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ORIGINAL ARTICLE

Food Allergy and Gastrointestinal Disease

Complementary feeding practices are related to the risk of food allergy in the ELFE cohort

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Abstract

Background: Conflicting results have been obtained when analyzing the relationship between complementary feeding (CF) practices and allergic diseases in childhood. This study aims to further explore the association between allergic diseases in early childhood (10.1016/j.jaci.2012.02.036) and the age at CF introduction (10.1016/S0140-6736(15)00149-X), food diversity in the first year of life (10.1016/j.ijporl.2019.109759) and the delayed introduction of major allergenic foods.

Methods: This analysis focused on 6662 children from the French nationwide ELFE cohort. Data on feeding practices were collected monthly from 3 to 10 months old. Their age at CF introduction was calculated alongside a diversity score, and the number of major allergenic foods (out of eggs, fish, wheat, and dairy products) not introduced at 8 and 10 months. Their associations with parent-reported allergy-related health events between 1 and 5.5 years were assessed using logistic regressions adjusted for confounding factors. A sensitivity analysis excluding early allergic cases (occurring between 2 months and 1 or 2 years) was conducted.

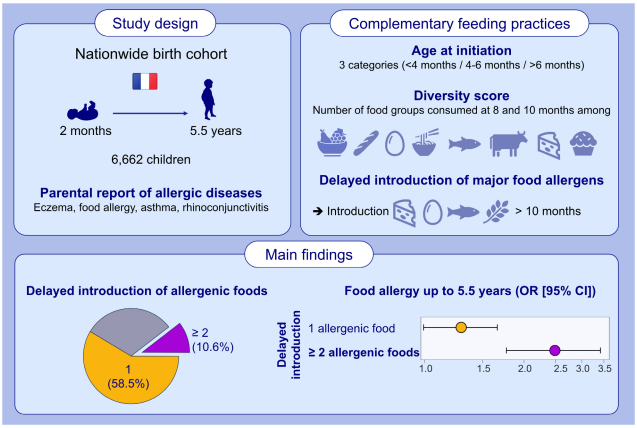
Abbreviations: CF, complementary feeding; ELFE, Étude Longitudinale Française depuis l'Enfance; PASTURE, protection against allergy: STUdy in rural environment.

Results: Late CF (>6 months) was related to a higher risk of food allergy (OR [95% CI] = 1.35 [1.02; 1.78]), a low diversity score at 8 months to a higher risk of asthma (OR [95% CI] = 1.22 [1.01; 1.48]), and two allergenic foods or more not being introduced at 10 months to a higher risk of rhinoconjunctivitis (OR [95% CI] = 1.20 [1.00; 1.44]) and food allergy (OR [95% CI] = 2.46 [1.77; 3.42]). Only this last association remained significant after the exclusion of early cases.

Conclusion: The delayed introduction of major allergenic foods is related to a higher risk of food allergy, which supports the updated guidelines for allergy prevention.

KEYWORDS

allergic rhinitis, asthma, childhood, complementary feeding, food allergy



GRAPHICAL ABSTRACT

The study aimed to explore the association between complementary feeding practices (age, food diversity and allergenic food) and the risk of food allergy, eczema, asthma, and rhinoconjunctivitis in early childhood. More than 50% children were not introduced with at least one major allergenic food (egg, wheat, fish, dairy products) at 10 months. This delayed introduction (after 10 months) of major allergenic food is associated with a higher risk of food allergy up to the age of 5.5 years.

Abbrevations: CI, confidence interval; ELFE, Étude Longitudinale Française depuis l'Enfance; OR, odds ratio

1 | INTRODUCTION

Many risk factors for allergic diseases have been identified, but some of them, such as gender, a family history of atopy, and pre-existing atopic diseases, are not modifiable.[1–3] Nevertheless, other risk factors are modifiable and they are far more interesting to those looking to bolster primary prevention; these include active or passive smoking, feeding practices[1–3] [particularly the age at which complementary feeding (CF) is initiated] and food diversity during this period. Non-modifiable factors such as, a family history of atopy[4,5] or early signs of allergic diseases,[6,7] further influence allergic disease through modifications to CF practices.

Current European guidelines define early CF as the introduction of CF occurring before the age of 4 months whereas late CF is considered to be when the introduction of CF occurred after the age of 6 months.[8] They recommend offering a varied diet to infant and the introduction of allergenic foods when CF is commenced any time after 4 months.[8] In most studies, early CF (<4 months) is not related to a higher risk of atopic dermatitis, food allergy, asthma, or rhinoconjunctivitis.[4–6,9] In contrast, late CF (after 6–7 months) is associated with a higher risk of food allergy after 5 years of age[10] but it is not associated with asthma, atopic dermatitis, or allergic rhinitis in the majority of studies.[11–13]

Some studies suggest that increased food diversity in the first year of life is linked to a lower risk of having food allergy,[11,13] asthma,[13,14] atopic dermatitis,[6,14] or allergic rhinitis.[14] However, other research reports that there is no association with atopic dermatitis,[9,12] asthma,[9] or allergic rhinitis.[9,14]

When considering the introduction of specific food allergens, the early introduction of peanuts in high-risk infants reduces the risk of a peanut allergy at 5 years of age but it does not affect other food allergies or allergic diseases.[15] Results are more conflicting when it comes to other food allergens, such as eggs, dairy products, and wheat, with some studies showing that there is a protective effect when introducing allergens at the beginning of CF on the risk of food allergy,[14,16] while other analysis found no association.[10,17–19] There is no link to the other allergic diseases.[6,9,12,18–20] A recent study highlighted the benefits of the early

introduction (between 3 and 4 months) and regular consumption up to 36 months, of four allergenic foods (peanut, cow's milk, egg and wheat), on the development of an allergy to these foods.[21] Hence, evidence concerning the relationship between CF practices and the risk of allergic diseases remains limited, and findings need to be confirmed in larger studies that provide more detailed information on the influence of CF.

In this context, our study aims to explore the link between several dimensions of CF practices (age at initiation, food diversity, introduction of main food allergens) and the risk of allergic diseases (food allergy, eczema, asthma, and rhinoconjunctivitis) up to 5.5 years of age among a large birth cohort in France.

2 | METHODS

2.1 | Study population

The Étude Longitudinale Française depuis l'Enfance (ELFE) is a multidisciplinary nationwide birth cohort that comprises 18,329 children born in 2011 in a random sample of 349 maternity wards in mainland France.[22] The inclusion criteria were single children or twins born after 33 weeks of gestation to mothers aged 18 years or older who were not planning to move outside of metropolitan France in the next 3 years.

2.2 | Ethical statement

Participating mothers had to provide written consent for their own and their child's participation. Fathers signed the consent form for the child's participation when present at inclusion, or they were informed about their rights to oppose it. The ELFE study is approved by the Advisory Committee for Treatment of Health Research Information (Comité Consultatif sur le Traitement des Informations pour la Recherche en Santé), the National Data Protection Authority (Commission Nationale Informatique et Libertés), and the National Statistics Council.

2.3 | Maternal and newborn characteristics

Mothers were interviewed in the maternity ward to obtain medical information about their pregnancy, their newborn, their demographic, their socioeconomic, and lifestyle-related characteristics and their eating habits during pregnancy. This was supplemented with data collection from obstetric and pediatric medical records. At 2 months postpartum, mothers and fathers were interviewed by phone, and more details on demographic and socioeconomic characteristics were collected. Meanwhile, the family's region of residence was determined using their postal code.

Parental and sibling history of allergy was also gathered during the 2-month interview. Children were considered to have a family history of allergy if at least one parent or sibling had experienced an allergic disease.

2.4 | Infant feeding practices

During each interview (monthly from 2 to 10 months), the following feeding practices were recorded: the consumption of solely breast milk, solely infant formula, both breast and formula milk (including plant-based infant formula), animal milk, or a plant-based beverage. The exact age of the child at breastfeeding cessation was recorded, alongside their age when formula milk was introduced, allowing us to calculate the predominant breastfeeding duration.[23]

Complementary feeding practices were also collected monthly from 3 to 10 months using a 26-item questionnaire.[24] The age at CF initiation was defined as the age in months when foods or beverages other than water, breast milk or infant formula were consumed for the first time more than once a month.[25] This was categorized into early (before 4 months), recommended (between 4 and 6 months), and late (after 6 months) strata.

A diversity score was derived from the one used in the PASTURE cohort,[19] and it consisted of the number of food groups (fruit or vegetables, meat, fish, eggs, grains, dairy products, bread and biscuits) that were consumed by the child at a given age. Data regarding consumption of some food items (chocolate, soy, and nuts) collected in the PASTURE study were not available in the ELFE study, so they were not considered in the diversity score. For each month, the diversity score was calculated as a total count of the number of different food groups consumed at least once in a given month, and it varied between 0 (no food diversity) and 8 (the highest food-diversity score). For the present study, the diversity score was considered at 8 and 10 months because of the low variability in food diversity at earlier ages (Figure S1). As we hypothesized that very low diversity was associated with a higher risk of allergy, we defined low diversity as the consumption of 0–2 food groups, intermediate diversity as the consumption of 3–5 food groups, and high diversity as the consumption of 6–8 food groups.

To study the impact of the late introduction of major allergenic foods on allergic diseases, we calculated the number of major allergenic foods (dairy products, hen's eggs, wheat, and fish) that were yet to be introduced at 8 and 10 months. Dairy products were considered to have been introduced if the infant consumed at least one item out of whole, skimmed, or semi-skimmed cow's milk, cheese, or yogurt. Egg was considered introduced if the infant ate the whites or the yokes of eggs. Meanwhile, wheat was considered introduced if the infant consumed at least one item out of pasta, rice, infant cereals, bread, or biscuits.

2.5 | Allergic diseases

Parents reported their children's health data during phone interviews at the ages of 2 months, 1, 2, 3.5, and 5.5 years and each interview covered the period since the last follow-up. Children were considered as prevalent cases and then excluded from all analysis if

parents reported an itchy rash, wheezing, or a medical diagnosis of cow's milk allergy at the 2-month interview.

Children were considered to have wheezing/asthma/eczema, respectively, between 2 months and 5.5 years if the parents reported that the child had at least one wheezing episode(s)/a medical diagnosis of asthma/eczema symptoms during the 1-, 2-, 3.5-, or 5.5-year interviews. As food allergy data were not collected at the 1-year interview, children were considered to have had a food allergy between 2 months and 5.5 years of age if their parents reported that they have been given a medical advice at least once to avoid any type of food due to an allergy at the 2-, 3.5-, or 5.5-year interviews.[26] Data about rhinoconjunctivitis were not collected at the 1- and 2-year interviews, so the children were considered to have had rhinoconjunctivitis between the ages of 3.5 and 5.5 years if parents reported at least one episode of allergic conjunctivitis or rhinitis at the 3.5- or 5.5-year interview.

The variable "any allergic disease" was defined as having at least one disease among food allergy, eczema, asthma, or rhinoconjunctivitis between 2 months and 5.5 years.

The children were considered as early cases if eczema or wheezing was reported at the 1-year interview or if a food allergy was reported at the 2-year interview.

2.6 | Sample selection

Analyses were based on the complete case sample, and the selection steps are presented in Figure 1. All of the analyses were conducted after the exclusion of prevalent cases at the age of 2 months.

2.7 | Statistical analysis

To compare the included families with their excluded ELFE counterparts, we used chi-squared tests for categorical variables and Student's *t*-tests for continuous variables.

Both unadjusted and adjusted associations between CF characteristics and atopic diseases were assessed using logistic regression models. For the adjusted models, potential confounding factors were identified from the literature and then selected using the direct acyclic graph method.[27] These included maternal characteristics (age at delivery, education level, employment status, migration, smoking status during pregnancy, region of residence, and urban/rural area), household characteristics (income per consumption unit, the number of older children at home), infant characteristics (cesarean-section delivery, infant's gender, birth weight, gestational age), predominant breastfeeding duration, family history of allergy, and variables related to the study's design (recruitment wave and maternity unit size) (Figure S2).

To explore the potential moderating effect of some factors, such as family history of allergy, the models also included the interaction term between the family history of allergy and the variables describing the CF practices that were tested. As a significant interaction between a family history of allergy and the child's age at the beginning of CF was only found for eczema, stratified analyses on the family history of allergy were only performed for this particular association.

To explore the issues relating to reverse causation, a sensitivity analysis was conducted after the exclusion of early cases (defined as cases of allergy occurring between the 2 month interview and the

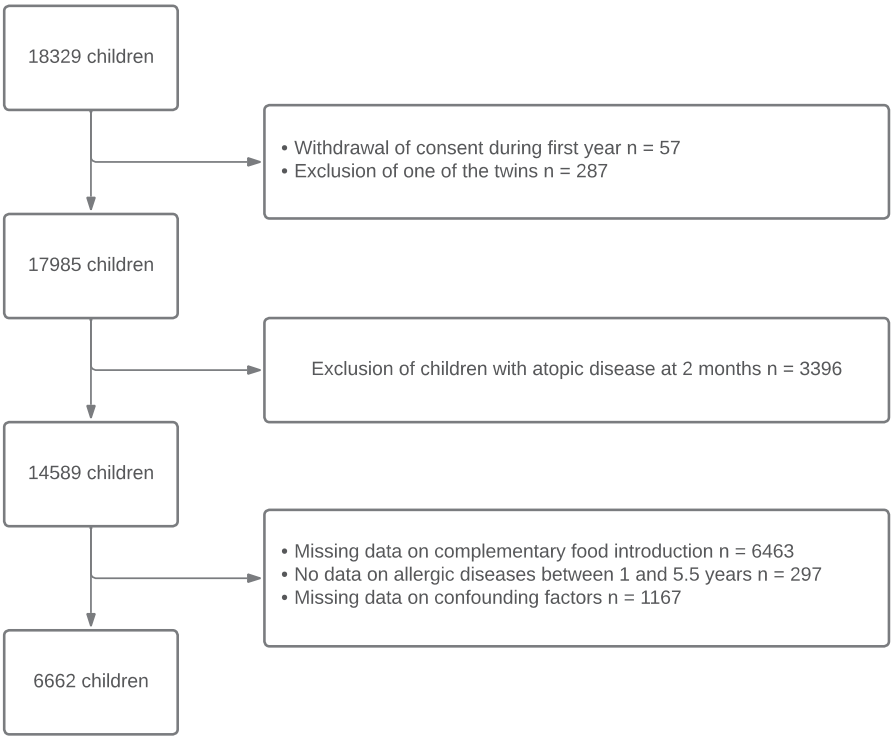


FIGURE 1 Flow chart of the study's sample selection.

1- or 2-year interviews) as we cannot guarantee that these cases did not occur between the 2-month interview and the beginning of CF. However, this sensitivity analysis also excludes potential incident cases occurring a few months after CF initiation.

To deal with selection and attrition bias, a sensitivity analysis was conducted with weighted data. The weighting was calculated to take the inclusion procedure and biases with regard to non-consent or attrition into account. It also included calibration on the margins from the state register's statistical data and the 2010 French National Perinatal study[28] on the following variables: age, region, marital status, migration status, level of education, and primiparity (https://www.elfe-france.fr/fichier/rte/178/Coté%20recherche/Weighting-Elfe-surveys-general-document.pdf). A specific weighting was calculated for each subsample.

All analyses were carried out with SAS software version 9.4 (SAS Institute), and the statistical significance was defined as $p < .05$.

3 | RESULTS

3.1 | Descriptive statistics

In comparison with the 6662 children who were included in the study, the excluded children were more likely to be born to a younger mother (30.4 vs 31.4 years) with a lower educational level (16.8% vs 24.8% with a Master's degree) and a lower income (€ 1514 ± 1049 vs € 1790 ± 936 per consumption unit) who smoked throughout their pregnancy (19.2% vs 11.3%). They were also less likely to have a family history of allergy (47.3% vs 52.5%).

The characteristics of the study's population are described in Table 1. The average age at CF initiation was 5.4 months (SD 1.1 months).

Food diversity was low before 6 months of age and increased thereafter up to 10 months (Figure S1). At 8 months, 18.8% of infants had a low diversity score, while 17.0% exhibited a high diversity score. Meanwhile, at 10 months, 2.4% had a low food-diversity score, and 55.6% demonstrated a high diversity score.

At least two major allergenic foods (out of dairy products, fish, wheat and eggs) were not introduced in 43.5% and 10.6% of children at 8 and 10 months, respectively (Figure S3). Additionally, more than half of the children had not been introduced to at least one major allergenic food by the age of 10 months.

3.2 | Age at complementary feeding introduction

As a moderating effect with regard to a family history of allergy (p for interaction = .03) was found on the associations between the age at CF introduction and the risk of eczema, these associations were stratified in accordance with this variable. Compared to the recommended CF initiation (4–6 months), a late CF initiation was associated to a lower risk of eczema among children without a family history of allergy (OR [95% CI] = 0.74, IC [0.57;0.95]), but this was not the case among those with a family history of allergy (OR [95% CI] = 1.15, [0.94; 1.40]). Meanwhile, an early CF introduction was related to the risk of eczema neither in children without a family history of allergy (OR [95% CI] = 0.94, [0.69; 1.29]), nor in children with a family history of allergy (OR [95% CI] = 1.16, [0.88; 1.58]). Furthermore, the negative association between a late CF initiation and the risk of eczema in children without a family history of allergy was not anymore significant after the exclusion of early cases (OR [95% CI] = 0.75, [0.54; 1.04]).

TABLE 1 Sample description ($n = 6662$).

Maternal characteristics	
Age at delivery (years)	31.4 (4.5)
Master's degree	24.8% (1655)
Employed during pregnancy	80.5% (5363)
Household income (€/month/consumption unit)	1790 (936)
Born in country other than France	5.6% (370)
Smoking during pregnancy	
Non smoker	59.2% (3941)
Smoker only before pregnancy	26.2% (1747)
Smoker only in early pregnancy	3.3% (223)
Smoker throughout pregnancy	11.3% (751)
Pre-pregnancy BMI (kg/m2)	23.3 (4.6)
Rural area	24.4% (1625)
Number of older children	
Firstborn	45.8% (3054)
Secondborn	37.8% (2517)
At least thirdborn	16.4% (1091)
Child's characteristics	
Birthweight (kg)	3.3 (0.5)
Gestational age (weeks)	39.3 (1.4)
Boys	50.8% (3387)
C-section delivery	17.0% (1131)
Predominant breastfeeding duration (months)	2.3 (3.6)
Family history of allergy	52.5% (3499)
Age at complementary feeding introduction	
<4 months	7.5% (499)
4 to 6 months	77.6% (5169)
>6 months	14.9% (994)
Allergic diseases between 2 months and 5.5 years	
Any allergy	64.2% (4279)
Eczema	33.5% (2158)
Food allergy	5.8% (373)
Asthma	26.6% (1770)
Rhinoconjonctivitis	39% (2394)

Note: Values are % (*n*) or mean (SD).

TABLE 2 Adjusted associations between complementary feeding characteristics and allergic diseases up to 5.5 years.

	Any allergy	Eczema	Food allergy	Asthma	Rhinoconjunctivitis
N	6662	6445	6433	6662	6140
Age at complementary feeding introduction					
<4 months	1.03 [0.84; 1.25]	1.06 [0.86; 1.30]	0.90 [0.58; 1.41]	1.17 [0.95; 1.45]	0.99 [0.81; 1.22]
4–6 months	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
>6 months	1.03 [0.89; 1.20]	0.95 [0.82; 1.11]	1.35 [1.02; 1.78]	0.96 [0.82; 1.13]	1.06 [0.91; 1.23]
Diversity score at 8 months					
Low diversity (0–2 food groups)	1.09 [0.91; 1.30]	1.01 [0.84; 1.21]	1.50 [1.02; 2.20]	1.22 [1.01; 1.48]	1.09 [0.91; 1.31]
Intermediate diversity (3–5 food groups)	1.09 [0.95; 1.25]	1.02 [0.88; 1.18]	1.32 [0.95; 1.83]	1.09 [0.93; 1.28]	1.03 [0.89; 1.19]
High diversity (6–8 food groups)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Diversity score at 10 months					
Low diversity (0–2 food groups)	1.05 [0.75; 1.46]	1.03 [0.73; 1.45]	1.57 [0.87; 2.85]	1.01 [0.70; 1.45]	1.43 [1.02; 2.01]
Intermediate diversity (3–5 food groups)	1.05 [0.95; 1.17]	1.10 [0.99; 1.23]	1.21 [0.97; 1.51]	1.02 [0.91; 1.15]	1.15 [1.03; 1.28]
High diversity (6–8 food groups)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Allergenic foods[a] at 8 months					
All 4 allergenic foods introduced	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
1 allergenic food not introduced	1.13 [0.95; 1.34]	0.93 [0.78; 1.12]	1.42 [0.92; 2.20]	1.17 [0.96; 1.42]	1.05 [0.88; 1.25]
At least 2 allergenic foods not introduced	1.18 [0.99; 1.40]	0.99 [0.82; 1.18]	2.03 [1.32; 3.13]	1.13 [0.93; 1.38]	1.16 [0.97; 1.39]
Allergenic foods[a] at 10 months					
All 4 allergenic foods introduced	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
1 allergenic food not introduced	1.17 [1.04; 1.31]	1.04 [0.92; 1.17]	1.29 [0.99; 1.67]	1.25 [1.10; 1.42]	1.07 [0.95; 1.21]
At least 2 allergenic foods not introduced	1.20 [1.003; 1.44]	1.11 [0.92; 1.34]	2.46 [1.77; 3.42]	1.13 [0.92; 1.38]	1.20 [1.002; 1.44]

Note: Values are OR [95% CI] from logistic regressions adjusted for maternal characteristics: age at delivery (18–24, 25–29, 30–34, ≥35 years), education level (up to lower secondary school, upper secondary school, intermediate, 3-year university degree, at least 5-year university degree), employment status (employed, unemployed, not in the labor force), migration (majority population, descendants of migrants, born in a foreign country under a foreign citizenship), smoking status during pregnancy (never smoker, smoker only before pregnancy, smoker in early pregnancy, smoker throughout pregnancy), region of residence (Paris region, North, East, Paris Basin–East, Paris Basin–West, West, Southwest, Southeast, Mediterranean), urban/rural area; household characteristics: monthly family income per consumption unit (≤€750; €751–1111; €1112–1500; €1501–1944; €1945–2500; >€2500), number of older children at home (no sibling, one sibling, at least two siblings); infant characteristics: cesarean section delivery, infant's sex, birthweight, gestational age; predominant breastfeeding duration family history of allergy, and variables related to study design (recruitment wave, maternity unit size). One model was run separately for each complementary feeding variable and each allergic outcome.

[a]Four allergenic foods were considered in the present study: dairy products, eggs, fish and wheat.

When compared with recommended CF initiation, late CF initiation (>6 months) was associated with a higher risk of food allergy up to 5.5 years (Table 2). Nevertheless, this association was attenuated and nonsignificant after the exclusion of early cases (occurring between the 2-month interview and the 1- or 2-year interview; Table 3). Early CF initiation was not related to the risk of food allergy.

TABLE 3 Adjusted associations between complementary feeding characteristics and allergic diseases up to 5.5 years, after exclusion of early allergic cases (any allergy occurring between the 2-month follow-up and the 1- or 2- year follow-up).

	Any allergy	Eczema	Food allergy	Asthma	Rhinoconjunctivitis
N	4359	4217	4208	4359	4011
Age at complementary feeding introduction					
<4 months	1.03 [0.81; 1.31]	1.08 [0.82; 1.41]	0.59 [0.21; 1.65]	1.11 [0.78; 1.58]	1.10 [0.84; 1.43]
4–6 months	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
>6 months	0.98 [0.82; 1.17]	0.92 [0.75; 1.12]	1.10 [0.62; 1.96]	0.92 [0.71; 1.21]	1.07 [0.88; 1.30]
Diversity score at 8 months					
Low diversity (0–2 food groups)	1.11 [0.90; 1.37]	1.01 [0.79; 1.29]	1.17 [0.56; 2.46]	1.37 [0.998; 1.87]	1.03 [0.82; 1.29]
Intermediate diversity (3–5 food groups)	1.12 [0.95; 1.33]	1.16 [0.95; 1.40]	1.12 [0.60; 2.09]	1.13 [0.87; 1.47]	1.01 [0.84; 1.21]
High diversity (6–8 food groups)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Diversity score at 10 months					
Low diversity (0–2 food groups)	0.93 [0.63; 1.37]	0.88 [0.55; 1.41]	1.57 [0.54; 4.61]	0.92 [0.51; 1.69]	1.47 [0.96; 2.24]
Intermediate diversity (3–5 food groups)	1.02 [0.90; 1.16]	1.07 [0.93; 1.24]	1.01 [0.66; 1.56]	0.99 [0.82; 1.19]	1.07 [0.93; 1.22]
High diversity (6–8 food groups)	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Allergenic foods[a] at 8 months					
All four allergenic foods introduced	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
One allergenic food not introduced	1.10 [0.90; 1.35]	0.98 [0.78; 1.23]	1.86 [0.71; 4.82]	1.18 [0.86; 1.62]	0.95 [0.76; 1.19]
At least two allergenic foods not introduced	1.16 [0.94; 1.43]	0.99 [0.78; 1.25]	2.41 [0.93; 6.21]	1.09 [0.79; 1.50]	1.10 [0.88; 1.38]
Allergenic foods[a] at 10 months					
All four allergenic foods introduced	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
One allergenic food not introduced	1.12 [0.98; 1.28]	1.13 [0.97; 1.32]	1.55 [0.92; 2.60]	1.10 [0.90; 1.35]	0.98 [0.85; 1.14]
At least 2 allergenic foods not introduced	1.02 [0.82; 1.28]	1.06 [0.82; 1.36]	2.32 [1.18; 4.59]	0.99 [0.71; 1.38]	1.06 [0.84; 1.35]

Note: Values are OR [95%CI] from logistic regressions adjusted for maternal characteristics (age at delivery, education level, employment status, migration, smoking status during pregnancy, region of residence, urban/rural area), household characteristics (income per consumption unit, number of older children at home), infant characteristics (cesarean section delivery, infant's sex, birthweight, gestational age), predominant breastfeeding duration, family history of allergy, and variables related to study design (recruitment wave, maternity unit size). One model was run separately for each complementary feeding variable and each allergic outcome.

[a]Four allergenic foods were considered in the present study: dairy products, eggs, fish, and wheat.

Moreover, the age at CF initiation was not associated with the risk of asthma and rhinoconjunctivitis.

Similar results were observed in unadjusted or weighted analyses (Tables S1 and S2).

3.3 | Food diversity during complementary feeding

In relation to a high food-diversity score, a low food-diversity score (0–2 food groups consumed) at 8 months was associated with a higher

risk of asthma and food allergy (Table 2), and a low or intermediate food-diversity score at 10 months was associated with a greater risk of rhinoconjunctivitis. These associations were attenuated and nonsignificant after the exclusion of early cases (occurring between the 2-month interview and the 1- or 2-year interview; Table 3). In addition, the food-diversity scores were not related to the risk of any allergy or eczema.

Similar results were observed in unadjusted or weighted analyses (Tables S1 and S2).

3.4 | Delayed introduction of major allergenic foods (out of dairy products, hen's eggs, wheat, and fish)

When compared to children that were introduced to all four allergenic foods, children with at least two allergenic foods not introduced at 8 months old were at a higher risk of food allergy (Table 2). Moreover, children with at least two allergenic foods not introduced at 10 months of age were at a higher risk of food allergy and rhinoconjunctivitis. The association between the number of allergenic foods not introduced at 10 months and food allergy remained significant after the exclusion of early cases (occurring between the 2-month interview and the 2-year interview; Table 3).

Similar results were observed in unadjusted or weighted analyses (Tables S1 and S2).

4 | DISCUSSION

In this nationwide birth cohort, food diversity increased regularly during the CF period, but at 10 months old, at least one major allergenic food out of dairy products, egg, fish, and wheat had still not been introduced to more than half of the children (most frequently egg). Late CF introduction, low food-diversity by the age of 10 months and the delayed introduction of major allergenic foods appeared to be associated with a higher risk of allergic diseases, especially food allergy and rhinoconjonctivitis. However, only the association between the delayed introduction of allergenic foods and the risk of food allergy remained significant after the exclusion of early allergic cases (occurring between the 2-month interview and the 1-year interview or, for the food allergy only, the 2-year interview).

In this study, CF introduction after 6 months was associated with a higher risk of food allergy. Hicke-Roberts et al.[11,12] uncovered similar results with regard to a higher risk of food allergy among infants that were introduced to CF after 7 months, but most studies found no significant association between late CF initiation and food allergy.[4,5] As the association was attenuated and nonsignificant after the exclusion of early cases, we cannot rule out the possibility that it was due to a reverse causation bias where parents of children with early allergic diseases delayed the introduction of complementary food.

A previous study reported a positive association between the food-diversity score at 6 months old and the risk of food allergy at 1 year.[12] During our research, even if late CF was shown to be associated with a higher risk of food allergy, we did not find a clear association between food diversity and the risk of food allergy. As was the case in our study, previous studies underlined an association between a low food-diversity score in infancy and a higher risk of asthma[17,18] or rhinoconjunctivitis.[18] However, the associations in our study were not uniform across the ages, which therefore limits the generalizability of our findings. Moreover, in the present paper, the diversity score was based on the food groups consumed during a given month, whereas previous papers have mostly examined the food groups introduced during a set period.[12,17,18] The frequency of consumption might play a role, but research exploring the association between the frequency of consuming several food items and allergic diseases is very scarce.[29] It would consequently be of interest to conduct further studies exploring the potential influence of both the frequency of consumption of each food group and the impact of food diversity on allergic diseases.

Regarding the delayed introduction of allergenic foods, several studies reported that it was associated with a higher risk of food allergy, but most of them focused on a given allergenic food and the risk of allergy in relation to this allergenic food.[20,30,31] In this study, we showed that the delayed (>10 months) introduction of at least two major allergenic foods (out of dairy products, wheat, egg, and fish) is associated with a higher risk of food allergy or rhinoconjunctivitis. Furthermore, the association with food allergy persisted after the exclusion of early allergic cases (any allergy occurring between the 2-month follow-up and the 2-year follow-up), indicating that this association was not explained by reverse causation. Egg was the most frequent allergenic food not introduced at 10 months of age; nevertheless, it is worth noting here that we were unable to take the introduction of baked eggs (in processed foods like cakes) into account because of the questionnaire's design. This might lead to an overestimate in terms of how delayed the introduction of egg was, but our results suggest that the introduction of a whole egg into infant diets is an important part of food allergy prevention. Indeed, earlier research demonstrate that a weekly protein intake of more than 2 g is important to prevent allergies,[29,32] so the consumption of lower levels of egg protein through processed foods might not be sufficient to prevent egg allergy.[33] Although several studies found a higher risk of atopic dermatitis or asthma among children with late or scarce amounts of fish being introduced into their diet,[19,29,32] the delayed introduction of food allergens (including fish) was not associated with the risk of eczema in our study. Meanwhile, some research found an association between the delayed introduction of fish after the age of 11 months and an increased risk of asthma and rhinoconjunctivitis,[17,34] yet most studies found no link between the introduction of allergenic foods and asthma or rhinoconjunctivitis.[5,6,9,13,17,19] When the ELFE cohort was launched, French nutritional guidelines recommended delaying the introduction of allergenic food to children with a family history of allergy, and European guidelines were unclear whether parents should delay their introduction or not.[35]

Our findings support the updated guidelines, indicating that the introduction of food allergens should not be delayed and should occur "when CF is initiated any time after 4 months"[8] and "as early as the CF is initiated that is to say between 4 and 6 months" (updated French guidelines from the Public Health France website, September 2021).[36] Recent studies underline the need for public health communications to disseminate and explain this change in the guidelines to parents and professionals who work with children.[37,38]

The very large sample and the collection of detailed socio-demographic and economic data ensure the presence of more statistical power and a favorable level of control over potential confounders. As in most observational studies, the selection/attrition bias was quite important, but the weighted analyses suggest that this bias had a limited impact on our findings. Indeed, the prospective design allowed for limited memory bias with regard to both exposure and outcome variables. However, the health data were reported by parents and not validated by medical records, which could lead to a potential measurement bias, even if the items used were derived from international questionnaires.[39] In particular, parental reporting could lead to an overestimation of allergic diseases. As children were considered to have food allergies when medical advice was given to avoid one specific food, due to a food allergy, then it was not possible to distinguish non-IgE-mediated food allergies from IgE-mediated food allergies. As allergy outcomes were not reported between 2 months and 1 year or even 2 years for food allergies, allergies reported at the 1 or 2-year interview could have occurred at any time between 2 months and 1 or 2-year of age. It was subsequently not possible to distinguish those occurring before CF introduction (prevalent cases) from those occurring after CF introduction (real incident cases). By comparing our main analysis and our sensitivity analysis (excluding all cases reported at 1 or 2 years for food allergies), we concluded that for some associations (those not significant in the sensitivity analyses), the reverse causation could not be excluded, whereas the association between the delayed introduction of allergenic foods and food allergy is unlikely to be due to this reverse causation.

In this nationwide cohort study, some aspects of CF practices were shown to be related to the risk of allergic diseases up to 5.5 years; this was mainly the case in relation to food allergy. In fact, delayed introduction (after 8 or 10 months) of major allergenic foods (dairy products, wheat, fish, and egg) was linked to a higher risk of food allergies up to 5.5 years (this more than doubled if there was a delayed introduction of at least two of them), even after excluding cases that occurred during the first 2 years of life. Our results support the updated guidelines for CF practices on early CF practices for food allergy prevention.

AUTHOR CONTRIBUTIONS

T. Adam: conceptualization (lead); formal analysis (lead); writing – original draft (lead). A. Divaret-Chauveau: conceptualization (lead); methodology (lead); supervision (lead); writing—review and editing (lead). C. Roduit: methodology (equal); writing—review and editing (equal). K. Adel-Patient: methodology (equal); resources (equal); writing—review and editing (equal). A. Deschildre: writing—review and editing (supporting). C. Raherison: resources (equal); writing—review and editing (supporting). M.-A. Charles: resources (equal); writing—review and editing (supporting). S. Nicklaus: methodology (equal); resources (equal); writing—review and editing (equal). B. de Lauzon-Guillain: conceptualization (lead); resources (lead); methodology (lead); supervision (lead); formal analysis (lead); writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

T. Adam reports support for attending meetings from Stallergens, ALK, and Sanofi. A. Divaret-Chauveau reports receiving support for this manuscript from the French National Research Agency (ANR-19-CE36-0008) and the University of Lorraine, grants for other studies from Don du Souffle, Fondation du Souffle, Novartis, and the Association Régionale d'Aide aux Insuffisants Respiratoires de Lorraine (ARAIRLOR). The author also had a contract with the French public agency ANSES as an expert in allergies and pediatrics for the Human Nutrition Committee, received consulting fees from Stallergens, ALK,

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DATA AVAILABILITY STATEMENT

The data underlying the findings in this study cannot be made freely available for ethical and legal reasons because they include a substantial number of variables that, together, could be used to identify the participants based on a few key characteristics and could then be used to access other personal data. Therefore, the French ethics authority strictly forbids making these data freely available. However, they can be obtained upon request from the ELFE principal investigator. Readers may contact marie-aline.charles@inserm.fr to request the data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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