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## **Title: Infant feeding clusters are associated with respiratory health and allergy at school age in the PARIS birth cohort**

**Short title: Infant feeding and respiratory health/allergy at 8 years**

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## **Author contributions**

IM contributed to the implementation of the PARIS birth cohort. IM and FR coordinated the PARIS cohort follow-up. JJ, NB and MBH supervised the medical examination and lung function tests at 8 years at Trousseau Hospital. GL supervised the medical examination and lung function tests at 8 years at Necker Hospital. BLG contributed to the interpretation of feeding data. HA performed the statistical analysis and drafted the manuscript. IM and FR supervised data analysis and manuscript preparation. All authors were involved in the interpretation of the results, critically revised the manuscript and approved the final version as submitted.

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## Abbreviations

95% CI: 95% confidence interval

$a\beta$ : adjusted beta regression coefficient

aOR: adjusted odds ratio

CMP: cow's milk protein

eHF: extensively hydrolysed formula

ETS: environmental tobacco smoke

FeNO: fractional exhaled nitric oxide

FEV<sub>1</sub>: forced expiratory volume in one second

FVC: forced vital capacity

IgE: immunoglobulin E

PARIS: Pollution and asthma risk: an infant study

pHF: partially hydrolysed formula

pHF-HA: partially hydrolysed formula with hypoallergenic label

RCT: randomised clinical trial

WHO: World health organization

## Abstract

**Background:** As infant feeding may influence allergy development, we aimed to identify groups of infants based on feeding practices and to examine their associations with respiratory health/allergy at 8 years in the PARIS birth cohort.

**Methods:** Data on breastfeeding, consumption of infant formula (regular, pre-/probiotics, partially hydrolysed with hypoallergenic label [pHF-HA], extensively hydrolysed [eHF], soya) and solid food introduction were collected using repeated questionnaires at 1, 3, 6, 9 and 12 months. Infants with similar feeding practices over the first year of life were grouped using multidimensional longitudinal cluster analysis. Respiratory/allergic morbidity was studied at 8 years as symptoms, doctor's diagnoses (asthma, hay fever, eczema, food allergy), and measurement of lung function, FeNO and specific IgE. Associations between feeding-related clusters and respiratory/allergic morbidity were investigated using multivariable logistic and linear regression models adjusted for potential confounders including early respiratory/allergic outcomes and parental history of allergy.

**Results:** Five clusters were identified among 3,446 infants: Cluster 1 (45%) mainly fed with regular formula, Cluster 2 (27%) exclusively breastfed during the first 3 months, and three other clusters consuming different types of formula (pre-/probiotics for Cluster 3 [17%], pHF-HA for Cluster 4 [7%], eHF/soya for Cluster 5 [4%]). Compared to Cluster 1, children from Cluster 2 tended to have a lower risk of asthma and children from Cluster 4 had a significant lower lung function (FEV<sub>1</sub>, FVC), higher FeNO and higher risk of sensitisation at 8 years.

**Conclusion:** Early pHF-HA use was negatively associated with objective measures of respiratory/allergic morbidity at school age, while children breastfed for at least 3 months seem protected against asthma at 8 years old.

**Keywords:** allergic morbidity, birth cohort, breastfeeding, hypoallergenic infant formula, lung function

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## Introduction

The prevalence of allergic diseases has been rising for several decades and allergy represents one of the most common chronic diseases in children according to the World Health Organization (WHO)<sup>1</sup>. Many factors can influence their occurrence such as heredity, environment and lifestyle. Infant feeding practices arise many questions. Exclusive breastfeeding for all babies up to six months and at least for four months is recommended by current guidelines<sup>2,3</sup>. Systematic reviews show moderate evidence for a protective effect of breastfeeding on childhood asthma risk and limited evidence regarding other allergic diseases<sup>4,5</sup>.

Different types of infant formula have been developed for infants not exclusively breastfed. Standard infant formulas are based on cow's milk protein (CMP). Thickened formulas with starch and carob are intended for use by infants with reflux<sup>6</sup>. Formulas with pre- or probiotics are used in clinical practice to improve intestinal transit in infants. Partially hydrolysed formulas (pHF) may prevent food allergy among high-risk infants<sup>3,7</sup>, whereas soya and extensively hydrolysed formulas (eHF) are specific formulas to feed infants with CMP allergy.

The potential impact of the type of formula feeding on later allergy is unclear. Von Berg et al<sup>8,9</sup> and Szajewska et al<sup>10</sup> showed pHF had a protective effect on allergic disorders, particularly eczema, whereas two recent reviews found no evidence to support pHF compared to CMP formula to prevent allergy<sup>11,12</sup>. Formula with prebiotics has been suggested to decrease the risk of eczema<sup>13</sup> but the current evidence does not support the use of prebiotics<sup>13</sup> or probiotics<sup>14</sup> for allergy prevention.

Concerning the age at solid food introduction, the recent guidelines recommend introducing all foods between four and six months<sup>3,15,16</sup>. Several studies have shown that delayed introduction of food did not protect against developing allergy, but conversely increased the risk of allergy<sup>17–20</sup>.

As part of the PARIS (Pollution and Asthma Risk: an Infant Study) birth cohort, the aims of the present study were (i) to identify, during the first year of life, feeding-related clusters and their sociodemographic and health determinants and (ii) to investigate their associations with respiratory health/allergy at 8 years.

## Methods

### Population and study design

This research is based on data from the PARIS birth cohort, including 3,840 healthy babies born between 2003 and 2006 in five Parisian maternity hospitals, their parents living in Paris or in the suburbs, as previously described<sup>21</sup>. Data were prospectively collected through repeated self-administered questionnaires and health check-up at 18 months and 8 years of age. The French ethics committees approved the PARIS study (permission nos. 031153, 051289, and ID-RCB 2009-A00824-53). Written informed consent was obtained from all parents.

### **Feeding practices**

Feeding practices were collected regularly during the first year using parental questionnaires at 1, 3, 6, 9 and 12 months. Parents were asked whether their child was breastfed exclusively (only breast milk), partially (both breast milk and infant formula), or not (only infant formula). If applicable, they were also asked to give the name of the infant formulas they used. Four categories of infant formula were considered: (a) regular, gathering standard CMP and thickened formula, (b) pHF with hypoallergenic label (pHF-HA), (c) with pre-/probiotics, (d) soya or eHF (grouped together due to the small number of infants consuming soya formula). Regarding the introduction of solid foods, parents were asked if their infants had eaten fruits, vegetables, egg white, meat or fish since the last questionnaire. Nuts/hazelnuts/peanuts/almonds, celery, kiwi or exotic fruits, egg white and fish were regarded as "allergenic" foods.

### **Health data**

Early wheezing, eczema symptoms and adverse food reactions were collected at each time point during the first year. Ever doctor-diagnosed food allergy was documented at age 6 years. Symptoms and medications in the last 12 months, as well as doctor's diagnoses of asthma, eczema and hay fever ever in life were collected by a paediatrician during the health check-up at 8 years taking place in two reference asthma and allergy medical centres in Paris (Necker and Trousseau hospitals). Current asthma, eczema and rhinitis were defined according to the MEDALL consortium<sup>22</sup>. Current asthma was based on asthma ever doctor-diagnosed, asthma medication and wheezing in the last 12 months (presence of at least two of the three criteria). Current rhinitis was defined as a positive answer to the two following questions from the International Study of Asthma and Allergies in Childhood (ISAAC)<sup>23</sup>: "Has your child had problems with sneezing, or a runny, or blocked nose when he/she did not have a cold or flu?" and "In the past 12 months, has this nose problem been accompanied by itchy–watery eyes?". Current eczema was defined as a positive answer to the following three ISAAC questions<sup>23</sup>: "Has your child ever had an itchy rash which was coming and going for at least six months?"; "Has

your child had this itchy rash at any time in the last 12 months?” and “Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?”. For each child, the best forced vital capacity (FVC) and forced expiratory volume in one second (FEV<sub>1</sub>) among three reproducible spirometry tests performed by trained technicians were recorded<sup>24</sup>. In addition, measurement of the fraction of exhaled nitric oxide (FeNO) was performed using a NIOX MINO<sup>®</sup> electrochemical analyser (Circassia Pharmaceuticals Inc., Chicago, USA). IgE were first analysed in serum with ImmunoCAP Trophatop<sup>®</sup> fx26, fx27, fx28 and Phadiatop<sup>®</sup> (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). In case of positive result of Trophatop<sup>®</sup> or Phadiatop<sup>®</sup>, allergen-specific IgE towards all respective food items and 7 aeroallergens were measured, as previously described<sup>25</sup>. Children were considered as sensitised if they were positive to at least one specific IgE ( $\geq 0.35$  kU<sub>A</sub>/L).

### **Covariates**

Other variables were documented during follow-up using standardised questionnaires:

- parental history of asthma, allergic rhinitis, eczema and food allergy;
- family socioeconomic status (SES) (low, medium, high) based on the highest position among parents, place of residence at birth (Paris city, suburbs), maternal geographic origin (metropolitan France, other), maternal age at delivery, older siblings;
- maternal smoking during pregnancy, number of medical consultations during pregnancy, delivery mode (vaginal, instrumental extraction, caesarean);
- day care attendance, exposure to environmental tobacco smoke (ETS);
- child's sex, weight (kg) and height (cm).

### **Statistical analysis**

To identify groups based upon the course of infant feeding, a version of K-means adapted to the analysis of joint trajectories was used (KmL3D package<sup>26</sup>). Six variables were considered at 5 time periods (1, 3, 6, 9 and 12 months): breastfeeding (no/mixed/exclusive); type of formula consumed: regular (no/yes), pHF-HA (no/yes), with pre-/probiotics (no/yes), eHF/soya (no/yes); and solid food introduction (no/yes: 0, 1,  $\geq 2$  “allergenic” foods). Before entering in the cluster analysis, the breastfeeding and food introduction variables were standardised by dividing each entry by the range. Infants were partitioned into clusters so that the Euclidean distance between infants and the mean trajectory of their respective clusters was minimised. The model was repeatedly fitted with 2 to 8 clusters. The optimal classification was determined using the Calinski-

Harabasz criterion. The analysis was performed on 3,446 infants with data available at least at three time points for each variable (Figure 1). Missing values were imputed by linear interpolation method<sup>24</sup>. Sensitivity analyses were conducted among infants with complete data (n=2,825).

Sociodemographic and health factors associated with these clusters were examined using stepwise multinomial logistic regression models including variables associated with a p-value less than 0.20 in bivariate analyses. As the occurrence of allergic disorders during the first year of life might have influenced parental choice of infant formula, we used Cox models to study whether the early occurrence of wheezing, eczema symptoms or adverse food reactions was associated with the first consumption of pHF-HA and eHF.

Associations of the feeding-related clusters with respiratory/allergic morbidity were studied in children participating in the health check-up at 8 years (N=1,068) (Figure 1). Associations with doctor-diagnosed asthma, hay fever, eczema and food allergy, sensitisation, FeNO >20 ppb<sup>27</sup>, and respiratory indices (FEV<sub>1</sub> [mL], FVC [mL], FEV<sub>1</sub>/FVC ratio [%]) were studied using multivariable logistic and linear regression models, adjusted for potential confounders identified using a directed acyclic graph (DAG)<sup>28</sup>, including parental history of allergy and early respiratory/allergic outcomes. Possible effect modification by parental history of allergy was explored by testing multiplicative interactions using a significance level of 0.15, and stratified models were built if necessary.

Results from regression models were expressed as adjusted odds ratios (aOR) and beta coefficients ( $\alpha\beta$ ) with their 95% confidence intervals (95% CI). The significance level was 0.05. Cluster analyses were conducted using R Studio (version 3.5.2, R foundation for Statistical Computing, Vienna, Austria). Regression analyses were performed using Stata/SE 15.1 (StataCorp, College Station, Texas, USA).

## Results

### Participants

Compared with PARIS infants who were not included in the infant feeding cluster analysis, those participating were more likely to live in a family with high SES, to have older siblings, parental history of allergy, and to be less exposed to ETS during pregnancy and at home at birth. However, they did not differ regarding sex, place of residence at birth and parental history of asthma (Table 1).

## **Description of feeding habits**

In infants with complete data, the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any and exclusive breastfeeding was 3 [0-6] months and 1 [0-3] month, respectively. About 88% of infants had received regular formula at least once by the age of 1 year, 15.2% pHF-HA, 31.1% formula with pre-/probiotics, and 5.8% eHF/soya. The median period of solid food introduction was 3-6 months for any solid food, and 6-9 months for “allergenic” foods.

## **Identification of feeding-related clusters**

The analysis showed optimal classification for five clusters (Figure 2, Table S1):

- Cluster 1 considered as reference (44.7% of infants) included infants mainly fed with regular formula; the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any breastfeeding was 1 [0-3] month;
- Cluster 2 (27.2%) was characterised by infants all breastfed at 3 months (exclusively for 94% of them); the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any and exclusive breastfeeding was 6 [3-9] months and 3 [3-6] months, respectively;
- Cluster 3 (17.1%) used pre-/probiotic-enriched formula; the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any breastfeeding was 1 [0-3] month;
- Cluster 4 (7.3%) used pHF-HA at 3 months then regular formula; the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any breastfeeding was 3 [1-3] months;
- Cluster 5 (3.7%) had an increasing use of eHF or soya formula over the first year; the median duration [25<sup>th</sup>-75<sup>th</sup> percentile] of any breastfeeding was 3 [0-6] months.

The median period at introduction of solid food was 3-6 months for Clusters 1, 2, 3, and 6-9 months for Clusters 4 and 5. The clusters did not differ regarding the median period when “allergenic” solid foods were introduced (6-9 months), except Cluster 5 with significant later introduction (after 12 months). Sensitivity analyses performed in infants with complete data led to similar clusters (Figure S1).

## **Factors associated with feeding-related clusters**

Compared to infants in Cluster 1, infants from all other clusters had more often parental history of allergy, and infants from Clusters 2, 4 and 5 had higher family SES (Table 2). Infants from Cluster 2 had less often a mother from metropolitan France, more often older siblings, less adverse food reactions in the first three months, and less often attended day care at 3 months

Parental history of asthma, eczema, allergic rhinitis and food allergy, as well as early eczema symptoms were more frequent in Cluster 4. However, the additional Cox analysis showed that adverse food reactions were not associated with the initiation of pHF-HA. Infants starting pHF-HA feeding had even less often wheezing and eczema symptoms than other children (model 1, Table S2).

Infants from Cluster 5 were more likely to suffer from eczema symptoms or adverse food reactions in the first three months and to have a weight below the 25<sup>th</sup> percentile of the WHO Growth Standards at 3 months. Cox analysis confirmed that infants consuming eHF/soya formula had a higher risk of adverse food reactions before eHF/soya formula was initiated (model 2, Table S2).

### **Feeding-related clusters and respiratory/allergic morbidity at school age**

Regarding doctor-diagnosed diseases, compared to Cluster 1, children from Cluster 5 were more likely to have been diagnosed with food allergy since birth (aOR= 15.00, 95% CI: 4.68, 48.13). Children from Cluster 2 tended to have a lower risk of current asthma at 8 years (aOR= 0.53, 95% CI: 0.27, 1.04). Clusters 3 and 4 did not differ from Cluster 1 (Table 3).

Concerning lung function, compared to Cluster 1, children from Cluster 4 had lower FEV<sub>1</sub> ( $\alpha\beta$ = -61.6 mL, 95% CI: -112.8, -10.5) and FVC ( $\alpha\beta$ = -85.6 mL, 95% CI: -146.6, -24.5). In addition, they were more likely to have FeNO >20 ppb (aOR= 2.64, 95% CI: 1.33, 5.24) and to be sensitised (aOR= 2.10, 95% CI: 1.18, 3.73). Clusters 2, 3, and 5 did not differ from Cluster 1 (Table 4).

Among children from Cluster 4, those without parental history of allergy had a higher risk of being sensitised (aOR= 5.02, 95% CI: 1.69, 14.91) but not those with parental allergy (aOR= 1.43, 95% CI: 0.71, 2.89) (p for interaction=0.09).

## **Discussion**

### **Key results**

Among a population-based birth cohort and using an unsupervised classification method based on three main features of infant feeding (breastfeeding, infant formula, solid food introduction), five clusters were identified. These clusters differed in terms of sociodemographic characteristics,

parental history of allergy, and early respiratory/allergic outcomes. Compared to the group of infants mainly fed with regular formula, three clusters were associated with respiratory/allergic morbidity:

- lower risk of current asthma at 8 years in children exclusively breastfed during the first 3 months;
- lower lung function and higher risk of airway inflammation and sensitisation at 8 years in children who received pHF-HA in the first 3 months;
- higher risk of food allergy diagnosis in children who received eHF, suggesting a reverse causality as expected.

### **Strengths and limitations**

One of the main strengths of this study is the good quality of data prospectively collected from PARIS participants. Indeed, data relied on medical diagnoses, standardised questionnaires and objective parameters measured during a health check-up carried out in two reference paediatric asthma and allergy medical centres. In addition, detailed infant feeding data were prospectively documented all along the first year of life. A large number of potential confounding factors related to both infant feeding and later respiratory/allergic morbidity have been taken in consideration. Few previous studies have used unsupervised and multidimensional statistical approaches without a priori hypothesis to characterise infant feeding practices<sup>29–31</sup>. Several sensitivity analyses were conducted to examine the potential impact of biases such as selection bias (imputation and analysis with complete data) and reverse causality (additional Cox analyses).

In our study, we considered all types of pHF-HA together due to the small number of infants consuming pHF-HA. Pooling all pHF-HA might result in imprecision which could dilute the effect of a particular type. Indeed, the potential benefit of a hydrolysed formula in allergy prevention may depend not only on the degree of hydrolysis, but also on the method of hydrolysis and the protein source (whey/casein)<sup>32</sup>. Furthermore, it was not possible to deepen the study of formulas enriched with pre-/probiotics due to the lack of data on the strains and quantity. Finally, in our study the attrition rate at 8 years represented about one third of the initial cohort, mainly due to the high mobility of the Paris population. Families moving to the province or abroad had to stop their participation in the PARIS cohort follow-up. Among children still followed at 8 years, almost half of them attended the 8-year health check-up including blood sampling. This check-up took half a day and many families could not make themselves available.

### **Interpretation**

## Infant feeding groups

Our cluster analysis led to five clusters mainly determined by infant formula or breastmilk consumption. The period of solid food introduction did not seem to drive their structure probably because it was quite homogeneous in all infants, mainly between 3 and 6 months, except in Clusters 4 and 5 where it was later. Indeed, the French dietary guidelines recommended no solid food before age 6 months for infants with a family history of allergy<sup>7</sup>.

Three teams previously used unsupervised methods (cross-sectional principal component analyses<sup>29,30</sup>, latent class transition analyses<sup>31</sup>) to identify early feeding patterns. Differences between these studies in terms of design, statistical methods and variables make comparisons difficult. Nevertheless, all the authors found a breastfeeding pattern<sup>29–31</sup>, gathering 23–26% of infants receiving direct breastfeeding in months 1–4 in the study by Karmaus et al<sup>31</sup>, which is comparable to 27.2% of PARIS cohort infants in Cluster 2. None of these studies examined types of infant formula in detail.

Conversely, infant formula consumption was well described in the ELFE cohort<sup>33</sup>. At 2 months, around 30% of infants received regular formula, 58.1% formula enriched in prebiotics/probiotics, 31.5% thickened formula, 1.4% eHF, and pHF concerned 6.5% of infants at 2 months and only 3.6% at 10 months. Their results are consistent in terms of proportions with our data, except for formula enriched in pre-/probiotics which was less used in our study, as in the EDEN cohort<sup>34</sup>, probably because their large introduction on the market started from around 2010 in France, after the recruitment of PARIS infants.

## Factors associated with infant feeding groups

Parents of breastfed infants or who used specific infant formula were more likely to have history of at least one allergic disease than parents who early used regular formula. Indeed, allergic parents are more prone or advised to try preventing allergy in their child through infant feeding<sup>3</sup>.

In our study, the choice of pHF-HA was especially strongly driven by parental history of asthma, allergic rhinitis, eczema or food allergy and high parental SES, consistently with the literature where pHF use had already been positively associated with parental history of allergy<sup>33,34</sup>, high family income<sup>33</sup> and maternal education<sup>34</sup> compared with regular formulas. Interestingly, the choice of pHF-HA was not driven by infant's early allergic outcomes in the PARIS cohort.

In the present study, breastfeeding during the first three months was associated with high parental SES, older siblings and mother from outside metropolitan France, which is consistent with the literature. In previous studies, the “breastfeeding pattern” was positively associated with maternal age<sup>29–31</sup>, education<sup>29–31</sup> and older siblings<sup>29</sup>. Families with higher SES are generally

more compliant with public health recommendations<sup>35,36</sup>. Moreover, in developed countries, women born outside the country appear to breastfeed more than the native-born<sup>37,38</sup>.

PARIS infants who received pre-/probiotics formula were more likely to be breastfed at maternity for a short period (median 1 month) and to live in Paris city at birth. Short breastfeeding duration was also associated with pre-/probiotics formula in the ELFE cohort<sup>33</sup>.

Unsurprisingly, PARIS infants with early adverse food reaction (including diarrhoea and vomiting) and low weight at 3 months were more likely to receive eHF/soya. Indeed, the use of eHF is recommended in the presence of such symptoms evocative of CMP allergy<sup>39</sup>. Similarly, in the ELFE cohort, parental concern at 2 months related to diarrhoea was associated with eHF consumption<sup>33</sup>.

#### Infant feeding groups and respiratory/allergic morbidity

Our feeding-related clusters were associated with respiratory/allergic morbidity at 8 years. Children breastfed for at least 3 months tended to have a lower risk of later asthma but there were no associations with lung function or FeNO, as also recently found by Gorlanova et al<sup>40</sup> in healthy children. The beneficial effect of breastfeeding on allergic disorders which might come from an immunomodulatory role remains unclear<sup>41</sup>. In the BAMSE cohort, Kull et al<sup>42</sup> showed that exclusive breastfeeding for 4 months or more reduced the risk of asthma by the age of 4 years (OR= 0.72; 95% CI: 0.53, 0.97). In their meta-analysis, Lodge et al<sup>4</sup> described some evidence that breastfeeding is protective for asthma (at 5-15 years) but this result was not confirmed in the meta-analysis by Victora et al<sup>43</sup> restricted to high quality studies. Neither of these two meta-analyses<sup>4,43</sup> found evidence for a protective effect of breastfeeding on eczema or rhinitis.

In our study, after adjusting for parental history of allergy and early allergic disorders, children who received all types of pHF-HA studied together were not at lower risk of later respiratory/allergic outcomes but surprisingly, at higher risk, which did not seem to be due to reverse causality. We however cannot rule out residual confounding explaining these observed associations. Currently only one randomised-controlled trial conducted among children at high risk of allergy, the GINI trial, has demonstrated a beneficial effect of pHF (whey-based pHF) in the first four months on atopic dermatitis during the first 3 years, but not on asthma, allergic urticaria or food allergy<sup>8</sup>. The cumulative incidence of eczema from birth to 15 years and the prevalence of allergic rhinitis between 11 to 15 years were lower compared to children who received standard formula<sup>9</sup>. Although the target of pHF are infants at high risk of allergy, it is noteworthy that in our population, more than a third of consumers did not have any parental history of allergy. The Cochrane systematic review<sup>11</sup> as well as a clinical report from the American Academy of

Pediatrics<sup>44</sup> found no evidence to support pHF compared with regular formula for allergic diseases prevention. Deleterious associations were even reported in a recent study in France<sup>45</sup>, consistently with our results. The authors showed that pHF-HA and whey-based pHF use at 2 months, compared to non-hydrolysed formula, was associated with wheezing and food allergy in infancy<sup>45</sup>.

For pre-/probiotics formula, no associations with respiratory/allergic morbidity were found in our study. A Cochrane review<sup>13</sup> concluded in 2013 there was no evidence for a beneficial effect of prebiotics regarding allergy, but the meta-analysis of four studies found a significant reduction in eczema (typical risk ratio=0.68, 95% CI: 0.48, 0.97). Grouping together all the prebiotics and probiotics regardless of the type of strains could partly explain the lack of association in our study<sup>34,46</sup>.

## Conclusion

Children breastfed for at least 3 months tended to be protected against asthma at 8 years of age. Consumption of pHF-HA was negatively associated with objective measures of respiratory/allergic morbidity at school age, even after adjusting for parental history of allergy and studying possible reverse causation bias. These results question the use of pHF-HA in all infants notably those without parental history of allergy. The efficacy of pHF-HA in reducing the risk of developing allergy deserve to be confirmed by more randomised-controlled trials, as it is now required at the European level<sup>47</sup>.

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## Tables

**Table 1.** Characteristics of the 3,446 infants from the PARIS cohort included in the infant feeding cluster analysis compared to those not included.

|                                                                       | Included<br>N= 3,446 | Not included<br>N= 394 | p <sup>†</sup>   |
|-----------------------------------------------------------------------|----------------------|------------------------|------------------|
| <b>Sex</b>                                                            |                      |                        |                  |
| Male, n (%)                                                           | 1,768 (51.3)         | 202 (51.3)             | 0.99             |
| Female, n (%)                                                         | 1,678 (48.7)         | 192 (48.7)             |                  |
| <b>Family socioeconomic status</b>                                    |                      |                        |                  |
| High, n (%)                                                           | 2,208 (64)           | 186 (47.2)             | <b>&lt;0.001</b> |
| Medium, n (%)                                                         | 947 (27.5)           | 133 (33.8)             |                  |
| Low, n (%)                                                            | 291 (8.5)            | 75 (19.0)              |                  |
| <b>Older sibling(s)</b>                                               |                      |                        |                  |
| None, n (%)                                                           | 1,978 (57.4)         | 201 (51.0)             | <b>&lt;0.001</b> |
| One, n (%)                                                            | 1,144 (33.2)         | 132 (33.5)             |                  |
| Two or more, n (%)                                                    | 324 (9.4)            | 61 (15.5)              |                  |
| <b>Place of residence at birth</b>                                    |                      |                        |                  |
| Paris city, n (%)                                                     | 2,180 (63.3)         | 253 (64.2)             | 0.72             |
| Paris suburbs, n (%)                                                  | 1,265 (36.7)         | 141 (35.8)             |                  |
| <b>Maternal age at birth above 35 years, n (%)</b>                    | 844 (24.6)           | 101 (25.6)             | 0.62             |
| <b>Parental history of asthma, n (%)</b>                              | 694 (20.2)           | 70 (17.9)              | 0.27             |
| <b>Parental history of asthma, allergic rhinitis or eczema, n (%)</b> | 1,842 (53.6)         | 186 (47.5)             | <b>0.02</b>      |
| <b>Maternal smoking during pregnancy, n (%)</b>                       | 372 (10.8)           | 61 (15.5)              | <b>0.01</b>      |
| <b>Exposure to ETS at home at birth, n (%)</b>                        | 702 (20.65)          | 95 (29.4)              | <b>&lt;0.001</b> |

ETS: environmental tobacco smoke

<sup>†</sup> Chi-squared test. Bold p-values were used to highlight significant associations (p<0.05).

**Table 2.** Factors associated with infant feeding clusters: multivariable multinomial regression model in infants from the PARIS birth cohort.

|                                                            | Cluster 1<br>n=1,241 | Cluster 2<br>n=774              | Cluster 3<br>n=474          | Cluster 4<br>n=205           | Cluster 5<br>n=111       |
|------------------------------------------------------------|----------------------|---------------------------------|-----------------------------|------------------------------|--------------------------|
|                                                            | Ref.                 | aOR (95% CI)                    | aOR (95% CI)                | aOR (95% CI)                 | aOR (95% CI)             |
| <b>Environmental characteristics and lifestyle</b>         |                      |                                 |                             |                              |                          |
| Breastfeeding at maternity (yes vs. no)                    | Ref.                 | <b>59.48</b><br>(26.28, 134.59) | <b>1.98</b><br>(1.52, 2.59) | <b>5.82</b><br>(3.36, 10.08) | 1.38<br>(0.85, 2.24)     |
| Place of residence at birth (Paris city vs. Paris suburbs) | Ref.                 | 1.07 (0.87, 1.31)               | <b>1.38 (1.10, 1.74)</b>    | 1.23 (0.89, 1.70)            | 1.12 (0.73, 1.73)        |
| Maternal geographic origin (other vs. metropolitan France) | Ref.                 | <b>1.32 (1.02, 1.71)</b>        | 0.91 (0.67, 1.24)           | 0.84 (0.54, 1.31)            | 0.57 (0.30, 1.08)        |
| Day care at 3 months (yes vs. no)                          | Ref.                 | <b>0.16 (0.11, 0.24)</b>        | 0.93 (0.72, 1.20)           | 1.01 (0.71, 1.44)            | 0.62 (0.37, 1.04)        |
| Maternal smoking during pregnancy (yes vs. no)             | Ref.                 | 0.88 (0.64, 1.23)               | 0.95 (0.68, 1.33)           | 0.92 (0.56, 1.51)            | <b>0.36 (0.16, 0.84)</b> |
| Mode of delivery                                           |                      |                                 |                             |                              |                          |
| Vaginal                                                    | Ref.                 | Ref.                            | Ref.                        | Ref.                         | Ref.                     |
| Instrumental extraction                                    | Ref.                 | 1.01 (0.76, 1.34)               | 1.18 (0.88, 1.59)           | 1.03 (0.68, 1.58)            | 1.21 (0.67, 2.15)        |
| Caesarean                                                  | Ref.                 | 0.96 (0.73, 1.27)               | 1.28 (0.96, 1.71)           | 1.07 (0.70, 1.62)            | <b>1.68 (1.00, 2.82)</b> |
| Maternal age at birth (≥median vs. <median) <sup>†</sup>   | Ref.                 | 0.96 (0.78, 1.18)               | 1.07 (0.85, 1.34)           | 0.97 (0.70, 1.34)            | <b>1.76 (1.13, 2.73)</b> |
| Parental SES at birth (high vs. low, medium)               | Ref.                 | <b>1.30 (1.06, 1.61)</b>        | 0.99 (0.79, 1.24)           | <b>1.54 (1.09, 2.17)</b>     | <b>1.60 (1.01, 2.54)</b> |
| Older siblings                                             |                      |                                 |                             |                              |                          |
| No                                                         | Ref.                 | Ref.                            | Ref.                        | Ref.                         | Ref.                     |
| Yes, 1                                                     | Ref.                 | <b>1.29 (1.03, 1.63)</b>        | 0.88 (0.68, 1.13)           | 0.99 (0.70, 1.42)            | 1.14 (0.71, 1.82)        |
| Yes, 2 or more                                             | Ref.                 | <b>1.92 (1.34, 2.74)</b>        | 0.86 (0.55, 1.32)           | 0.85 (0.43, 1.66)            | 0.65 (0.26, 1.65)        |
| <b>Parental history of allergy</b>                         |                      |                                 |                             |                              |                          |
| Asthma (yes vs. no)                                        | Ref.                 | 1.18 (0.91, 1.52)               | 1.05 (0.79, 1.39)           | <b>1.79 (1.26, 2.54)</b>     | 1.34 (0.82, 2.18)        |
| Eczema (yes vs. no)                                        | Ref.                 | 1.10 (0.84, 1.43)               | 1.00 (0.75, 1.34)           | <b>1.50 (1.04, 2.16)</b>     | <b>2.31 (1.47, 3.64)</b> |
| Food allergy (yes vs. no)                                  | Ref.                 | 1.12 (0.77, 1.62)               | 0.88 (0.58, 1.34)           | <b>1.73 (1.08, 2.77)</b>     | 1.04 (0.51, 2.12)        |
| Allergic rhinitis (yes vs. no)                             | Ref.                 | <b>1.44 (1.17, 1.79)</b>        | <b>1.49 (1.19, 1.88)</b>    | <b>1.74 (1.27, 2.39)</b>     | 1.18 (0.77, 1.82)        |

| Child's characteristics                                  |      |                          |                   |                          |                          |
|----------------------------------------------------------|------|--------------------------|-------------------|--------------------------|--------------------------|
| Sex (girl vs. boy)                                       | Ref. | 0.99 (0.81, 1.21)        | 1.07 (0.86, 1.32) | 0.82 (0.61, 1.12)        | 0.67 (0.44, 1.02)        |
| Adverse food reaction in the first 3 months (yes vs. no) | Ref. | <b>0.59 (0.38, 0.92)</b> | 0.65 (0.41, 1.03) | 0.53 (0.26, 1.07)        | <b>5.23 (3.22, 8.49)</b> |
| Eczema symptoms in the first 3 months (yes vs. no)       | Ref. | 0.96 (0.76, 1.21)        | 0.88 (0.67, 1.14) | <b>1.51 (1.08, 2.11)</b> | <b>2.84 (1.87, 4.32)</b> |
| Wheezing in the first 3 months (yes vs. no)              | Ref. | 0.69 (0.42, 1.14)        | 0.72 (0.41, 1.27) | 0.95 (0.47, 1.93)        | 1.79 (0.83, 3.67)        |
| WHO weight percentile at 3 months                        |      |                          |                   |                          |                          |
| <25 <sup>th</sup>                                        | Ref. | 0.94 (0.75, 1.18)        | 1.10 (0.86, 1.40) | 1.10 (0.79, 1.55)        | <b>1.58 (1.03, 2.44)</b> |
| 25 <sup>th</sup> -75 <sup>th</sup>                       | Ref. | Ref.                     | Ref.              | Ref.                     | Ref.                     |
| >75 <sup>th</sup>                                        | Ref. | 0.95 (0.71, 1.26)        | 1.18 (0.87, 1.60) | 0.84 (0.52, 1.36)        | 0.59 (0.28, 1.25)        |

aOR: adjusted odds ratio, 95% CI: 95% confidence interval, SES: socioeconomic status, WHO: world health organization. † The median of maternal age at birth is 32 years. The odds ratios in bold differ significantly from the reference (p<0.05).

1 **Table 3.** Adjusted associations of infant feeding clusters with (a) ever doctor-diagnosed respiratory/allergic diseases at 8 years and (b) current  
2 respiratory/allergic disease at 8 years in children from the PARIS birth cohort.

|                                                  | Cluster 1      |              | Cluster 2      |                   | Cluster 3      |                   | Cluster 4     |                   | Cluster 5     |                            |
|--------------------------------------------------|----------------|--------------|----------------|-------------------|----------------|-------------------|---------------|-------------------|---------------|----------------------------|
|                                                  | n/N<br>%       | aOR (95% CI) | n/N<br>%       | aOR (95% CI)      | n/N<br>%       | aOR (95% CI)      | n/N<br>%      | aOR (95% CI)      | n/N<br>%      | aOR (95% CI)               |
| <b>Ever doctor-diagnosed diseases at 8 years</b> |                |              |                |                   |                |                   |               |                   |               |                            |
| Asthma ever                                      | 33/327<br>10.1 | Ref.         | 22/245<br>9.0  | 0.82 (0.44, 1.52) | 18/140<br>12.9 | 1.38 (0.73, 2.61) | 11/61<br>18.0 | 1.80 (0.82, 3.97) | 3/25<br>12.0  | 0.96 (0.26, 3.61)          |
| Hay fever ever                                   | 15/330<br>9.0  | Ref.         | 16/243<br>6.6  | 1.27 (0.56, 2.88) | 8/140<br>5.7   | 1.37 (0.54, 3.48) | 2/61<br>3.3   | 0.62 (0.13, 2.98) | 2/25<br>8.0   | 1.56 (0.29, 8.30)          |
| Eczema ever                                      | 70/329<br>21.3 | Ref.         | 58/244<br>23.8 | 1.12 (0.72, 1.74) | 39/139<br>28.1 | 1.52 (0.93, 2.47) | 15/60<br>25.0 | 0.98 (0.50, 1.95) | 9/24<br>37.5  | 1.59 (0.62, 4.09)          |
| Food allergy ever                                | 12/301<br>4.0  | Ref.         | 7/221<br>3.2   | 0.99 (0.34, 2.82) | 3/123<br>2.4   | 0.76 (0.19, 2.90) | 1/56<br>1.8   | 0.30 (0.03, 2.76) | 9/25<br>36.0  | <b>15.00 (4.68, 48.13)</b> |
| Allergy ever                                     | 47/362<br>13.0 | Ref.         | 39/267<br>14.6 | 0.95 (0.58, 1.57) | 17/147<br>11.6 | 0.75 (0.41, 1.39) | 11/65<br>16.9 | 1.13 (0.53, 2.39) | 12/29<br>41.4 | <b>4.99 (2.08, 11.97)</b>  |
| <b>Current diseases at 8 years</b>               |                |              |                |                   |                |                   |               |                   |               |                            |
| Current asthma                                   | 33/354<br>9.3  | Ref.         | 16/263<br>6.1  | 0.53 (0.27, 1.04) | 12/146<br>8.2  | 0.83 (0.41, 1.72) | 6/64<br>9.4   | 0.94 (0.36, 2.45) | 5/28<br>17.9  | 1.88 (0.62, 5.66)          |

|                  |                |      |                |                   |                |                   |               |                   |              |                   |
|------------------|----------------|------|----------------|-------------------|----------------|-------------------|---------------|-------------------|--------------|-------------------|
| Current rhinitis | 24/362<br>6.6  | Ref. | 23/266<br>8.7  | 1.11 (0.58, 2.11) | 14/147<br>9.5  | 1.35 (0.66, 2.78) | 5/65<br>7.7   | 0.94 (0.33, 2.65) | 4/29<br>13.8 | 2.23 (0.66, 7.56) |
| Current eczema   | 46/345<br>13.3 | Ref. | 36/253<br>14.2 | 1.04 (0.62, 1.79) | 19/143<br>13.3 | 0.95 (0.52, 1.74) | 13/61<br>21.3 | 1.39 (0.67, 2.90) | 6/25<br>24.0 | 1.50 (0.53, 4.21) |

1 aOR: adjusted odds ratio, 95% CI: 95% confidence interval.

2 The odds ratios in bold differ significantly from the reference ( $p < 0.05$ ). N total for each model may vary due to missing information.

3 All models were adjusted for the following variables: child's sex, mode of delivery, maternal age at birth, breastfeeding at maternity, maternal geographic origin, day care at  
4 3 months, parental socioeconomic status at birth, older siblings at birth, maternal smoking during pregnancy, exposure to environmental tobacco smoke during the first year  
5 of life, parental history of asthma, eczema, allergic rhinitis, and food allergy, adverse food reaction in the first 3 months, eczema symptoms in the first 3 months, wheezing in  
6 the first 3 months, lower respiratory infection (bronchitis or bronchiolitis) during the first year, body mass index for age and sex at 8 years based on the WHO child growth  
7 standards.

**Table 4.** Adjusted associations of infant feeding clusters with respiratory parameters and allergic sensitisation at 8 years in children from the PARIS birth cohort.

|                           | Cluster 1       |                    | Cluster 2      |                    | Cluster 3      |                     | Cluster 4     |                              | Cluster 5     |                     |
|---------------------------|-----------------|--------------------|----------------|--------------------|----------------|---------------------|---------------|------------------------------|---------------|---------------------|
|                           | N               | a $\beta$ (95% CI) | N              | a $\beta$ (95% CI) | N              | a $\beta$ (95% CI)  | N             | a $\beta$ (95% CI)           | N             | a $\beta$ (95% CI)  |
| FEV <sub>1</sub> (mL)     | 342             | Ref.               | 255            | 8.7 (-23.7, 41.1)  | 139            | -5.9 (-43.0, 31.1)  | 62            | <b>-61.6 (-112.8, -10.5)</b> | 27            | 17.1 (-56.8, 91.0)  |
| FVC (mL)                  | 342             | Ref.               | 255            | -0.5 (-39.1, 38.2) | 139            | -0.0 (-44.5, 43.9)  | 62            | <b>-85.6 (-146.6, -24.5)</b> | 27            | 24.9 (-63.2, 113.1) |
| FEV <sub>1</sub> /FVC (%) | 342             | Ref.               | 255            | 0.39 (-0.54, 1.32) | 139            | -0.59 (-1.65, 0.48) | 62            | 0.56 (-0.91, 2.03)           | 27            | -0.12 (-2.24, 2.00) |
|                           | n/N %           | aOR (95% CI)       | n/N %          | aOR (95% CI)       | n/N %          | aOR (95% CI)        | n/N %         | aOR (95% CI)                 | n/N %         | aOR (95% CI)        |
| FeNO >20 ppb              | 51/307<br>16.6  | Ref.               | 46/226<br>20.4 | 1.06 (0.65, 1.74)  | 24/123<br>19.5 | 1.22 (0.69, 2.16)   | 18/57<br>31.6 | <b>2.64 (1.33, 5.24)</b>     | 3/26<br>11.5  | 0.44 (0.12, 1.68)   |
| Allergic sensitisation    | 113/345<br>32.8 | Ref.               | 92/247<br>37.2 | 1.20 (0.82, 1.76)  | 48/135<br>35.6 | 1.17 (0.75, 1.81)   | 32/63<br>50.8 | <b>2.10 (1.18, 3.73)</b>     | 12/27<br>44.4 | 1.52 (0.66, 3.51)   |

a $\beta$ : adjusted regression coefficient, aOR: adjusted odds ratio, 95% CI: 95% confidence interval, FeNO: fraction of exhaled nitric oxide, FEV<sub>1</sub>: forced expiratory volume in one second, FVC: forced vital capacity.

The regression coefficients and odds ratios in bold differ significantly from the reference ( $p < 0.05$ ). N total for each model may vary due to missing information.

All models were adjusted for the following variables: child's sex, mode of delivery, maternal age at birth, breastfeeding at maternity, child's ethnicity (FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC models) or maternal geographic origin (FeNO and IgE models), day care at 3 months, parental socioeconomic status at birth, older

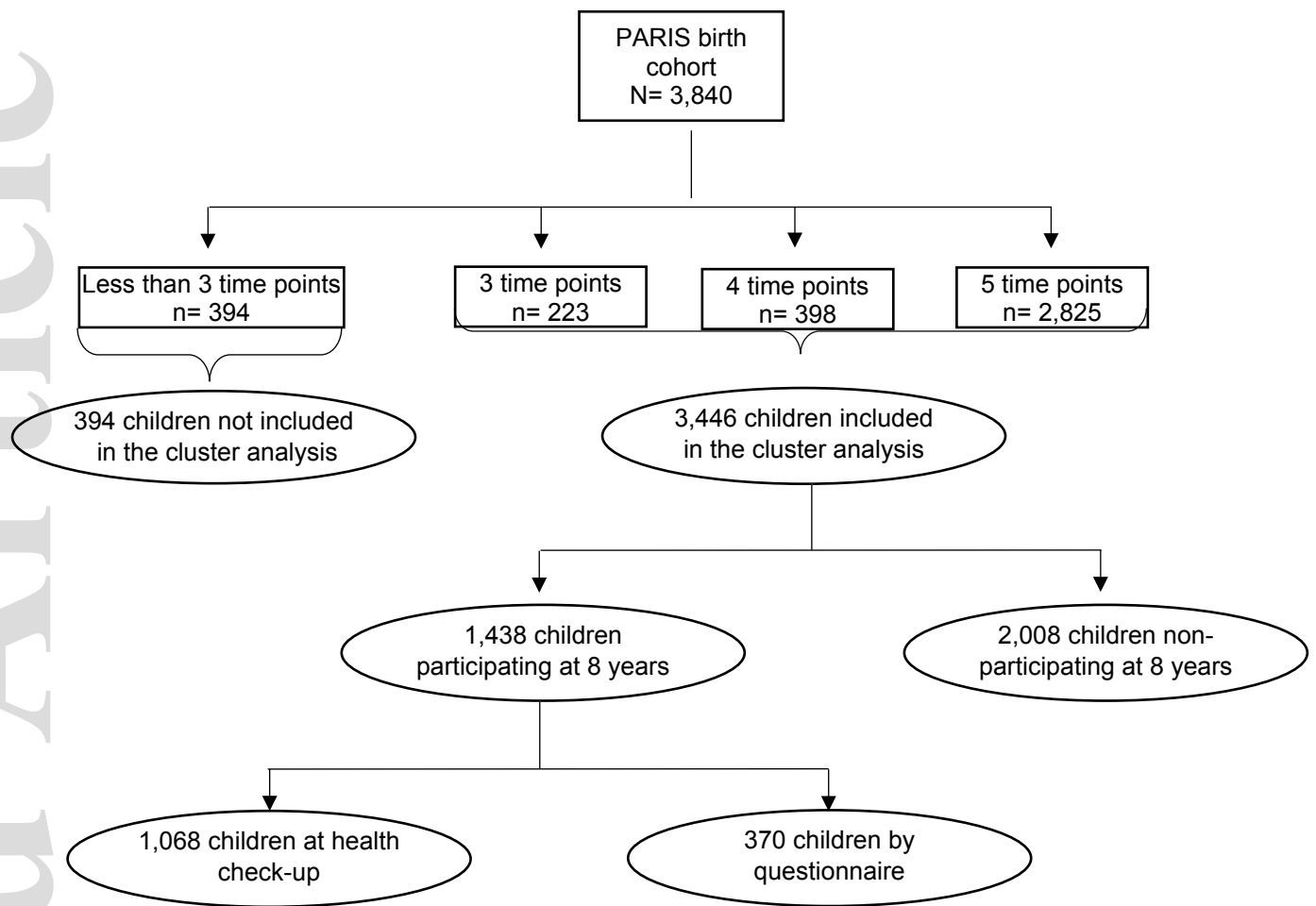
siblings at birth, maternal smoking during pregnancy, exposure, environmental tobacco smoke during the first year of life, parental history of asthma, eczema, allergic rhinitis, and food allergy, adverse food reaction in the first 3 months, eczema symptoms in the first 3 months, wheezing in the first 3 months, lower respiratory infection (bronchitis or bronchiolitis) during the first year, body mass index for age and sex at 8 years based on the WHO child growth standards. FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC models were also adjusted for age and height at health check-up. FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC models were further adjusted for inhaled medication use, and FeNO model for inhaled corticosteroids use at age 8 years.

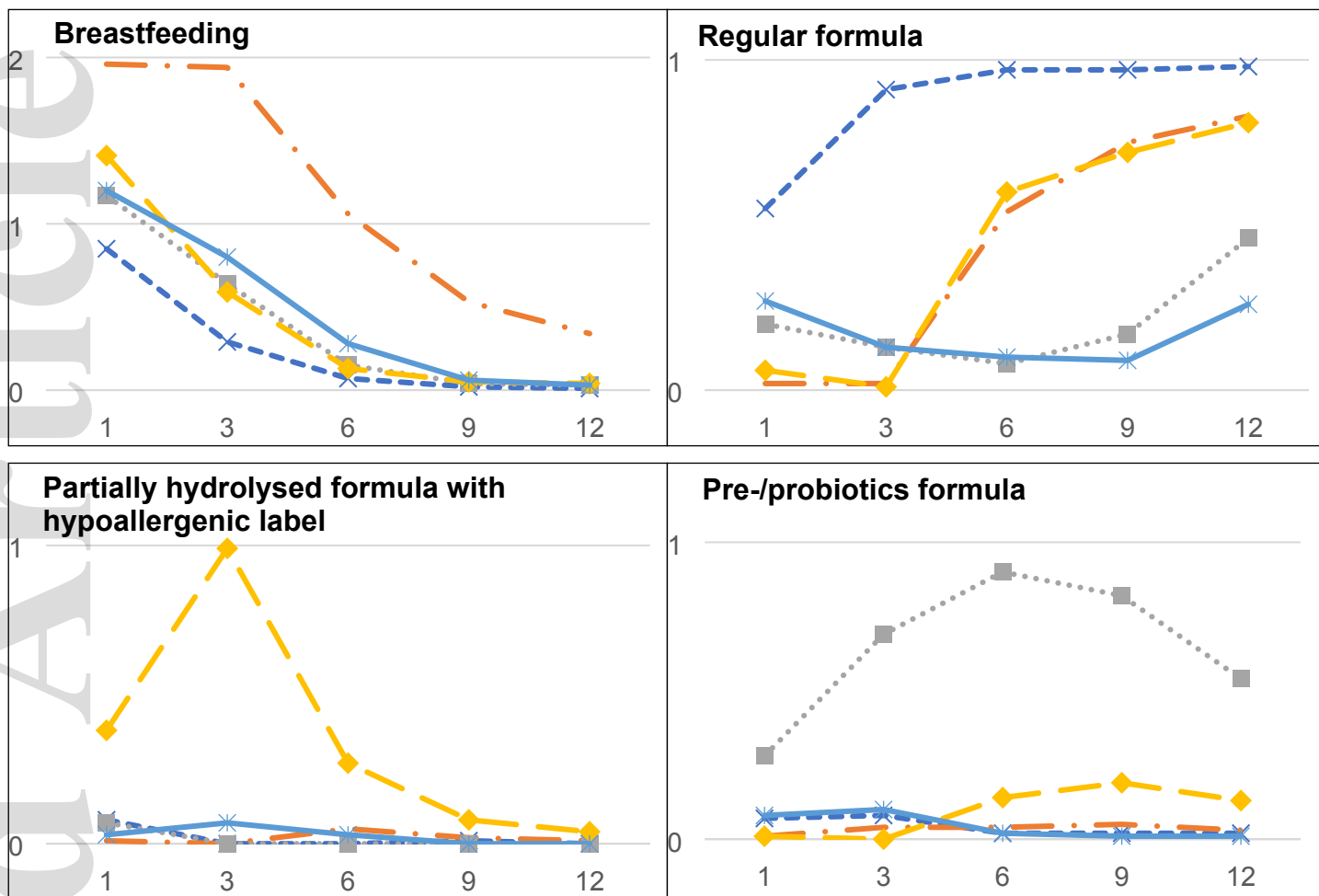
## Figure legends

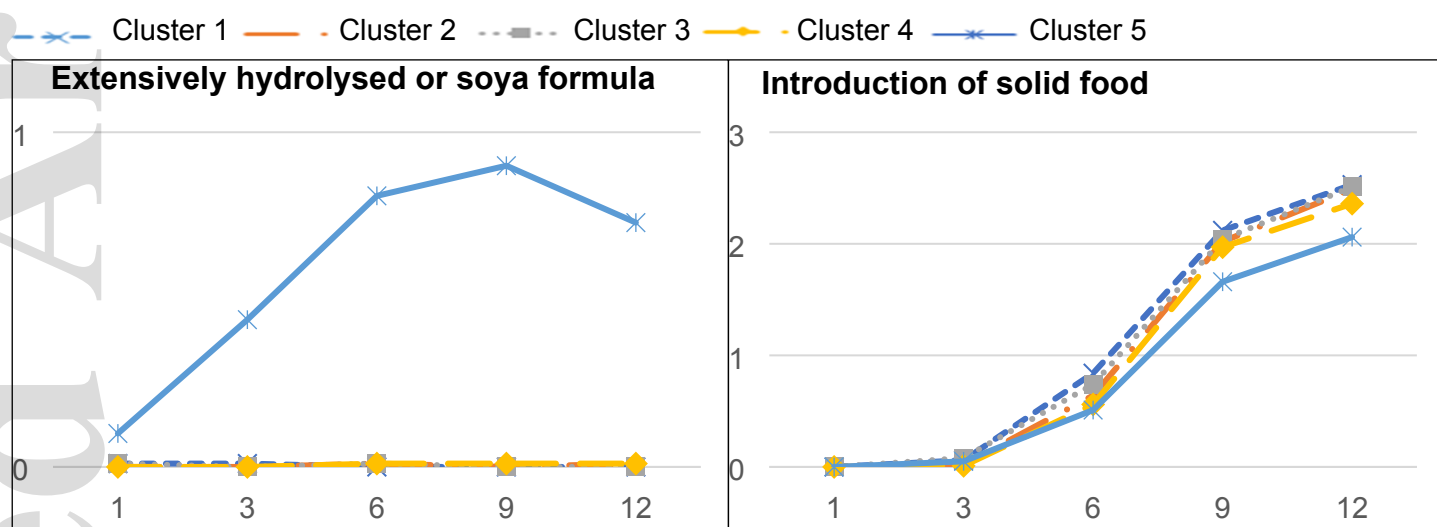
**Figure 1.** Flow chart of the PARIS cohort children participating in the present study.

**Figure 2.** Infant feeding clusters identified during the first year of life in the PARIS birth cohort (n=3,446)

Legend: The x-axis indicates age (in months) and y-axis the mean value of the feeding variables in each cluster at each time point. The 6 variables are coded as follows: breastfeeding (0=no, 1=mixed, 2=exclusive), partially hydrolysed formula with hypoallergenic label (0=no, 1=yes), formula enriched with pre-/probiotics (0=no, 1=yes), extensively hydrolysed or soya formula (0=no, 1=yes), solid food introduction (0=no solid food, 1=non-allergenic solid food, 2=one allergenic solid food, 3=at least two allergenic foods).







## **APPENDICES**

**Title: Infant feeding clusters are associated with respiratory health and allergy at school age in the PARIS birth cohort**

**Short title: Infant feeding and respiratory health/allergy at 8 years**

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**Table S1.** Best Calinski-Harabasz criterion values for each number of clusters after 500 iterations.

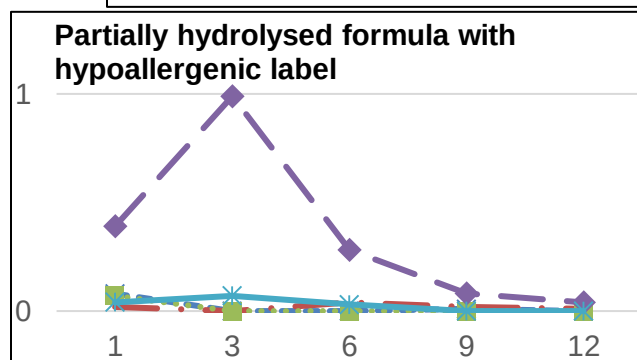
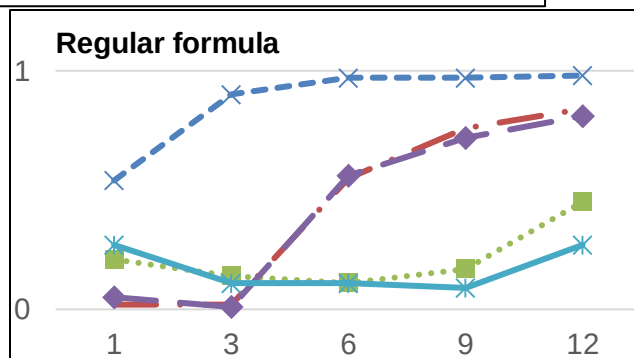
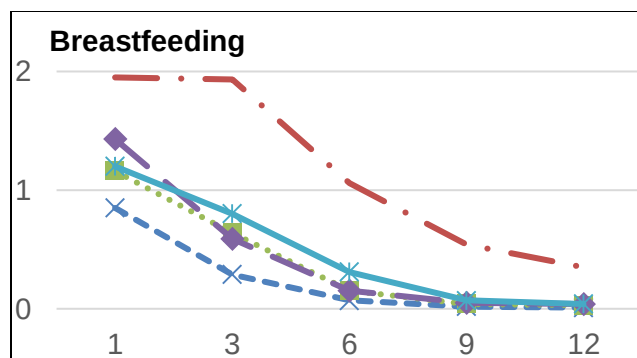
| Number of clusters | Calinski-Harabasz criterion |
|--------------------|-----------------------------|
| 2                  | 585.63                      |
| 3                  | 653.48                      |
| 4                  | 683.48                      |
| 5                  | 706.09                      |
| 6                  | 665.08                      |
| 7                  | 647.59                      |
| 8                  | 611.75                      |

**Table S2.** Factors associated with hydrolysed formula initiation in infants from the PARIS birth cohort (multivariable Cox regression models).

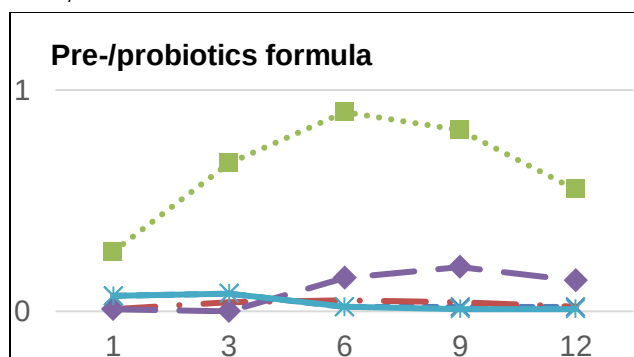
|                                                                    | <b>Model 1:</b> Initiation of partially hydrolysed formula with hypoallergenic label |                          | <b>Model 2:</b> Initiation of extensively hydrolysed or soya formula |                          |
|--------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------|----------------------------------------------------------------------|--------------------------|
|                                                                    | Ref.                                                                                 | aHR (95% CI)             | Ref.                                                                 | aHR (95% CI)             |
| <b>Environmental characteristics and lifestyle</b>                 |                                                                                      |                          |                                                                      |                          |
| Breastfeeding at maternity (yes vs. no)                            | Ref.                                                                                 | <b>2.25 (1.66, 3.05)</b> | Ref.                                                                 | <b>0.61 (0.44, 0.86)</b> |
| Place of residence at birth (Paris city vs. Paris suburbs)         | Ref.                                                                                 | 0.95 (0.79, 1.14)        | Ref.                                                                 | 1.11 (0.82, 1.51)        |
| Maternal geographic origin (other vs. metropolitan France)         | Ref.                                                                                 | 0.79 (0.61, 1.02)        | Ref.                                                                 | 0.71 (0.46, 1.11)        |
| Day care at 3 months (yes vs. no)                                  | Ref.                                                                                 | 1.06 (0.85, 1.34)        | Ref.                                                                 | 0.94 (0.65, 1.35)        |
| Maternal smoking during pregnancy (yes vs. no)                     | Ref.                                                                                 | 1.07 (0.80, 1.45)        | Ref.                                                                 | <b>0.50 (0.28, 0.90)</b> |
| Mode of delivery                                                   |                                                                                      |                          |                                                                      |                          |
| Vaginal                                                            | Ref.                                                                                 | Ref.                     | Ref.                                                                 | Ref.                     |
| Instrumental extraction                                            | Ref.                                                                                 | 1.12 (0.88, 1.44)        | Ref.                                                                 | 1.02 (0.68, 1.53)        |
| Caesarean                                                          | Ref.                                                                                 | 1.18 (0.93, 1.49)        | Ref.                                                                 | 1.11 (0.75, 1.64)        |
| Maternal age at birth ( $\geq$ median vs. $<$ median) <sup>†</sup> | Ref.                                                                                 | 1.09 (0.90, 1.32)        | Ref.                                                                 | <b>1.37 (1.00, 1.86)</b> |
| Parental SES at birth (high vs. low-medium)                        | Ref.                                                                                 | <b>1.23 (1.01, 1.50)</b> | Ref.                                                                 | 1.12 (0.82, 1.54)        |
| Older siblings                                                     |                                                                                      |                          |                                                                      |                          |
| No                                                                 | Ref.                                                                                 | Ref.                     | Ref.                                                                 | Ref.                     |
| Yes, 1                                                             | Ref.                                                                                 | 1.05 (0.85, 1.29)        | Ref.                                                                 | 1.22 (0.88, 1.70)        |
| Yes, 2 or more                                                     | Ref.                                                                                 | 0.67 (0.45, 1.01)        | Ref.                                                                 | 0.62 (0.31, 1.22)        |
| <b>Parental history of allergy</b>                                 |                                                                                      |                          |                                                                      |                          |
| Asthma (yes vs. no)                                                | Ref.                                                                                 | <b>1.54 (1.26, 1.89)</b> | Ref.                                                                 | 1.36 (0.97, 1.91)        |
| Eczema (yes vs. no)                                                | Ref.                                                                                 | <b>1.59 (1.30, 1.95)</b> | Ref.                                                                 | 1.39 (0.99, 1.96)        |
| Food allergy (yes vs. no)                                          | Ref.                                                                                 | <b>1.34 (1.00, 1.80)</b> | Ref.                                                                 | 0.94 (0.55, 1.60)        |
| Allergic rhinitis (yes vs. no)                                     | Ref.                                                                                 | <b>1.30 (1.08, 1.56)</b> | Ref.                                                                 | 1.00 (0.74, 1.35)        |
| <b>Child's characteristics</b>                                     |                                                                                      |                          |                                                                      |                          |
| Sex (girl vs. boy)                                                 | Ref.                                                                                 | <b>0.83 (0.69, 0.99)</b> | Ref.                                                                 | <b>0.60 (0.45, 0.81)</b> |
| Adverse food reaction before the first use of formula (yes vs. no) | Ref.                                                                                 | 0.84 (0.60, 1.17)        | Ref.                                                                 | <b>6.04 (4.48, 8.16)</b> |

|                                                              |      |                          |      |                          |
|--------------------------------------------------------------|------|--------------------------|------|--------------------------|
| Eczema symptoms before the first use of formula (yes vs. no) | Ref. | <b>0.45 (0.37, 0.56)</b> | Ref. | 0.89 (0.66, 1.19)        |
| Wheezing before the first use of formula (yes vs. no)        | Ref. | <b>0.24 (0.16, 0.35)</b> | Ref. | <b>0.48 (0.32, 0.73)</b> |
| WHO weight percentile at 3 months                            |      |                          |      |                          |
| <25 <sup>th</sup>                                            | Ref. | 0.95 (0.78, 1.16)        | Ref. | <b>1.73 (1.28, 2.36)</b> |
| 25 <sup>th</sup> -75 <sup>th</sup>                           | Ref. | Ref.                     | Ref. | Ref.                     |
| >75 <sup>th</sup>                                            | Ref. | 0.86 (0.65, 1.13)        | Ref. | 0.89 (0.53, 1.49)        |

aHR: adjusted hazard ratio, 95% CI: 95% confidence interval, SES: socioeconomic status, WHO: world health organization. † The median of maternal age at birth is 32 years. The hazard ratios in bold differ significantly from the reference (p<0.05).



--x-- Cluster 1 n= 1,245   
 -.- Cluster 2 n= 775   
 -.- Cluster 3 n= 476   
 -.- Cluster 4 n= 221   
 -x- Cluster 5 n=108



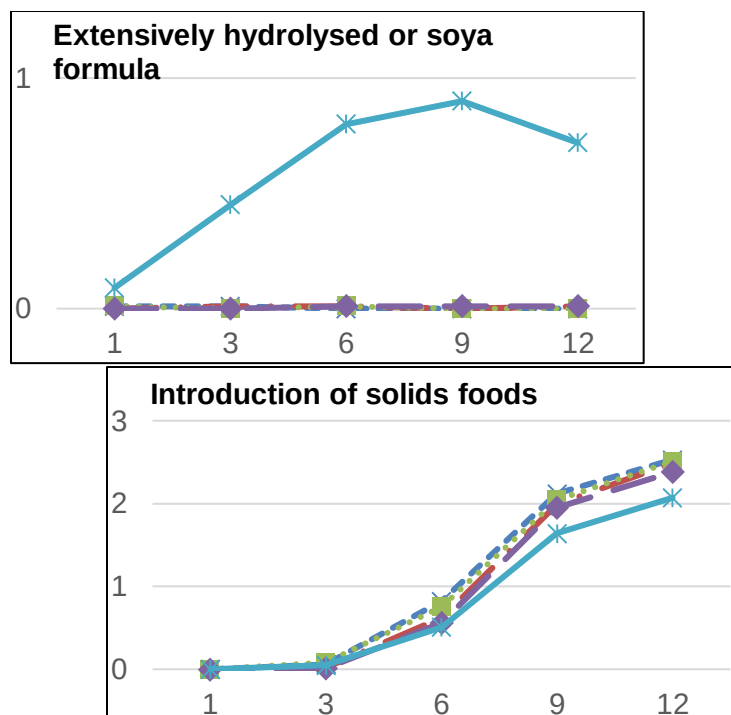


**Figure S1.** Infant feeding clusters identified during the first year of life in infants from the PARIS birth cohort with complete data (n=2,825).

Legend: The x-axis indicates age (in months) and y-axis the mean value of the feeding variables in each cluster at each time point. The 6 variables are coded as follows: breastfeeding (0=no, 1=mixed, 2=exclusive), partially hydrolysed formula with hypoallergenic label (0=no, 1=yes), formula enriched with pre-/probiotics (0=no, 1=yes), extensively hydrolysed or soya formula (0=no, 1=yes), solid food introduction (0=no solid food, 1=non-allergenic solid food, 2=one allergenic solid food, 3=at least two allergenic foods).