









ORIGINAL ARTICLE

Epidemiology and Genetics

Prevalence and early-life risk factors of school-age allergic multimorbidity: The EuroPrevall-iFAAM birth cohort

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Abstract

Background: Coexistence of childhood asthma, eczema and allergic rhinitis is higher than can be expected by chance, suggesting a common mechanism. Data on allergic multimorbidity from a pan-European, population-based birth cohort study have been lacking. This study compares the prevalence and early-life risk factors of these diseases in European primary school children.

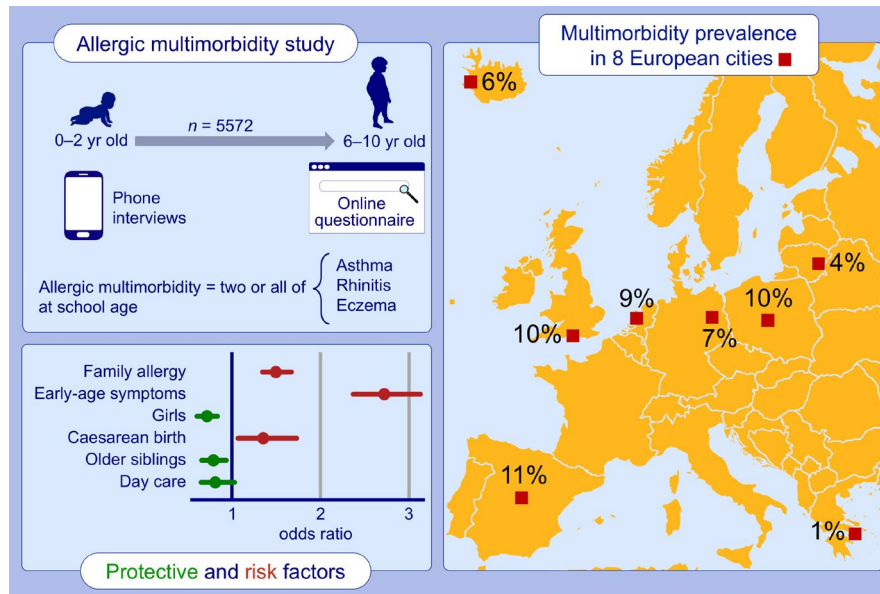
Methods: In the prospective multicentre observational EuroPrevall-iFAAM birth cohort study, we used standardized questionnaires on sociodemographics, medical history, parental allergies and lifestyle, and environmental exposures at birth, 12 and 24 months. At primary school age, parents answered ISAAC-based questions on current asthma, rhinitis and eczema. Allergic multimorbidity was defined as the coexistence of at least two of these.

Results: From 10,563 children recruited at birth in 8 study centres, we included data from 5,572 children (mean age 8.2 years; 51.8% boys). Prevalence estimates were as follows: asthma, 8.1%; allergic rhinitis, 13.3%; and eczema, 12.0%. Allergic multimorbidity was seen in 7.0% of the whole cohort, ranging from 1.2% (Athens, Greece) to 10.9% (Madrid, Spain). Risk factors for allergic multimorbidity, identified with AICc, included family-allergy-score, odds ratio (OR) 1.50 (95% CI 1.32–1.70) per standard deviation; early-life allergy symptoms, OR 2.72 (2.34–3.16) for each symptom; and caesarean birth, OR 1.35 (1.04–1.76). Female gender, OR 0.72 (0.58–0.90); older siblings, OR 0.79 (0.63–0.99); and day care, OR 0.81 (0.63–1.06) were protective factors.

Conclusion: Allergic multimorbidity should be regarded as an important chronic childhood disease in Europe. Some of the associated early-life factors are modifiable and may be considered for prevention strategies.

KEYWORDS

allergic multimorbidity, allergic rhinitis, asthma, children, eczema



GRAPHICAL ABSTRACT

Allergic multimorbidity (coexistence of asthma, eczema and allergic rhinitis) is common among European children at primary school age, with 7% of study participants affected. Protective factors identified in the study include female sex, having older siblings and attending day care. Risk factors include history of allergic diseases in first-degree family members, early-age symptoms and caesarean birth.

1 | INTRODUCTION

Interest in multiple coexisting allergic diseases (allergic multimorbidity) has been increasing, and several recent studies address prevalence and risk factors focusing on childhood and adolescence. Allergic multimorbidity is often defined as two or more allergic diseases: asthma, allergic rhinitis and eczema. The German birth cohort Multicentre Allergy Study (MAS) found an allergic multimorbidity prevalence of 2% at age 9 in those with no family history, compared with 11% of those with at least one allergic parent.¹ The Mechanisms of the Development of ALLergy (MeDALL) meta-analysis showed a relatively high occurrence of coexisting asthma, allergic rhinitis and eczema in 4- and 8-year-old children in many European cohorts suggesting a common mechanism.² In their combined data analysis, as well as in the Swedish BAMSE birth cohort,³ allergic multimorbidity prevalence increased with age up to adolescence.

The iFAAM study is a continuation of the EuroPrevall birth cohort study that recruited newborns in 2005–2010^{4,5} and completed its last follow-up assessment at 6–10 years in eight European cities.⁶ It gives a unique opportunity to estimate the influence of prenatal and postnatal environmental, lifestyle and sociodemographic early-life factors on the prevalence of asthma (allergic and non-allergic), allergic rhinitis, eczema and allergic multimorbidity at primary school age in Europe, which is indeed the aim of the current analysis.

2 | METHODS

2.1 | Study design, setting and population

The study design and baseline characteristic of the study population have been described in detail previously.^{4–7} In summary, the prospective multicentre birth cohort study (funded by the European Commission) recruited 12,049 newborns in 2005–2010 in 9 European centres (Figure 1). After a perinatal baseline interview, regular standardized parental telephone interviews were conducted at 12 and 24 months of age. Sociodemographics, medical history, parental allergies, parental lifestyle, dietary habits, environmental exposures and other potentially influential factors for developing allergies were assessed. Excluded were children born before 34 weeks, with a 5-min APGAR score <7, and parents with insufficient skills of the local language.⁴

During the years 2014–2017, at primary school age, all the study centres except Milan participated in a follow-up assessment, iFAAM (also funded by the European Commission). Parents answered questions online, including questions on symptoms of current allergic diseases. A few parents who were unable or unwilling to access/complete the questionnaire by themselves were invited to the study centre or questioned via telephone interviews.

Ethical approval was obtained individually for both study periods from the local ethics committee in each participating country. Informed parental consent was also obtained for each assessment, in written form for the early childhood period, and online at school age.

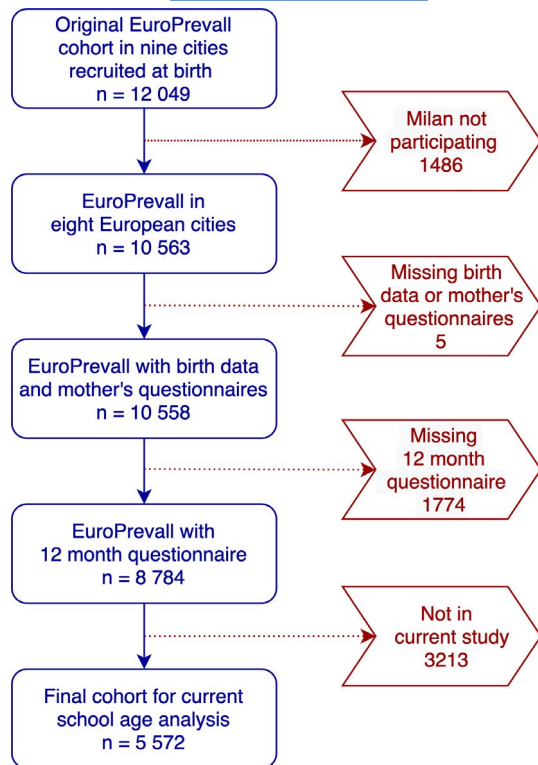


FIGURE 1 Flow chart of the population-based pan-European birth cohort study showing the EuroPrevall and iFAAM participants up to inclusion in the current analysis. The EuroPrevall study centre Milan did not participate in the iFAAM project. The eight participating cities were as follows: Reykjavík, Iceland; Southampton, UK; Amsterdam, the Netherlands; Berlin, Germany; Lodz, Poland; Vilnius, Lithuania; Madrid, Spain; and Athens, Greece. 'Not in current study' are children whose parents were not reachable or were not interested in participation at school age

2.2 | Key outcomes

The iFAAM questionnaire was based on stringent epidemiological definitions and validated and widely used questions in population-based cross-sectional childhood and teenage studies such as the International Study of Asthma and Allergies in Childhood (ISAAC project).⁸⁻¹¹

Current asthma at school age was defined as present if at least three of the following five parent-reported criteria were fulfilled: (a1) wheezing or whistling, (a2) breathing difficulties, (a3) dry cough at night, (a4) asthma medication, all in the past 12 months and (a5) doctor-diagnosed asthma ever. Asthma was also considered to be present if criteria (a4) and (a5) were both fulfilled without any of the three symptoms (a1–a3), indicating a well-managed disease.

Current allergic rhinitis at school age was defined as present if at least two of the following three criteria were fulfilled: (r1) sneezing, or a runny or blocked nose, without having a cold, (r2) nasal allergy/hay fever medication, both in the past 12 months, and (r3) doctor-diagnosed allergic rhinitis or hay fever ever.

Current eczema at school age was defined as present if both of the following criteria were fulfilled: (e1) an itchy rash, which was

intermittently coming and going, and (e2) doctor-diagnosed eczema/atopic dermatitis ever.

Current allergic multimorbidity at school age was defined as present if at least two of current asthma, allergic rhinitis and eczema were coexisting.

2.3 | Definition of covariates

Many of the early-age covariates were simple yes-no questions: *sex*, *caesarean-birth*, *child's* and *mother's antibiotics-at-birth*, *cows-milk-in-first-week*, *pets-at-home* (cats/dogs), *live-on-a-farm* and *mould* in the house. Other early-age covariates require more explanation. *Mothers-age* is a simple continuous variable, *parent-education* is also continuous, sum of mother's and father's education codes, each of these in the range 1–4 according to education level. *Family-allergy-score* at baseline is also a continuous variable and computed as previously described (Appendix S1).¹² *Breastfeeding* is true if the child was breastfed for ≥ 6 months (possibly along with other feeding). Breastfeeding for ≥ 4 months was also evaluated. *Vitamin-D* was true if the child received daily vitamin D supplementation starting within the first 2 months. *Older-siblings* (dichotomous) is true if other children, ≤ 10 years older, were living in the household. *Day-care* is true if the child attended day care before the age of 18 months for ≥ 8 h/week with ≥ 2 other children. *Pregnancy-smoking* is true if the mother reported smoking ≥ 5 cigarettes/d during pregnancy. *Smoking-at-home* (dichotomous variable) is true if ≥ 10 cigarettes/d were smoked at home.

The continuous variable *early-age-symptoms* was defined as the sum of three dichotomous variables: symptoms associated with asthma, allergic rhinitis and eczema. The first of these is 1 if the child had wheezing or whistling in the chest between 12 and 24 months of age; otherwise, it is 0. The second is 1 if the child had at least 2 of the following 3 criteria before age 2: (1) sneezing, or a runny or blocked nose, without having a cold, (2) itchy, watery eyes and (3) doctor-diagnosed hay fever. The third is 1 if the child had an itchy rash or eczema that lasted for at least 7 days, in the fold of the elbows, behind the knees, in front of the ankles, on the cheeks or around the neck, ears or eyes, before age 2.

A crucial variable considered was the study centre. This variable was treated as giving a multiplicative centre effect, as described in more detail in the statistics section below.

Finally, the iFAAM study included a question on current heavy traffic, which was the only school-age covariate considered.

2.4 | Data processing and statistical analysis

Data were processed with Unix and MATLAB (version 9.3; The MathWorks Inc.). To assess the significance of covariates, a logistic regression model was constructed, where centre effect was included as a multiplicative factor:

Odds = (center effect) × (effect of covariate 1) × (effect of covariate 2) × ...

The covariates entering the model were selected using the AICc criterion (Akaike information criterion with correction). One advantage of using AICc is that it is independent of (arbitrary) statistical significance levels: it selects the model with the smallest expected mean squared error.¹³ Forest plots were used to show 95% confidence intervals.

Note that in the model all individuals weight equally, and therefore, the centres are effectively weighted by the participant count in each one, as in inverse probability weighting.¹⁴

3 | RESULTS

3.1 | Study prevalence of allergic diseases

Of 10,563 recruited children in the eight participating centres, 5572 (52.8%) fulfilled the eligibility criteria listed in Section 2.1 (Figure 1). Table S1 shows a breakdown of the dropout by study centre. The participation in individual centres is shown in Figure 2. The children were aged between 6 and 10 years when the last parental questionnaire was answered. The allergic outcomes at school age were as follows: asthma, 8.1%; allergic rhinitis, 13.3%; eczema, 12.0%; allergic multimorbidity, 7.0%; and all three diseases, 1.3% (Table 1).

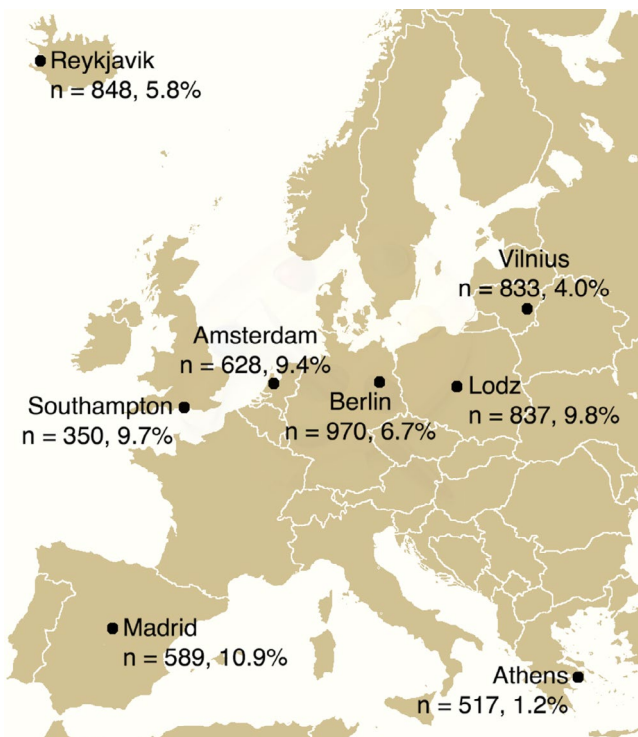


FIGURE 2 The eight centres of the population-based EuroPrevall-IFAAM birth cohort study, the number of children who participated in each one at the school-age follow-up assessment (in total 5572 children) and the proportion of these with allergic multimorbidity (overall proportion 7.0%)

TABLE 1 Prevalence of individual allergic diseases at primary school age according to study centre (%), and breakdown according to the number and type of coexisting diseases

| Centre | n | Age, y, mean (SD) | Prevalence, % | | | | | Number of allergic diseases, % | | | | | Single diseases, % | | | Double diseases, % | | | |
|--------------|------|-------------------|---------------|----------|--------|--------|-----|--------------------------------|------|------|-----|------|--------------------|--------|----------|--------------------|-------|-------|-------|
| | | | Asthma | Rhinitis | Eczema | 2 or 3 | 0 | 1 | 2 | 3 | 0 | 1 | 2 | Asthma | Rhinitis | Eczema | A & R | A & E | R & E |
| Reykjavik | 848 | 8.0 (0.6) | 7.1 | 12.4 | 12.0 | 5.8 | 0.6 | 5.2 | 19.3 | 74.9 | 3.5 | 7.3 | 8.5 | 2.2 | 0.7 | 2.2 | 2.2 | 0.7 | 2.2 |
| Southampton | 350 | 7.9 (0.7) | 12.3 | 12.3 | 15.1 | 9.7 | 2.3 | 7.4 | 18.0 | 72.3 | 4.6 | 4.9 | 8.6 | 3.1 | 2.3 | 2.0 | 3.1 | 2.3 | 2.0 |
| Amsterdam | 628 | 6.7 (0.8) | 11.3 | 11.3 | 17.5 | 9.4 | 1.6 | 7.8 | 19.7 | 70.9 | 4.3 | 4.0 | 11.5 | 3.3 | 2.1 | 2.4 | 3.3 | 2.1 | 2.4 |
| Berlin | 970 | 8.3 (0.9) | 7.8 | 10.9 | 12.5 | 6.7 | 1.4 | 5.3 | 16.4 | 76.9 | 3.0 | 5.1 | 8.4 | 2.6 | 0.8 | 1.9 | 2.6 | 0.8 | 1.9 |
| Lodz | 837 | 8.7 (0.6) | 10.0 | 23.3 | 9.9 | 9.8 | 1.4 | 8.4 | 22.2 | 68.0 | 2.5 | 13.9 | 5.9 | 5.7 | 0.4 | 2.3 | 5.7 | 0.4 | 2.3 |
| Vilnius | 833 | 8.6 (0.5) | 4.2 | 11.4 | 5.4 | 4.0 | 1.3 | 2.6 | 11.8 | 84.3 | 1.7 | 7.4 | 2.6 | 1.2 | 0.0 | 1.4 | 1.2 | 0.0 | 1.4 |
| Madrid | 589 | 8.7 (0.6) | 11.0 | 16.5 | 20.5 | 10.9 | 1.5 | 9.3 | 24.8 | 64.3 | 2.7 | 8.1 | 13.9 | 4.2 | 2.5 | 2.5 | 4.2 | 2.5 | 2.5 |
| Athens | 517 | 8.9 (0.6) | 3.7 | 5.8 | 6.2 | 1.2 | 0.2 | 1.0 | 13.2 | 85.7 | 2.9 | 4.8 | 5.4 | 0.4 | 0.2 | 0.4 | 0.4 | 0.2 | 0.4 |
| All children | 5572 | 8.2 (0.9) | 8.1 | 13.3 | 12.0 | 7.0 | 1.3 | 5.8 | 18.1 | 74.9 | 3.0 | 7.3 | 7.8 | 2.9 | 1.0 | 1.9 | 2.9 | 1.0 | 1.9 |

Note: The bolded italic column, headed '2 or 3', shows the prevalence of allergic multimorbidity, that is two or more of asthma, allergic rhinitis and eczema. The section headed 'Single diseases' shows the percentage of children having one specific disease, and the section headed 'Double diseases' shows the percentage having exactly two specific diseases.

TABLE 2 Early-life covariates according to study centre. The table shows only covariates that AICc selected into the model for allergic multimorbidity, or into a model for one of the individual diseases

| Centre | n | Avg. family allergy score | Girls (%) | Caesarean birth (%) | Older siblings (%) | Day care (%) | Pregnancy smoking (%) | Allergy-like symptoms before age 2 (%) | | |
|-------------------------------|-------------|---------------------------|-------------|---------------------|--------------------|--------------|-----------------------|--|------------|-------------|
| | | | | | | | | Wheezing | Rhinitis | Eczema |
| Participants in current study | | | | | | | | | | |
| Reykjavik | 848 | 1.5 | 47.9 | 12.6 | 54.4 | 77.6 | 4.7 | 15.7 | 9.4 | 15.0 |
| Southampton | 350 | 1.7 | 44.3 | 31.7 | 43.7 | 45.4 | 1.1 | 10.3 | 10.6 | 16.3 |
| Amsterdam | 628 | 1.5 | 48.7 | 11.6 | 52.7 | 69.9 | 5.4 | 9.6 | 9.1 | 21.3 |
| Berlin | 970 | 1.4 | 47.9 | 32.1 | 36.3 | 66.0 | 3.3 | 10.1 | 6.0 | 12.7 |
| Lodz | 837 | 0.7 | 49.0 | 38.2 | 27.5 | 4.9 | 0.0 | 0.7 | 9.6 | 10.0 |
| Vilnius | 833 | 0.3 | 48.0 | 18.8 | 34.7 | 10.8 | 2.5 | 2.0 | 0.4 | 4.0 |
| Madrid | 589 | 1.0 | 48.9 | 3.2 | 42.1 | 61.6 | 10.4 | 2.4 | 2.5 | 12.1 |
| Athens | 517 | 0.7 | 46.8 | 44.7 | 40.6 | 10.4 | 8.5 | 2.7 | 6.8 | 5.8 |
| Total | 5572 | 1.1 | 48.0 | 23.9 | 40.8 | 43.9 | 4.2 | 6.8 | 6.6 | 11.8 |
| Not participating | 3212 | 1.0 | 48.2 | 22.9 | 43.1 | 35.9 | 6.0 | 6.2 | 5.6 | 10.2 |

Note: Family-allergy-score is standardized to have SD = 1. The table also shows a summary for the EuroPrevall children who did not participate in primary school-age follow-up assessment (iFAAM project). See section 2.3 for detailed definitions and Table S3 for other covariates. There is a significant difference (according to a two-tailed test at the 5% level), for day care, pregnancy smoking and all the early-age allergy-like symptoms (shown in bold italics).

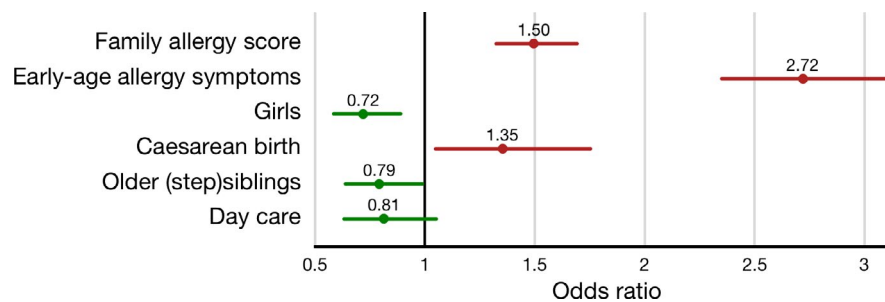


FIGURE 3 Odds ratios and 95% confidence intervals for protective factors (green) and risk factors (red) of allergic multimorbidity at school age [of a model selected according to AICc]. *Family-allergy-score* is standardized to have SD = 1. *Early-age-symptoms* is in the range 1–3 and counts the number of allergic symptoms (of allergic rhinitis, eczema, asthma) observed before age 2. All the remaining variables are dichotomous. The OR for family-allergy-score shows the multiplicative effect for each standard deviation, and somewhat similarly, the OR for early-age symptoms shows the multiplicative effect of each such symptom that is present. The factors shown are the ones present in a multivariate logistic model that maximizes the AICc model selection criterion

The difference between the centres was considerable, with only 1.2% allergic multimorbidity in Athens and 4.0% in Vilnius, reaching 9.4–10.9% in Amsterdam, Southampton, Lodz and Madrid, with Reykjavik and Berlin falling in-between. Asthma had the largest prevalence in Southampton, allergic rhinitis in Lodz and eczema in Madrid (Table 1).

3.2 | Differences between non-participating and participating school-age children

Tables 2 and S1 show a summary of the covariates for the two groups: the 3212 children dropping out in the last step in Figure 1 and the final study population for the current analysis. There were fewer day care children in the dropout group (two-tailed,

$p < .01$), and that group also had fewer children with early-age symptoms of allergic diseases ($p = .04$). There were more smoking at home, more pregnancy smoking, less breastfeeding, more dogs and more children but fewer mothers receiving antibiotics at birth, parent education level was lower ($p < .01$ for all), and there was less vitamin D supplementation in the non-participating group ($p = .03$).

3.3 | Risk factors

The logistic regression model included six covariates for allergic multimorbidity, selected according to AICc: *family-allergy-score*, *early-age-symptoms*, *sex*, *caesarean-birth*, *older-siblings* and *day-care* before 18 months of age (Table 2, Figure 3). Female sex, older-siblings and

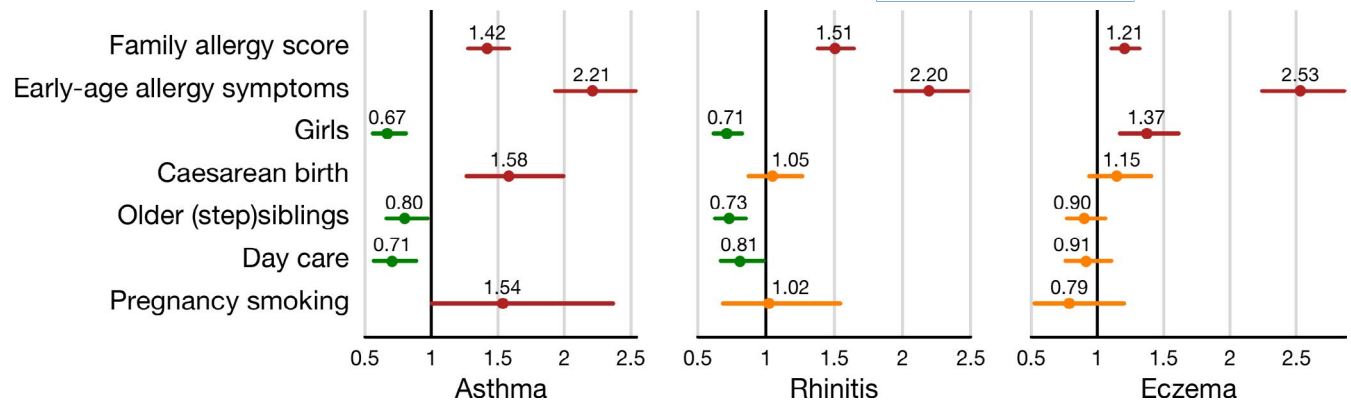


FIGURE 4 Odds ratios and 95% confidence intervals for covariates that are predictors for one or more of the individual diseases considered in the study (secondary outcomes). Covariates for which the confidence intervals do not contain 1 are coloured green if the factor is protective and red if it poses a risk. Confidence intervals of variables that are not selected into a corresponding model are shown in orange. See also explanations in the caption of Figure 3

day-care were independently protective for multimorbidity, whereas the *family-allergy-score*, *caesarean-birth* and *early-age-symptoms* posed a risk. The low occurrence of caesarean birth in Madrid is explained by the recruitment in the maternity ward where scheduled c-sections were absent (Table 2). Note that this deviation does not change the modelling result: in a model without Madrid, AICc selects the same six covariates as the full data model, with very similar estimated odds ratios (S5).

The AICc procedure selects many of the same covariates for individual diseases (Figure 4). Day care provides a protective effect against asthma and allergic rhinitis, and the same applies to having older siblings. Female sex lowers the risk for both asthma and allergic rhinitis, but interestingly, it increased the risk for eczema. Caesarean birth increased the risk only for asthma, but not for the other two allergic diseases. Smoking during pregnancy was included in the asthma model according to the AICc value as a risk factor. Finally, both high *family-allergy-score* and many *early-age-symptoms* are positively related to all three individual diseases.

All the other covariates listed in Section 2.3, *mothers-age*, *parent-education*, *antibiotics-at-birth*, *cows-milk-in-first-week*, *breastfeeding*, *vitamin-D* supplementation, *pets-at-home*, *smoking-at-home*, *live-on-a-farm* and *mould* in the house, were not selected into the models, neither for multimorbidity nor for any of the individual diseases. Of these variables, *live-on-a-farm* had the largest estimated effect, but the statistical power is low as indicated by a wide confidence interval (OR = 0.67, 95% CI 0.26–1.71).

Models including only specific early-age symptoms were also considered. AICc selected early symptoms of both allergic rhinitis and eczema as predictors of school-age allergic multimorbidity by themselves, but not wheezing. However, when combined with one or both of the other two symptoms, wheezing increased the estimated risk, and it was also selected as a predictor of school-age asthma (Table S7).

Current heavy *traffic exposure* was identified as a risk factor for asthma, but not for the other two diseases (Table S8).

3.4 | Consistency of the statistical model

To check the consistency of the modelling, multimorbidity models with each covariate as the only variable apart from centre effect were constructed. Table S2 shows the odds ratios and AICc values for these models and some additional models, including the final 6-variable model of Figure 3. The results were consistent. To further check the stability of the results, the final model was fitted 8 times, each time leaving out one centre, and again, the results were consistent (Tables S4 and S5).

To further check the sanity of the models, and to demonstrate that the multiplicative effect of the number of predictive early-age symptoms was realistic, we analysed two examples: there were 176 children with two early-age symptoms. According to the model, the odds for these children was increased by a factor of $2.72^2 = 7.4$. The model can be used to predict the rate of allergic multimorbidity at school age among these children (adjusting for all the other variables). Such computation predicts 46.7 children, while the actual count is 47. A similar investigation for all three early-age symptoms gives 38 children, 17 of which are multimorbid, while the model predicts 19.3.

4 | DISCUSSION

4.1 | Current study prevalence and comparison with other studies

In our study with children aged 6–10 years, allergic rhinitis and eczema were more common than asthma. There was considerable difference between the study centres with allergic multimorbidity (two or more allergic diseases) ranging from 1.2% in Athens to 10.9% in Madrid. We did not see any clear geographical prevalence gradient across the participating European centres, such as from north to south or west to east, as found in a previous population-based cross-sectional evaluation.¹⁵ While other studies that we considered

defined multimorbidity also as having at least two of asthma, allergic rhinitis and eczema, they sometimes used different definitions of the individual diseases, however often based on original ISAAC questions.⁸

In the Swedish BAMSE birth cohort study in Stockholm, about 12 years before our study, the prevalences at 8 years were similar with 7.1%, 14.7%, 17.0% and 5.5% for asthma, allergic rhinitis, eczema and allergic multimorbidity, respectively;^{3,16} however, the Scandinavian mainland was not part of our study. In the rural Isle of Wight study (UK), multimorbidity in 4- and 10-year-old children was 7.8% and 10.5%, respectively, in 1993–1999¹⁷ as compared to 9.7% in 7.9-year-old children in Southampton in the current study. In that study, the prevalence of allergic multimorbidity increased further to 15.8% in 18-year-olds. A recent Polish cross-sectional multicentre study found 10.7% of 6- to 7-year-old children having allergic multimorbidity,¹⁸ compared with the current study prevalence in Lodz, 9.8%. In the Dutch PIAMA birth cohort, including many rural areas, the published asthma prevalence for 8-year-old children in 2003–2004 was 7.2%,¹⁹ thus lower than the 11.4% for the city of Amsterdam in the current study. Study prevalence of allergic multimorbidity in Berlin was similar to the risk-enriched population-based German MAS study, about 20 years earlier, when compared separately for high-risk and low-risk children (Table S6).¹

In 116,863 children at 6–7 years from 22 affluent and non-affluent countries that participated in phase III of the global cross-sectional International Study of Asthma and Allergies in Childhood (ISAAC), performed 2000–2003, the prevalence for asthma was 9.7%, for allergic rhinitis 8.9%, for eczema 7.3% and for allergic multimorbidity 5.0%,²⁰ somewhat lower than our findings across Europe.

The differences in definitions of the allergic diseases between studies and study settings make it hard to draw conclusions on whether allergic multimorbidity is a waxing problem in Europe. However, our prevalence estimates ranging up to 11% in Madrid considering only the three most common allergic diseases shows that allergic multimorbidity is a common problem for many primary school-aged children in Europe.

In our assessments in children up to 2.5-year-olds, Athens (Greece) had the second lowest wheezing prevalence and lowest prevalence of confirmed food allergy,^{21–23} and now has the lowest study prevalence of all three single diseases, as well as allergic multimorbidity. It also has, by far, the lowest estimate for school-age food allergy.⁶ However, Madrid, also in Mediterranean Europe, has the highest observed prevalence of both allergic multimorbidity and eczema, and high percentage for the other two diseases.

The considerable differences between cities (Section 3.1) evidently cannot be explained by the geographical locations. Genetic susceptibility and/or environmental factors such as diet may play a role. The relatively low prevalence in Reykjavik could be partly due to the widespread supplementation of fish oil to infants,¹² or possibly less pollution.

4.2 | Risk factors

As expected, *family-allergy-score* had a large effect not only on single allergic diseases but also on allergic multimorbidity. Interestingly, allergic family history appeared to influence the occurrence of eczema less than respiratory allergy.

Also, as expected, the best predictor for allergic multimorbidity at school age were *early-age-symptoms* of allergic diseases. Early-age symptoms are of course not a risk factor, strictly speaking. Multimorbidity models without *early-age-symptoms* give odds ratios for the other factors that are comparable to those of the full model (Figure 3, Table S2). The same holds for individual diseases (data not shown). If the aim is to predict school-age allergic diseases, one would use all available data, including the early-age-symptoms, but if the aim is to study the causal pathway, this variable should be excluded.

Being a *girl* is protective against allergic multimorbidity, asthma and allergic rhinitis at school age, but carries a risk for eczema. These findings confirm results from MAS, PARIS, and BAMSE.^{1,10,16,24} In MAS, boys with eczema had more allergic multimorbidity than girls with eczema. This was confirmed by our study, 40% and 30% for boys and girls, respectively ($p = .07$; data not shown). The PARIS study also showed boys to be at higher risk of allergic sensitization to aeroallergens and food allergens, and at much higher risk of being multisensitized.

Pregnancy-smoking was not found to affect allergic multimorbidity; however, according to the AICc criterion, it is a risk factor for primary school-age asthma (OR = 1.54, 95% CI = 0.99–2.38). This is in agreement with multiple other studies, where smoking during pregnancy increased the risk for early-life wheezing and school-age asthma, even more than other tobacco smoke exposure.^{25–30}

Figure 4 indicates that pregnancy smoking primarily affects non-atopic asthma,^{28,31} and the same applies to *caesarean-birth*, which is a risk factor for multimorbidity and asthma, but not for allergic rhinitis or eczema. The result for asthma confirms findings of a recent meta-analysis, albeit with considerable statistical heterogeneity, with mainly retrospective and cross-sectional studies, showing an increased asthma risk by caesarean birth.³² Not included in this meta-analysis were two separate evaluations of long-term prospective population-based birth cohorts, focusing on asthma and allergy, which did not find association between caesarean birth and asthma at age 15³³ and 20 years.³⁰

In previous studies, having *older siblings* and *day-care attendance* were both protective for respiratory allergic diseases at school age.^{20,34,35} The protective effects of natural birth, older siblings and day care attendance have been explained by the increased exposure to protective bacteria in infancy,^{36,37} whereas the protection by older siblings was also hypothesized of being an in utero immune priming effect.³⁵

The negative effect of current *traffic* on asthma is consistent with earlier findings (Table S7).¹⁹ We did not have accessible information on traffic at early age.

4.3 | Allergic multimorbidity is a disease in its own right

Several studies show that allergic multimorbidity can be considered as a special disease.^{2,16} This is supported by a genetic study.³⁸

In our study, asthma concurrent with allergic rhinitis and/or eczema accounted for about half of the asthma cases, 3.9% (2.9% +1.0%; Table 1) out of 8.1%, approximately twice as often as would be expected if the diseases were independent. If they were independent, the prevalence of all three being concurrent would be 0.13% ($0.081 \times 0.133 \times 0.120 = 0.0013$), whereas the actual cohort prevalence of the triple multimorbidity is ten times higher, 1.3% (Table 1).

We concentrated on allergic diseases at the age around 8 years; however, the coexistence of the diseases may have developed in different patterns from infancy. A study using machine learning identified 8 such patterns, leading to different combinations of the diseases at school age.³⁹ A study on atopic endotypes in childhood identified four patterns of disease development.⁴⁰

4.4 | Strengths and weaknesses of the study

The current study involves multiple countries from all climatic regions in Europe, it uses prospectively collected data from birth to school age by the same standardized methods, and it is to date the largest such single study. It had sufficient statistical power to examine potential risk factors in a single model. To a certain extent, some of these risk and protective factors are modifiable (pregnancy smoking, caesarean birth, day care and traffic exposure). Being a prospective study, early-life risk factors can be determined without relying on long-term memory of the parents.

However, the generalizability of the cohort to the whole populations has not been formally assessed and may be limited. Furthermore, a considerable number of children were lost to follow-up after 6–10 years since birth, possibly exaggerating the estimated multimorbidity percentage. It is also possible that the differences in loss between centres introduce bias in the estimates from the regression; however, it is not easy to analyse the nature of this bias. Also, several interesting and probably important potential early-life factors are not considered, for example paracetamol and antibiotic use, diet and IgE sensitization. The BAMSE birth cohort, the Isle of Wight study and PARIS birth cohort showed food and airborne sensitization in infancy to be risk factors for later allergic multimorbidity.^{3,17,24}

5 | CONCLUSIONS

Allergic multimorbidity should be considered as a relevant chronic childhood condition in Europe and probably around the globe. Importantly, some of the associated early-life factors that this study identified are modifiable and thus can be considered for prevention

strategies. Future research on allergic diseases should focus on individuals with multimorbidity, for better understanding of the underlying mechanisms, with the ultimate aim for improved disease management. Knowledge gaps include the age bracket from childhood to adulthood, associations with other allergic and non-allergic comorbidities, and effects of the diseases on quality of life in families with allergic multimorbidity. The currently ongoing COVID-19 pandemic will further direct the focus on the link between viral infections and chronic respiratory diseases and allergies.

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CONFLICT OF INTEREST

Dr. Roberts reports grants from EU and grants from Food Standards Agency, during the conduct of the study; Dr. Grimshaw reports grants from Food Standards Agency UK, during the conduct of the study; Dr. Papadopoulos reports personal fees from Novartis, personal fees from Nutricia, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI, personal fees from MYLAN/MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT Biotech, personal fees from Boehringer Ingelheim, grants from Gerolymatos International SA and grants from Capricare, outside the submitted work; Dr. Xepapadaki reports personal fees from Uriach, personal fees from Novartis, personal fees from Nestle and personal fees from Nutricia, outside the submitted work; Dr. Fiandor reports personal fees and non-financial support from AstraZeneca, outside the submitted work; Dr. Quirce reports personal fees and non-financial support from GSK, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Novartis, personal fees and non-financial support from Mundipharma, personal fees and non-financial support from Teva, and personal fees and non-financial support from Allergy Therapeutics, outside the submitted work; Dr. Sprikkelman reports grants from Nutricia Advanced Medical Nutrition Netherlands, grants from AstraZeneca, Netherlands, grants from TEVA Netherlands and grants from GlaxoSmithKline Netherlands, during the conduct of the study, and grants from Aimmune, outside the submitted work; Dr. Couch reports grants

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AUTHOR CONTRIBUTIONS

ENCM was overall coordinator of the collaborative research initiatives EuroPrevall and iFAAM; KB was initiator, principal investigator and iFAAM theme leader of the birth cohort study, and participated in planning of the present analysis, interpretation of results and writing of the manuscript; TK was co-PI of the birth cohort (both in EuroPrevall and in iFAAM), initiated, planned and supervised the present analysis, and participated in the writing of the manuscript; STS was PI in Iceland, initiated, planned and supervised the present analysis, and wrote the first draft of the manuscript; KJ planned and carried out statistical analysis and wrote the first draft of the manuscript; MC participated in the planning and interpretation of the results of the present study, and the manuscript writing; LG coordinated the iFAAM school-age follow-up of the birth cohort, carried out data cleaning, and participated in planning the present analysis, interpretation of results and writing of the manuscript; RvR was responsible for laboratory analyses for the whole project, participated in the planning of the birth cohort and was PI in the Netherlands; MFR was responsible for laboratory analyses including skin prick tests and participated in the planning of the study design and was PI for the SERMAS-iFAAM team; PC was responsible for all central IT aspects including the central database and participated in the planning of the school-age follow-up; and AR was responsible for the central data management, and participated in the cohort management and planning of the study. All authors participated in the planning and/or local implementation of the various assessments including study management, parental interviews and clinical visits of the birth cohorts, reviewed and commented the draft of the manuscript and approved the final version.


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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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