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The Introduction of Allergenic Foods and the Development of Reported Wheezing and Eczema in Childhood

The Generation R Study

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Objective: To examine whether the timing of introduction of the allergenic foods cow's milk, hen's egg, peanuts, tree nuts, soy, and gluten is associated with eczema and wheezing in children 4 years of age or younger.

Design: Population-based prospective cohort study from fetal life until young adulthood.

Setting: Rotterdam, the Netherlands, from April 2002 through January 2006.

Participants: A total of 6905 preschool children participating in the Generation R study.

Main Exposure: Timing of introduction of cow's milk, hen's egg, peanuts, tree nuts, soy, and gluten collected by questionnaires at 6 and 12 months of age.

Main Outcome Measures: Information on the outcomes eczema and wheezing were obtained by questions from the age-adapted version of the "International Study of Asthma and Allergies in Childhood" core ques-

tionnaire and questionnaire data on parentally reported physician diagnosis for eczema.

Results: Of 6905 children, wheezing was reported in 31% at age 2 years and in 14% at ages 3 and 4 years. Eczema was reported in 38%, 20%, and 18% of children at the ages of 2, 3, and 4 years, respectively. The introduction of cow's milk, hen's egg, peanuts, tree nuts, soy, and gluten before the age of 6 months was not significantly associated with eczema or wheezing at any age after adjustment for potential confounders ($P > .10$ for all comparisons). The results did not alter after stratification according to the child's history of cow's milk allergy and parental history of atopy.

Conclusion: This study does not support the recommendation for delayed introduction of allergenic foods after age 6 months for the prevention of eczema and wheezing.

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THE PREVALENCE OF ATOPIC DISEASES in children has been increasing over the past few decades¹ and varies throughout the world.² Atopic diseases, including atopic eczema, asthma, allergic rhinitis, and food allergy, are common in childhood and cause a very significant burden.^{3,4} Atopic diseases are complex and multifactorial, involving genetic and environmental factors.⁵ An important environmental factor that may influence the development of atopic diseases is early childhood nutrition. The first year of life includes many transitions in food consumption.⁶ Introduction of complementary feeding is essential for both developmental and nutritional concerns. The timing of complementary feeding is particularly im-

portant given the maturation of the gastrointestinal and renal systems.⁷ Health risks that have been suggested to be associated with early complementary feeding include excessive child weight gain,⁸ increased body mass index,⁹ respiratory illness during childhood,¹⁰ and autoimmune diseases (eg, type 1 diabetes mellitus¹¹ and celiac disease¹²).

Recommendations for the timing of complementary feeding vary. The European Academy of Allergology and Clinical Immunology,¹³ The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN),¹⁴ and the American Association of Pediatrics¹⁵ recommend delaying introduction of solid foods until a child is 4 to 6 months of age. However, the ESPGHAN recommends that

introduction of complementary feeding should not be delayed beyond the age of 6½ months.¹⁴ There is no current convincing evidence that delayed complementary feeding beyond the age of 4 to 6 months is protective for the development of atopic diseases.^{13,15-18} In addition, few studies found early complementary feeding to be associated with an increased risk of atopic disorders such as eczema.^{16,19,20} Some studies even found an increased risk for atopic disease in relation to delayed food introduction.^{21,22}

It has been suggested that a family history of atopic disease is associated with a significantly increased risk for development of atopic disease in childhood.²³ However, avoidance or delayed introduction of potentially allergenic foods has not been convincingly shown to reduce allergies, either in children considered at risk for the development of allergy or in those not considered to be at risk.¹⁴ Muraro et al²³ found that most children who develop atopic disease, particularly recurrent wheezing and asthma, during early childhood do not belong to high-risk groups for development of atopic disease.

Whether delayed introduction of allergenic foods could decrease the risk of atopic diseases is controversial. Therefore, our aim was to examine whether the timing of introduction of the following allergenic foods—cow's milk, hen's egg, peanuts, tree nuts, soy and gluten—is associated with eczema and wheezing in children up to 4 years of age. In addition, we aimed to assess whether the association differs between children with and those without a history of cow's milk allergy in the first year of life and those children with and those without a parental history of atopy.

METHODS

PARTICIPANTS AND STUDY DESIGN

This study was embedded in the Generation R study, a population-based prospective cohort study from fetal life until young adulthood, and has been described in detail previously.^{24,25} Consent for postnatal follow-up was provided by a total of 7893 mothers with a delivery date between April 2002 and January 2006. The study was approved by the medical ethical review board of the Erasmus Medical Center, Rotterdam, the Netherlands.

ECZEMA AND WHEEZING

For children aged 2, 3, and 4 years, questions from the age-adapted version of the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires on asthma and eczema were used. These questions were made suitable for younger children and have been used in several articles on this cohort.²⁶ Information was also available from questionnaire data on parentally reported physician diagnosis for eczema. Questionnaire response rates were 69%, 64%, and 63% at the ages of 2, 3, and 4 years, respectively. Eczema and wheezing were defined as present or absent in the child's second, third, and fourth years of life.

INTRODUCTION OF ALLERGENIC FOODS AND GLUTEN IN THE FIRST YEAR OF LIFE

When the child was 6 and 12 months old, parents were asked by questionnaire about the child's age at first introduction of cow's

milk (4855 children), hen's egg (4505 children), peanuts (4478 children), tree nuts (4431 children), soy (4658 children), and gluten (4734 children) in their infant's diet. Also at these times, parents were asked to complete a short food-frequency questionnaire about food products frequently consumed, according to a Dutch food consumption survey in children.²⁷ Subsequently, the reported food products introduced were cross-checked with the short food-frequency questionnaires. For example, if, when their child was 12 months old, the parents indicated that they had never introduced peanuts into their child's diet, yet when their child was 6 months old, the parents had indicated that their child had consumed peanut butter more than once, the introduction of this allergen was considered to be at or before 6 months of age. In addition, the first introductions of cow's milk and soy were also cross-checked with the type of bottle feeding (soy-based or based on fully hydrolyzed whey protein or not) used at the ages of 6 and 12 months.

COVARIATES

Variables possibly related to eczema and wheezing, such as sex, gestational age, and birth weight, were obtained from obstetric records assessed in midwife practices and hospital registries.²³ In addition, potential confounders and mediators were accessed through a combination of prenatal and postnatal questionnaires completed by both parents and included information on race/ethnicity; maternal socioeconomic status (SES); maternal smoking; parity; and family history of asthma, eczema, hay fever or allergic rhinitis, and allergy to house dust. The race/ethnicity of the child was defined as follows: if both parents were born in the Netherlands, the race/ethnicity of the child was defined as Dutch; if one of the parents was born in a country other than the Netherlands, that country applied; if parents were born in countries other than the Netherlands, the country of the mother applied.²⁸ Maternal SES was defined according to educational level as follows: low level was defined as no education, primary school, or less than 3 years of secondary school; midlevel as more than 3 years of secondary school, higher vocational training, or a bachelor's degree; and high level as an academic education.²⁹ Postnatal questionnaires completed by the mothers at 6, 12, and 24 months included information on the general health of the child (ie, medication use, comorbidity), day care attendance, and the consumption of food products. Data on breastfeeding were collected by delivery reports and postnatal questionnaires at the ages of 2, 6, and 12 months. Breastfeeding was classified as (1) never; (2) exclusively for 6 months; (3) exclusively for 4 months and partially at 6 months; (4) exclusively for 4 months, with no breastfeeding at 6 months; (5) partially for 6 months; or (6) partially for 4 months, with no breastfeeding at 6 months. In addition, information on the presence of cow's milk allergy was obtained by questionnaire at the ages of 6 and 12 months by asking parents whether their child had been seen by a physician because of cow's milk allergy. When the child was 24 months old, parents were asked about the number of physician-attended respiratory tract infections acquired by the child and use of antibiotics during the past 12 months. Information on gastroenteritis was obtained by asking parents about their child's bowel movements and defined as any episode of diarrhea accompanied by fever. Body mass index (BMI) at 24 months was calculated from the child's weight and height available from child health centers. Being overweight was defined according to age- and sex-dependent BMI thresholds for young children from Cole et al.³⁰

POPULATION FOR ANALYSES

To avoid the influence of metabolic disorders and clustering, the following children were excluded in the analyses for this

study: twinborn (238 children); siblings within the Generation R cohort (343 children); those with presence of a congenital heart condition (47 children); those with anemia between the ages of 12 and 24 months (58 children); and those with growth retardation, defined as height for age minus 2 standard deviations based on the Netherlands growth curves of children 12 to 24 months old (163 children).³¹ The presence of a congenital heart condition and anemia were defined according to parentally reported physician diagnosis obtained by questionnaire. Children whose parents did not provide informed consent for the use of questionnaire data were also excluded (135 children). To prevent bias associated with missing data, variables with missing values were multiple imputed (5 imputations) based on the correlation between the variable with missing values with other patient characteristics^{32,33} according to the Markov Chain Monte Carlo method. Consequently, data for 6905 children were available after multiple imputation for statistical analyses.

STATISTICAL ANALYSIS

Logistic regression analyses were performed with eczema and wheezing at ages 2, 3, and 4 years separately as dependent variables. Introductions of allergenic foods in the first year of life were analyzed as independent variables and adjusted for potential confounders and mediators (ie, sex, maternal SES, race/ethnicity, maternal smoking, gestational age, birth weight, parity, breastfeeding, use of any antibiotics, day care attendance, gastroenteritis, number of respiratory tract infections, overweight, parental history of atopy). The selection of potential confounders and mediators was performed by the alteration in odds ratios (ORs). The potential confounder or mediator was kept in the multivariate model in case of an alteration of 10% or greater in OR. To assess whether the association between the timing of allergenic food introduction and wheezing and eczema was different among children with a history of cow's milk allergy and parental history of atopy vs those without, statistical interaction was evaluated by adding the product term of the independent variable and subgroup (independent variable $\times$ subgroup) as covariate to the univariate model. Stratified analyses by history of cow's milk allergy or parental history of atopy were performed when the statistical interaction was significant (eTables 1-4; <http://www.archpediatrics.com>). The pooled results of the 5 imputed data sets are reported in this article as ORs and 95% confidence intervals (CIs). $P < .05$ was considered as statistically significant. The statistical analyses were performed using SPSS software (version 17.0 for Windows; SPSS Inc, Chicago, Illinois).

RESULTS

STUDY POPULATION

Maternal and child characteristics of the study population are presented in **Table 1**. Of 6905 children, 31% had reported wheezing at age 2 years and 14% at ages 3 and 4 years. Eczema was reported in 38%, 20%, and 18% of children at the ages of 2, 3, and 4 years, respectively.

INTRODUCTION OF ALLERGENIC FOODS AND GLUTEN

The introduction of tree nuts before the age of 6 months was significantly associated with wheezing at 2 years of age

Table 1. Maternal and Child Characteristics in 6905 Preschool Children Participating in the Generation R Study

Characteristics	No. (%)
Mother	
Socioeconomic status	
Low	766 (11)
Mid	4746 (69)
High	1393 (20)
Ever smoked during pregnancy	
No	5064 (73)
Yes	1841 (27)
Parents with a history of atopy	3274 (47)
Parity	2899 (42)
Child	
Male sex	3496 (51)
Race/ethnicity	
Dutch/Western	4380 (63)
Non-Western	2525 (37)
Gestational age at delivery, mean (SD), mo	39.9 (1.6)
Birth weight, mean (SD), g	3431 (540)
History of cow's milk allergy in first year of life	846 (12)
Breastfeeding	
Never	781 (11)
6 mo exclusive	345 (5)
4 mo exclusive, partially at 6 mo	1296 (19)
4 mo exclusive, no breastfeeding at 6 mo	357 (5)
6 mo partially	795 (12)
4 mo partially, no breastfeeding at 6 mo	3331 (48)
Use of any antibiotics ^a	2839 (41)
Overweight ^a	1755 (25)
Respiratory tract infections, No. ^a	
0	3322 (48)
1-3 times	2369 (34)
≥ 4 times	1213 (18)
Day care attendance ^a	5137 (74)
Gastroenteritis ^a	4599 (67)

^aFrom ages 12 to 24 months.

(OR, 2.69; 95% CI, 1.25-5.73). However, this association was explained by sex, maternal SES, race/ethnicity, maternal smoking, gestational age, birth weight, parity, breastfeeding, use of any antibiotics, day care attendance, gastroenteritis, number of respiratory tract infections, overweight, and parental history of atopy (**Table 2**). No significant association was found between early introduction to tree nuts and wheezing at age 3 years (OR, 1.24; 95% CI, 0.70-2.20) or 4 years (OR, 1.30; 95% CI, 0.79-2.13) (Table 2). In addition, no significant association was found between early introduction to tree nuts and eczema up to age 4 years (**Table 3**). The introduction of cow's milk, hen's egg, peanuts, soy, and gluten to an infant's diet before the age of 6 months was not significantly associated with wheezing (Table 2) or eczema (Table 3) at any age. These results were independent of sex, maternal SES, race/ethnicity, maternal smoking, gestational age, birth weight, parity, breastfeeding, use of any antibiotics, day care attendance, gastroenteritis, number of respiratory tract infections, overweight, and parental history of atopy. Additional adjustment for potential mediator history of cow's milk allergy did not alter the results for wheezing or eczema (data not shown).

Table 2. Association Between the Introduction of Allergenic Foods and Wheezing at Ages 2, 3, and 4 Years in 6905 Preschool Children Participating in the Generation R Study

Allergenic Food Introduced at Age ≤6 mo	Children, No. (%)	Age 2 y		Age 3 y		Age 4 y	
		Univariate Model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a	Univariate Model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a	Univariate Model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a
Cow's milk	4757 (69)	0.83 (0.43-1.57)	0.80 (0.44-1.43)	1.02 (0.84-1.23)	1.02 (0.85-1.22)	0.97 (0.77-1.21)	0.96 (0.77-1.19)
Hen's egg	1466 (21)	1.83 (0.95-3.51)	1.39 (0.84-2.28)	1.26 (0.83-1.91)	1.13 (0.84-1.51)	1.30 (0.99-1.70)	1.11 (0.91-1.34)
Peanuts	1069 (15)	2.16 (0.75-6.13)	1.71 (0.60-4.83)	1.25 (0.81-1.93)	1.14 (0.77-1.66)	1.25 (0.79-1.97)	1.05 (0.69-1.61)
Tree nuts	875 (13)	2.69 (1.25-5.73) ^b	2.41 (0.83-7.00)	1.24 (0.70-2.20)	1.11 (0.68-1.79)	1.30 (0.79-2.13)	1.12 (0.75-1.67)
Soy	2002 (29)	1.73 (0.99-3.01)	1.54 (0.96-2.46)	1.11 (0.80-1.53)	1.05 (0.80-1.38)	1.16 (0.87-1.55)	1.06 (0.84-1.35)
Gluten	3203 (46)	1.30 (0.94-1.79)	1.17 (0.86-1.60)	1.07 (0.86-1.31)	1.02 (0.83-1.26)	1.10 (0.94-1.28)	1.03 (0.87-1.20)

Abbreviations: CI, confidence interval; OR, odds ratio (compared with introduction at age older than 6 months).

^aAdjusted for sex, socioeconomic status of the mother, race/ethnicity, smoking during pregnancy, gestational age at birth, birth weight, parity, breastfeeding, use of any antibiotics from ages 12 to 24 months, day care attendance from ages 12 to 24 months, gastroenteritis from ages 12 to 24 months, number of respiratory tract infections from ages 12 to 24 months, overweight from ages 12 to 24 months, and parental history of atopy.

^b $P = .06$ after adjustment for unequal variances.

Table 3. Association Between the Introduction of Allergenic Foods and Eczema at Ages 2, 3, and 4 Years in 6905 Preschool Children Participating in the Generation R Study

Allergenic Food Introduced at Age ≤6 mo	No. (%)	Age 2 y		Age 3 y		Age 4 y	
		Univariate Model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a	Univariate Model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a	Univariate model, OR (95% CI)	Multivariate Model 1, Adjusted OR (95% CI) ^a
Cow's milk	4757 (69)	0.92 (0.68-1.23)	0.91 (0.67-1.23)	0.88 (0.75-1.03)	0.88 (0.74-1.03)	0.95 (0.77-1.17)	0.95 (0.77-1.15)
Hen's egg	1466 (21)	1.27 (0.52-3.10)	1.10 (0.51-2.32)	0.84 (0.65-1.09)	0.87 (0.69-1.10)	1.11 (0.88-1.39)	1.05 (0.81-1.35)
Peanuts	1069 (15)	1.36 (0.48-3.87)	1.11 (0.34-3.61)	0.95 (0.72-1.26)	0.99 (0.72-1.36)	0.94 (0.70-1.26)	0.87 (0.65-1.16)
Tree nuts	875 (13)	1.64 (0.46-5.85)	1.54 (0.35-6.69)	1.09 (0.72-1.65)	1.16 (0.76-1.76)	1.12 (0.79-1.60)	1.06 (0.72-1.56)
Soy	2002 (29)	1.47 (0.74-2.92)	1.33 (0.72-2.44)	0.92 (0.75-1.14)	0.95 (0.75-1.19)	1.01 (0.82-1.23)	0.97 (0.80-1.17)
Gluten	3203 (46)	0.94 (0.69-1.28)	0.90 (0.71-1.14)	0.88 (0.76-1.02)	0.90 (0.76-1.06)	1.05 (0.85-1.29)	1.02 (0.81-1.27)

Abbreviations: CI, confidence interval; OR, odds ratio (compared with introduction at age older than 6 months).

^aAdjusted for sex, socioeconomic status of the mother, race/ethnicity, smoking during pregnancy, gestational age at birth, birth weight, parity, breastfeeding, use of any antibiotics from ages 12 to 24 months, day care attendance from ages 12 to 24 months, gastroenteritis from ages 12 to 24 months, number of respiratory tract infections from ages 12 to 24 months, overweight from ages 12 to 24 months, and parental history of atopy.

PARENTAL HISTORY OF ATOPY AND INFANT'S HISTORY OF COW'S MILK ALLERGY

A history of cow's milk allergy in the first year of life was more frequently found in children with reported wheezing and eczema than in children without reported wheezing and eczema ($P \leq .05$ for difference in history of cow's milk allergy at the ages of 2, 3, and 4 years). A parental history of atopy was also more frequently found in children with reported wheezing ($P = .24$, $P < .01$, and $P = .11$ for difference in parental history at the ages of 2, 3, and 4 years, respectively) and eczema ($P < .05$ for difference in parental history at the ages of 2, 3, and 4 years) (eTable 1). Although a significant interaction was found with a history of cow's milk allergy for the introduction of peanuts and gluten (eTable 2), no significant association was found after stratification by history of cow's milk allergy (eTable 3). No interaction was found between the timing of introduction of food allergens and parental history of atopy (eTable 4).

COMMENT

This population-based prospective birth cohort study failed to demonstrate that the timing of introduction of allergenic foods (cow's milk, hen's egg, peanuts, tree nuts, soy, and gluten) was associated with eczema and wheezing in children 4 years or younger. The results did not alter after stratification for history of cow's milk allergy or parental history of atopy.

Various current feeding guidelines recommend complementary feeding to be introduced when a child is older than 4 to 6 months.¹³⁻¹⁵ However, there is no current convincing evidence that delayed complementary feeding until a child is older than 4 to 6 months is protective for the development of atopic disease.^{13,15-18} Few previous studies found earlier complementary feeding, before a child is 4 months of age, to be positively associated with atopic diseases as eczema and wheezing.^{10,19,34} In a birth cohort in the Christchurch Child Development Study in New Zealand, eczema rates were found to be significantly higher in infants who were in-

roduced to solid foods before 4 months of age.^{19,34} A study of a cohort of children in Dundee, Scotland, found solid feeding before 15 weeks to be associated with an increased probability of wheezing during childhood.¹⁰ However, these studies did not assess whether a longer delay of complementary feeding, until a child is older than 6 months, had an additional protective effect on eczema and wheezing.

The results of this study are in agreement with the findings of other birth cohort studies. The Influences of Life-style-related Factors on the Immune System and the Development of Allergies in Childhood (LISA) birth cohort study found no evidence supporting a delayed introduction of solid foods beyond age 6 months for the prevention of eczema at age 2 years³⁵ and no evidence supporting a delayed introduction beyond ages 4 or 6 months for the prevention of asthma at age 6 years.¹⁷ Filipiak et al¹⁸ also did not find evidence supporting delayed introduction of solid foods beyond 4 months of age or delayed introduction of the most potentially allergenic solids beyond 6 months for the prevention of eczema. In addition, a birth cohort study in the United Kingdom found no evidence for a protective effect of late introduction for the development of eczema or wheezing at ages 5 to 5 1/2 years.²² Conversely, this last study found a significantly increased risk of eczema in relation to late introduction of the allergenic foods egg and milk. The KOALA birth cohort study²¹ found that a delayed introduction of cow's milk was associated with a higher risk of eczema in the first 2 years of life. The latter association could possibly be explained by reverse causation since parents with a family history of atopy or infants with early symptoms of allergy may delay complementary feeding. Possible distortion by reverse causality has been suggested previously.³⁵

An important strength of this study is the large study population drawn from the general population. Several other studies selected children of atopic parents who are at higher risk of developing atopic diseases, which might have led to selection bias since atopic parents are more likely to introduce allergenic foods later in the infant's diet. An additional strength is the use of multiple imputation for missing data. Consequently, attrition bias was of minimum concern.^{32,33}

Some limitations of the study have to be considered in the interpretation of the results. Information on the timing of allergenic food introduction was asked retrospectively when the child was 6 and 12 months old; therefore, minor misclassification because of recall bias cannot be excluded. However, this would have influenced our results only if parents of children with wheezing or eczema tended to misclassify having introduced allergenic foods after 6 months of age instead of before 6 months of age. Eczema and wheezing were diagnosed on the basis of parent-reported questionnaires. This could have led to misclassification of the outcome since physician diagnosis provides more accurate outcome diagnosis. Yet, we do not expect this misclassification to have influenced the effect of timing of food allergen introduction in particular, given that the outcome was measured after the introduction period. Another limitation of this study was that it could not examine the effect of aller-

genic food introduction before the age of 4 months in relation to eczema and wheezing. Thus, our study precludes conclusions on the effect of very early introduction of allergenic foods. However, Zutavern et al¹⁷ found no evidence supporting a delayed introduction of solid foods beyond 4 or 6 months of age for the prevention of asthma at the age of 6 years. For eczema any effect of a delayed introduction of solids could not be excluded.

Asthma assessment among young children is based on asthmalike symptoms, such as wheezing, often reported by parents through self-administered written questionnaires. Early wheezing in infancy is, however, not a very strong and independent predictor of childhood asthma. Diagnosis of asthma is difficult in young children, owing to the nonspecificity of the symptoms and the fact that conventional lung function tests cannot be performed at such a young age.³⁶ Therefore, our results do not allow for conclusions regarding the introduction of allergenic foods and later development of asthma. However, previous studies found that an infant's diet has a greater effect on short-term outcomes of atopic diseases than on long term-outcomes.⁷ Therefore, we do not expect the effect of the introduction of allergenic foods to influence the results for eczema and wheezing differently at ages older than 4 years.

We considered confounding and reverse causality in our analysis by adjusting for potential confounders and by evaluating statistical interaction for history of cow's milk allergy and parental history of atopy. However, residual confounding and residual reverse causality cannot be fully excluded. Reverse causation may occur if a delayed introduction of allergenic foods is truly protective for wheezing and eczema and parents of high-risk infants were more likely to delay the introduction of allergenic foods after 6 months of age, which may cancel out the effect.

In conclusion, the results presented in this study do not support a delayed introduction of allergenic foods at an age older than 6 months for the prevention of atopic diseases eczema and wheezing. Further studies in our cohort should focus on asthma and eczema at later ages in order to elucidate whether late introduction of food allergens delays the onset of atopic disease.

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