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Characteristics of infant formula consumed in the first months of life and allergy in the EDEN mother–child cohort

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Abstract

The evidence regarding the association between infant formula (IF) composition and the prevention of allergy and respiratory diseases remains sparse and inconclusive. This study aimed to evaluate whether some IF characteristics were associated with the risk of allergy or respiratory diseases in childhood. Among 1243 formula-fed children from the EDEN mother–child cohort, IF characteristics concerning long-chain polyunsaturated fatty acids (LCPUFAs) enrichment, prebiotic/probiotic enrichment, and hydrolysis of proteins were identified from the ingredients list. Eczema, wheezing, food allergy, asthma, and allergic rhinitis up to age 8 years were prospectively collected and summarized into four allergic and respiratory multimorbidity clusters. Associations between 4-month IF characteristics and risk of allergy or respiratory diseases were tested using logistic regressions adjusted on main confounders. The consumption of LCPUFA-enriched formula was not linked to allergic and respiratory multimorbidity clusters, but to a lower risk of any allergy, eczema, and wheezing. Probiotic-enriched formula consumption was associated with a lower risk of belonging to the 'Allergy without asthma' cluster (odds ratio [OR] [95% confidence interval, CI] = 0.63 [0.40–0.99]), and consumption of a formula enriched in *Bifidobacterium lactis* was associated with a lower risk of any allergy (OR [95% CI] = 0.59 [0.41–0.85]). Partially hydrolysed formula (pHF) consumption was associated with a higher risk of belonging to the 'Allergy without asthma' cluster (OR [95% CI] = 2.73 [1.65–4.51]). This study

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confirms the positive association between pHF consumption and the risk of allergy found in previous observational studies and suggests that consumption of LCPUFA-enriched or probiotic-enriched formula was associated with a lower risk of allergy.

KEYWORDS

allergy, infant formula, long-chain polyunsaturated fatty acids, partially hydrolysed formula, probiotics

1 | INTRODUCTION

Over the last decades, there has been an increase in the prevalence of allergic diseases, which is attributed to changes in environmental factors and lifestyles. In general, these diseases share some common risk factors, including parental history of allergy, exposure to air pollutants or cigarette smoke, low microbial exposure, and inadequate early feeding practices (e.g. short breastfeeding duration, solid food introduction before 4 months of age or beyond 6 months of birth) (Beasley et al., 2015; Halken, 2004; Pawankar et al., 2013).

Exclusive breastfeeding for the first 6 months of life, or at least 4 months, is the recommended feeding option for all newborns because it provides all of their nutritional needs to grow and develop a healthy immune system (WHO, 2003), while protecting the infant from various infections. However, several studies have shown a high level of non-compliance with these recommendations (Cai et al., 2012; Schiess et al., 2010; Victora et al., 2016). For non-breastfed and partially breastfed infants, a large range of infant formula (IF) is available (de Lauzon-Guillain et al., 2018), including IF enriched in long-chain polyunsaturated fatty acids (LC-PUFAs) such as docosahexaenoic acid (DHA), arachidonic acid (ARA) or eicosapentaenoic acid (EPA), IF enriched in prebiotics, probiotics, or a combination of both, and partially hydrolysed formula (pHF).

Although IF composition must comply, within European countries, with strict regulations, existing data regarding the potential effect of their components on the risk of allergy are limited or inconclusive (Adjibade, DAVISSE-PATURET, Bernard, et al., 2022; Arslanoglu et al., 2008; Birch et al., 2010; Cuello-Garcia et al., 2017; Foiles et al., 2016; Lapillonne et al., 2014; Pastor et al., 2006; Sierra et al., 2015). Available studies on the potential effect of LCPUFA enrichment support a beneficial effect of DHA/ARA-enriched formula on allergic diseases (Birch et al., 2010; Foiles et al., 2016; Lapillonne et al., 2014) and a recent observational study reported that DHA/ARA/EPA-enriched formula consumption at 2 months was associated with a lower use of asthma medications up to 3.5 years (Adjibade, DAVISSE-PATURET, Bernard, et al., 2022). For formula enriched in prebiotics, probiotics, or symbiotics, randomized control trials (RCTs) led to inconsistent findings and the Committee on Nutrition from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition concluded that data were insufficient to recommend their routine use (Braegger et al., 2011). Available systematic reviews also concluded that

Key messages

- The study aimed to explore, among formula-fed infants, the association between infant formula characteristics and allergic or respiratory multimorbidity clusters in early childhood.
- Probiotic-enriched formula consumption was associated with a lower risk of belonging to the 'Allergy without asthma' cluster.
- Partially hydrolysed formula consumption was associated with a higher risk of belonging to the 'Allergy without asthma' cluster, even after exclusion of cases reported at 1 year.

current evidence was not conclusive to recommend the routine use of probiotic-, prebiotic- or symbiotic-enriched formula in healthy term infants (Arslanoglu et al., 2008; Cuello-Garcia et al., 2017; de Silva et al., 2020; Sierra et al., 2015; Skórka et al., 2018). Regarding pHF, a recent systematic review concluded that evidence was not sufficient to support the use of hydrolysed formula for the prevention of allergic diseases (Osborn et al., 2018). In addition, two observational studies reported that infants consuming pHF had lower lung capacity (Amazouz et al., 2021) and a higher risk of wheezing and food allergy (Davisse-Paturet et al., 2019) in childhood than those consuming regular formula.

Most studies have considered allergic and respiratory diseases separately, whereas children can suffer from multiple allergic and respiratory diseases (Anto et al., 2017). In fact, according to the atopic march, children with atopic dermatitis in infancy are more likely to develop allergic rhinitis and asthma later in childhood, and these phenotypes may persist for several years, leading to allergic and respiratory multimorbidity (Paller et al., 2019). In a previous paper from the EDEN mother-child study (Delvert et al., 2022), four allergy and respiratory multimorbidity clusters were highlighted offering the opportunity to study them jointly. In this context, the purpose of this observational study was to evaluate, under real conditions of use, the associations between the characteristics of IF (enrichment in LCPUFA, enrichment in probiotics or prebiotics, and partial proteins hydrolysis) consumed in the first months of life and allergic and respiratory multimorbidity in childhood.

2 | MATERIALS AND METHODS

2.1 | Study population

Our analyses were based on data from the EDEN (Etude des déterminants pré et post natals précoces du développement psychomoteur et de la santé de l'enfant) mother-child cohort, a prospective study designed to assess the prenatal and early postnatal determinants of child development and health. The study protocol has been described in detail elsewhere (Heude et al., 2016). Briefly, the study included 2002 pregnant women recruited from 2003 to 2006 in two French university hospitals (Poitiers and Nancy), before 24 weeks of amenorrhoea. Exclusion criteria were multiple pregnancies, known diabetes before pregnancy, French illiteracy, and planning to move outside the region within the next 3 years. The study was approved by the ethics committee (CCPPRB) of Kremlin-Bicêtre Hospital on 12 December 2002 and the National Agency Regulating Data Protection (Commission National de l'Informatique et des Libertés [CNIL]). Written consent was obtained from both parents.

2.2 | Data collection

2.2.1 | Infant feeding

Data on infant feeding was collected by using 3-day dietary records at the 4-month follow-up. Parents were asked to report the brand and product name of all formulas used. The ingredient list and nutritional composition were then used to identify the nutritional characteristics of all reported formulas. The nutritional characteristics examined in the present study were: enrichment in LCPUFA (not enriched, enriched), enrichment in prebiotics or probiotics (not enriched, enriched in prebiotics, enriched in probiotics, enriched in prebiotics, or probiotics without precision) and protein hydrolysis (intact proteins, partially hydrolysed proteins). Within probiotics, specific enrichments were considered: *Bifidobacterium* (not enriched, enriched in *Bifidobacterium lactis*, enriched in *Bifidobacterium breve*, enriched in probiotics but no sufficient details to classify), and *Streptococcus thermophilus* (not enriched, enriched in *S. thermophilus*, enriched in probiotics but no sufficient details to classify). For this study, we only used the data collected at the 4-month follow-up to limit the residual confounding related to other sources of LCPUFA, prebiotics or probiotics in the diet. Infants receiving both breast milk and IF at 4 months were classified according to the type of formula they consumed.

2.2.2 | Allergy and respiratory diseases

Data on allergy and respiratory diseases were collected using the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher & Weiland, 1998) completed by parents at the

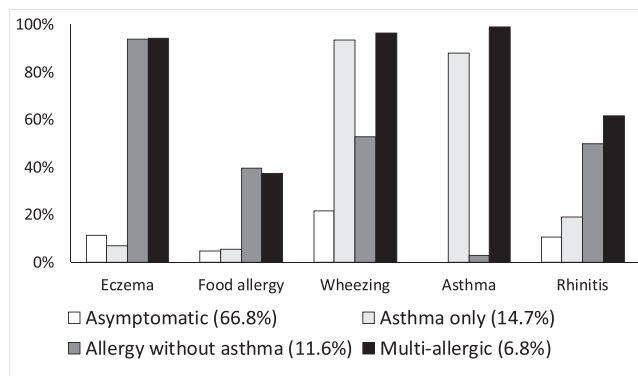


FIGURE 1 Frequency of symptoms in each of the five identified allergic and respiratory multimorbidity clusters ($n = 1243$).

8-month and, 1-, 2-, 3-, 4-, 5- and 8-year follow-ups. As some atopic diseases may be more prevalent in infancy (e.g., eczema), whereas others may appear later in childhood (e.g., rhinitis), we decided to account for the larger possible period. Consequently, in this study, allergy-related outcomes considered were wheezing up to age 8 years, eczema up to age 8 years, food allergies up to age 8 years, current asthma up to age 8 years, and allergic rhinitis from age 1 to 8 years. Eczema, current asthma, and allergic rhinitis were defined according to the MEDALL consortium criteria (Pinart et al., 2014). In this study, children were considered to have ever wheezing, ever eczema, ever food allergy, ever asthma or ever allergic rhinitis if the parents reported at least once the considered health event during follow-up. In addition, if the parents reported at least one of the allergic diseases mentioned above, children were considered to have 'any allergy' for up to 8 years.

In previous work, four allergy and respiratory multimorbidity clusters were highlighted using Latent Class Analysis (Delvert et al., 2022): the 'asymptomatic' cluster, including children with lower prevalence of all allergic and respiratory outcomes; the 'asthma-only' cluster, including children with higher prevalence of wheezing and asthma but lower prevalence of food allergies and eczema; the 'allergies without asthma' cluster, including children with higher prevalence of food allergy, eczema, and rhinitis, but lower prevalence of asthma; and the 'multi-allergic' cluster, including children with higher prevalence of all allergic and respiratory outcomes (Figure 1). Children were assigned to their most likely cluster.

2.2.3 | Other variables

Several data on familial socio-demographic and birth characteristics were collected during pregnancy or at birth in the medical records. Maternal and household characteristics considered in this study were: maternal age at delivery (years), primiparity (yes/no), maternal education level (years of education), monthly household income (<€1500, €1501–2300, €2301–3000 and >€3000) and family history of allergy (including maternal, paternal and sibling history of asthma,

eczema, allergic rhinitis and food allergy; yes/no). The child's characteristics included sex, gestational age (weeks), and age at introduction to IF (months) (Betoko et al., 2013).

2.3 | Selection of the study sample

Among the 1899 newborns included in the EDEN cohort and for whom birth weight data were available, we excluded exclusively breastfed infants at age 4 months ($n = 253$), infants without data regarding the IF consumed at age 4 months ($n = 282$), those who had a medical diagnosis of cow's milk protein allergy reported at 4 months ($n = 10$) and those without data on allergic and respiratory multimorbidity considered in the present study ($n = 111$). Finally, the main analyses involved 1243 children.

2.4 | Statistical analyses

Children included in this study were compared to excluded children using chi-square test for categorical variables and Student's *t* test for continuous variables. In this study, some covariates had missing values, but the proportion of missing values was <2% for all variables. We thus handled missing covariates data by using the Hot Deck method, which consists of replacing the missing value with that of respondents with the same characteristics (Andridge & Little, 2009).

The associations between characteristics of the formula consumed at age 4 months and allergic and respiratory multimorbidity clusters were assessed with logistic regression models adjusted for potential confounders. These confounders were identified from the literature and selected by using the directed acyclic graph method (Shrier & Platt, 2008). All analyses were then adjusted for recruitment centre, maternal characteristics (age at delivery, primiparity and education level), monthly household income, family history of allergy, and child's characteristics (sex, gestational age and age at introduction to IF). In the main analyses, separate logistic regression models were performed for each combination of outcome and IF characteristic. The potential modulating effect of family history of allergy, maternal history of allergy, and any breastfeeding duration were tested, and the analyses were stratified when the *p* value for interaction was <0.10.

Several sensitivity analyses were performed to evaluate the influence of potential bias and test the robustness of our findings. First, we examined the associations with the type of formula consumed, considering all nutritional characteristics in a single 4-category variable (regular IF, IF enriched in LCPUFA only or in combination with prebiotics or probiotics, IF enriched in prebiotics or probiotics only, partially hydrolysed formula). Second, to examine the potential influence of the reverse causation bias, the main analyses were repeated among (1) infants who consumed IF with the same characteristics during their first 4 months of life ($n = 824$) and (2) infants without early cases (reported at least once up to

8 months) ($n = 909$). In addition, our analyses were repeated among infants who were not breastfed or breastfed for less than 1 month ($n = 492$) to partially account for the fact that infants consuming both breast milk and IF may also benefit from LCPUFAs, prebiotics, and probiotics contained in breast milk. A sensitivity analysis was also conducted using any allergy variable, and the individual allergic or respiratory outcomes were considered separately.

All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Sample characteristics

As compared with excluded children, including children were more often the firstborn (48.5% vs. 37.1%), born to an older mother (29.6 ± 4.8 years vs. 29.3 ± 5.0 years), with a higher education level (13.8 ± 2.6 years vs. 13.2 ± 2.8 years), and in a household with a higher monthly income (13.0% vs. 24.8% for an income ≤ 1500 euros and 29.2% vs. 23.0% for an income > 3000 euros). No difference was highlighted between included and excluded children on family history of allergy, gestational age and child sex.

The characteristics of the included children are described in Supporting Information S1: Table 1. At 4 months, 60.8% of infants consumed a regular IF, 5.9% LCPUFA-enriched formula, 27.4% prebiotic- or probiotic-enriched formula and 10.9% pHF. Regarding probiotic-enriched formula, the probiotics added to IF were often *B. breve* combined with *Streptococcus thermophilus*, and *B. lactis* alone or combined with *S. thermophilus* (Figure 2). The prevalence of any allergy at each age according to the IF consumed at 4 months is described in Supporting Information S1: Figure 1.

3.1.1 | LCPUFA enrichment

Unadjusted associations between infant feeding practice variables and growth parameters are presented in Supporting Information S1: Table 2. We describe below the associations obtained with the adjusted models and compare them with sensitivity analyses.

The main analyses showed that the consumption of a formula enriched with LCPUFAs at 4 months of age was not associated with allergic and respiratory multimorbidity clusters (Table 1). Sensitivity analyses yielded similar findings.

However, when 'any allergy' was considered or when allergic and respiratory outcomes were considered separately, consumption of LCPUFA-enriched formula at 4 months was associated with a lower risk of any allergy, eczema, and wheezing compared to consumption of non-LCPUFA-enriched formula (Supporting Information S1: Table 3). No significant association was found for food allergy, asthma, and allergic rhinitis although the trend was similar for food allergy and allergic rhinitis.

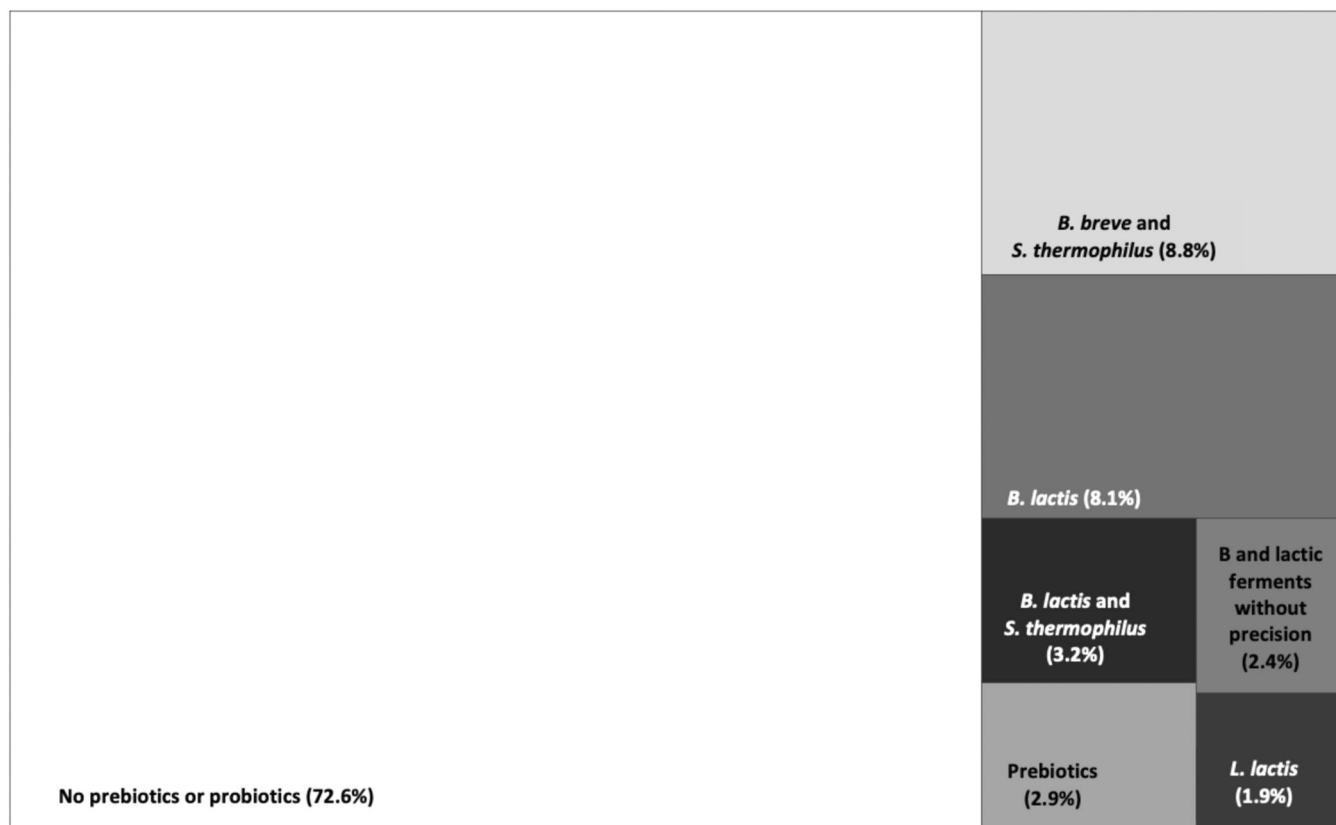


FIGURE 2 Consumption of pre- or probiotic-enriched formula at age 4 months among formula-fed infants ($n = 1243$). *B.* *Bifidobacterium*; *L.* *Lactococcus*; *S.* *Streptococcus*.

3.1.2 | Prebiotics and probiotics enrichment

Consumption of prebiotic- or probiotic-enriched formula at 4 months is related to a lower risk of belonging to the cluster 'Allergy without asthma' (Table 2). Exclusion of infants who changed the type of IF before the age of 4 months or early cases did not change the results, consumption of prebiotic- or probiotic-enriched formula at 4 months also related to a lower risk of belonging to the cluster 'Asthma only'. After excluding infants breastfed longer than 1 month, the association with the risk of belonging the cluster 'Allergy without asthma' was similar but not any more significant (odds ratio [OR] [95% confidence interval, CI = 0.67 [0.31–1.44] vs. OR [95% CI = 0.63 [0.40–0.99]).

However, when 'any allergy' was considered or when allergic and respiratory outcomes were considered separately (Supporting Information S1: Table 3), a negative association was only found for food allergy.

Considering the strains of probiotics, no association was found with the allergic and respiratory multimorbidity clusters (Supporting Information S1: Table 4). However, the consumption of a formula enriched in *B. lactis* was associated with a lower risk of any allergy, but not when considering allergic or respiratory diseases individually.

3.1.3 | Partially hydrolysed protein

Compared to consumption of intact-protein formula at 4 months, the consumption of pHF at 4 months was associated with a higher risk of belonging to the 'Allergy without asthma' cluster (Table 3). This association remained consistent after excluding infants who changed formula type or early cases. Additionally, after excluding infants breastfed longer than 1 month, the consumption of pHF at 4 months was also associated with a higher risk of belonging to the 'asthma-only' cluster.

When any allergy was considered or allergic and respiratory outcomes were considered separately, pHF consumption at 4 months was associated with a higher risk of any allergy, eczema, food allergy and allergic rhinitis (Supporting Information: Table 3). However, there was no association found between pHF consumption and wheezing or asthma.

Maternal history of allergy had a moderating effect on the association between pHF consumption and some allergic outcomes (p value for interaction term: 0.02 for any allergy, 0.009 for food allergy). In the analyses stratified on maternal history of allergy, the association for any allergy was significant in the subgroup of infants whose mothers had a history of allergy (OR [95% CI] = 4.03 [1.64–9.95]) but not in the subgroup of infants whose mothers had no history of allergy (OR [95% CI] = 1.21 [0.75–1.94]), whereas the reverse was found for food allergy (history of allergy: OR [95% CI] = 0.79 [0.31–2.03]; no history of allergy: OR [95% CI] = 3.46 [1.86–6.43]).

TABLE 1 Adjusted associations between the enrichment in LC-PUFA of formula consumed at 4 months and the allergic and respiratory multimorbidity clusters in the main sample as in specific sub-samples, EDEN study.^a

	Asthma only	Allergy without asthma	Multi-allergic
Main sample, <i>n</i> = 1243			
Enrichment in LC-PUFA			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Enriched	0.53 [0.22–1.26]	0.48 [0.19–1.23]	1.22 [0.50–2.99]
Infant breastfed <1 month, <i>n</i> = 492			
Enrichment in LC-PUFA			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Enriched	0.56 [0.16–1.96]	0.70 [0.20–2.48]	2.41 [0.71–8.21]
Infants with the same formula up to 4 months, <i>n</i> = 824			
Enrichment in LC-PUFA			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Enriched	0.58 [0.20–1.69]	0.68 [0.23–2.02]	1.89 [0.67–5.33]
Exclusion of early cases (occurring before 8 or 12 months), <i>n</i> = 909			
Enrichment in LC-PUFA			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Enriched	0.37 [0.09–1.58]	0.44 [0.10–1.86]	1.28 [0.28–5.94]

Abbreviations: CI, confidence interval; LCPUFA, long-chain polyunsaturated fatty acid; OR, odds ratio.

^aValues are OR [95% CI] from multinomial logistic regressions (reference group = 'Asymptomatic' cluster) adjusted for recruitment centre, maternal characteristics (age at delivery, education level, primiparity), household income, family history of allergy and child's characteristics (sex, gestational age, age at infant formula introduction). Separate logistic regression models for each combination of outcome and infant formula characteristics.

4 | DISCUSSION

In this observational study, the consumption of LCPUFA-enriched formula at 4 months of age was not linked to allergic and respiratory multimorbidity clusters, but it was associated with a lower risk of any allergy, eczema, and wheezing when considered separately. Probiotic-enriched formula consumption at 4 months was associated with a lower risk of belonging to the 'Allergy without asthma' cluster, and consumption of a formula enriched in *B. lactis* was associated with a lower risk of any allergy. The associations with the risk of allergic or respiratory diseases considered individually were not statistically significant although in the same direction. Conversely, partially hydrolysed formula consumption at 4 months was associated with a higher risk of belonging to the 'Allergy without asthma' cluster and a higher risk of food allergy, especially in infants without a maternal history of allergy.

As in our observational study, one RCT involving healthy term infants from two cohorts showed a protective effect of DHA/ARA-enriched formula on any allergy during the first 3 years of life (Birch et al., 2010). Another RCT of healthy term infants also found a protective effect of DHA/ARA-enriched formula on any allergic disease during the first year of life, but not up to 4 years of life (Foiles et al., 2016). However, in this RCT, the protective effect of

DHA/ARA-enriched formula was found for (1) any allergic diseases during the first 4 years of life only when the mother had no allergies and (2) wheezing/asthma only when the mother had allergies. This modulating effect of maternal history of allergy was not observed for DHA/ARA-enriched formula consumption in the present study. Regarding available observational studies, one found that the consumption of DHA/ARA-enriched formula at 2 months was not associated with the risk of wheezing, itchy rash, asthma medication and food allergy up to age 5.5 years, but the consumption of DHA/ARA/EPA-enriched formula was associated with a lower risk of asthma medication (Adjibade, Davaisse-Paturet, Bernard, et al., 2022). Another observational study also found no association between the consumption of DHA/ARA-enriched formula and the risk of eczema during the first year of life (Lapillonne et al., 2014), but consumption of DHA/ARA-enriched formula was associated with a lower risk of having an increased number of eczema episodes. In the present study, LC-PUFA enrichment was not related to the allergic and respiratory multimorbidity cluster but was related to a lower risk of any allergy, eczema and wheezing.

Overall, studies that have evaluated the effect of prebiotic-enriched formula on allergy in childhood are limited and showed inconsistent findings (Adjibade, Davaisse-Paturet, Divaret-Chauveau, et al., 2022; Cuello-Garcia et al., 2017; Sierra et al., 2015; Skórka et al., 2018).

TABLE 2 Adjusted associations between the enrichment in pre/probiotics of formula consumed at 4 months and the allergic and respiratory multimorbidity clusters in the main sample as in specific sub-samples, EDEN study.^a

	Asthma only	Allergy without asthma	Multi-allergic
Main sample, n = 1243			
Enrichment in pre/probiotics			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Prebiotics	1.24 [0.51–3.03]	0.70 [0.20–2.39]	0.76 [0.17–3.35]
Probiotics	0.79 [0.53–1.17]	0.63 [0.40–0.99]	0.89 [0.52–1.52]
Infant breastfed <1 month, n = 492			
Enrichment in pre/probiotics			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Prebiotics	2.05 [0.65–6.40]	1.15 [0.24–5.59]	– ^b
Probiotics	0.95 [0.51–1.77]	0.67 [0.31–1.44]	1.48 [0.65–3.37]
Infants with the same formula up to 4 months, n = 824			
Enrichment in pre/probiotics			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Prebiotics	1.44 [0.42–4.94]	1.19 [0.25–5.72]	– ^b
Probiotics	0.54 [0.30–0.98]	0.44 [0.22–0.89]	0.89 [0.41–1.92]
Exclusion of early cases (occurring before 8 or 12 months), n = 909			
Enrichment in pre/probiotics			
Not enriched	1 [Ref]	1 [Ref]	1 [Ref]
Prebiotics	2.03 [0.70–5.84]	1.05 [0.24–4.73]	3.48 [0.70–17.38]
Probiotics	0.46 [0.24–0.90]	0.59 [0.30–1.17]	1.12 [0.45–2.82]

Abbreviations: CI, confidence interval; OR, odds ratio.

^aValues are OR [95% CI] from multinomial logistic regressions (reference group = 'Asymptomatic' cluster) adjusted for recruitment centre, maternal characteristics (age at delivery, education level, primiparity), household income and child's characteristics (sex, gestational age, age at infant formula introduction). Separate logistic regression models for each combination of outcome and infant formula characteristics.

^bInsufficient sample size to provide estimates.

Consistent with the results observed in the ELFE cohort (Adjibade, Davaise-Paturet, Divaret-Chauveau, et al., 2022), we found that consumption of prebiotic-enriched formula was not associated with the risk of allergy. Similarly, a Spanish RCT on healthy term infants also found no effect of enrichment of IF in galacto-oligosaccharides on allergic outcomes, including atopic dermatitis, wheezing and food allergy (Sierra et al., 2015).

Regarding probiotic-enriched formula, consumption of a formula enriched in *B. breve* or *S. thermophilus* at age 4 months was not associated with the risk of allergy, consistent with the results observed for itchy rash, wheezing, food allergy, and asthma in the ELFE cohort (Adjibade, Davaise-Paturet, Divaret-Chauveau, et al., 2022). In the present study, the only association found for probiotics was between *B. lactis* and a lower risk of any allergy. To our knowledge, no RCT has assessed the effect of probiotic-enriched formula on allergy risk. However, RCTs that evaluated the effect of pre and/or postnatal supplementation reported inconsistent results,

with a protective effect mostly found when probiotic supplementation was started during pregnancy (Sestito et al., 2020; Sun et al., 2021; Wei et al., 2020).

In the present study, consumption of pHF compared with intact protein formula was not associated with the risk of asthma, consistent with the results of available meta-analyses (Osborn et al., 2018). Conversely, consumption of pHF was associated with a higher risk of food allergy among infants whose mothers had no history of allergy, consistent with the results observed in the PARIS birth cohort, which found that consumption of pHF with the hypoallergenic label, compared to consumption of regular IF, was associated with a higher risk of being sensitized among infants without a parental history of allergy (Amazouz et al., 2021). In the ELFE cohort, with larger sample size, consumption of pHF with the hypoallergenic label was associated with a higher risk of food allergy in both infants with and without a family history of allergy (Davaise-Paturet et al., 2019). Regarding RCTs that have examined

TABLE 3 Adjusted associations between the protein hydrolysis level of formula consumed at 4 months and the allergic and respiratory multimorbidity clusters in the main sample as in specific sub-samples, EDEN study.^a

	Asthma only	Allergy without asthma	Multi-allergic
Main sample, <i>n</i> = 1243			
Protein hydrolysis level			
Intact proteins	1 [Ref]	1 [Ref]	1 [Ref]
Partially hydrolysed proteins	1.36 [0.79–2.33]	2.73 [1.65–4.51]	1.93 [0.98–3.80]
Infant breastfed <1 month, <i>n</i> = 492			
Protein hydrolysis level			
Intact proteins	1 [Ref]	1 [Ref]	1 [Ref]
Partially hydrolysed proteins	3.78 [1.26–11.37]	7.81 [2.48–24.6]	3.64 [0.84–15.7]
Infants with the same formula up to 4 months, <i>n</i> = 824			
Protein hydrolysis level			
Intact proteins	1 [Ref]	1 [Ref]	1 [Ref]
Partially hydrolysed proteins	1.58 [0.88–2.85]	2.31 [1.25–4.26]	2.02 [0.91–4.49]
Exclusion of early cases (occurring before 8 or 12 months), <i>n</i> = 909			
Protein hydrolysis level			
Intact proteins	1 [Ref]	1 [Ref]	1 [Ref]
Partially hydrolysed proteins	1.89 [0.95–3.74]	3.26 [1.63–6.53]	0.91 [0.24–3.41]

Abbreviations: CI, confidence interval; OR, odds ratio.

^aValues are OR [95% CI] from multinomial logistic regressions (reference group = 'Asymptomatic' cluster) adjusted for recruitment centre, maternal characteristics (age at delivery, education level, primiparity), household income and child's characteristics (sex, gestational age, age at infant formula introduction). Separate logistic regression models for each combination of outcome and infant formula characteristics.

the effect of pHF on the risk of allergic diseases, no effect was observed for asthma, rhinitis, and food allergy (Osborn et al., 2018), while some meta-analyses have found a protective effect for atopic dermatitis/eczema in high-risk infants (Vandenplas et al., 2019). We have to acknowledge that, in the present study, all pHF were considered in the same group, whereas protein origin (casein or whey) and the degree of hydrolysis may differ according to pHF brand.

In the present study, two complementary approaches were considered to examine allergic or respiratory outcomes. They were either considered individually or as multimorbidity clusters. Except for PUFA-enrichment, where the statistical power was more limited, findings were consistent across both approaches. For probiotics enrichment, a lower risk was highlighted for both the 'allergy without asthma' cluster and food allergy, but not eczema or allergic rhinitis, suggesting that the association for the cluster was mainly driven by food allergy. For pHF, a higher risk was highlighted for the 'allergy without asthma' cluster, but also for food allergy, eczema, and allergic rhinitis, suggesting that the association is not driven by one atopic disease but was common to all allergic diseases in contrast with respiratory diseases.

The present prospective study involved children from the EDEN mother-child cohort. Health data were reported by parents, and not

validated by medical records, which could lead to a potential measurement bias. However, to limit this bias, we used questionnaires and definitions validated in international consortia (Asher & Weiland, 1998; Pinart et al., 2014). We accounted for the frequent coexistence and inter-relations of allergic and respiratory diseases in children by using multimorbidity clusters. Given the observational design, we cannot entirely exclude reverse causality. However, several sensitivity analyses, performed to examine the robustness of our results and address reverse causation bias, showed similar findings, suggesting that these biases have limited influence on our findings. In particular, the association found between pHF consumption at 4 months remains consistent after excluding infants breastfed longer than 1 month, those consuming more than one IF from birth and early cases, suggesting that this result was not due to the reverse causation bias. Despite the wide range of confounders accounted for in our models, residual confounding cannot be excluded as some factors such as omega-3 or probiotics supplementation during pregnancy or infancy were not measured. Another limitation of this study is the low proportion of children consuming LCPUFA-enriched formula, which could lead to low statistical power to observe significant associations, especially for food allergy. The composition of IF evolved in the last decades and the part of IF enriched in LC-PUFA or in pre- or probiotics was higher in more recent birth cohorts,

whereas the part of IF with partially hydrolysed proteins was lower (Adjibade, Davaisse-Paturet, Bernard, et al., 2022; de Lauzon-Guillain et al., 2018), suggesting that the results have to be confirmed in other cohorts. However, the probiotic strains remained similar (Adjibade, Davaisse-Paturet, Divaret-Chauveau, et al., 2022). In the present study, we only considered milk feeding in the first months and no other dimensions of infant diet such as complementary feeding. Further studies are needed to examine whether accounting for some aspects of complementary feeding, such as delayed introduction of allergenic foods, may affect these findings. In addition, the generalization of our findings should be done with caution as the participants of the EDEN cohort have a higher education level and socioeconomic position than the general population. It would be of great interest to replicate such analyses in more vulnerable populations.

In conclusion, this observational study among formula-fed infants showed that, under real-life conditions, the consumption of pHF was associated with a higher risk of allergy without asthma, and increased food allergy, especially in infants without a maternal history of allergy. The consumption of an LCPUFA-enriched formula or a formula enriched in *B. lactis* appeared to be associated with a lower risk of allergy later in life, but these results were less consistent across analyses. Further observational studies and larger well-designed RCTs involving infants at high risk, but also at low risk of allergy are needed to confirm these results and to hypothesize on the causal nature of the observed associations.

AUTHOR CONTRIBUTIONS

Moufidath Adjibade was involved in data curation, formal analyses and writing—drafting or editing the initial manuscript. Lucille Vigneron was involved in investigation, data curation, and writing—drafting or editing the initial manuscript. Rosalie Delvert was involved in data curation, and writing—reviewing or editing the manuscript. Karine Adel-Patient was involved in supervision and writing—reviewing or editing the manuscript. Amandine Divaret-Chauveau was involved in formal analysis, supervision, and writing—reviewing or editing the manuscript. Isabella Annesi-Maesano was involved in methodology, and writing—reviewing or editing the manuscript. Barbara Heude was involved in funding acquisition, and writing—reviewing or editing the manuscript. Marie-Aline Charles was involved in funding acquisition, investigation, and writing—reviewing or editing the manuscript. Blandine de Lauzon-Guillain was involved in conceptualization, methodology, investigation, supervision, funding acquisition, data curation, formal analysis, writing—drafting the initial manuscript, and writing—reviewing or editing the manuscript.

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CONFLICT OF INTEREST STATEMENT

Amandine Divaret-Chauveau has been invited to allergology and pediatric congresses (inscription and accommodation) by Mead Johnson, Sodilac, and Nutricia. Karine Adel-Patient has been invited by Stallergènes to speak at a conference, outside of the submitted work. None of the other authors declare any conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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