

Systematic Review of the Relationship Between Early Introduction of Solid Foods to Infants and the Development of Allergic Disease

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Objective: To assess the evidence that early solid feeding (before age 4 months) increases the risk of allergic disease.

Data Sources: MEDLINE, the Cochrane Library, and the Drugs and Pharmacology section of EMBASE with key words "infant," "food," and "allergy."

Study Selection: We found 2719 article citations and reviewed references of relevant articles. We critically evaluated the methods and results of articles that met inclusion criteria. We identified 13 studies that met inclusion criteria. There was only 1 controlled trial.

Data Extraction: Allergic disease.

Data Synthesis: Five studies found a positive association between early solid feeding and eczema, with a per-

sistence of the association for 10 years in 1 study. Four studies found no association. One study found an association between early solid feeding and pollen allergy. We found no strong evidence to support the association between early solid feeding and the development of persistent asthma, persistent food allergy, allergic rhinitis, or animal dander allergy.

Conclusions: Systematic review of available evidence suggests that early solid feeding may increase the risk of eczema. However, there are little data supporting an association between early solid feeding and other allergic conditions. Since many studies had problematic methods, additional controlled trials are needed to help physicians as they advise parents about the allergic risks of early introduction of solids.

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THE AGE WHEN INFANTS ARE introduced to solid foods has varied greatly during the last century, from 1 year of age in the 1900s to a few weeks of age in the 1950s.¹ Currently, the American Academy of Pediatrics,² the World Health Organization,³ and the European Academy of Allergology and Clinical Immunology⁴ recommend avoidance of solid feeding for at least the first 4 months of life, citing studies that have suggested an increased risk of allergy associated with earlier introduction of solids. However, there has been no systematic review of the evidence that early solid feeding increases an infant's risk of allergic disease.

*For editorial comment
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The timing of introduction of solids to infants is an important issue that physicians frequently confront while caring for infants. Counseling parents is further complicated by the fact that, despite recommendations to the contrary, many par-

ents continue to feed their infants solids before the age of 4 months.^{5,6} The 1988-1994 National Health and Nutrition Examination Survey reported that 52% of nonbreastfed infants and 29% of breastfed infants were introduced to infant cereal at 2 to 3 months of age.²

Given that pediatricians are frequently asked for advice on when to start infants on solid foods and, to our knowledge, no systematic synthesis of the literature has been performed, we conducted a systematic review to evaluate the evidence of the effect of early solid feeding of infants on the risk of allergic disease.

METHODS

We searched MEDLINE (from January 1, 1966, through March 1, 2005), the Cochrane Library (as of March 1, 2005), and the Drugs and Pharmacology section of EMBASE (1991 through March 1, 2005) using the key words "infant" and "food" and "allergy" and restricted our search to human studies and English-language publications. We also reviewed the bibliographies of relevant articles to identify additional studies. We used a key-

word search because it was more robust than alternative literature searches using MeSH headings or key words of specific allergic conditions.

We designed this systematic review to follow a number of inclusion and exclusion criteria. We included randomized controlled trials and case-control and cohort studies. We chose to include cohort studies because some, but not all, of these cohort studies have been cited in feeding recommendations.^{2,4} Therefore, given the clinical influence that these cohort studies exert, we felt that they merited evaluation in our review.

We immediately eliminated articles that did not examine the relationship between the introduction of solid foods to infants and the development of any of the following allergic diseases: asthma, eczema, food allergy, pollen allergy, allergic rhinitis, and animal dander allergy. We did not include outcomes that frequently are due to nonallergic causes (such as cough, respiratory illness, or vomiting) in order to avoid type II error. We defined "solid foods" as any food other than breast milk, cow's milk, or formula.

Therefore, studies were included only if they met all of the following criteria: (1) explicit mention of early (at < 4 months of age) introduction of solids, (2) presence of a comparison group for early feeders, (3) absence of additional and simultaneous allergy reduction interventions (such as prenatal maternal diet restriction, environmental allergen avoidance, or additional infant hypoallergenic dietary restrictions), (4) measurement of 1 of the aforementioned clinically defined allergic diseases, and (5) English-language publication.

If a citation could not be excluded based on the title or abstract, then the entire article was reviewed. After articles that clearly did not meet the inclusion criteria were excluded, 2 of us (B.A.T. and C.M.S.) independently evaluated all remaining articles to determine if they met inclusion criteria; another of us (A.E.C.) resolved discrepancies. We did not blind authors to the titles, authors, or journal publication of the articles. We defined duplicate publications as multiple original articles that reported identical outcomes measured on the same population during the same period. For duplicate publications, we included the first published article unless minor differences between publications existed. In this latter case, we included the publication that provided the most information.

RESULTS

LITERATURE SEARCH

Our literature search identified 2719 article titles. Thirty-nine articles required joint review by 3 of us (B.A.T., C.M.S., and A.E.C.). None of these 39 articles was a randomized controlled trial. We found 2 sets (4 articles) of duplicate publications.⁷⁻¹⁰

Thirteen studies met inclusion criteria (**Table**). Major reasons for exclusion were (1) no information regarding timing of solid food introduction, (2) multiple simultaneous interventions in addition to timing of solids, (3) attempts to compare groups with confounding differences at baseline, (4) delay of only a select group of solids, (5) comparison groups were not "early" and "late" feeders, and (6) allergic disease was not clinically defined. The references for these excluded articles are available on request.

We also excluded studies in which the intervention consisted of a combined prenatal and postnatal dietary intervention because the methods (control group had neither maternal nor infant dietary restriction) did not permit evalu-

ation of the individual contribution of infant diet to the outcomes.²²⁻²⁴ Additionally, these studies evaluated the effect of delayed, not early, introduction of solid feeding.²²⁻²⁴

We present the studies according to the allergic outcomes reported; as a result, some studies appear multiple times. Furthermore, cohorts are followed up longitudinally and so some have been described in multiple publications. For simplicity, we refer to each follow-up publication for a cohort as a different study.

ECZEMA

Summary

Nine cohort studies evaluated the relationship between solids before the age of 3 to 4 months and eczema.^{7,9,11-17} Five of these studies found a positive association,^{7,11-14} while 4 studies found no association.^{9,15-17} Of these 9 studies, 5 were based on 2 cohorts followed up longitudinally.^{7,9,11,12,14}

Studies Finding a Positive Association Between Early Introduction of Solid Foods and Eczema

Two studies followed up the same birth cohort of 135 Finnish infants of atopic parent(s), evaluating them for eczema at 1 and 5 years of age.^{9,14} Sixty-five mothers initiated solid foods at 3 months of age (against protocol), but none introduced cow's milk before 6 months of age. An unreported, but "similar," number of infants in each group avoided fish, citrus fruit, and eggs by their mothers' initiative. Criteria for eczema were either (1) previous diagnosis by a physician and eczema noted during an examination by the author (a physician) or (2) eczema on examination at the 1- and 5-year study evaluations. No information on the blinding of the examining author was provided.

By 1 year of age, 24% of these Finnish infants were diagnosed with eczema: 14% of breastfed infants vs 35% of solid-fed infants ($P < .01$).¹⁴ However, by 5 years of age, 24% of both feeding groups had eczema.⁹ Although these cohort studies suggest that the association between early feeding of solids to infants of atopic parent(s) and eczema wanes by 5 years of age, these results merit cautious interpretation because 17% of participants were lost to follow-up.

Forsyth et al¹³ examined whether introduction of solid foods at a specific time before 3 months of age was associated with eczema in a birth cohort of 671 Scottish infants. The rate of eczema (adjusted for maternal age, social class, type of milk feed, and maternal history of allergic disease) during 1 to 2 years of age was significantly higher among infants introduced to solids at 8 to 12 weeks of age compared with other ages (<8 weeks, 5.4%; 8-12 weeks, 17%; >12 weeks, 8.3%; $P < .05$).

Three studies followed up a birth cohort during the Christchurch Child Development Study in New Zealand^{7,11,12} for 10 years. Since compliance with maternal diaries was only 61% by age 2 years, maternal recall and physicians' records provided the missing information. At age 2 years, eczema rates were significantly higher in infants fed solids before 4 months of age: before 4 months

Table. Characteristics of Included Studies*

Disease	No. of Subjects	Exclusive to Subjects With Atopic Family History	Age at Study Conclusion	Disease Risk
Eczema				
Fergusson et al ⁷	1265	No	10 y	Increased
Fergusson et al ¹¹	1265	No	2 y	Increased
Fergusson et al ¹²	1265	No	3 y	Increased
Forsyth et al ¹³	671	No	2 y	Increased
Kajosaari and Saarinen ¹⁴	135	Yes	1 y	Increased
Kajosaari ⁹	135	Yes	5 y	No difference
Moore et al ¹⁵	525†	Yes	1 y	No difference
Van Asperen et al ¹⁶	79	Yes	16-20 mo	No difference
Zutavern et al ¹⁷	642	No	5.5 y	No difference
Asthma				
Armentia et al ¹⁸	500‡	No	41.5 y ± 18.5§	Increased
Fergusson et al ¹⁹	1265	No	4 y	No difference
Kajosaari ⁹	135	Yes	5 y	No difference
Wheezing				
Forsyth et al ¹³	671	No	2 y	No difference
Van Asperen et al ¹⁶	79	Yes	16-20 mo	No difference
Wilson et al ²⁰	545	No	7.3 y (6.1-9.9)	Increased
Zutavern et al ¹⁷	642	No	5.5 y	No difference
Food allergy				
Kajosaari and Saarinen ¹⁴	135	Yes	1 y	Increased
Kajosaari ⁹	135	Yes	5 y	No difference
Allergic rhinitis				
Van Asperen et al ¹⁶	79	Yes	16-20 mo	No difference
Pollen allergy				
Kajosaari ⁹	135	Yes	5 y	Increased
Animal dander allergy				
Kajosaari ⁹	135	Yes	5 y	No difference
Allergic disease				
Parihar et al ²¹	425¶	No	0-2 y	Increased

*All studies are cohort design unless otherwise noted.

†Designed as randomized-controlled trial, analyzed as a cohort.

‡Case-control design.

§Mean age ± SD.

||Mean age (range).

¶Cross-sectional design.

of age, 17.8% vs after 4 months of age, 12.6% ($P < .05$).¹¹ Furthermore, the association was found to be dose dependent; rates of eczema increased with the number of different food types given: 0 foods, 13.4% had eczema; 1 to 2 types of foods, 17%; 3 to 4 types, 17.4%; and more than 5 types, 33.3% ($P < .05$).¹¹ However, this study found no association between eczema and either the specific types of foods or the estimated mean volume of solids. Parental history of atopy had an independent and stronger influence on rates of childhood eczema than early solid feeding (23.7% of children with atopic parents vs 13.0% of those without; $P < .001$).¹¹ No significant interaction was found between parental history, early solid feeding, and rate of eczema.

At 3 years of age, the positive association between early solid feeding and eczema persisted in the Christchurch cohort.¹² After adjusting for parental history and type of milk diet, the cumulative rates of eczema were found to be 16.6% for those offered no solids before 4 months, 20.5% for those offered 1 to 3 types of solid foods, and 25% for those offered 4 or more types ($P < .01$).¹²

At 10 years of age, the authors found a positive effect of early solids on recurrent eczema in the Christchurch

cohort.⁷ The authors defined recurrent eczema as having 3 previous physician visits for eczema, having at least 3 years of eczema symptoms, and receiving regular medications for eczema.⁷ Eighty-four percent of the original cohort was followed up for 10 years. Although the overall prevalence of recurrent eczema decreased, the adjusted prevalence increased significantly with increasing types of solid foods introduced: 5.4% for no solids, 7.5% for 1 to 3 solids, and 12.7% for 4 or more solids ($P < .05$).⁷ However, no particular food type was significantly associated with eczema.⁷ In summary, the strengths of the Christchurch cohort's findings are the length of follow-up and the dose-dependent nature of the relationship.

Studies Finding No Association Between Early Introduction of Solid Foods and Eczema

In addition to the 5-year follow-up study of the Finnish infant cohort,⁹ 3 studies found no association between early solid feeding and eczema.¹⁵⁻¹⁷ After studying 475 of 525 infants in a British birth cohort with a parental history of eczema or asthma, Moore et al¹⁵ found no sig-

nificant association between introduction of solids before 3 months of age and eczema (diagnosed through interval physical examinations) by 3, 6, or 12 months of age. Although initially designed as a randomized controlled trial to promote exclusive breastfeeding, poor compliance led to analysis of the study as a cohort. Multivariate analysis controlling for type of milk, early introduction of solids, social class, and family history of atopy found that only severity of atopic family history and type of milk independently predicted eczema at age 3 months (both $P < .01$) and severity of family history alone significantly predicted eczema at 6 and 12 months of age ($P < .02$). However, problematic study design warrants cautious interpretation of these results.

Van Asperen et al¹⁶ studied a birth cohort of 79 Australian infants with a parental history of atopic disease (confirmed by skin prick tests) and found no significant association between eczema and solid feeding before 4 months of age (<4 months of age, 48.5%; >4 months of age, 47.8%). However, this study had the following problems: (1) incomplete follow-up (100% retention at 16 months, 75% at 20 months), (2) small sample size, (3) no indication of a blinded determination of eczema status, and (4) no indication that results were adjusted for cow's milk intake.

Zutavern et al¹⁷ evaluated 604 of a birth cohort of 642 British children at 5.5 years of age and, in a multivariate analysis, found none of the early feeding exposures (rice by 3 months of age; fruits, vegetables, and cereals by 4 months of age; or any solid food by 3 months of age) to be significantly associated with development of eczema at 5.5 years of life. Unlike the previous study by Ferguson et al,¹¹ this study found no significant association between the numbers of food types introduced before age 4 months and eczema.

ASTHMA OR WHEEZING

Summary

One case-control and 6 cohort studies examined the association between early solid feeding and the development of asthma and/or wheezing.^{9,13,16-20} The case-control study found a positive association with asthma.¹⁸ Three cohort studies found no significant association with asthma by 4,¹⁹ 5,⁹ or 7²⁰ years of life, respectively. Three cohort studies found no significant association with episodes of wheezing,^{13,16,17} while 1 found a positive association.²⁰

Studies Finding a Positive Association Between Early Introduction of Solid Foods and Asthma

The case-control study compared 250 cases of grass-pollen asthma (identified by allergy and pulmonary testing) with 250 asthma-free controls from an allergy clinic.¹⁸ Grass pollen was the major aeroallergen responsible for allergic asthma in the geographic area; patients not native to the area were excluded. Cases and controls were not age matched (Table). Recall of exposure to cereals before 3 months of age was associated with grass-pollen asthma in an adjusted model (adjusted for mite asthma, animal asthma, food asthma, sex, and urban origin of pa-

tients; odds ratio, 6.24; $P = .71$). However, these findings should be interpreted cautiously because it is unclear whether the results were adjusted for family history and the exposure status is susceptible to recall bias.

Studies Finding No Association Between Early Introduction of Solid Foods and Asthma

A longitudinal evaluation of the Christchurch cohort found that introduction to solids before 4 months of age was not associated with the cumulative rate of asthma or "wheezy bronchitis" by 4 years of age (solid fed, 7.2% vs nonsolid fed, 6.2%) and parental asthma was the only factor significantly related to variation in asthma rates.¹⁹ Authors included "wheezy bronchitis" because it accounted for only 10 of the 77 "asthmatic" children¹⁹ and differentiating it from asthma is difficult at a young age.

Among the 135 Finnish infants of atopic parent(s), Kajosaari⁹ found no association between solid feeding at 3 months of age and asthma at 5 years of age. At 5 years of age, only 51 of 65 exclusively breastfed children and 62 of 70 children fed early solids were available for follow-up.⁹

Study Finding No Association Between Early Introduction of Solid Foods and Asthma But a Positive Association With Wheezing

Wilson et al²⁰ retrospectively evaluated a subset (81%) of the birth cohort of Scottish infants at a mean age of 7.3 years (range, 6.1-9.9 years) and found an increased risk of wheezing, but not asthma, with introduction of solids before age 15 weeks. The outcome of wheeze required either a history of persistent wheeze since birth or during the previous 12 months. The outcome of asthma required either a previous physician diagnosis or current treatment with asthma medications. After adjustment for parental history of atopy, sex, and social class, the estimated probability of ever wheezing was significantly higher for those introduced to solids before 15 weeks of age (21.0% [95% confidence interval, 19.9%-21.1%]) compared with after (9.7% [95% confidence interval, 8.6%-10.8%]; $P < .01$). Using the cutoff of 15 weeks of age, the probability of ever having asthma was not significantly associated with the timing of solid feeding.

Studies Finding No Association Between Early Introduction of Solid Foods and Wheezing

Forsyth et al¹³ studied the same Scottish birth cohort until 2 years of age and found no relationship between the timing of solid foods introduction and episodes of wheezing during various age intervals (adjusted for maternal age, social class, type of milk feed, and maternal history of allergic disease).

In the birth cohort of 79 British infants of atopic parent(s), Van Asperen et al¹⁶ found no significant association between introduction of solids before 4 months of age and wheezing (unadjusted for parental smoking or introduction of cow's milk).

Zutavern et al¹⁷ evaluated about 600 of 642 children in a British birth cohort and found no association between early solid feeding and "transient" and "pre-

school wheezing.” The authors defined “transient wheezing” as wheezing in the first 2 years of life only and “preschool wheezing” as either wheezing from age 1 to 4 years or wheezing during the fifth year of life with a history of at least 1 previous wheezing episode. Multivariate analysis revealed (1) no association between timing of solids (rice before age 3 months; fruits, vegetables, and cereals by 4 months of age; and any solid food by 3 months of age) and transient or preschool wheezing¹⁷ and (2) no significant association between the number of food types introduced before 4 months of age and wheezing.

FOOD ALLERGY

Longitudinal follow-up of the birth cohort of 135 Finnish infants of atopic parent(s) found early solid feeding to be significantly associated with food allergy by 1 year of age.¹⁴ Food allergy was defined as a “history of skin rash or heavy vomiting after ingestion of a food.” Allergy to fish, eggs, or citrus fruit prompted additional evaluation with an “elimination/challenge/rechallenge” protocol. At 1 year of age, infants who had received solids at 3 months of age were significantly more likely to have a history of food allergy compared with exclusively breastfed infants (37% vs 7%; $P < .001$).¹⁴ Even when considering a history of food allergy to either fish, eggs, or citrus fruit individually, solid-fed infants were still more likely to have a positive history of allergy (26% vs 7%; $P < .01$).¹⁴ However, evaluation of these food allergies with an elimination/challenge/rechallenge protocol decreased the proportion of food allergies in the solid-fed group to about 12%, and differences between the groups were no longer statistically significant.¹⁴ This finding raises the concern that some nonallergic children were misclassified as allergic. When the criteria for food allergy were modified to include a positive clinical history and positive skin prick tests (fish, milk, wheat), at 5 years of age, there was no difference in allergy to any food between the 2 feeding groups.⁹

ALLERGIC RHINITIS

In the birth cohort of 79 British infants of atopic parent(s), Van Asperen et al¹⁶ found no association between early solid feeding (<4 months of age) and rhinitis by 16 to 20 months of age (no solids, 51.5%; solids, 58.6%; $P > .05$). Rhinitis was defined as “any history of nasal discharge and/or blockage occurring continuously for at least 4 weeks and excluding obvious infective rhinitis.”^{16(p526)}

POLLEN ALLERGY

In the study of 135 Finnish infants of atopic parent(s), Kajosaari⁹ found that exclusively breastfed infants were significantly less likely to have pollen allergy at 5 years of age than infants introduced to solid foods at 3 months of age (no solids, 20%; solids <3 months of age, 37%; $P = .04$). The investigators defined pollen allergy as positive skin prick test results to birch, elm, timothy, or ragweed that matched a clinical history of pollen allergy.

ANIMAL DANDER ALLERGY

Kajosaari⁹ found no association between cumulative incidence of animal dander allergy and solid feeding at 3 months of age. Animal dander allergy was determined by clinical history and positive skin prick test results to dog or cat epithelium.

ANY ALLERGIC DISEASE

Using a cross-sectional study design, Parihar et al²¹ found introduction of solids before the age of 3 months to be significantly associated with “allergic disease” in children before the age of 2 years at a pediatric clinic in Chandigarh, India. A child with 1 or more major allergic conditions (allergic asthma, rhinitis, atopic dermatitis, and urticaria) was categorized as allergic. No mean age of the study population was provided, although the 2 groups (with and without allergic disease) were reportedly “well-matched” for age. However, the 2 groups differed with respect to family history of allergy and age of introduction of cow’s milk.

Parihar et al found that more children with allergic disease had been given semisolids before 3 months of age: 9.4% of children with allergies vs 1.4% of children without ($P < .01$). Significantly more children with allergies than those without had been fed cereals before 4 months of age and had received more solids during 4 to 6 months of life, although the authors didn’t provide confidence intervals. However, study results should be interpreted cautiously since it is unclear whether the results were adjusted for family history of allergy and age at introduction of cow’s milk.

COMMENT

The evidence that introduction of solid food to infants before 4 months of age increases the risk of allergic disease is conflicting and inconsistent. In general, there is insufficient evidence to suggest that, on its own, the early introduction of solids to infants is associated with an increased risk of asthma, food allergy, allergic rhinitis, or animal allergies. However, based on the current literature, we can make limited and cautious conclusions. There is a consistent association between the persistence of eczema and the introduction of solid foods before age 4 months that is supported by long-term follow-up studies and the dose-dependent nature of the association. The results of 1 cohort study suggest a relationship between pollen allergy and early solid feeding in children with an atopic family history.

Unfortunately, many of the reviewed studies lacked a rigorous design and so were susceptible to multiple biases. For example, there was only 1 controlled trial (non-randomized). While it is understandably difficult to evaluate the relationship of interest with a randomized controlled design, such a design would account for unmeasured and unknown confounders associated with early solid feeding. Moreover, some of the studies presented in this review failed to adjust for important known confounders, such as milk type used or parental history of atopy.

Exposure ascertainment was another important source of bias in identified studies. For example, some studies introduced recall bias by retrospectively collecting data

on feeding. Most studies failed to systematically define the quality and quantity of solid foods that were introduced. This latter issue is important given the finding of Fergusson et al¹¹ of a dose-response relationship between number of food types and eczema.

Some study results may have been influenced by outcome misclassification. For example, incidence of some clinical outcomes may vary substantially depending on definitions used. In the study of 135 Finnish infants, when food allergy was evaluated by history in combination with a food challenge protocol instead of by history alone, the proportion of children with food allergy decreased.¹⁴ Finally, lack of blinding to feeding history during study examinations may have led to a biased evaluation of outcome status.

There are a number of limitations to this systematic review that warrant consideration. We only evaluated articles in the English language and perhaps missed relevant studies published in other languages. We did not include studies that evaluated vomiting and/or diarrhea as outcomes because we felt that these were nonspecific symptoms of allergy. As a result, we may have missed a portion of children who had allergic gastrointestinal disorders. Additionally, some studies were based on the same ethnically homogeneous cohort of children^{9,14} and some populations may have different genetic tendencies toward allergy as well as variable local prevalence of certain health outcomes. Finally, the potential for delayed timing of solid food introduction to affect the risk of allergic disease either alone, in concert with additional hypoallergenic interventions (such as prenatal or environmental), or in certain susceptible subgroups are valid concerns. However, evaluation of these factors is beyond the scope of this article.

In summary, we found that the evidence linking early solid feeding of infants and allergic disease is inconsistent and conflicting. We propose that organizations modify their recommendations regarding the relationship between the timing of introduction of solid feeding of infants and allergic disease risk to reflect the evidence presented in this review. Physicians who counsel parents on infant feeding issues should both educate parents that early solids do not confer a nutritional advantage and temper strong parental concerns that feeding small amounts of solids before 4 months of age will inevitably cause their child to develop an allergic condition.

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