8–3.3), respectively (Table 1) [24, 42, 46, 59–66]. The rates of sensitization to soy based on SPTs were 0.1 (0.0–0.2), 12.7 (5.8–16.7), and 12.9 (CI<sub>95</sub> % NA) for the same groups (Table 2). The rates of sensitization based on specific IgE measurements were 0.7 (CI<sub>95</sub> % NA), 11.7 (7.2–15.6), and 27.1 (14.3–31.8) for the general population, referred population and atopic children groups, respectively (Table 3).

Finally, the prevalence of soy allergy based on self-reporting in the general population was 0.2 (0.0–0.30) (Table 4; Fig. 1).

Next, we evaluated the prevalence of allergy and sensitization to soy after the use of infant formula. We identified 21 articles covering 22 populations (Tables 5, 6, and 7). Many were cohort studies [15, 60, 67–73] or clinical trials [61, 65, 71, 74–77] of children with milk allergy or atopic dermatitis who used soy formula as a treatment modality. Others used soy-based formulas (SBFs) because of parental atopy or parental preferences. These studies determine sensitization to soy after ingestion of soy formulas, and are therefore expected to yield a higher rate of sensitization than studies examining children who were not exposed to soy yet. The evidence based on these studies, nevertheless, allowed us to establish a weighted prevalence of OFC-proven allergy of 2.5 %, (CI<sub>95</sub> %, 2.1–8.3) (Table 5) and a prevalence of sensitization to soy of 8.7–8.8 % (CI<sub>95</sub> %, 3.8–15.0), as determined by SPTs or serum sIgE to soy (Table 6a, b, respectively). The rate of self-reported prevalence to soy allergy in populations that used soy was 4.4 % (0–5.6) (Table 7; Fig. 2).

We identified 11 studies (12 populations) in which the sensitized patients underwent an OFC to soy or used soy regularly. In these studies, only 11.2 % of soy-sensitized children had clinical allergy (Table 8). Finally, we identified

**Table 9** Three studies in which infants were soy fed from birth

| Author, year (reference)  | Population      | Number | Allergic (%) | Diagnosis     | Sensitization |
|---------------------------|-----------------|--------|--------------|---------------|---------------|
| Bruno, 1997 [60]          | Atopic parents  | 243    | 1 (0.5)      | OFC           | 14            |
| Nachmias, 2010 [72]       | Parental choice | 982    | 0            | Self reported | ND            |
| Berger-Achituv, 2005 [70] | Various         | 205    | 1 (0.5)      | Self reported | ND            |
|                           |                 | 1,430  | 2 (0.1)      |               |               |

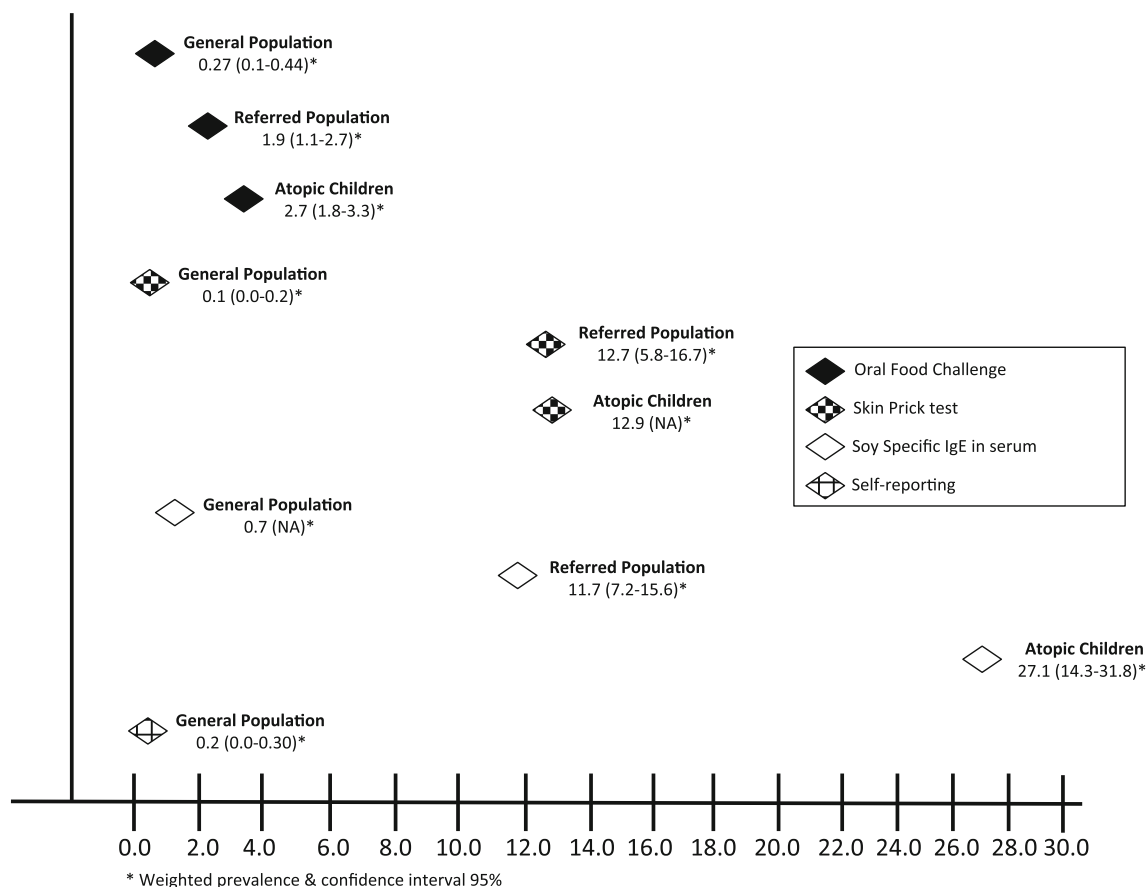


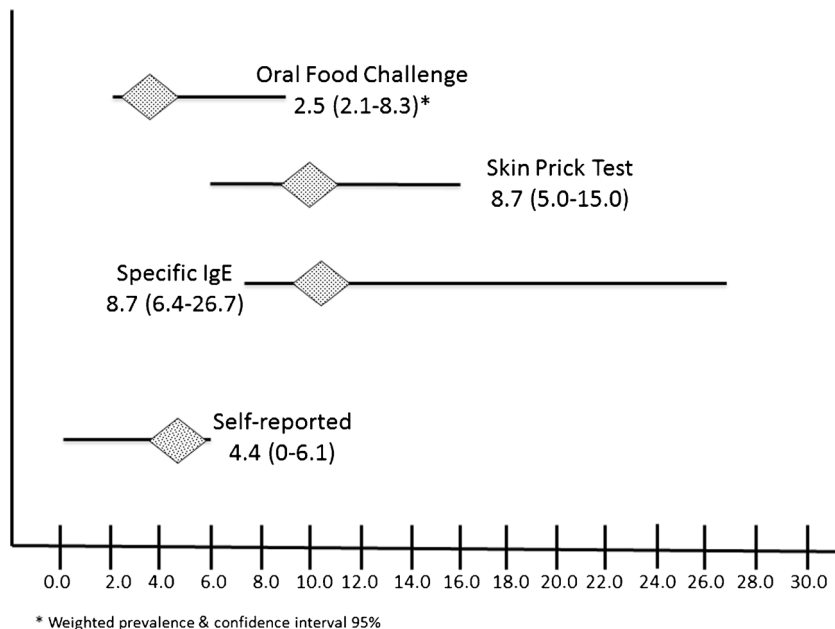
**Fig. 1** Represents data from Tables 1, 2, 3, and 4

only three studies totaling 1,430 individuals that evaluated for the risk soy allergy in infants younger than 6 months. Out of the 1,430 infants, only two likely had soy allergy and only one was diagnosed based on OFC (Table 9).

## Discussion and Conclusions

From the available evidence up to July 2013, we found only two studies that determined the prevalence of soy allergy in

**Fig. 2** Represents data from Tables 5, 6, 7, and 8



infants and children in the general population using an OFC [62, 63]. The cumulative prevalence in these studies was less than 0.3 %. Several lines of evidence indicate that this figure might in fact represent an overestimation. First, all four positive cases originated from one study [62]. Furthermore, in only one of these cases were cutaneous signs noted, which is by far the most common manifestation in reactions to allergenic food [78]. Second, this figure is in agreement with the self-reported soy allergy noted for the general population [63, 79–82]. This is somewhat surprising, as it is well accepted that self-reported food allergy is much higher than proven food allergy [83]. Thus, taken together, the true allergy to soy in infants and children in the general population might be even lower than 0.27 %.

Not surprisingly, the prevalence of soy allergy among selected populations is much higher. We identified four studies in which patients were referred to the allergy clinic for evaluation of food-related problems [59] or other allergic issues [24, 46, 60], and the reported soy allergy was 1.6 %. This figure was even higher (2.7 %) among children with food allergies or atopic dermatitis [42, 61, 64–66]. This last figure is very close to the prevalence of 2.5 %, which was extracted from 12 separate reports of soy allergy after a period of exposure to an SBF (Table 5). In 10 of these studies, all participants had IgE-CMPA. Therefore, the prevalence of soy allergy among IgE-CMPA is much lower and in sharp contrast with some earlier publications that have indicated rates of greater than 30 or 40 % [19, 20]. It is possible that in these latter studies, patients with IgE-mediated and non-IgE mediated soy allergy were grouped together. However, in a highly cited multicenter report, in which a precise distinction between IgE-mediated and non-IgE-mediated soy allergy was made, the prevalence of soy allergy was reported as 14 % [61]. In the present meta-analysis, this report [61] contributed 12 out of the 16 soy allergic children among those infants with IgE-CMPA. The likely explanation is that all 12 of these cases came from a single institution, which was a referral center for “multiple food allergy” [61], suggesting a possible bias. Interestingly, none of the other centers in that multicenter study contributed a single patient, and none of the 93 IgE-CMPA infants developed a soy allergy during the 1-year follow-up.

The self-reported “allergy” to soy was 0.2 %. This figure is surprisingly low and identical to the OFC-proven prevalence of soy allergy in the general population. This probably reflects the fact that in the general population soy is not perceived as a very allergenic food [83]. However, among the IgE-CMPA allergic infants, the prevalence of self-reported soy-related reactions was as high as 4.4 % (Table 6). Most of the patients in this group were from two out of six reported studies. The first is a study from Korea in which 38 infants with presumed IgE-CMPA were divided into two groups. In the first group, 12 out of 18 infants could not tolerate soy. In the second group, 4 out of 20 could not tolerate chicken soup, which is

not a known or recognized allergen [84]. In the second study, 90 patients were identified from a population of 1,000 CM allergic patients and were classified as nontolerant to soy and therefore were included with those who had self-reported soy allergy [73]. In that population, 290 (29 %) could not tolerate an extensively hydrolyzed formula, which is an unusually high figure for allergy to extensively hydrolyzed milk protein. These results raise significant doubts, suggesting that a significant part of the complaints in these two studies were non-IgE-mediated reactions. A third study of patients with IgE-CMA [76] contributed three patients with cutaneous or gastrointestinal symptoms that arose after 2 weeks of ingestion of SBFs. An additional two infants in that report had similar symptoms but, based on the negative SPTs, were not considered as having IgE-mediated allergy to soy. Thus, if we exclude the very low quality studies, the prevalence of self-reported soy allergy among infants who were exposed to soy was 0.1 (excluding 82, 90, and 93) to 0.3 % (including 82).

The rate of sensitization to soy in the unselected population is in the same range as OFC-proven allergy. However, among the selected populations, the rate of sensitization is much higher. The low rate of proven allergy to patients who are sensitized is shown in Table 8. This confirms the earlier observation of Ahrens [85] on the low rate of soy allergy to soy IgE sensitization compared with other foods, such as milk and peanut. An interesting observation by Masilamani [86] of the anti-allergic or allergy inhibition properties of soy might provide a partial mechanistic explanation. We identified only three studies totaling 1,430 individuals that evaluated for the risk of soy allergy in infants younger than 6 months. Out of the 1,430 infants, only two likely had soy allergy (Table 9), and in only one the diagnosis was based on an OFC. We extracted data for the risk of soy allergy among infants consuming SBFs in the first months of life from three studies only. We found that only two out of the 1,430 (0.1 %) infants had evidence of soy allergy. Thus, taken together, these findings do not substantiate the recommendations of the AAP and ESPHAGAN [87, 88] to postpone the introduction of SBFs in infants with IgE-CMPA the first 6 months of life based on the concern for an increased risk of allergy to soy.

## References

1. Forsyth D (1991) The history of infant feeding from Elizabethan times. *Proc Soc Med* 4:110–141
2. Holt I E (1902) The diseases of infancy and childhood, 2nd edn. Appleton, New York
3. Howarth, W. J. (1905), The influence of feeding on the mortality of infants. *Lancet* ii, 210–213
4. Stevens E, Patrick T, Pickler R (2009) A history of infant feeding. *J Perinat Educ* 18(2):32–39
5. Cantani A (1987) The struggle for breastfeeding. *Ann Allergy* 59:84

6. Ruhrah J (1909) The soybean in infant feeding. *Prelim Rep Arch Pediatr* 26:496–501
7. Shurtleff W, Aoyagi A (1984) Soymilk industry and market. The soy foods center, Lafayette
8. Hill I, Stuart H (1929) Soybean food preparation for feeding infants with milk idiosyncrasy. *JAMA* 93:985–987
9. Fomon SJ (1974) Infant nutrition, 2nd edn. WB Saunders, Philadelphia
10. The committee on nutrition of the American Academy of Pediatrics (1971) Vitamin K supplementation for infants receiving milk substitute infant formulas and for those with fat malabsorption. *Pediatrics* 48:483–487
11. United States Congress (1980) Infant Formula Act of 1980. United States Capitol Health Documents Room, Washington
12. Brooks JR, Morr CV (1985) Current aspects of soy protein fractionation and nomenclature. *J Am Oil Chem Soc* 62:1347–1350
13. Kay JL, Daeschner CW Jr, Desmond MM (1960) Evaluation of infants fed soybean and evaporated milk formulae from birth to 3 months. A comparison of weight, length, hemoglobin, hematocrit, plasma biochemical values. *AJDC* 100:264–276
14. The committee on nutrition of the American Academy of Pediatrics (1983) Soy-protein formulas: recommendations for use in infant feeding. *Pediatrics* 72:359–363
15. Cantani A, Ferrara M, Ragno W, Businco I (1990) Efficacy and safety of a soy-protein-formula for feeding babies with atopic dermatitis and cow milk hypersensitivity. *Eur Rev Med Pharmacol Sci* 12:311–318
16. European Society of Pediatric Gastroenterology and Nutrition. Committee on nutrition (1994) Comment on the composition of soy-protein based infant and follow-up formulas. *Acta Paediatr Scand* 79:1001–1045
17. Businco I, Rubaltelli F (1989) Management and prevention of cow's milk allergy in infants. *Wyeth-Ayerst Nutr Semin Ser* 1:41–64
18. Mimouni F, Campagne B, Neylan M, Tsang RC (1993) Bone mineralization in the first year of life in infants fed human milk, cow-milk formula, or soy-based formula. *J Pediatr* 122:348–354
19. Eastham EJ (1989) Soy protein allergy. In: Hamburger RN (ed) *Food intolerance in children*. Raven Press, New York, pp 223–236
20. Eastham EJ, Lichauco T, Grady MI, Walker WA (1978) Antigenicity of infant formulas: role of immature intestine on protein permeability. *J Pediatr* 93(4):561–564
21. Kjellman NI, Johansson SGQ (1979) Soy versus cow milk in infants with biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin Allergy* 9:347–358
22. Chandra RK, Singh G, Shridhara B (1989) Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants. *Ann Allergy* 63:102–106
23. Gerrard JW, Lubos MC, Hardy LW, Holmlund BA, Webster D (1967) Milk allergy: clinical picture and familial incidence. *Can Med Assoc J* 97:780–785
24. Giampietro PG, Ragno V, Daniele S, Cantani A, Ferrara M, Businco L (1992) Soy hypersensitivity in children with food allergy. *Ann Allergy* 69:143–146
25. Bock SA, Sampson HA, Atkins FM et al (1988) Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 82:986–997
26. Bock SA (1996) Food challenges in the diagnosis of food hypersensitivity. *Nestle Nutr Workshop Ser* 34:105–117
27. Halken S, Host A, Hansen LG, Osterballe O (1993) Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow's milk allergy: a clinical investigation. *Pediatr Allergy Immunol* 4:53–59
28. Gerrard JW, Mackenzie JWA, Goluboff N, Garson JZ, Maningis CS (1973) Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand Suppl* 234:1–21
29. Kuitunen P, Visakorpi JK, Savilahti E, Pelkonen P (1975) Malabsorption syndrome with cow milk intolerance. Clinical findings and course in 54 cases. *Arch Dis Child* 50:351–356
30. Jakobsson I, Lindberg T (1979) A prospective study of cow milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 68:835–839
31. Hill DJ, Ford RPK, Shelton MJ, Hosking CS (1984) A study of 100 infants and young children with cow milk allergy. *Clin Rev Allergy* 2:125–142
32. Bishop JM, Hill DJ, Hosking CS (1990) Natural history of cow milk allergy: clinical outcome. *J Pediatr* 116:862–867
33. Perkio M, Savilahti E, Kuitunen P (1981) Morphometric and immunohistochemical study of jejunal biopsies from children with intestinal soy allergy. *Eur J Pediatr* 137:63–69
34. Schwartz RH (1991) IgE-mediated allergic reactions to cow's milk. *Immunol Allergy Clin North Am* 11:717–741
35. Whitherly SA (1990) Soy formulas are not hypoallergenic. *Am J Clin Nutr* 51:705–706
36. Minford AMB, MacDonald A, Littlewood JM (1982) Food intolerance and food allergy in children: a review of 68 cases. *Arch Dis Child* 57:742–747
37. Hattevig G, Kjellman B, Johansson SGO, Bjorksten B (1984) Clinical symptoms and IgE responses to common food proteins in atopic and healthy children. *Clin Allergy* 14:551–559
38. Beningori N, Cantani A, Piccarazzi A, Osmelli S, Busingo L (1985) Management of atopic dermatitis by elimination diet: a useful but difficult approach. *Fisons SpA, Roma*, pp 95–104
39. Host A, Halken S (1990) A prospective study of cow milk allergy in Danish infants during the first three years of life. *Allergy* 45:587–596
40. Bergmann R I, Bergmann KE, Lau-Schadendorf S et al (1994) Atopic disease in infancy. The German multicenter atopy study (MAS-90). *Pediatr Allergy Immunol* 5(suppl 1):19–25
41. Kivity S, Dunner K, Marian Y (1994) The pattern of food hypersensitivity in patients with onset after 10 years of age. *Clin Exp Allergy* 24:19–22
42. Crespo JF, Pasqual C, Burks AW, Helm RM, Esteban MM (1995) Frequency of food allergy in a pediatric population from Spain. *Pediatr Allergy Immunol* 6:39–43
43. Noferi A, Fusghillo S, Iorio C (1995) Rilevanza epidemiologica e clinica deile arachidi quali causa di allergia. *Osservazioni personali Notiz Allergol* 14:113–117
44. Dean TP, Spurr M, Warner JO (1994) Soy sensitivity among cow's milk allergic children. *Clin Exp Allergy* 24:984A
45. Wilson NW, Hamburger RN (1988) Allergy to cow milk in the first year of life and its prevention. *Ann Allergy* 61:323–470
46. Magnolfi C, Zani G, Lacava L, Patria MF, Bardare M (1996) Soy allergy in atopic children. *Ann Allergy Asthma Immunol* 77:197–201
47. Branski D (1984) Specific etiologies of chronic diarrhea in infancy. *Nestle Nutr Workshop Ser* 6:107–145
48. The European Society of Pediatric Gastroenterology Working Group for the Diagnostic Criteria for Food Allergy (1992) Diagnostic criteria for food allergy with predominantly intestinal symptoms. *J Pediatr Gastroenterol Nutr* 14:108–112
49. Freier S, Eran M, Suranyi Y (1988) Antigen presentation. *Nestle Nutr Workshop Ser* 17:89–98
50. Kahn A, Mozin MJ, Rebuffat E et al (1988) Milk intolerance in children with persistent sleeplessness: a prospective double-blind crossover evaluation. *Pediatrics* 84:595–602
51. Johnstone DE, Roghmann KJ (1993) Recommendations for soy infant formula: a review of the literature and a survey of pediatric allergists. *Pediatr Asthma Allergy Immunol* 7:77–88
52. Hill LW (1942) The production of nonetiological skin hypersensitivity to foods by natural means in atopic persons. *J Allergy* 13:366–370
53. Cantani A, Lucenti P (1997) Natural history of soy allergy and/or intolerance in children, and clinical use of soy protein formulas. *Pediatr Allergy Immunol* 8:59–74
54. Sampson HA (1988) The role of food hypersensitivity and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 81:635–645
55. Sampson HA (1999) Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 103:981–989

56. Robinson KA, Dickersin K (2002) Development of a high sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol* 31:150–153
57. Wilczynski NL, Haynes RB, the Hedges Team (2004) Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2:23
58. GRADE Working Group (2004) Grading quality of evidence and strength of recommendations. *BMJ* 328:1490–1498
59. Bock SA, Atkins FM (1990) Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 117(4):561–567
60. Bruno G, Giampietro PG, Del Guercio MJ et al (1997) Soy allergy is not common in atopic children: a multicenter study. *Pediatr Allergy Immunol* 8(4):190–193
61. Zeiger RS, Sampson HA, Bock SA et al (1999) Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 134(5):614–622
62. Roehr CC, Edenharter G, Reimann S et al (2004) Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 34:1534–1541
63. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindeslev-Jensen C (2005) The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 16:567–573
64. Caminiti L, Passalacqua G, Barberi S et al (2009) A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc* 30:443–448
65. Klemola T, Kalimo K, Poussa T et al (2005) Feeding a soy formula to children with cow's milk allergy: the development of immunoglobulin E-mediated allergy to soy and peanuts. *Pediatr Allergy Immunol* 16:641–646
66. Niggemann B, Sielaff B, Beyer K, Binder C, Whan U (1999) Outcome of double-blind, placebo-controlled food challenge test in 107 children with atopic dermatitis. *Clinical Exp Allergy* 29:91–96
67. Dias A, Santos A, Pinheiro JA (2010) Persistence of cow's milk allergy beyond two years of age. *Allergol Immunopathol* 38(1):8–12, Madr
68. Antunes J, Borrego LM, Queiroz A et al (2009) Allergy to extensively hydrolysed formulas. *Allergol Immunopathol* 37(5):272–278, Madr
69. Buts JP, Di Sano C, Hansdorffer S (1993) Clinical evaluation of the tolerance for a soy-based special milk formula in children with cow's milk protein intolerance/allergy (CMPI/CMPA). *Minerva Pediatr* 45(5):209–213
70. Berger-Achituv S, Shohat T, Romano-Zelekha O et al (2005) Widespread use of soy-based formula without clinical indications. *JPGN* 41:660–666
71. Mehr SS, Kemp AS (2008) Feeding choice for children with immediate allergic reactions to cow's milk protein. *MJA* 189:178–179
72. Nachmias N, Landman Y, Danon YL, Levy Y (2010) Soy allergy following early soy feeding in neonates. *IMAJ* 12:684–686
73. Sladkevicius E, Nagy E, Lack G, Guest JF (2010) Resource implications and budget impact of managing cow milk allergy in the UK. *J Med Econ* 13:119–128
74. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E (2002) Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 140:219–224
75. Terracciano L, Bouygue GR, Sarratut T, Véglià F, Martelli A, Fiocchi A (2010) Impact of dietary regimen on the duration of cow's milk allergy: a random allocation study. *Clin Exp Allergy* 40:637–642
76. Agostoni C, Fiocchi A, Riva E et al (2007) Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol* 18:599–606
77. Arató A, Horváth J (1995) Soy formula in the feeding of infants with milk allergy. *Orv Hetil* 136(27):1433–1437
78. Katz Y, Rajuan N, Goldberg MR et al (2010) Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 126:77–82
79. Dalal I, Binson R, Reifen Z et al (2002) Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy* 57:362–365
80. Brugman E, Meulmeester JF, Spee-van der Wekke A, Beuker RJ, Radder JJ, Verloove-Vanhorick SP (1998) Prevalence of self-reported food hypersensitivity among school children in The Netherlands. *Eur J Clin Nutr* 52:577–581
81. van Bockel-Geelkerken M, Meulmeester JF (1992) Prevalence of putative food hypersensitivity in young children. *Ned Tijdschr Geneesk* 136:1351–1356
82. Eggesbo M, Halvorsen R, Tambs K, Botten G (1999) Prevalence of parentally perceived adverse reactions to food in young children. *Pediatr Allergy Immunol* 10:122–132
83. Altan DR, Chiamonte LT (1996) Public perception of food allergy. *J Allergy Clin Immunol* 97:1247–1251
84. Jirapinyo P, Densupsoontorn N, Wongarn R, Thamonsiri N (2007) Comparisons of a chicken-based formula with soy-based formula in infants with cow milk allergy. *Asia Pac J Clin Nutr* 16(4):711–715
85. Ahrens B, Niggemann B, Whan U, Beyer K (2012) Organ-specific symptoms during oral food challenge in children with food allergy. *J Allergy Clin Immunol* 130:549–551
86. Masilamani M, Wei J, Bhatt S, Paul M, Yákir S, Sampson HA (2011) Soybean isoflavins regulate dendritic cell function and suppress allergic sensitization to peanut. *J Allergy Clin Immunol* 128:1242–1250
87. Greer FR, Sicherer SH, Bruks AW (2008) Effects of early nutritional interventions on the development of atopic diseases in infants and children: the role of maternal dietary restrictions, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulae. *Pediatrics* 121:183–191
88. Koletzko S, Niggemann B, Arato A et al (2012) Diagnostic approach and management of cow's milk protein allergy in infants and children: ESPGHAN GI committee practical guidelines. *JPGN* 55:221–229
89. Arshad SH, Tariq SM, Matthews S, Hakim E (2001) Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 108:e33
90. Rance F, Grandmottet X, Grandjean H (2005) Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy* 35:167–172
91. Roberts G, Peckitt C, Northstone K et al (2005) Relationship between aeroallergen and food allergen sensitization in childhood. *Clin Exp Allergy* 35:933–940
92. Chiang WC, Kidon MI, Liew WK, Goh A, Tang J, Chay OM (2007) The changing face of food hypersensitivity in an Asian community. *Clin Exp Allergy* 37:1055–1061
93. Baatenburg de Jong A, Dikkeschei LD, Brand PLP (2011) Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized and polysensitized children. *Pediatr Allergy Immunol* 22:166–171
94. Matricardi PM, Bockelbrink A, Beyer K et al (2007) Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. *Clin Exp Allergy* 38:493–500
95. Ferrari GG, Eng PA (2011) IgE-mediated food allergies in Swiss infants and children. *Swiss Med Wkly* 141:w13269
96. Kristjansson I, Ardal B, Jonsson JS, Sigurdsson JA, Foldevi M, Björkstén B (1999) Adverse reactions to food and food allergy in young children in Iceland and Sweden. *Scand J Prim Health Care* 17:30–34
97. Katz Y, Goldberg MR, Zadik-Mnuhin G, Leshno M, Heyman E (2008) Cross-sensitization between milk proteins: reactivity to a “kosher” epitope? *IMAJ* 10:85–88
98. Ahn KM, Han YS, Nam SY, Park HY, Shin MY, Lee SI (2003) Prevalence of soy protein hypersensitivity in cow's milk protein-sensitive children in Korea. *J Korean Med Sci* 18:473–477