Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
DBPCOFC to peanut	12 months of peanut avoidance (peanut-avoidance versus peanut-consumption group based on primary trial)	Prevalence of peanut allergy at 72 months: Peanut-avoidance group: **18.6%** Peanut-consumption group: **4.8%** **P<0.001**	
DBPCOFC (peanut, cooked egg, cow milk, sesame, whitefish, and wheat)	Early Introduction Group (EIG): early introduction of 6 allergenic foods Or Standard Introduction Group (SIG): exclusive BF to ~6 months of age. After 6 months, the consumption of allergenic foods was allowed according to parental discretion.	Intention to Treat Analysis • Food allergy to ≥1 allergen (EIG versus SIG); RR=0.80 (0.51-1.25) • Food allergy to individual allergens: all nonsignificant Per Protocol analysis • Food allergy to ≥1 allergen (EIG versus SIG): **RR=0.33 (0.13-0.83)** • Food allergy to peanut (EIG versus SIG): **RR=0** • Food allergy to egg (EIG versus SIG): **RR=0.25 (0.08-0.82)** No significant effects with respect to milk, sesame, fish, or wheat	Low adherence to the protocol in the EIG (42.8%).

continued

TABLE C-4a Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
DuToit et al., 2015	RCT, UK	Infants, age least 4 months and less than 11 months at enrollment with severe eczema, egg allergy, or both	640	60 months

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Clinical history, SPT, OFC, DBPCOFC, sIgE (peanut) 530 had negative SPT at baseline 98 had positive SPT at baseline	Peanut intake (avoidance versus consumption)	Prevalence of peanut allergy at 60 months: *SPT Negative Group* **13.7% avoidance group** **1.9% consumption group** **(P<0.001)** (86.1% relative reduction in the prevalence of peanut allergy) *SPT Positive Group* **35.3% avoidance group** **10.6% consumption group** **(P=0.004)** (70.0% relative reduction in the prevalence of peanut allergy) No significant between-group difference in the incidence of serious adverse events	

continued

TABLE C-4a Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Palmer et al., 2013	RCT, Australia	Singleton term infants with symptoms of moderate-to-severe eczema. Infants who had begun solids before 4 months of age or who had any previous known direct ingestion of egg were excluded	86 49 egg group 37 rice group (control)	12 months

NOTE: CI = confidence interval; EIG = Early Introduction Group; IgE = immunoglobulin E; OFC = oral food challenge; SIG = Standard Introduction Group; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated egg allergy, as defined based on the results of an observed pasteurized raw egg challenge and SPT	1 teaspoon of pasteurized raw whole egg powder versus rice powder (control) daily from 4 to 8 months of age Cooked egg was introduced to both groups after an observed feed at 8 months	RR: 0.65 (0.38-1.11)	At 4 months of age, before any known egg ingestion, 36% (24/67) of infants already had egg-specific IgE levels of greater than 0.35 kilounits of antibody (kUA)/L. Egg-specific IgG4 levels were significantly (P<0.001) greater in the egg group at both 8 and 12 months.

TABLE C-4b Antigen Exposure Hypothesis (Observational Studies)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Diet Diversity				
Grimshaw et al., 2014	Nested case control, UK	Infants from the PIFA Study who had been diagnosed as having a food allergy and their 2 age-matched controls	41 cases 82 controls	2 years
Roduit et al., 2014	Prospective cohort, Europe	Children from rural areas in five European countries	856	Up to age 6 years

NOTE: CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; sIgE = food-specific serum IgE; SPT = skin prick testing; UK = United Kingdom.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Parent report, physical exam, SPT, sIgE, exclusion diet, DBPCOFC	Dietary patterns during first year of life	Scores were significantly different between the food allergic and control infants (P=0.002) for component 1 (diet high in fruits and vegetables)	Early infant feeding patterns did not have an association with the later development of food allergy. Children who did not have a food allergy by the age of 2 years had a dietary pattern in later infancy characterized by higher intake of fruits, vegetables, and home-prepared foods as compared to children who had a food allergy. Unadjusted analysis only.
Parent report of doctor diagnosis; sIgE (hen egg, cow milk, peanut, hazelnut, carrot, and wheat flour)	Food diversity during first year of life (1) 0-3 items (2) 4-5 items (3) 6 items (ref) (4) diversity score, continuous	(1) **4.43 1.62-12.10** (2) **1.85 1.02-3.35** (3) 1 (4) **0.70 (0.57-0.86)**	Adjusted for center, farmer, parents with allergy, sex, breast-feeding, siblings, and maternal education.

TABLE C-5 Nutritional Immunomodulation Hypothesis (Observational Studies)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Lipids/Omega-3 Fatty Acids (see systematic reviews below)				
Vitamin D				
Koplin et al., 2016	Prospective cohort, Australia	Infants participating in the HealthNuts study	5,276	1 year
Baek et al., 2014	Cross-sectional, Korea	Children with atopic dermatitis or suspected food allergy, who had not been on vitamin supplementation for at least 1 month before the study	226	3-24 months

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
SPT, sIgE, OFC	Serum $25(OH)D_3$ ≤50 nmol/L = vitamin D insufficiency 51-74 nmol/L = intermediate vitamin D ≥75 nmol/L = high vitamin D	Infants with GG genotype (insufficient versus intermediate): 6.0 (0.9-38.9) Infants with GT/TT phenotypes (insufficient versus intermediate): 0.7 (0.2-2.0) Infants with GG genotype (high versus intermediate): 4.0 (1.3-12.9)	Adjusted for infants' consumption of egg and formula use and parents' country of birth and used a seasonally adjusted measure of serum $25(OH)D_3$.
History of acute reaction + sIgE ≥0.35 kU/L or >95% predictive decision points	Serum $25(OH)D_3$ Deficiency: <20ng/mL Insufficiency: 20-29ng/mL Sufficiency: ≥30ng/mL	Deficient versus sufficient Food allergens: 5.0 (1.8-14.1) Milk: 10.4 (3.3-32.7) Wheat: 4.2 (1.1-15.8)	Vitamin D deficiency increased the risk of sensitization to food allergens, especially to milk and wheat. The Scoring Atopic Dermatitis index was independently related to 25(OH)D levels after adjusting for the level of sensitization.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Norizoe et al., 2014	Longitudinal Study, Japan	Infants with facial eczema and their mothers	164	3-24 months
Wawro et al., 2014	Cross-sectional, Germany	Samples from two German birth cohort studies	2,815	10 years
Allen et al., 2013	Cross-sectional, Australia	Infants from HealthNuts population-based cohort	5,276	1 year

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Doctor-diagnosed allergic incidents, including atopic dermatitis, food allergy with or without being positive for IgE food allergens, or wheeze or asthma with or without being positive for IgE inhaled allergens	Maternal vitamin D (800 IU/day) supplement	RR=**3.42 (1.02-11.77)**	Vitamin D supplementation may not decrease the severity of infantile eczema at 3 months of age, but may rather increase the risk of later food allergy up to 2 years of age. Unadjusted analysis only.
sIgE >0.35 kU/l	Serum 25(OH)D Q1: <57.9 (nmol/L) Q2: 57.9- <71.5 Q3: 71.5- <87.8 Q4: ≥87.8 Continuous variable	 1 0.91 (0.67-1.25) 1.25 (0.93-1.69) 1.30 (0.97-1.75) **1.07 (1.02-1.11)**	Lifetime prevalence also was significantly related to vitamin D status.
OFCs + SPT/ sIgE ≥0.35 kU/L	Vitamin D ≥50 nmol/L (insufficiency) (1) All infants (2) Infants with one or both parents born overseas (3) Infants with both parents born in Australia	Any food allergy versus none: (1) 1.29 (0.51-3.25) (2) 0.39 (0.08-1.76) **(3) 3.08 (1.10-8.59)** Peanut allergy versus none (infants with both parents born in Australia): **11.51 (2.01-65.79)** Egg allergy versus none (infants with both parents born in Australia): **3.79 (1.19-12.08)**	

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Liu et al., 2013	Prospective longitudinal cohort study, US	Children in the Boston Birth cohort	460	0-3 years
Weisse et al., 2013	Prospective longitudinal cohort study, Germany	Mother–child pairs from the Lifestyle and environmental factors and their Influence on Newborns Allergy risk (LINA) cohort study	378	First 2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
sIgE >0.35 kU/l	Vitamin D (ng/ml) cord blood/ postnatal	All children:	There was no association between low vitamin D status and food sensitization at any single time point alone.
	≥11 / ≥30 (reference)	1	
	≥11 / <30	0.73 (0.42-1.29)	
	<11 / ≥30	0.90 (0.54-1.51)	
	<11 / <30	**2.03 (1.02-4.04)**	
		Children with C allele of rs2243250:	Adjusted for a child's sex and ancestry proportion, breastfeeding, postnatal maternal smoking, household income, and maternal age.
		1	
		0.52 (0.23–1.18)	
		1.26 (0.65–2.43)	
		3.23 (1.37-7.60)	
Parental report of a doctor diagnosis. tIgE levels >0.7 kU/l in cord blood and >3.8 kU/l at age of 1 or 2 yrs, or sIgE >0.35 kU/l	Maternal vitamin D Median = 22.2 ng/ml (55.41 nmol/ml)	1st year of life: 1.27 (0.67–2.40)	Adjusted for sex, number of siblings, increased cord blood tIgE levels, family atopy history, cotinine levels during pregnancy, breastfeeding, UV intensity at birth and vitamin D supplementation within the first year of life.
		2nd year of life: **3.66 (1.36–9.87)**	
		2-year lifetime period: **1.91 (1.09–3.37)**	
	Cord blood vitamin D Median = 10.95 ng/ml (27.33 nmol/ml)	1st year of life: 0.92 (0.45–1.85)	
		2nd year of life: **4.65 (1.50–14.48)**	
		2-year lifetime period: 1.70 (0.92-3.14)	

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Jones et al., 2012	Prospective longitudinal cohort study, Australia	High-risk infants	231	12 months
Liu et al., 2011	Prospective longitudinal birth cohort, US	Mother-infant pairs in the Boston Birth Cohort	649 children	Around 2 years
Lipids/Omega-3 Fatty Acids (see systematic reviews below)				
Folate				
Okupa et al., 2013	Cohort study, US	Children at high risk of developing asthma and allergic disease	138	2, 4, 6, and 8 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
SPT History of immediate symptoms + SPT	Cord blood vitamin D <50 nmol/L versus ≥75 nmol/L (reference)	Risk of allergen sensitization: 1.0 (0.9-1.01) Risk of developing IgE-mediated food allergy: 1.00 (0.99-1.02)	Adjusted for season of birth, pets in the home, infant sex, maternal age, maternal education, and ethnicity.
sIgE (milk, egg white, peanut, soy, shrimp, walnut, cod fish, and wheat)	Cord blood plasma total 25(OH)D concentrations (<11 ng/ml = deficiency)	Vitamin D deficient versus not deficient (reference) Any food sensitization: 1.16 (0.83-1.63) Egg sensitization: 0.84 (0.56-1.27) Milk sensitization: 1.15 (0.76-1.73) Peanut sensitization: 1.06 (0.64-1.75)	
Allergic sensitization (sIgE to milk/ egg/ peanut for years 1 to 3 and egg/peanut for years 5+)	Plasma folate levels	High versus low folate levels at or before age 6 years): 8% versus 26% (P=0.02)	Unadjusted analysis only.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Dunstan et al., 2012	Prospective cohort, Australia	Pregnant women (healthy nonsmokers with uncomplicated term pregnancies)	628 women 484 infants	12 months
Magdelijns et al., 2011	Prospective birth cohort, the Netherlands	Children in the KOALA birth cohort	2,834	2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy was defined as a history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food Allergic sensitization (milk, peanut, whole egg) was assessed by SPT at 1 year of age	Tertiles of maternal folate intake from supplements (FFQ during 3rd trimester) (1) <200 mg/day (2) 200-499 mg/day (3) >500 mg/day Tertiles of cord blood folate at delivery (1) <50.3 nmol/l (2) 50.3-75.1 nmol/l (3) >75.1 nmol/l	Folate intake: IgE-mediated food allergy (1) reference group (2) 1.4 (0.7-3.0) (3) 1.1 (0.5-2.4) Sensitized to food allergens (1) reference group (2) 1.3 (0.7-2.3) (3) 1.1 (0.6-2.0) Cord blood folate: IgE-mediated food allergy (1) 1.7 (0.5-5.6) (2) reference group (3) 2.6 (0.9-8.1) Sensitized to food allergens (1) 2.2 (0.9-5.6) (2) reference group (3) 1.1 (0.5-2.4) All ORs adjusted for maternal allergy and infant postnatal diet	Also looked at maternal intake of folate from food, but found no differences in the maternal dietary folate intakes of infants with any allergic outcomes. Because of the focus on allergy in the primary study, sensitized allergic mothers were over represented (70.6%). All ORs adjusted for maternal allergy and infant postnatal diet.
sIgE (hen egg, cow milk, peanut, and aeroallergens)	Folic acid supplement use during pregnancy (measured as quintiles of intracellular folate status during 3rd trimester)	Folic acid supplement use versus no use (reference) Increased sIgE: 1.06 (0.67-1.68)	Allergic sensitization was to both food allergens and aeroallergens.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Other Nutrient Intakes				
West et al., 2012	Prospective cohort, Australia	Pregnancy cohort with a family history of allergic rhinitis, asthma, eczema, food or other allergy	300 mother–infant pairs	12 months

NOTE: CI = confidence interval; FFQ = food frequency questionnaire; IgE = immunoglobulin E; OFC = oral food challenge; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; sIgE = food-specific serum IgE; SPT = skin prick test; tIgE = total IgE; UK = United Kingdom; US = United States; UV = ultraviolet.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy was defined as a history of immediate symptoms after contact with and/or ingestion and a positive SPT at 12 months (milk, egg, peanut)	Quartiles of daily maternal dietary and total intakes during pregnancy (1) β-carotene (2) vitamin C (3) vitamin E (4) copper (5) zinc Quartiles Q1 lowest (reference) Q2 Q3 Q4 highest Measured by semiquantitative FFQ administered after 28 weels gestation	(1) β-carotene 0.40 (0.12-1.32) 1.16 (0.43-3.11) 0.38 (0.11-1.27) P_{trend}=0.2 (2) Vitamin C **0.22 (0.06-0.78)** 0.75 (0.27-2.06) 0.46 (0.16-1.36) P_{trend}=0.1 (3) Vitamin E 0.96 (0.32-2.84) 0.86 (0.29-2.54) 0.57 (0.19-1.72) P_{trend}=0.8 (4) copper 0.60 (0.22-1.60) 0.40 (0.13-1.22) **0.38 (0.11-0.95)** P_{trend}=0.2 (5) zinc 0.67 (0.22-2.03) 1.28 (0.46-3.53) 0.52 (0.16-1.73) P_{trend}=0.4	Adjusted for maternal education, paternal history of allergic disease, birth weight, and exposure to furred pets at home; all were included in the multiple logistic regression model.

TABLE C-6 Systematic Review Summaries

Author, year	Best et al., 2016
Aims/Key questions	To develop a clearer understanding of the effect to the developing fetus, before commencement of the progression of atopy ("atopic march") and establishment of allergic disease symptoms.
Study eligibility criteria	Inclusion criteria: • Study design: prospective studies, including longitudinal observational studies and RCTs and quasi-randomized trial. • Exposure: maternal fish or n-3 LCPUFA intake during pregnancy. • Intervention and comparator: intervention modifying maternal n-3 LCPUFA intake during pregnancy with a parallel control group or placebo. • Outcome measures: Incidence of atopic disease (i.e., IgE-mediated allergic disease) or sensitization in the offspring during infancy, childhood, or adolescence. The presence of IgE-mediated allergic disease is defined as a clinician diagnosis, parent report of symptoms of allergic disease, or parent report of a physician's diagnosis. Sensitization is defined as a positive SPT or IgE serology indicating sensitization. Exclusion criteria: • Animal studies, cross-sectional studies, and retrospective and case-control studies. • Studies of maternal n-3 LCPUFA consumption or supplementation in the postnatal period only (breastfeeding or direct supplementation of the infant). • Studies that reported immune biomarkers by laboratory assessment in the absence of evaluation of symptoms or clinical diagnosis of allergic disease in the offspring.
Literature search dates or year range	Inception to July 30, 2015
Number of food allergy studies included	3 RCTs (based on SPT)
Synthesis methods	Summary tables and meta-analysis

TABLE C-6 Continued

Key findings	Three RCTs with sensitization outcomes at age 12 months were combined in meta-analysis. Definitions of sensitization were inconsistent. Overall risk of bias of the three RCTs was low to moderate. One RCT was rated high risk of bias for incomplete outcome data reporting and one was rated high risk of bias for selective reporting. • Fixed effect meta-analysis showed a significant reduction in "sensitization to egg" at 0-12 months (pooled RR: 0.55; 95% CI: 0.39-0.76; P=0.0004) • Fixed effect meta-analysis showed a significant reduction in "sensitization to any food" at 12 months (pooled RR: 0.59; 95% CI: 0.46-0.76; P<0.0001)
Limitations	• This systematic review did not focus on food allergy. • Fixed effect meta-analysis ignores clinical heterogeneity (e.g., different doses of n-3 fatty acids) and produced more significant results. Note: Discordant results with Klemens et al. (2011) meta-analysis. Overlaps in two RCTs. Best et al. (2016) did not include one study that was included in Klemens et al. (2011). Klemens et al. (2011) performed random-effects meta-analysis while Best et al. (2016) performed fixed-effects meta-analysis.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	N
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	N
Likelihood of publication bias assessed?	Y (the authors noted that the risk of publication bias cannot be excluded because only published studies were included in meta-analysis)
Conflict of interest (COI) stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

continued

TABLE C-6 Continued

Author, year	Boyle et al., 2016
Aims/Key questions	To determine whether feeding infants with hydrolyzed formula reduces their risk of allergic or autoimmune disease.
Study eligibility criteria	Interventions and comparators: • Inclusions: Any hydrolyzed formula of cow milk origin compared with any nonhydrolyzed cow milk formula, human milk, or another type of hydrolyzed cow milk formula. Also included were studies in which hydrolyzed formula was given as part of a multifaceted intervention, which the authors defined as an intervention with at least two other components in addition to the hydrolyzed formula—for example, exclusion of allergenic food from the mother's diet, promotion of breastfeeding, delayed introduction of solid food, or measures to avoid exposure to house dust mite. Studies in which other interventions were applied to both intervention and control groups, such as exclusion of cows' milk from the mother's diet during lactation also were included. • Exclusions: Studies of hydrolyzed formula of milk other than cow milk, such as hydrolyzed rice, goat milk, or soy formula. Study designs of interest: All intervention trials. Populations of interest: • Inclusions: Studies of infant feeding between birth and age 12 months. • Exclusions: Studies in which infants or their mothers were defined by the presence of a pre-existing disease state, including very low birth weight or premature infants. Outcomes of interest: • Atopic outcomes included were asthma (categorized as wheeze, recurrent wheeze, atopic wheeze, bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate, forced expiratory volume in 1 second), eczema, allergic rhinitis and/or conjunctivitis, food allergy, allergic sensitization (that is, SPT or sIgE assessment, or tIgE level). • Autoimmune outcomes included were type 1 diabetes mellitus (defined serologically and/or clinically), celiac disease (defined serologically and/or clinically), inflammatory bowel disease, autoimmune thyroid disease, juvenile rheumatoid arthritis, vitiligo, or psoriasis.
Literature search dates or year range	The Cochrane Library (2013, issue 7), EMBASE (1947 to July 2013), LILACS (1982 to July 2013), Medline (1946 to July 2013), and Web of Science (1970 to July 2013). Searches run on July 25, 2013, and rerun on April 17, 2015.

TABLE C-6 Continued

Number of food allergy studies included	13
Synthesis methods	Narrative text and meta-analysis
Key findings	There was no significant difference in risk of "any food allergy" with partially (pooled RR: 1.73; 95% CI: 0.79-; I^2=42%) or extensively (pooled RR 0.86; 95% CI: 0.26-2.82; I^2=42%) hydrolyzed formula compared with standard formula at age 0-4 years, nor for extensively hydrolyzed formula at age 5-14 years. [Note that number of studies included in each meta-analysis was not reported in text.] No difference was found in food allergy to cow milk, egg, or (partially hydrolyzed formula only) peanut. Direct comparison of the two formulas (egg allergy) and casein versus whey dominant extensively hydrolyzed formula showed no significant difference in risk of food allergy. [Note: no other details reported in text.] There was no significant difference in risk of allergic sensitization to cow milk with partially (pooled RR: 1.30; 95% CI: 0.65-2.60; I^2=0%; seven studies) or extensively (pooled RR: 0.77; 95% CI: 0.09-6.73; I^2=77%; three studies) hydrolyzed formula, and no significant difference between groups for risk of allergic sensitization to "any allergen" or raised total IgE level. The strength of evidence was graded as moderate for partially hydrolyzed formula, and as very low for exclusively hydrolyzed formula.
Limitations	Many studies of allergic outcomes included in this review had unclear or high risk of bias and evidence of conflict of interest, often because of inadequate methods of randomization and treatment allocation (selection bias) and support of the study or investigators from manufacturers of hydrolyzed formula. In many cases study participants were infants with early full formula feeding, so findings might not be applicable to populations with more typical feeding patterns.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y – Appendix 1
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Partially – List of excluded studies was not reported
Characteristics of included provided?	Y – Characteristics of included studies are summarized in tables A and B in appendix 3.

continued

TABLE C-6 Continued

Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y – GRADE approach
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y

Author, year	Cuello-Carcia et al., 2016
Aims/Key questions	To provide evidence-based recommendations about the use of prebiotic supplements for the primary prevention of allergies.
Study eligibility criteria	According to the evidence profiles table, the study eligibility criteria can be assumed to be: • Population: healthy infants • Intervention: prebiotic supplementation • Comparison: no prebiotic supplementation • Main outcomes: development of allergy, nutritional status, adverse effects • Setting: outpatient
Literature search dates or year range	Up to January 2015, with an update on July 29, 2015
Number of food allergy studies included	1
Synthesis methods	GRADE approach

Key findings	Outcome	Without prebiotics (per 1,000)	With prebiotics (per 1,000)	Difference (95% CI) (per 1,000)	Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Food allergy	170	48 (14 to 170)	122 fewer (0 to 156 fewer)	RR 0.28 (0.08 to 1.00)	VERY LOW

TABLE C-6 Continued

Conclusions and research needs	The guideline panel determined that there is a low certainty of a net benefit from using prebiotics in infants. Based on the body of available evidence, it is likely that prebiotic supplementation in infants reduces the risk of developing recurrent wheezing and possibly also the development of food allergy. There is very low certainty prebiotics have an effect on other outcomes. However, because of low certainty of evidence or no published information about other outcomes, the fact that the authors did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.
Limitations	This publication is a guideline paper. Although the guideline appears to be based on a systematic review, the methods of systematic review were not fully reported in this publication. No other source or citation to the systematic review was found.

AMSTAR rating	
An a priori design?	Yes
Duplicate study selection and data extraction?	Not reported
Comprehensive literature search?	Yes
Status of the publication as an inclusion criterion?	Not reported
List of studies (included and excluded) provided?	Partially – Excluded studies were not reported
Characteristics of included provided?	Yes
Scientific quality of the included studies assessed and reported?	Yes
Scientific quality used in formulating conclusions?	Yes
Methods used to combine the findings appropriate?	Yes
Likelihood of publication bias assessed?	No
Conflict of interest stated?	Yes

continued

TABLE C-6 Continued

Author, year	Newberry et al., 2016
Aims/Key questions	To update a prior systematic review on the effects of omega-3 fatty acids (n-3 fatty acids) on maternal and child health and to assess the evidence for their effects on, and associations with, additional outcomes. Key Question 2: Fetal/childhood exposures – What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 fatty acids) or n-3 fatty acid-supplemented infant formula or intakes of n-3 fatty acids from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants? • Growth patterns • Neurological development • Visual function • Cognitive development • Autism • Learning disorders • ADHD • Atopic dermatitis • Allergies (Note: including food allergies) • Respiratory illness
Study eligibility criteria	Populations of interest: • Healthy preterm or term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy. • Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth. • Healthy preterm or term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding. • Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy.

TABLE C-6 Continued

	Interventions of interest: • N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination); • N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 fatty acid content • High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl) o Exclude doses of more than 6g/d, except for trials that report adverse events • N-3 fatty acid fortified infant formulae o E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance® o N-3 fatty acid fortified follow-up formula o Exclude parenterally administered sources • Marine oils, including fish oil, cod liver oil, menhaden oil, and algal with quantified n-3 fatty acid content • Algal or other marine sources (e.g., phytoplankton) of omega-3 fatty acids with quantified n-3 content Exposures of interest: • Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires • Breast milk n-3 fatty acids (KQ2) • Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following: o Plasma fatty acids o Erythrocyte fatty acids o Adipocyte fatty acids Comparators of interest: • Inactive comparators: o Placebo o Nonfortified infant formula • Active comparators: o Different n-3 sources o Different n-3 concentrations o Alternative n-3 fortified infant formula o Soy-based infant formula o Diet with different level of Vitamin E exposure Outcomes of interest: • Risk for allergies. Validated allergy assessment procedures, preferably challenge (SPT or validated blood tests accepted) Timing of interest: • Interventions implemented within 1 month of birth or exposures measured within 1 month of birth • Follow-up duration is 0 to 18 years
Literature search dates or year range	Update searches were from the year 2000. For the newly added topics (e.g., allergies), the authors "reference mined" articles that they identified to determine whether any studies conducted and published before 2000 should be obtained and included.

continued

TABLE C-6 Continued

Number of food allergy studies included	3 RCTs
Synthesis methods	Narrative text and meta-analysis
Key findings	All three RCTs recruited pregnant women whose infants were at high risk of atopy (e.g., parent diagnosis of allergy, or sibling has diagnosed or suspected allergy). • Among the three prenatal n-3 interventions and two follow-up studies, three found associations between maternal n-3 fatty acid supplementation (DHA + EPA, varying doses ranging from 0.8 to 3.09 g/d) and lower risk of allergies (denoted by sensitization to egg allergen and positive skin prick test). However, in all but one study, these relationships were no longer observed or became marginal after adjusting for potential confounders or after long-term follow-up. • Meta-analysis of three RCTs (N=949) with 12-month food allergy outcomes yielded an insignificant summary effect size for DHA+EPA supplementation and risk of food allergy (OR: 0.54; 95% CI 0.05-6.2; I^2=42.3%). • Note that the strength of evidence was graded as low for the conclusion of no significant effect of DHA or DHA+EPA supplementation during pregnancy on food allergies.
Limitations	• The risk for allergies is an additional outcome of interest that was not included in the original review. • The search strategy was not designed specifically for food allergies outcomes.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y/N (The search strategy was not designed to specifically for food allergies outcomes because "food allergies" were not one of the pre-specified outcomes of interest)
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y

TABLE C-6 Continued

Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N (only published studies were included)
Conflict of interest stated?	Y

Author, year	Cuello-Carcia et al., 2015
Aims/Key questions	To synthesize the evidence supporting use of probiotics to prevent allergies and inform World Allergy Organization guidelines on probiotic use. Three key questions of this systematic review are: 1. Should supplementation of probiotics versus no such supplementation be used in pregnant women to prevent development of allergy in their children? 2. Should supplementation of probiotics versus no such supplementation be used in breastfeeding mothers to prevent development of allergy in their children? 3. Should supplementation of probiotics versus no such supplementation be used in infants to prevent development of allergy?
Study eligibility criteria	• Types of studies: RCTs with a minimum follow-up of 4 weeks that compared any type of probiotic with placebo, irrespective of their language or publication status. • Types of participants: Pregnant women, breastfeeding mothers, and infants and children (up to age 9 years). • Types of interventions: Any probiotic supplementation, irrespective of formulation (capsules, oil droplets, suspension, and supplements in infant formulas or cereals), microorganism, supplement composition (single versus multiple strains), or dose. • Types of outcome measures: The World Allergy Organization guideline panel members in a formal process determined the outcomes of interest. The following outcomes were deemed critical to the decision whether to use probiotics to prevent allergies: eczema, asthma and/or wheezing, food allergy, allergic rhinitis, any adverse effects, and severe adverse effects.
Literature search dates or year range	From inception to December 2014
Number of food allergy studies included	6 RCTs [Note: some RCTs contributed data for more than one meta-analysis.]
Synthesis methods	Narrative text, meta-analysis, and GRADE

continued

TABLE C-6 Continued

Key findings

- No RCTs for the comparison of probiotics versus no probiotics in pregnant women for prevention of allergy in their children (direct evidence).
- No RCTs for the comparison of probiotics versus no probiotics in breastfeeding women for prevention of allergy in their children (direct evidence)

				Anticipated absolute effects	
Outcomes	**No. of participants (studies)**	**Strength of evidence (GRADE)**	**Relative effect, RR (95% CI)**	**Risk with no probiotics**	**Risk difference with probiotics**
Probiotics versus no probiotics in pregnant women for prevention of allergy in their children (indirect evidence)					
Food allergy, follow-up: range, 12-24 months	355 (3 RCTs)	●○○○ Very low	1.08 (0.73-1.59)	Study population	
			Note: 1.49 (0.58, 3.81) in the forest plot	39 per 1,000	3 more per 1,000 (11 fewer to 23 more)
Probiotics compared with no probiotics in breastfeeding women to prevent allergies in their children (indirect)					
Food allergy, follow-up: range, 12-24 months	167 (2 RCTs)	●○○○ Very low	1.7 (0.58-4.96)	Study population	
				59 per 1,000	41 more per 1,000 (25 fewer to 233 more)
Probiotics compared with no probiotics in infants to prevent allergies (direct)					
Food allergy, follow-up: range, 6-24 months	349 (3 RCTs)	●○○○ Very low	0.88 (0.55-1.43)	Study population	
				167 per 1,000	20 fewer per 1,000 (75 fewer to 72 more)

TABLE C-6 Continued

Outcomes	No. of participants (studies)	Strength of evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects: Risk with no probiotics	Anticipated absolute effects: Risk difference with probiotics
Probiotics compared with no probiotics in infants to prevent allergies (indirect)					
Food allergy, follow-up: range, 6-24 months	295 (2 RCTs)	●○○○ Very low	1 (0.25-3.91)	Study population	
				27 per 1,000	0 fewer per 1,000 (20 fewer to 79 more)

Limitations

- There were moderate-to-serious concerns about the risk of bias in most studies.
- Some inconsistency in reporting of the meta-analysis results.
- Confidence that one would observe effects in real life is low to very low (low to very low certainty in the evidence). This is a result of the relative paucity of direct evidence in any of the three groups in whom probiotics could be used, the high likelihood of bias in primary studies, and the serious imprecision of the estimated pooled effects.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y – Table E3 and online repository
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Gunaratne et al., 2015
Aims/Key questions	To assess the effect of n-3 LCPUFA supplementation in pregnant and/or breastfeeding women on allergy outcomes (food allergy, atopic dermatitis [eczema], allergic rhinitis [hay fever] and asthma/wheeze) in their children.
Study eligibility criteria	Inclusion criteria: • Types of studies: RCTs focusing on n-3 LCPUFA supplementation of pregnant and/or breasfeeding women (compared with placebo or no treatment) and assessed allergy outcomes of the infants or children. Quasi-RCTs and RCTs using a cluster-randomized design were eligible for inclusion but none were identified. • Types of participants: Women and their children, with either a normal or high risk of developing allergic disease, were included. A fetus or a child with a first degree relative with medically diagnosed allergies, or a positive SPT, or a positive RAST was defined as being at high risk of allergies. Infants were also considered at high risk of allergies if their cord blood IgE level was above 0.70 IU/mL. • Types of interventions: All randomized comparisons of n-3 LCPUFA supplementation given to pregnant or lactating women (either with or without arachidonic acid), with placebo or no supplementation as a control, regardless of dose regimens and duration of intervention. Trials in which fish was the intervention were included if appropriately controlled, for example, if the diet was appropriately adjusted to match the protein contribution of fish. • Primary outcomes: o Medically diagnosed any allergy with sensitization, i.e., IgE-mediated allergies where both the signs and symptoms of the allergic disease and a positive SPT and/or RAST test are present. o Medical diagnosis or parental report (using validated questionnaire) of any allergy, +/– IgE sensitization. • Secondary outcomes: Children with specific forms of allergy, including food allergy, atopic dermatitis (eczema), asthma/wheeze, allergic rhinitis (hay fever) with IgE sensitization and +/– IgE sensitization, SPT results, and parent-reported allergies using non-validated questionnaires. Exclusion criteria: • Types of studies: Trials published in abstract form only, trials using a crossover design, and trials examining biochemical outcomes only.

TABLE C-6 Continued

Literature search dates or year range	Inception to August 2014
Number of food allergy studies included	Five
Synthesis methods	Narrative text and meta-analysis
Key findings	Three of the five trials had high risk of bias for incomplete outcome data (attrition bias) and/or selective reporting bias. • N-3 LCPUFA supplementation reduced the incidence of IgE-mediated food allergies in children up to 12 months of age (117 infants, RR: 0.13; 95% CI: 0.02-0.95), but there were no clear differences found between the intervention and control groups at any other age (12 to 36 months, 825 children, average RR: 0.58; 95% CI: 0.18-1.88; >36 months, 706 children, RR: 1.43; 95% CI: 0.63-3.26). • When food allergies +/– IgE sensitivity were considered, results showed few differences from those for IgE-mediated allergies with no differences in the direction of findings from those for IgE-mediated allergies: o Up to 12 months of age, 117 infants, RR: 0.13; 95% CI: 0.02-0.95. o Between 12 and 36 months, random-effects meta-analysis of four trials (973 children) showed pooled RR: 0.72; 95% CI: 0.40-1.30. o >36 months of age, 706 children, RR: 1.43; 95% CI: 0.63-3.26.
Limitations	• Review authors MM and CTC were investigators on two trials included in the review. • Studies included in this review used differing doses, DHA to EPA ratios, and duration of n-3 LCPUFA supplementation, and did not take into account the baseline n-3 LCPUFA status of the women.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	de Silva et al., 2014
Aims/Key questions	This systematic review is one of the series of systematic reviews for developing EAACI *Guidelines for Food Allergy and Anaphylaxis*. This systematic review examined ways to prevent the development of food allergy in children and adults.
Study eligibility criteria	• This review focused solely on studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. Studies seeking to prevent potential manifestations of food allergy, such as atopic dermatitis (eczema) or asthma, but not including an explicit diagnosis of sensitization to food or food allergy, were not included. • Systematic reviews and meta-analyses, RCTs, quasi-RCTs, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies were eligible. • No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.
Literature search dates or year range	The following databases were searched: Cochrane Library, MEDLINE, Embase, CINAHL, ISI Web of Science, TRIP Database, and Clinicaltrials.gov from inception to September 30, 2012
Number of food allergy studies included	74
Synthesis methods	Narrative synthesis and summary tables

TABLE C-6 Continued

Key findings	Table 1 summarized key evidence about prevention strategies: • Overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women at normal or high risk. Although breastfeeding may have many other benefits, the evidence in relation to the prevention of food allergy is not strong. This, to a large extent, reflects the ethical challenges of randomizing infants to a nonbreastfeeding arm. • There is more evidence about the benefits of alternatives to cow milk formula for babies at high risk. Extensively hydrolyzed whey or casein formula and partially hydrolyzed formula may have a protective effect, but it appears that soy formula does not protect against food allergies. • Probiotics do not seem to be protective in infants at high or normal risk, and neither does delaying the introduction of solid foods until later than the recommended minimum weaning age. Combining dietary with environmental modifications during infancy may be the best way forward for infants at high risk.
Limitations	• The studies included were heterogeneous, and as a result, it was not appropriate to quantitatively synthesize this evidence. • There are also limitations with the studies themselves. To date, the focus of research has largely been on preventing IgE-mediated food allergy rather than on non-IgE-mediated food allergy. Many studies are small, short term, and focus on the surrogate measure of food sensitization rather than food allergy. Sensitization may be a normal, harmless, and transitory phenomenon, which does not necessarily correlate with allergic disease.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y (protocol published elsewhere)
Status of the publication as an inclusion criterion?	Y (protocol published elsewhere)
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Kong et al., 2014
Aims/Key questions	To investigate the preventive effect of probiotics on pediatric food allergy.
Study eligibility criteria	• Study design of interest: RCTs with any sample size. • Population of interest: Infants and their mothers whose first-degree relatives have a history of allergic disease (asthma, allergic nose inflammation, allergic conjunctivitis, allergic eczema, food allergies, etc.). • Interventions of interest: Probiotics may be of single or multiple mixed bacteria type with any treatment course and dose. • Outcome of interest: Incidence of food allergy diseases.
Literature search dates or year range	Last search conducted September 30, 2013
Number of food allergy studies included	10
Synthesis methods	Meta-analysis
Key findings	• Total 1,349 subjects in the probiotics groups and 1,352 subjects in the control groups. Individual study sample size ranged from 60 to 888. • Fixed-effects meta-analysis of 10 RCTs showed no significant difference in the incidence of food allergies (pooled RR: 0.88; 95% CI: 0.76-1.03) with moderate heterogeneity (I^2=33%) comparing prenatal and postnatal probiotics supplementation with placebo or control.
Limitations	• Major sources of heterogeneity include: follow-up durations (ranging from 1 to 7 years); flora types of probiotic bacteria; dose and concentration of probiotics. • Individual study characteristics were not reported, overall risk of bias (or quality) for the included 10 RCTs was moderate, and some methodological concerns regarding the systematic review (see AMSTAR rating below). • Food allergy outcome definitions were not reported.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	N – Only one database used
Status of the publication as an inclusion criterion?	N

TABLE C-6 Continued

List of studies (included and excluded) provided?	N – Excluded studies not provided
Characteristics of included provided?	N
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	N – COI not provided for either the review of the included studies

Author, year	Marrs et al., 2013
Aims/Key Questions	To systematically review the evidence on the associations between microbial exposure and food allergies.
Study eligibility criteria	Inclusion criteria: • Food allergy outcomes included food challenge data, physician-diagnosed food allergy, reported doctor diagnosis of food allergy or food sensitization diagnosed by either SPT or elevated sIgE levels. • Using a study design appropriate to assess impact of microbial exposure. [Note: not explicitly defined.] Exclusion criteria: • Management guidance documents, reviews and studies investigating celiac disease, food intolerance and animal models were excluded.
Literature search dates or year range	Medline from inception to July 2012
Number of food allergy studies included	46
Synthesis methods	• Summary tables. • Qualitative synthesis using a pragmatic score (quality grading/rating scores) developed for this study. Publications were awarded greater weight of evidence if they used food challenge data rather than reported doctor diagnosis or only sensitization data (challenge-proven food allergy +2; [reported] physician-diagnosis +1, SPT or IgE measurement sensitization +0).

continued

TABLE C-6 Continued

Key findings	• Mode of delivery: All 13 studies reported that being born by caesarean was associated with an increased risk of developing food allergy or food sensitization, except the study of lowest quality. Six of these associations were significant. However, only two pertained to clinical food allergy diagnoses. The overall quality of these 13 studies was moderate (2 studies received a quality score of 4, 4 received a score of 3, 5 received a score of 2, and 2 received a score of 1). • Farming lifestyle and animal exposure: Of four studies investigating farm and animal exposure on food allergy, the Healthnuts Study found significantly less challenge-proven egg, sesame and peanut allergy among infants living with a dog during the first year of life (aOR: 0.6 [0.5-0.8]). However the quality of this study was poor (score of 2). • Endotoxin exposure: Two studies were included but the quality was very poor (score of 0 and 1). • Childhood infections: No studies investigated the association between viral and bacterial infections and challenge-proven food allergy. • Childhood vaccinations: No association was found for any of the recommended childhood vaccinations. • Antibiotic use: Some evidence suggests that antibiotic exposure increases the risk of eczema, but no such relationship has been found for food allergy. • Gut microbiota: Five studies investigated gut microbiota characteristics, two of which compared data with respect to food challenge outcomes and the other three used food sensitization parameters. The two studies ranking highest in quality originated from the same Spanish infants who were diagnosed with IgE-mediated cow milk allergy by milk challenge at a tertiary referral center. [Note that studies were not summarized in the summary tables. Summary of individual study findings was provided in text.] • Pro- and prebiotics: Eleven probiotic RCTs (quality score ranged from 0 to 3) have assessed whether microbial supplementation may be used in the prevention or treatment of food allergy or sensitization, but results have been disappointing overall.

TABLE C-6 Continued

Limitations	• Some methodological concerns regarding the search and study selection process. The authors seem to "up-play" some positive results, not taking into account the quality scores in their synthesis. Most of the studies were rated poor quality. • With exception of probiotics, all studies for other microbial exposures were observational studies. • The studies selected were highly heterogeneous in design and quality. • Most studies were primarily designed to investigate respiratory allergies or eczema, and hence lacked objective characterization of clinical food allergy and statistical power to detect significant risk estimates.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Not reported
Comprehensive literature search?	N (Medline only)
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	No but available on request
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N – COI of the systematic review authors were reported but COI not provided for the included studies

Author, year	Kramer and Kakuma, 2012
Aims/Key questions	To assess the effects of prescribing an antigen avoidance diet during pregnancy or lactation, or both, on maternal and infant nutrition and on the prevention or treatment of atopic disease in the child; positive SPTs to dietary antigens; and cord blood levels of IgE (a predictor of subsequent atopic disease).

continued

TABLE C-6 Continued

Study eligibility criteria	Inclusion criteria: • Study design: All acceptably controlled (randomized or quasi-randomized) comparisons of maternal dietary antigen avoidance prescribed to pregnant (at any time during pregnancy) or lactating women at high risk, regardless of degree (number of foods eliminated from the diet) or duration. • Population: Pregnant or lactating women at high risk of giving birth to an atopic child, based on a history of atopic disease (eczema, asthma, or hay fever) in the mother, father, or a previous child. Lactating mothers of infants with established atopic eczema. • Intervention: Prescription of diet with exclusion (or reduced quantity) of potentially antigenic foods such as cow milk, egg, peanut, fish, and chocolate. • Outcome measures: o Primary outcomes: Occurrence and severity of atopic disease in the child. o Secondary outcomes: Nutritional status of mother (gestational weight gain) and fetus (birth weight); other pregnancy outcomes (e.g., preterm birth); positive SPT to ingested antigen (especially egg and milk); and cord blood IgE levels. Exclusion criteria: • Trials of multimodal interventions that include, in addition to maternal dietary antigen avoidance, manipulation of the infant's diet other than breast milk or of other non-dietary aspects of the infant's environment (i.e., exposure to inhaled allergens).
Literature search dates or year range	Unspecified; search conducted on July 6, 2012
Number of food allergy studies included	Three (based on SPT results)
Synthesis methods	Summary tables and meta-analysis

TABLE C-6 Continued

Key findings	• Antigen avoidance during pregnancy: Results from two trials involving 334 pregnant women at high risk of atopic offspring suggest a lower incidence of positive SPT to egg antigen at 6 months of age, but the effect was no longer evident at 18 months, nor was any benefit apparent at either age for SPT to milk antigen (random-effects meta-analysis pooled RR: 0.95; 95% CI: 0.52-1.74). The risk of bias of the two trials is mixed (one was low risk and one was high risk of bias). • Antigen avoidance during lactation: A larger included trial (N=497) did not report on atopic eczema or other allergic disease outcomes, but found no evidence of sensitization to milk, egg, or peanut antigen on SPT at 1, 2, or 7 years of age. The risk of bias of this trial was unclear because the information available is based solely on a published abstract.
Limitations	• This Cochrane systematic review did not focus on food allergies or sensitization. Out of 12 trials, only 3 reported SPT results. • Food sensitization outcomes were based on SPT results only. • Included trials had small sample sizes.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y/N (funding sources of included studies were not reported but the systematic review authors reported no conflict of interest)

Author, year	Fisher et al., 2011
Aims/Key questions	To determine whether specific oral tolerance induction is more effective than avoidance in inducing tolerance in children ages 0 to 18 years who have IgE-mediated food allergy.

continued

TABLE C-6 Continued

Study eligibility criteria	Inclusion criteria: • Population: Children ages 0 to 18 years with IgE-mediated food allergy proven by DBPCOFC at the start of the study. • Outcome measures: The success of specific oral tolerance induction was objectively assessed using oral food challenge or DBPCOFC for tolerance but DBPCOFC for allergy. • Quality of trial: Scored ≥1+ using the National Institute for Health and Clinical Excellence (NIHCE) criteria for quality assessment. • Other: English language publications.
Literature search dates or year range	1950 to July 2009
Number of food allergy studies included	Three
Synthesis methods	Summary tables and meta-analysis
Key findings	• All three RCTs examined the effect of oral tolerance induction to cow milk protein, with one study enrolling children who were exquisitely sensitive, reacting at <1 ml of whole cow milk at the start of the study. Age ranges of children included in each RCT were wide (0.6-12.9; 5-17; 6-17 years). • One RCT also performed oral tolerance induction to hen egg, although each child was desensitized to only one food (cow milk or hen egg) during the study. In two RCTs, children who were not randomized to receive specific oral tolerance induction practiced avoidance of the relevant allergen. Children in the third RCT consumed a placebo, although no details of the substance used for the placebo were provided. • Meta-analysis: Total of 127 children were included in the meta-analysis. Although a reduction in allergy after treatment is highlighted, this fails to meet statistical significance (pooled RR: 0.61; 95% CI: 0.32-1.12; P=0.1302). Cochran Q (8.87; P=0.0118) and I^2 (77.5%; 95% CI: 0%-91%) found high heterogeneity between studies, which further reduces the significance of findings.
Limitations	• One author reviewed the studies using the NIHCE quality framework, but no details about quality assessment were reported. It is unclear how many studies were excluded based on quality score. • Included studies performed specific oral tolerance induction only to cow milk or hen egg, and although these are the most common childhood food allergens trials had small sample size.

TABLE C-6 Continued

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	N (only one author conducted the search and one author reviewed the studies)
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

Author, year	Klemens et al., 2011
Aims/Key questions	To determine if n-3 PUFA supplementation during pregnancy and lactation reduces risk for childhood allergic disease.
Study eligibility criteria	Inclusion criteria: • RCTs comparing supplementation in pregnancy and lactation with n-3 PUFA or placebo for primary prevention of allergic disease in neonates, infants, and children. • Study participants were pregnant or lactating women and their offspring. • Studies had to report on one of the following clinical or immunological outcomes in neonates, infants, or children: asthma, atopy, and food allergy as a clinical diagnosis or as response to the egg SPT at any time during the first 12 months of life. Diagnoses must be verified by medical or nursing clinicians.
Literature search dates or year range	1950 to October 2010
Number of food allergy studies included	Three
Synthesis methods	Summary tables, meta-analysis and narrative synthesis

continued

TABLE C-6 Continued

Key findings	• Three RCTs (N=264) reported on clinical diagnoses of food allergy in children. All RCTs were rated high quality. • Random-effects meta-analysis showed no significant difference in food allergy between children of mothers who received n-3 PUFA supplementation and children of mothers receiving placebo (6/128 versus 16/136, pooled OR: 0.46; 95% CI: 0.156-1.38). There was no significant between-study heterogeneity (P=0.226, I^2=32.777) nor was there evidence of publication bias (Egger's regression intercept P=0.998). o When only RCTs in which supplementation was started during pregnancy were considered, fewer children with food allergies were born to n-3 PUFA-supplemented mothers than to placebo-supplemented mothers, but this difference was not significant (4/92 versus 15/108, pooled OR: 0.34; 95% CI: 0.10-1.15). • Two of the included studies (N=187) reported on the period prevalence of positive response to the egg SPT in children up to age 12 months after maternal n-3 PUFA supplementation during pregnancy. Supplementation significantly reduced a positive SPT response to egg (12/87 versus 32/100, pooled OR: 0.33; 95% CI: 0.16-0.70). There was no significant between-study heterogeneity (P=0.957, I^2=0.000).
Limitations	• The different doses of supplementation in the combined studies also may represent a weakness of this meta-analysis, given that n-3 PUFA supplementation may have an inverted U-shaped dose–response curve, with moderate doses conferring more benefit than high doses in some models. • Although a positive SPT indicates the presence of food-specific IgE antibodies, a positive response may be seen in tolerant individuals and does not necessarily represent food allergy.

AMSTAR rating

An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y

TABLE C-6 Continued

Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)
Author, year	Osborn and Sinn, 2006
Aims/Key questions	• To determine the effect of feeding hydrolyzed formulas on allergy and food intolerance in infants and children compared to adapted cow milk or human breast milk. If hydrolyzed formulas are effective, to determine what type of hydrolyzed formula is most effective, including extensively and partially hydrolyzed formulas. • To determine which infants benefit, including infants at low or high risk of allergy and infants receiving early, short-term, or prolonged formula feeding.
Study eligibility criteria	Inclusion criteria: • Types of studies: RCTs and quasi-RCTs that compare the use of a hydrolyzed infant formula to human milk or an adapted cow milk formula. Random and quasi-random (e.g., using alternation) trials with ≥80% follow-up of participants were eligible for inclusion. • Types of participants: Infants in the first 6 months of life without clinical evidence of allergy. • Types of interventions: Hydrolyzed cow milk and soy formulas, and extensively and partially hydrolyzed formulas. Hydrolyzed formulas may be used for either o early, short-term supplementary or sole formula feeding in infants unable to be exclusively breastfed in the first days of life; o prolonged supplementation of breastfed infants or sole formula feeding in infants in the first months of life; or o weaning from the breast using infant formula. • Type of controls: The control group may include infants who receive exclusive human milk (either breast fed or expressed) or an adapted cow milk formula. • Primary outcomes: o All allergy including asthma, atopic dermatitis, allergic rhinitis or food allergy. o Food intolerance.
Literature search dates or year range	Inception to March 2006
Number of food allergy studies included	Five

continued

TABLE C-6 Continued

Synthesis methods	Meta-analysis, summary table, narrative text
Key findings	For Comparison 01 Early short-term feeding: Hydrolyzed formula versus human milk feeding among low-risk infants: • (90 infants) no significant difference in any allergy (RR: 1.43; 95% CI: 0.38-5.37), food allergy (RR: 1.43; 95% CI: 0.38-5.37), and cow milk allergy (RR: 7.11; 95% CI: 0.35-143.84) at age 3 years. • (3,559 infants) no significant difference in cow milk allergy up to mean age of 27 months (RR: 0.87; 95% CI: 0.52-1.46). For Comparison 03 Early short-term feeding: Hydrolyzed formula versus cow milk formula: • (77 infants) no significant difference in childhood allergy incidence (RR: 1.37; 95% CI: 0.33-5.71), childhood food allergy (RR: 1.37; 95% CI: 0.33-5.71), and childhood cow milk allergy (RR: 5.13; 95% CI: 0.25-103.43). • (3,478 infants) a reduction in infant cow milk allergy of borderline significance (RR: 0.62; 95% CI: 0.38-1.00). For Comparison 04 Prolonged feeding: Hydrolyzed formula versus cow milk formula: • (141 infants) no significant difference in infant food allergy (RR: 1.82; 95% CI: 0.64-5.16). • (67 infants) a significant reduction in infant cow milk allergy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 07 Prolonged feeding: Extensively hydrolyzed formula versus cow milk formula: • (96 infants) no significant difference in food allergy (RR: 1.15; 95% CI: 0.33-4.02). For Comparison 08 Prolonged feeding: Partially hydrolyzed formula versus cow milk formula: • (91 infants) no significant difference in infant food allergy (RR: 2.56; 95% CI: 0.86-7.56). • a significant reduction in cow milk allergy in infancy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 09 Prolonged feeding: Extensively hydrolyzed formula versus partially hydrolyzed formula: • Meta-analysis of two studies (N=341) found a significant reduction in infant food allergy (typical RR: 0.43; 95% CI: 0.19-0.99). • (246 infants) no significant difference in infant cow milk allergy (RR: 0.13; 95% CI: 0.01-1.16).

TABLE C-6 Continued

Key findings (continued)	For Comparison 11 Prolonged feeding: Hydrolyzed formula versus cow milk formula: Allergy/intolerance confirmed by test: • (141 infants) no significant difference in infant food allergy confirmed by specific IgE (RR: 1.82; 95% CI: 0.64-5.16). • significant reduction in infant cow milk allergy confirmed by specific IgE (RR: 0.36; 95% CI: 0.15-0.89). • no significant difference in infant food intolerance confirmed by DBPCOFC (RR: 0.48; 95% CI: 0.07-3.33). For Comparison 14 Prolonged feeding: Partially hydrolyzed whey formula versus cow milk formula: • significant reduction in infant cow milk allergy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 15 Prolonged feeding: Partially hydrolyzed casein containing formula versus cow milk formula: • (91 infants) no significant difference in infant food allergy (RR: 2.56; 95% CI: 0.86-7.56). For Comparison 17 Prolonged feeding: Extensively hydrolyzed casein containing formula versus cow milk formula: • (96 infants) no significant difference in infant food allergy (RR: 1.15; 95% CI: 0.33-4.02).
Limitations	• Many "meta-analyses" of small number of studies. • Infant and childhood allergy had different definitions, timing of measurement and methods for measurement from study to study. Most studies were small or had methodological limitations, with benefits not persisting when analysis was restricted to trials with blinding of measurement to study formula or to studies of adequate methodology.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	N (many "meta-analysis" had one study)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Kramer and Kakuma, 2004
Aims/Key questions	To assess the effects on child health, growth, and development, and on maternal health, of exclusive breastfeeding for 6 months versus exclusive breastfeeding for 3 to 4 months with mixed breastfeeding (introduction of complementary liquid or solid foods with continued breastfeeding) thereafter through 6 months.
Study eligibility criteria	Inclusion criteria: • Study design: Controlled clinical trials and observational studies, published in all languages, examining whether or not exclusive breastfeeding until age 6 months has an impact on growth, development, morbidity, and survival of healthy, term infants and their mothers. • Comparison: The comparisons must have been based on one group of infants who received exclusive breastfeeding for at least 3 but less than 7 months and mixed breastfeeding until 6 months or later (i.e., infants were introduced to liquid or solid foods between 3 and 6 months of age), and another group of infants who were exclusively breastfed for at least 6 months. Studies comparing infants receiving prolonged exclusive breastfeeding (more than 6 months) to those exclusively breastfed for 6 months and continued mixed breastfeeding after 6 months also were included. Among infants exclusive breastfeeding for at least 3 months, the interventions/exposures compared were continued exclusive breastfeeding versus mixed breastfeeding. The "complementary" foods used in mixed breastfeeding included juices, formula, other milks, other liquids, or solid foods. Although the WHO defines exclusive breastfeeding as breastfeeding with no supplemental liquids or solid foods other than medications or vitamins, few studies strictly adhered to the WHO's definition. • Population: Lactating mothers and their healthy, term, singleton infants.

TABLE C-6 Continued

Study eligibility criteria (continued)	• Outcome measures: Any infant or maternal health outcomes. The infant outcomes specifically sought (but not necessarily found) included growth (weight, length, and head circumference and z-scores (based on the WHO/CDC reference) for weight-for-age, length-for-age, and weight-for-length), infections, morbidity, mortality, micronutrient status, neuromotor and cognitive development, asthma, atopic eczema, other allergic diseases, type 1 diabetes, blood pressure, and subsequent adult chronic diseases such as coronary heart disease, hypertension, type 2 diabetes, and inflammatory and autoimmune diseases. Maternal outcomes sought included postpartum weight loss, duration of lactational amenorrhea, and such chronic diseases as breast and ovarian cancer and osteoporosis. Exclusion criteria: • Studies of (or including) low birthweight (less than 2,500 g) infants were not excluded, provided that such infants were born at term (at least 37 completed weeks). Only those studies with an internal comparison group were included in the review, i.e., the authors excluded studies based on external comparisons (with reference data). • Studies comparing exclusive breastfeeding and mixed breastfeeding from birth were excluded, as were those that investigated the effects of age at introduction of nonbreast milk liquid or solid foods but did not ensure exclusive breastfeeding at least 3 months before their introduction.
Literature search dates or year range	Inception to June 15, 2011
Number of food allergy studies included	One cohort study
Synthesis methods	Narrative synthesis; meta-analysis (N/A for food allergy outcome because only one study was included)
Key findings	• 1 cohort study enrolled 135 healthy Finnish infants of atopic parents reported food allergy outcome. This study was rated unclear overall risk of bias. • For the comparison of exclusive breastfeeding for 6-7 months versus 3-4 months, this study also reported a reduced risk of a history of food allergy at 1 year but double food challenges showed no significant risk reduction (RR: 0.77; 95% CI: 0.25-2.41).
Limitations	• This systematic review did not focus on food allergy. Only 1 cohort study reported food allergy outcomes.

continued

TABLE C-6 Continued

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	N
Methods used to combine the findings appropriate?	N (many "meta-analysis" only has 1 study)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	N

NOTE: ALA = alpha-linolenic acid; CDC = Centers for Disease Control and Prevention; CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EAACI = European Academy of Allergy & Clinical Immunology; EPA = eicosapentaenoic acid; IgE = immunoglobulin E; IU = international units; LCPUFA, long-chain polyunsaturated fatty acid; N/A = not available; OR = odds ratio; PUFA = polyunsaturated fatty acid; RAST = radioallergosorbent; RCT = randomized controlled trial; RR = relative risk; SDA = stearidonic acid; SPT = skin prick test; tIgE = total IgE; WHO = World Health Organization.

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Appendix D

Acronyms and Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology
AAFA	Asthma and Allergy Foundation of America
AAP	American Academy of Pediatrics
ACAA	Air Carrier Access Act
ACAAI	American College of Allergy, Asthma & Immunology
ACD	allergic contact dermatitis
ACP	allergen control plan
AD	atopic dermatitis
ADA	American Diabetes Association
ADA	Americans with Disabilities Act
aOR	adjusted odds ratio
AP	allergenic proctocolitis
APC	antigen-presenting cell
APT	atopy patch test
ASCIA	Australasian Society of Clinical Immunology and Allergy
BAT	basophil activation test
BEAT	Beating Egg Allergy Trial
CAC	Codex Alimentarius Commission
CCP	critical control point
CD14	cluster of differentiation 14
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CPSC	Consumer Product Safety Commission

CRD	component resolved diagnostics
DBPCOFC	double-blind, placebo-controlled oral food challenge
DC	dendritic cell
DMP	differentially methylated probe
DOJ	U.S. Department of Justice
DOT	U.S. Department of Transportation
EAACI	European Academy of Allergy & Clinical Immunology
EAT	Enquiring About Tolerance
ECHO	Environmental Influences on Child Health Outcomes
ED	eliciting dose
EFSA	European Food Safety Authority
EG	eosinophilic gastroenteritis
EHF	extensively hydrolyzed cow's milk formula
ELISA	enzyme-linked immunosorbent assay
EoE	eosinophilic esophagitis
EPIT	epicutaneous immunotherapy
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
EU	European Union
EWAS	epigenome-wide association study
FAA	Federal Aviation Administration
FALCPA	Food Allergen Labeling and Consumer Protection Act
FAMPP	Food Allergy Management and Prevention Plans
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FDEIA	food-dependent, exercise-induced allergy
FNS	U.S. Food and Nutrition Service
FPIES	food protein–induced enterocolitis syndrome
FSIS	Food Safety and Inspection Service
FSMA	Food Safety Modernization Act
GI	gastrointestinal
GINI	German Infant Nutritional Intervention
GWAS	genome-wide association study
GxE	genome–environment
HACCP	hazard analysis and critical control point
HEAP	Hen's Egg Allergy Prevention

HHS	U.S. Department of Health and Human Services
HLA	human leucocyte antigen
HRQL	health-related quality of life
ICD	*International Classification of Diseases*
ICN	Institute of Child Nutrition
ICSA	interval censoring survival analysis
IDEA	Individuals with Disabilities Education Act
IEP	individualized education program
IFN	interferon
IgE	immunoglobulin E
ILSI-EU	International Life Sciences Institute-Europe
IOM	Institute of Medicine
ITP	Interstate Travel Program
JCAAI	Joint Council of Allergy, Asthma & Immunology
LEAP	Learning Early About Peanut Allergy
LOAEL	lowest-observed-adverse-effect level
MAPK	mitogen-activated protein kinase
MED	minimal eliciting done
Mis-BAIR	Melbourne Infant Study-BCG for Allergy and Infection Reduction
MMR	measles, mumps, rubella
NAS	National Academy of Sciences
NCHS	National Center for Health Statistics
NEISS	National Electronic Injury Surveillance System
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHMRC	National Health and Medical Research Council
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NSAID	nonsteroidal anti-inflammatory drug
OFC	oral food challenge
OIT	oral immunotherapy
OR	odds ratio

PAL	precautionary allergen labeling
PASTURE	Protection against Allergy Study in Rural Environments
PCR	polymerase chain reaction
PFAS	pollen-associated food allergy syndrome
PHF	partially hydrolyzed formula
PIFA	Prevalence of Infant Food Allergy; Pertussis Immunisation and Food Allergy
PreventADALL	Preventing Atopic Dermatitis and Allergies in Children
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RAST	radioallergosorbent test
RCT	randomized controlled trial
RFR	Reportable Food Registry
RR	relative risk
sIgE	allergen-specific IgE (or food-specific IgE)
SLIT	sublingual immunotherapy
SNP	single nucleotide polymorphism
SOP	standard operating procedure
SPT	skin prick test
STEP	Starting Time for Egg Protein
SyMBIOTA	Synergy in Microbiota
TNO	Netherlands Organization for Applied Scientific Research
TTB	U.S. Tax and Trade Bureau
TWG	Threshold Working Group
USDA	U.S. Department of Agriculture
VDR	vitamin D receptor
VITAL®	Voluntary Incidental Trace Allergen Labeling
WAO	World Allergy Organization
WHO	World Health Organization

Appendix E

Definitions

Acceptable level of risk: A risk management decision regarding the degree of risk that would be acceptable within the affected population.

Allergen-specific IgE (sIgE): An IgE that recognizes a specific allergen and that is formed by the immune systems of some individuals after they have been exposed to that allergen in food. Also referred to in the text as food-specific IgE.

Allergy/allergic disease: A disease caused by immunologic dysfunction that falls under one of two key classifications: immunoglobin E (IgE)-mediated or non-IgE-mediated.

Anaphylaxis: An acute, potentially life-threatening syndrome with multi-systemic manifestations due to the rapid release of inflammatory mediators.

Atopic disorder: Disorder characterized by exaggerated or hypersensitive immune reactions to foreign antigens.

Atopic march: Refers to the idea that atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma.

Atopy patch test (APT): A test performed in a manner similar to patch testing that is routinely used for evaluation of allergic contact dermatitis, except that foods are used. The food, presented as a fresh extract or powder, is generally placed under an aluminum disc on the skin for 48

hours then removed. The final test result is determined at 72 hours after application. Current guidelines do not recommend the APT for the routine diagnosis of food allergies.

Auto-injector of epinephrine: A device used in first-aid management to self-inject epinephrine.

Basophil activation test (BAT): A test conducted by exposing the basophils in a test tube to various concentrations of the allergen to be tested, either an extract or individual component proteins in the test tube. The readout is the number of cells responding, or the concentration of allergen at which 50 percent of the cells respond. About 10 percent of people are BAT non-responders, even though they are allergic and have positive skin tests. The test is a functional assay akin to a provocation test, such as a skin prick test.

Basophils (basophilic granulocytes): The least abundant of the granulocytes (the others being neutrophils and eosinophils). Basophils can release histamine, lipid mediators, and cytokines in response to the aggregation of their cells surface FcεRI, which is induced when IgE bound to these FcεRI recognizes specific allergens, including those from foods. Unlike mast cells, basophils mature in the bone marrow and circulate in the blood, but can enter tissues at sites of allergic inflammation.

Component resolved diagnostics: A test sometimes referred to as molecular testing. This test involves measuring sIgE against individual allergenic food proteins.

Cross-contact: A situation in which an unintended allergen may be present in an otherwise allergen-free food because of contact between the unsafe and safe foods.

Cytokines: Small proteins produced by various immune cells and other cell types that carry signals to facilitate communication and interaction between cells.

Desensitization: A state of clinical and immunological nonresponsiveness to an allergen, including food allergens, that can be induced by the careful, physician-guided administration of gradually increasing amounts of the offending allergen over a relatively short period of time (hours to days). The maintenance of such desensitization typically requires continued regular exposure to the offending allergen (also see **Tolerance**).

Epinephrine: Also known as adrenaline, first-line therapy for food-induced anaphylaxis. Recommended to be injected intramuscularly.

Epitopes: Specific fragments of food allergens (antigens) that the immune system recognizes; if recognized by IgE bound to FcεRI on the surface of mast cells and basophils, epitopes can trigger an allergic reaction that may include anaphylaxis.

Exposure assessment: An action that plays an essential role in determining whether the hazardous properties of a substance will translate to adverse health effects. For foods, the exposure assessment estimates the amounts (or range of amounts) of the hazard that are likely to be consumed. If these amounts exceed a Reference Dose or the established maximum level in foods (established using a hazard assessment), then a risk of adverse health consequences to the exposed (sub)population is predicted. In contrast, an exposure at or below the Reference Dose or maximum level in foods is assumed to be safe for the vast majority of individuals. In the case of food allergens, the Reference Dose could also be used as an action level to determine when precautionary allergen labeling should be applied to a product package. (Also see **Hazard identification and hazard characterization** and **Reference Dose**.)

FcεRI: The high-affinity receptor for IgE that binds IgE and thereby permits cells bearing FcεRI on their surface (e.g., mast cells, basophils, some dendritic cells, and macrophages) to become "sensitized" so that they can be activated to release inflammatory mediators by allergens recognized by the bound IgE. For the FcεRI to initiate the cell signaling that results in activation of mast cells and basophils to release their mediators requires that the receptors are aggregated when their bound IgE reacts with allergens that are at least bivalent (e.g., have two epitopes that can bind IgE). This permits such allergens to bridge adjacent IgE molecules and to aggregate the FcεRI receptors that bind such IgE.

Food: Any substance—whether processed, semiprocessed, or raw—that is intended for human consumption. Food includes drinks, chewing gum, food additives, and dietary supplements.

Food allergens: The components within foods that trigger adverse immunologic reactions; these are most often specific glycoproteins that can interact with the body's immune cells in a way that initiates the development of a food allergy.

Food allergy: An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food, and that can be either IgE-mediated or non-IgE-mediated.

Food intolerance: An adverse reaction to foods or food components that lacks an identified immunologic pathophysiology.

Food protein-induced enterocolitis syndrome and food protein-induced allergic proctocolitis: Non-IgE-mediated disorders that lack current means of simple laboratory testing to identify causal foods or to confirm the diagnosis. Guidelines suggest using the medical history, resolution of signs and symptoms during dietary elimination, and recurrence of signs and symptoms upon exposure, for example during an oral food challenge, as a means of diagnosis.

Hazard: An inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or given population is exposed to that agent.

Hazard identification and hazard characterization: The two components of the hazard assessment process. Hazard identification includes a determination that the substance with the hazardous properties is present, but also more generally refers to the identification of the type and nature of the adverse effects that an agent can cause in an organism, system, or given population. In the hazard identification of an allergenic food, the prevalence and severity of the specific food allergy would be considered. Hazard characterization involves a qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. Hazard characterization encompasses the dose–response relationship. A hazard assessment (involving both hazard identification and hazard characterization) can be used to derive safe levels of exposure, for instance through the elaboration of a Reference Dose.

Immunoglobulin E (IgE): An antibody that can trigger intense inflammatory reactions. IgE causes the IgE-mediated allergic response by binding strongly to IgE receptors (FcεRI) found on the surface of mast cells and basophils, and triggering these cells to release powerful inflammatory mediators once the cell-bound IgE recognizes the offending food allergen.

Lowest-observed-adverse-effect level (LOAEL): The lowest dose of a hazard (e.g., allergen, expressed as milligrams (mg) of total protein from the allergenic food) that can provoke an observable reaction in an individual or population. Also known as the minimal eliciting dose.

Mast cells: Cells derived from hematopoietic precursors that mature after migrating into essentially all vascularized tissues, where they can reside for long periods of time. Mast cells are present within the mucosal tissues of the entire gastroinstestinal tract (and many other anatomical sites, including the skin and airways) and contain cytoplasmic granules rich in histamine, proteoglycans (depending on the mast cell population, these consist of heparin and/or chondroitin sulfates), serine proteases (depending on the mast cell population, these can consist of carboxypeptidase A3, tryptases and/or chymase). Upon activation by IgE and specific antigens (including food allergens), mast cells can release such granule-associated inflammatory mediators and also secrete newly synthesized lipid mediators and cytokines. Mast cells also can be activated by diverse agents that act independently of IgE, which can result in the release of the same products produced by mast cells activated through IgE.

No-observed-adverse-effect level (NOAEL) or threshold: The highest dose of a hazard (e.g., allergen, expressed as mg of total protein from the allergenic food) that will not provoke an observable reaction in an individual or population.

Objective response: A reaction that can be independently verified by a clinically trained observer (e.g., urticaria [hives], vomiting, flushing, angioedema).

Oral food challenge (OFC): A feeding test that typically involves a gradual, medically supervised ingestion of increasingly larger doses of the food being tested as a possible food allergen. Guidelines recommend using the OFC to diagnose food allergy, particularly in individuals whose clinical history and other test results do not definitively establish the diagnosis of food allergy. There are three types of OFCs depending on the protocol. An open OFC is one where the food is in its natural form; a single-blind OFC is one where the food is masked from the patient's perspective so less patient bias occurs because of anxiety; a double-blind, placebo-controlled oral food challenge (DBPCOFC) involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested. A DBPCOFC is considered the "gold standard" for diagnosis of food allergy.

Pollen-associated food allergy syndrome (oral allergy syndrome): A type of food allergy with signs and symptoms that include itching or swelling of the lips, mouth, or throat in response to eating certain raw fruits and vegetables that typically develops in adults with hay fever. The specific IgE antibodies formed exhibit reactivity with both proteins found in pollens and similar proteins found in certain fruits and vegetables.

Reference Dose: The lowest dose of a hazard (e.g., allergen, expressed in mg of total protein from the allergenic source) that is predicted to elicit symptoms of a reaction when ingested by a defined, small percentage of the population of individuals who are known to experience adverse reactions to that hazard.

Risk: The probability of an adverse effect in an organism, system, or (sub) population caused under specified circumstances by exposure to an agent.

Risk characterization: A process that can be used to assess the likelihood of risk even in cases where a Reference Dose or maximum level has not been established. The risk characterization is the determination of quantitative probability, including attendant uncertainties, that adverse health effects will occur in a given individual or (sub)population, under defined conditions of exposure.

Safety: The control of recognized hazards to achieve an acceptable level of risk.

Sensitization: A condition in which an individual produces detectable IgE to a particular allergen or allergens. It precedes and is required for the cell manifestations of a food allergy, but not all individuals with detectable IgE will experience a food allergy reaction to the allergen recognized by that IgE.

Skin prick test: An allergy detection test performed by puncturing the surface of the skin to introduce an allergen and evaluating the area of the induced wheal (small swelling) and flare (redness) responses that can be measured.

Subjective response: A mild transitory reaction that cannot be independently confirmed by a clinically trained observer (e.g., palatal itching or stomach cramping).

T cells: Lymphocytes produced by the thymus that guide many aspects of the immune system, particularly its adaptability and ability to recognize threats.

Tolerance: A state of relatively unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response. It can be natural (e.g., to the body's own proteins) or acquired (e.g., to

external proteins). It also is said that some persons can "grow out" of an allergy; this can be envisioned as a form of acquired tolerance to the offending allergen(s). In some instances, the state of tolerance may be transient (also see **Desensitization**); in others it can be durable.

Appendix F

Committee Members Biographical Sketches

Virginia A. Stallings, M.D. (*Chair*) is the Jean A. Cortner Endowed Chair in Gastroenterology, and Director of the Nutrition Center at The Children's Hospital of Philadelphia, and Professor of Pediatrics at the Perelman School of Medicine, University of Pennsylvania. Her research interests include pediatric nutrition, evaluation of dietary intake and energy expenditure, and nutrition-related chronic disease. Dr. Stallings has been a member of the National Academy of Medicine since 2005 and has served on several National Academies of Sciences, Engineering, and Medicine committees: Committee on Nutrition Standards for National School Lunch and Breakfast Programs, Committee on Nutrition Services for Medicare Beneficiaries, Committee on the Scientific Basis for Dietary Risk Eligibility Criteria for WIC (Women, Infants, and Children) Programs, the Committee to Review the WIC Food Packages, and the Committee to Review Child and Adult Care Food Program Meal Requirements. She is a former member (1997-2000) and co-vice chair (2000-2002) of the Food and Nutrition Board. Dr. Stallings is board certified in pediatrics and clinical nutrition. She received the Fomon Nutrition Award from the American Academy of Pediatrics and is a Fellow of the American Society of Nutrition. Dr. Stallings earned a B.S. in Nutrition and Foods from Auburn University, an M.S. in Human Nutrition and Biochemistry from Cornell University, and an M.D. from the University of Alabama at Birmingham School of Medicine.

Katrina (Katie) Allen, Ph.D., is Director of the Population Health Research Theme, Murdoch Childrens Research Institute, Professor of Paediatrics at the University of Melbourne, Australia, and holds a Chair in Food

Allergy at the University of Manchester, United Kingdom. She is an active pediatric allergist and gastroenterologist at the Royal Children's Hospital, Melbourne. Her research focuses on the evolving field of food allergy and her vision is to prevent food allergy in children. She is a National Health and Medical Research Council (NHMRC) Practitioner Fellow and Chief Investigator on five NHMRC-funded studies, which seek to answer questions about population health and evolution of the allergy epidemic, including gene-environment and epigenetic associations with food allergy. Dr. Allen also is Director of the NHMRC-funded Australian Centre of Food & Allergy Research, which aims to translate research findings into clinical practice and public health policy to ensure the best outcomes for children with food allergy.

A. Wesley Burks, M.D., is Executive Dean for the University of North Carolina (UNC) School of Medicine. In this role he provides overall academic leadership for the School of Medicine and the UNC Health Care System. He also is the Curnen Distinguished Professor in Pediatrics. Dr. Burks joined the UNC system in November 2011. His research interests are in the allergic diseases, particularly adverse reactions to foods. Dr. Burks heads a research team whose work centers on identifying the allergens in specific foods at a molecular level, improving understanding of the mechanism of adverse food reactions, and developing treatments for food allergy in animal models and in clinical studies. Dr. Burks and his colleagues are currently conducting clinical studies with different types of mucosal immunotherapy. His laboratory funding comes from many sources, including the National Institutes of Health (NIH) and private foundations. He is a past Chair and member of the NIH Hypersensitivity, Autoimmune, and Immune-mediated Diseases study section and is Past President of the American Academy of Allergy, Asthma & Immunology. He received an M.D. from the University of Arkansas for Medical Sciences and completed a fellowship in Allergy and Immunology at Duke University Medical Center.

Nancy R. Cook, Sc.D., is a Professor in the Department of Medicine at the Brigham & Women's Hospital and Harvard Medical School, and Professor of Epidemiology at the Harvard School of Public Health. Dr. Cook is a biostatistician involved in the design, conduct, and analysis of several large randomized trials, including the Women's Health Study, the Physicians' Health Study, and the VITamin D and OmegA-3 TriaL (VITAL). She leads the Trials of Hypertension Prevention (TOHP) Follow-up Study, an observational follow-up of participants in Phases I and II of TOHP. Dr. Cook's methodologic efforts focus on the predictive modeling of observational data and developing risk prediction scores using clinical biomarkers. She was a member of the National Academy of Sciences, Engineering, and Medicine's

Committee on the Consequences of Sodium Reduction in Populations. She received her M.S. and Sc.D. from the Harvard School of Public Health.

Sharon M. Donovan, Ph.D., R.D., is Professor and Melissa M. Noel Endowed Chair in the Department of Food Science and Human Nutrition at the University of Illinois at Urbana-Champaign. Her research focuses on pediatric nutrition, with an emphasis on optimization of neonatal intestinal development. She compares the biological effects of human milk and infant formulas on intestinal function in human infants and neonatal piglets and in various models of intestinal disease. Dr. Donovan is actively involved in several professional societies and served as the President of the American Society for Nutrition (2011-2012). She is the recipient of several awards in recognition of her research, including the Mead Johnson Award and the Norman A. Kretchmer Award from the American Society for Nutrition. She is currently a member of the National Academies of Sciences, Engineering, and Medicine's Food and Nutrition Board. Dr. Donovan received her B.S. and Ph.D. in Nutrition from the University of California, Davis, and completed a post-doctoral fellowship in Pediatric Endocrinology at the Stanford University School of Medicine.

Stephen J. Galli, M.D., was chair of the Department of Pathology (1999-2016), and since 1999 has been the Mary Hewitt Loveless, M.D. Professor, and Professor of Pathology and of Microbiology and Immunology at the Stanford University School of Medicine. He also was the Co-Director of the Stanford Center for Genomics and Personalized Medicine from 2009-2016. He served on the faculty of Harvard Medical School from 1979 to his arrival at Stanford. Dr. Galli's research has focused on the development and function of mast cells and basophils and the development of new animal models for studying the roles of these cells in health and disease, with particular interests in the roles of these cells in asthma, anaphylaxis, and food allergies, and the roles of mast cells and IgE in innate and acquired host defense against venoms. He is currently principal investigator of a National Institute of Allergy and Immune Diseases (NIAID) Asthma and Allergic Diseases Cooperative Research Center (AADCRC) at Stanford (2013-2018), for a project entitled "Integrated Genomic and Functional Studies of Tolerance Therapy for Peanut Allergy." Dr. Galli served as one of two Co-Chairs of an NIAID Food Allergy Research Expert Panel (2006) and is a member of the National Allergy and Infectious Diseases Council of the NIH (2014-2018). Dr. Galli was a member of the National Research Council committee that wrote the report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Dr. Galli was elected to the Collegium Internationale Allergologicum (serving as president from 2010-2014) and the National Academy of Medicine. He

also is a foreign member of the *Accademia Nazionale dei Lincei* (National Academy of the Lynxes) in Rome. Dr. Galli received a MERIT Award from the NIAID/NIH (1995), Scientific Achievement Awards from the International Association of Allergy & Clinical Immunology (1997) and the World Allergy Organization (2011), the Rous-Whipple Award of the American Society for Investigative Pathology (2014), and the Karl Landsteiner Medal of the Austrian Society of Allergology and Immunology (2014). Dr. Galli received an M.D. from Harvard Medical School, and completed a residency in Anatomic Pathology at Massachusetts General Hospital.

Bernard Guyer, M.D., M.P.H., is the Zanvyl Krieger Professor of Children's Health, Emeritus, at the Johns Hopkins Bloomberg School of Public Health in Baltimore. A physician trained in both pediatrics and preventive medicine, Dr. Guyer's 40-year career in public health has been devoted to advancing the health of mothers, children, and families worldwide. Retired in 2011, he continues to be actively involved in the Women's and Children's Health Policy Center at the Bloomberg School of Public Health, where he lectures, teaches, and advises students and faculty. He is a member of the National Academy of Medicine and chaired the National Academy of Sciences, Engineering, and Medicine's Board on Children, Youth, and Families (2007-2013). Dr. Guyer received his B.S. from Antioch College, his M.D. from the University of Rochester School of Medicine, and his M.P.H. from the Harvard School of Public Health.

Gideon Lack, M.B.B.Ch., is Head of the Children's Allergy Service at Guy's and St. Thomas' National Health Service Foundation Trust, Professor of Paediatric Allergy and Head of Department of Paediatric Allergy at King's College London. His research has focused on severe childhood asthma, peanut allergy, and new strategies to prevent and treat food allergies, eczema, asthma, and hay fever in children and adults. His clinical expertise includes allergic asthma, anaphylaxis, and desensitizing vaccines to treat hay fever and other allergies. Dr. Lack is principal investigator of a current randomized controlled clinical trial designed to determine the best strategy to prevent peanut allergy in young children, the LEAP-On (Learning Early About Peanut Allergy) study and principal investigator of the EAT (Enquiring About Tolerance) study. He is a member of the British Medical Association, the British Society of Allergy and Clinical Immunology, the European Academy of Allergy & Clinical Immunology, the Medical Research Council Asthma UK Centre in Allergic Mechanisms of Asthma, and the Collegium Internationale Allergolicum. He also is a Fellow of the Royal College of Paediatrics and Child Health. Dr. Lack obtained his medical degree from the University of Oxford Medical School and his specialization in Allergy

and Immunology from the National Jewish Centre for Immunology and Respiratory Medicine in Denver, Colorado.

Ann S. Masten, Ph.D., LP, is Regents Professor and Irving B. Harris Professor of Child Development in the Institute of Child Development at the University of Minnesota. Dr. Masten's research focuses on understanding processes that promote competence and prevent problems in human development, with a focus on adaptive processes and pathways, developmental tasks and cascades, and resilience in the context of high cumulative risk, adversity, and trauma. She directs the Project Competence studies of risk and resilience, including studies of normative populations and high-risk young people exposed to war, natural disasters, poverty, homelessness, and migration. Dr. Masten co-chairs the Forum on Investing in Young Children Globally and serves on the Board of Children, Youth, and Families for the National Academies of Sciences, Engineering, and Medicine. She is a member of the U.S. National Committee of Psychology, a past-president of the Society for Research in Child Development, and recipient of the Bronfenbrenner Award for Lifetime Contributions to Developmental Psychology in the Service of Science and Society from the American Psychological Association. Her publications include the 2014 book *Ordinary Magic: Resilience in Development* and numerous empirical articles. She completed her Ph.D. in psychology at the University of Minnesota and her clinical psychology internship at the University of California, Los Angeles.

Jose M. Ordovas, Ph.D., is Professor of Nutrition at the Friedman School of Nutrition Science and Policy, Professor of Genetics at the Sackler School of Graduate Biomedical Sciences at Tufts University and Senior Scientist at the U.S. Department of Agriculture (USDA) Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts, where he also is the Director of the Nutrition and Genomics Laboratory. He is a Senior Collaborating Scientist at the Centro Nacional de Investigaciones Cardiovasculares and Instituto Madrileño de Estudios Avanzados en Alimentación (IMDEA), both in Madrid, Spain. Dr. Ordovas's major research interests focus on the genetic factors predisposing to cardiovascular disease and obesity and their interaction with the environment and behavioral factors, with special emphasis on diet. Throughout his career, Dr. Ordovas has received multiple honors for his scientific achievements, including the USDA Secretary's Award, the Centrum American Nutrition Society Award, the Mary Swartz Award from the Dietetic Association, the Garry-Labbe Award from the American Association for Clinical Chemistry, the Francisco Grande Memorial Lecture for Excellence in Nutrition Research, The Rafael del Pino Foundation Lecture, the Turkish Genetics Society Award, the Jaén Paraíso Interior and Asociación Española de Municipalidades del

Olivo (AEMO) awards for his contributions to the diffusion of the Mediterranean diet and the olive oil, the Good Cholesterol award from Aviles and the Danone Foundation Award for achievements in Nutrition Research, the Gold Medal of the Spanish Society of Cardiology, and the Francisco Grande Award from the Fundacion Dieta Mediterranea. He has been awarded an honorary degree in Medicine from the University of Cordoba in Spain and the title of Member of the Royal Academies of Sciences, Medicine, Nutrition and Pharmacy, all of them in Spain. Dr. Ordovas serves on multiple editorial boards and is active with multiple international peer review and steering committees. He served on the National Academy of Sciences, Engineering, and Medicine's Food and Nutrition Board (2005-2011). Dr. Ordovas was educated in Spain at the University of Zaragoza where he completed his undergraduate work in chemistry and received his doctorate in human lipoprotein metabolism. He did postdoctoral work at the Massachusetts Institute of Technology, Harvard, and Tufts.

Hugh A. Sampson, M.D., is the Kurt Hirschhorn, M.D. and Children's Center Foundation Professor of Pediatrics and the Director of the Jaffe Food Allergy Institute at Mount Sinai's Icahn School of Medicine. Dr. Sampson's research interests have focused on food allergic disorders, and now include work on the pathogenesis of food-induced anaphylaxis, characterization of allergenic food proteins and their processing by the immune system, genetics of food allergy, development of novel diagnostic tests, and mechanisms of immunotherapeutic strategies for treating food allergies, including basic studies and clinical trials in oral, sublingual, and epicutaneous immunotherapy and the potential use of biologics, such as anti-IgE and anti-cytokine monoclonal antibodies. Dr. Sampson is past chair of the Section on Allergy & Immunology of the American Academy of Pediatrics and the past-president of the American Academy of Allergy, Asthma & Immunology. He has served on several editorial boards, including 20 years on the *Journal of Allergy and Clinical Immunology,* and as Chair of the Medical Advisory Board for *Food Allergy & Anaphylaxis Network/Food Allergy Research and Education* for 25 years. He also has served as a Director of the American Board of Allergy and Immunology. Dr. Sampson is a member of the National Academy of Medicine. He received his M.D. from the University at Buffalo, the State University of New York.

Scott H. Sicherer, M.D., is the Elliot and Roslyn Jaffe Professor of Allergy, Immunology and Pediatrics at the Icahn School of Medicine at Mount Sinai, Chief of the Division of Pediatric Allergy and Immunology, and Medical Director of Mount Sinai's Clinical Research Unit. His research interests include the following aspects of food allergy: natural history, gastrointestinal manifestations, epidemiology, psychosocial and quality of life issues,

modalities to educate physicians and parents, and treatment modalities (including novel therapies). He is a co-author of three Practice Parameters (two on food allergy and one on diagnostic testing), and participated as a member of the Coordinating Committee for the NIAID/NIH-supported food allergy Guidelines. He is also a co-author of four American Academy of Pediatrics (AAP) Clinical Reports covering allergy prevention, diagnostics, use of epinephrine for anaphylaxis, and school issues for management of food allergy. Dr. Sicherer was the AAP representative for drafting the Centers for Disease Control and Prevention's guidelines for managing food allergies in schools. He is past chair of the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology, the board of directors of the American Board of Allergy and Immunology, and the Section on Allergy and Immunology of the AAP. He is associate editor of *The Journal of Allergy and Immunology, In Practice*. Dr. Sicherer received his M.D. from the Johns Hopkins University School of Medicine and his pediatric training, including a chief residency, at Mount Sinai in New York City. He completed a fellowship in allergy and immunology at Johns Hopkins.

Anna Maria Siega-Riz, Ph.D., was the Associate Dean for Academic Affairs and Professor in the Departments of Epidemiology and Nutrition at the Gillings School of Global Public Health, the University of North Carolina (UNC) at Chapel Hill at the start of this report. She is now a Professor in the Departments of Public Health Sciences and Obstetrics and Gynecology at the University of Virginia School of Medicine. She has focused her research on maternal nutritional status, including maternal obesity and gestational weight gain and their effect on the short- and long-term outcomes of the mother and child. She studies dietary patterns among Hispanic adults and children. She was a member of the 2015 Dietary Guidelines Advisory Committee and has served on multiple committees for the National Academy of Sciences, Engineering, and Medicine, examining topics from the WIC (Special Supplemental Nutrition Program for Women, Infants, and Children) food packages to standards for systematic reviews in health care. She currently serves on the advisory council of the National Heart, Lung, and Blood Institute and on the USDA working group preparing for the Dietary Guidance during pregnancy for the 2020 report. Dr. Siega-Riz earned a B.S. in Public Health in Nutrition from the UNC Gillings School of Global Public Health, an M.S. in Food, Nutrition, and Food Service Management from UNC–Greensboro, and a Ph.D. in Nutrition (Minor in Epidemiology) from the UNC Gillings School of Global Public Health.

Stephen L. Taylor, Ph.D., is Co-Founder and Co-Director of the Food Allergy Research and Resource Program, and Professor in the Department

of Food Science and Technology at the University of Nebraska–Lincoln. His research interests involve food allergies and allergy-like illnesses, including the development, evaluation, and improvement of immunochemical methods for the detection of allergens and allergenic foods; the determination of threshold doses for allergenic foods and implementation of risk assessment approaches for allergenic foods; and the effect of food processing on food allergens. Dr. Taylor has served on several committees and was a member of the National Academy of Sciences, Engineering, and Medicine's Food and Nutrition Board (1999-2004). He received his B.S. and M.S. in Food Science and Technology from Oregon State University and his Ph.D. in Biochemistry from the University of California, Davis.

Xiaobin Wang, M.D., M.P.H., Sc.D., is Zanvyl Krieger Professor in Child Health, Director of the Center on the Early Life Origins of Disease, and Professor of Pediatrics at the Johns Hopkins Bloomberg School of Public Health and School of Medicine. In the past 16 years, Dr. Wang has served as the principal investigator in a number of large scale molecular epidemiological studies funded by NIH. She has led a multi-institution, multidisciplinary team to investigate environmental, nutritional, genetic and epigenetic factors during critical developmental windows (preconception, in utero, infancy, and childhood) aiming to elucidate the root causes of high-impact pediatric and adult diseases, including adverse reproductive and pregnancy outcomes, obesity/diabetes/metabolic syndrome, and food allergies. In particular, her team has conducted a series of innovative studies on food allergies and related traits or conditions in three unique study cohorts (the Boston Birth Cohort, Chicago Family Cohort, and Chinese Twin Cohort) and contributed to an improved understanding of the role of genetics, gene–environment interactions, and epigenetics in the development of food allergies. Dr. Wang previously served as a member of the Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Dr. Wang received her M.D. from Peking University (formerly, Beijing Medical University) in Beijing, China, and M.P.H. from the School of Public Health and Tropical Medicine at Tulane University in New Orleans. She also received an Sc.D. degree from the Department of Maternal and Child Health at the Johns Hopkins Bloomberg School of Public Health in Baltimore. She completed a 3-year research fellowship in Environmental Epidemiology at the Harvard School of Public Health and a residency in pediatrics at the Boston University Medical Center.