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# Childhood food allergy and food allergen sensitisation are associated with adult airways disease: a birth cohort study

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## Conflict of interest

The authors declare that they do not have any relevant conflicts of interest.

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## Ethical approval

This study had ethical approval from the IOW Local Research Ethics Committee (06/Q1701/34).

## Abstract

### **Background:**

Childhood food allergy (FA) and food allergen sensitisation (FAS) are associated with allergic airway disease(s) [AAD] (asthma and rhinitis) in childhood. However, the associations between childhood FA/FAS and AAD in adulthood are not well described.

### **Methods:**

We investigated the longitudinal relationship between childhood FA/FAS to common food allergens and AAD at 18 and 26 years, in the Isle of Wight birth cohort. Study subjects (N=1456) were followed-up at fixed timepoints from ages 1 to 26 years for FA/FAS status. AAD were evaluated from 4 years onwards. The associations between FA/FAS and AAD were assessed with univariate analyses and then multivariable logistic regression, adjusting for clinically relevant co-variables.

### **Results:**

FA at 4 years was significantly associated with asthma at 18 years [Adjusted Odds ratio (aOR): 2.75, 95% CI: 1.53-4.92, P=0.001] and 26 years (aOR: 2.62, 95% CI: 1.32-5.20, P=0.006). Conversely, childhood FA was not associated with adulthood rhinitis whatsoever. While FAS at ages 4 and 10 were associated with both AAD, the associations between FAS and rhinitis were less robust relative to asthma.

## **Conclusion:**

Childhood FA increased the odds of asthma during adulthood by nearly 3-fold. Additionally, childhood FAS was also associated with increased odds of asthma in adulthood. Conversely, FAS but not FA in childhood was associated with rhinitis in adulthood. We suggest that children with FA/FAS should be followed-up to facilitate early detection and intervention of subsequent AAD, particularly asthma.

## **Keywords:**

asthma; cohort studies; food hypersensitivity; longitudinal studies; respiratory hypersensitivity; rhinitis.

## **Key message**

Our study is the first to provide unselected, longitudinal birth cohort data to show that childhood food allergy and food allergen sensitisation were associated with increased odds of asthma and to a lesser extent rhinitis, in adulthood. Given our findings, clinicians should consider following-up children with food allergy and food allergen sensitisation for early detection and treatment of subsequent allergic airways disease, particularly asthma.

## **Abbreviations used**

AAD: Allergic airways disease(s)

DBPCFC: double-blind placebo-controlled food challenges

FA: Food allergy

FAS: Food allergen sensitisation

IgE: Immunoglobulin E

IOW: Isle of Wight

SPT: Skin prick test

## Introduction

Allergic airway disease(s) [AAD] (asthma and rhinitis) continue to be major global health problems among children (1) and are associated with substantial morbidity, impaired quality-of-life and significant economic burden (2,3). The clinical expression of AAD is dependent upon a complex interaction between multiple genetic and environmental factors. A key area of research is clarifying the role of food allergy (FA) and food allergen sensitisation (FAS) in AAD development. The time-order relationship between FA and AAD in childhood has been investigated, and it has been shown that early FA predicts a higher likelihood of developing aeroallergen sensitisation and AAD (4–6). FA has also been implicated in increasing paediatric asthma morbidity and life-threatening exacerbations (7,8).

However, there is a limited evidence base around the associations of childhood FA/FAS in relation to AAD presentation and persistence in adulthood. Also, it is unclear whether FA and FAS show different associations with asthma and rhinitis over the life-course. Characterising this relationship is crucial, given the allergy epidemic (9) and the aforementioned mutually detrimental relationship between FA and asthma. As such, to address these questions, we analysed longitudinal data collected from the Isle of Wight (IOW) birth cohort, where data on FA, FAS and AAD up to 26 years were available (10). Our objectives were to 1. Assess the associations between childhood FA/ FAS and adult AAD. 2. Assess the effect of childhood FA / FAS on asthma persistence into adulthood. 3. Assess the relationship between childhood FA/ FAS and adult aeroallergen sensitisation .

## Methods

The parents of every child (N=1536) born between 1 January 1989 and 28 February 1990, on the IOW, UK, were approached to participate in this longitudinal study. All children after exclusion (N=1456) were then followed up at regular intervals: age 1 (94.4%), 2 (84.5%), 4 (83.6%), 10 (94.3%), 18 years (90.2%), and 26 years (70.9%). This study had approval from the IOW Local Research Ethics Committee (06/Q1701/34) and written informed consent was obtained for all participants at recruitment and each follow-up. Detailed study methodology, characteristics and the development of allergic disease in this cohort have been described elsewhere (10).

## Definitions

Clinical definitions for FA, FAS, aeroallergen sensitisation, asthma and rhinitis are described elsewhere (10–12). Briefly, for FA, three criteria were defined *a priori*, and all three needed to be met for the diagnosis of food allergy. These included; 1. A reaction to a recognised food allergen as defined by the European Union (13) and the Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment (14), 2. the report of recognised allergic symptoms (15) and 3. Symptoms developing within 4 hours of food ingestion. Food challenges were not performed in our study (10–12).

Food and aero- allergen sensitisation status was ascertained using skin prick tests (SPTs). This included common food and aero- allergens such as cow's milk, hen's egg, cod, wheat, soya and peanut (food panel) plus house dust mite, grass pollen mix, tree pollen mix, cat epithelia, dog epithelia, *Alternaria alternata* and *Cladosporium herbarum* (aeroallergen panel) (extracts from ALK-Abello, Horsholm, Denmark). Additional allergens were used depending on clinical history. Positive (histamine) and negative (saline) controls were performed as reference measurements. At ages 1 and 2 years, SPTs were only performed in symptomatic children. At subsequent assessments, SPTs to both food and aeroallergen panels were routinely performed on subjects attending the follow-ups. Positive sensitisation was defined as having an SPT reaction to an allergen with a mean wheal diameter of 3 mm greater than the negative control. The patterns of food allergen sensitisation of the cohort up to 18 years of age have been published elsewhere (12).

Asthma was defined as having a history of physician diagnosed asthma plus either the presence of wheezing in the prior 12 months or requirement for asthma medications in the last 12 months (16). Rhinitis was defined by a positive questionnaire response to the presence of a sneezing, running or congested nose in the last 12 months in the absence of a cold or flu (17).

Persistent asthma was defined as asthma which is present at two consecutive time-points, i.e.: 10 and 18 years, 18 and 26 years (18). Atopic asthma and rhinitis were defined by meeting study criteria for the respective airway disease alongside positive allergen sensitisation at the time. Non-atopic asthma and rhinitis were conversely defined as meeting study criteria for the respective airway disease in the absence of allergen sensitisation.

## **Statistical Analysis**

Data analysis was performed with SPSS software (Version 26; IBM, USA). Categorical variables were assessed using the Chi-squared test or Fisher's exact test where appropriate. A P-value <0.05 was deemed as being statistically significant.

Multivariable logistic regressions were used to further assess the associations between FA/FAS and AAD. For categorical variables with zero counts of certain categories, penalized logistic regression models were applied instead (19). Listwise deletion was used to address missing data in logistic regression modelling. For all logistic regression analyses, 95% confidence intervals (CIs) were used and a P-value <0.05 was regarded as being statistically significant. We did not correct for multiple comparisons as our hypotheses and analysis plan was determined a-priori (20) rather than randomly selected.

### **Covariates**

Potential confounding variables based on the literature around allergic disease and from our previous reports (4,10–12,18,21) were examined using univariate analyses. These included sex (dichotomous), family (maternal, paternal or sibling) history of asthma, rhinitis, eczema or food allergy (dichotomous, questionnaire at birth), cord Immunoglobulin E (IgE) (>0.5kU/L, dichotomous), maternal smoking (dichotomous, questionnaire at birth). Additionally, 'family social status cluster' was also examined as one of the potential co-variables. This was a composite variable derived from a combination of parental occupation (socioeconomic status), family income, and number of children in a child's bedroom during ages 4-10 (21). Eczema, which was diagnosed based on the criteria of Hanifin and Rajka (ie, itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution) was also examined as a potential covariate (22). Since early aeroallergen sensitisation showed a high overlap with FA and FAS (Online Repository Table E1), it was not included in our models as a covariate to avoid collinearity. Covariates trending towards significance ( $p < 0.1$ ) in univariate analyses were treated as candidate independent variables and included in the final models of logistic regressions (23).

## **Results**

### **Study Population Description**

1536 children were enrolled in the IOW cohort study at birth, of which 1456 were available for subsequent assessments. The study reflected a dynamic cohort whereby some subjects missed one follow-up but returned to participate in future assessments (10). Overall, high retention rates

were consistently achieved at these follow-ups, apart from the 26-year SPT (Figure 1). Relevant clinical characteristics of the IOW birth cohort are described in Table 1.

### **Food allergy, food allergen sensitisation and allergic airways diseases in adulthood**

Based on results from multivariable logistic regressions, FA at 4 years was significantly associated with asthma at both 18 and 26 years (Table 2). Additionally, FA at 1 or 2 years was also associated with asthma at age 26 years. Childhood FAS had stronger associations with adult asthma whereby FAS at ages 4 and 10 was associated with increased odds of asthma at both 18 and 26 years (Table 2). Additionally, among infants at age 1 or 2 years with symptoms of possible FA, FAS was also associated with an increased odds of asthma at ages 18 and 26 years (Table 2).

In contrast, childhood FA was not associated at all with rhinitis at 18 and 26 years. Again, FAS had stronger associations with rhinitis, whereby FAS at 4 years was associated with rhinitis at 18 years and FAS at 10 years was associated with rhinitis at both ages 18 and 26 (Table 3).

### **Food allergy, food allergen sensitisation and asthma persistence into adulthood**

There were no statistically significant associations between childhood FA and FAS with asthma persistence (Table 4).

### **Food allergy, food allergen sensitisation and aeroallergen sensitisation in adulthood**

FA was not associated with aeroallergen sensitisation at 18 years and only FA at 1 or 2 years was significantly associated with aeroallergen sensitisation at 26 years. Conversely, FAS at ages 4 and 10 were associated with aeroallergen sensitisation at 18 years and 26 years (Table 5). Similarly, among infants at age 1 or 2 years with symptoms of possible FA, FAS was also associated with an increased odds of aeroallergen sensitisation at ages 18 and 26 years (Table 5).

### **Food allergy, food allergen sensitisation with atopic and non-atopic airways disease in adulthood**

Based on results from logistic regressions, childhood FA (except age 10) was associated with atopic asthma at 26 but not 18 years. However, childhood FA was not associated with atopic rhinitis (Online Repository Table E2 and E3). Again, childhood FAS displayed stronger associations with atopic asthma and rhinitis. FAS at ages 4, 10, as well as FAS in symptomatic infants at ages 1 or 2 were associated with adult atopic asthma. Conversely, only FAS at ages 4 and 10 were associated with adult atopic rhinitis (Online Repository Table E2 and E3).

Conversely, apart from FA at age 4, childhood FA and FAS had no associations to non-atopic AAD. (Online Repository Table E4 and E5).

### **Subgroup and sensitivity analysis of subjects with complete follow-up to age 26**

Due to the loss of follow-up at age 26 years for a larger number of participants compared to other ages, we compared the group not seen at age 26 against the group who were. We found that these two groups were not significantly different with regards to most variables (aeroallergen sensitisation, FA, FAS, eczema, rhinitis and early asthma) apart from the not seen group having a lower proportion of females (37.6% vs 54.2%) and a lower prevalence of asthma at age 18 (13.8% vs 19%) (Online repository Table E6).

To further clarify whether the loss of follow up and the differences between the seen and not-seen groups would affect our main results, we performed sensitivity analyses of our main age 18 findings in subjects (N=1033) where information was available at age 26. The findings at age 18 based on this subset were consistent with the overall results (Online repository Table E7). Similar analyses were applied to the subgroup at 26 with complete SPT (N=556). Similarly, the findings at age 18 based on data in N=556 subjects were consistent apart from the association between FAS at age 4 and asthma at age 18 (Online repository Table E8).

This sensitivity analysis was also repeated on our atopic AAD findings. Similarly, our results were largely intact, apart from the associations between FAS in symptomatic infants at ages 1 or 2 and asthma at age 18 (Online repository Tables E9 and E10).

## Discussion

To the author's best knowledge, this study is the first to describe the longitudinal associations of childhood FA/FAS with asthma and rhinitis in adulthood, in a well-characterised, unselected birth cohort. A key finding was that childhood FA/FAS were associated with adulthood AAD, especially asthma, even after adjusting for clinically relevant covariates. Additionally, our findings are novel in that we described the differential associations of childhood FA/FAS with adult asthma and rhinitis. We also explored the relationship of early FA/FAS on asthma persistence into adulthood. Our data fill the aforementioned gap in the understanding of the role of childhood FA/FAS on adult AAD. These findings also suggest that children with FA/FAS should be followed-up to facilitate early detection of these diseases, particularly asthma.

Similar to what is observed in childhood asthma, FA at 1 or 2 and 4 years had strong associations with asthma in adulthood. These associations can partly be due to the observations that FA at these years is predictive of an atopic phenotype and future respiratory allergies (4–6,24). The apparent weaker association between FA at age 10 and AAD may coincide with the acquisition of natural tolerance to early-childhood FA (11). The discrepancy between FA and FAS, whereby FAS displays overall stronger associations with AAD, and aeroallergen sensitisation, may reflect our definition of FA. In our study, FA was defined clinically and did not require the presence of allergic sensitisation (12). We did not use allergen sensitisation as a criterion to be inclusive of both IgE and non-IgE mediated FA in line with our outcomes of interest. Conversely, the presence of FAS represents a true IgE-mediated process, thereby explaining its stronger associations as the majority of AAD is IgE mediated. However, atopy is one among many factors driving FA and asthma associations and hence we examined FA and FAS separately as risk factors, and asthma and aeroallergen sensitisation as outcomes. Indeed, our study showed that childhood FAS was associated with adult asthma.

The exact pathophysiologic mechanisms by which FA and FAS influence AAD are unclear. A commonly accepted hypothesis is based on the 'atopic march', where in atopic individuals, early FA and FAS are associated with a higher subsequent risk of IgE-mediated aeroallergen sensitisation and future AAD development (25). This may be partially supported by our previous work (26) and our findings whereby childhood FAS potentiated the odds of later aeroallergen sensitisation in our cohort. This was especially so with regards to FAS at age 10 and aeroallergen sensitisation at age 26, whereby the extremely wide confidence intervals were observed due to

overly strong information, i.e. a 'perfect' association between the two processes (Online Repository Table E11). However, the atopic march hypothesis has been challenged where allergic comorbidities rather than atopic march is described as truly reflecting these associations (27,28). Our data describe epidemiological observations and are not set out to weigh towards either hypothesis. The associations seen in our data may be due to the release of inflammatory mediators in the respiratory tract secondary to food allergen exposure in the gastrointestinal tract. Alternatively, indirect entry of food allergens may occur via inhalation of aerosolized food proteins (29). Additionally, they could also be due to the absorption of food allergens via damaged eczematous skin (30). Indeed eczema is well known to be associated with FA/FAS and AADs (26,31). We have previously shown the increased risk of FA and FAS in children with filaggrin mutations only occurs if they have eczema (12) and have also shown that those children with filaggrin mutations develop aeroallergen sensitisation and asthma at age 10 only in the presence of early eczema (26). However, expanding on our previous findings and findings of the German Multicenter Allergy Study, where childhood FA and FAS were related to asthma at age 13 (32), our data show the associations between childhood FA/FAS extends to adulthood asthma and to a lesser extent adulthood rhinitis, even after adjusting for eczema in our models. The independence of FA and FAS from eczema in increasing the odds of subsequent AAD may be contrary to the proposed natural history described by the atopic march, whereby eczema is thought to be the key 'entry point' for subsequent allergic airways disease (25–27). This may also suggest that while eczema is important in the pathogenesis of later life AAD, FA and FAS are independently associated with AAD, especially with regards to asthma.

Asthma and rhinitis are regarded as similar disorders in the "one airway one disease" paradigm (33), this study uniquely revealed that FA/FAS were associated with different trajectories of long-term outcomes in these diseases. FA at 1 or 2 and 4 years were associated with adult asthma. In contrast, FA at those ages was not associated with rhinitis in adulthood. Additionally, although FAS had stronger associations with rhinitis, compared to FA, these associations were still less robust compared to asthma. Furthermore, the differences in associations were not lost, even when we looked specifically at atopic rhinitis and atopic asthma. This is somewhat contrary to the "atopic march" hypothesis as rhinitis is regarded as the culmination of atopic march and a more typical atopic manifestation than asthma, which is a more heterogeneous condition (25). The disparities observed here alongside the differences in trends of prevalence (34,35), may suggest these conditions have different underlying pathophysiologic mechanisms. It may also suggest both diseases are indeed heterogeneous, given their differing associations with FA and FAS. Few studies have been performed to

ascertain the degree of contribution from FA and FAS in the separate development of the respective airway diseases. Tikkanen et al demonstrated that early cow's milk allergy increased the risk of asthma by almost 7-fold whereas the risk of rhinitis was increased by about 2-fold by 10 years of age (6). Our findings corroborate this, but also expand on it by showing that while the associations between childhood FA and rhinitis is lost after age 10, it persists in asthma. An explanation could be that nasal passages have a greater degree of exposure to aeroallergens compared to the lower airways, whereas airway smooth muscles are more susceptible to systemic inflammatory mediators (36). Unlike asthma where bronchial wall damage may result from inflammatory cytokine release, nasal epithelial disruption has not been demonstrated in allergic rhinitis (37). Thus, the associated inflammation arising from FA and FAS is more likely to affect the lower airways, thereby explaining the increased association seen in asthma.

Our study has several strengths. For one, it is the first to investigate the longitudinal associations of childhood FA/FAS on AAD, into early adulthood. Furthermore, our study was unselected, used prospective data, had high retention rates, and had repeated collection of information. Our study had limitations. The IOW population is homogenous and consists predominately of Caucasians. While this may limit generalisability, a homogenous population is advantageous in testing hypotheses. Additionally, in our study, we opted to define FA based on detailed symptoms corroborated with the clinical impression of clinicians to minimize misclassification bias based on self-reporting. While we have validated and published extensively using these methods, the gold-standard investigation, double-blind placebo-controlled food challenges (DBPCFC), were not performed as this was not routine practice at the time. Nonetheless, we have shown that our prevalence rates of FA are comparable to others, despite not using DBPCFC nor including allergen sensitisation as a criterion (11). Similarly, the diagnoses of asthma and rhinitis were determined primarily based on clinical definitions and medication usage, and objective investigations such as spirometry were not routinely performed. Another limitation of the study was the high loss of follow-up at age 26, especially with regards to skin prick test. However, our subgroup and sensitivity analyses of those who had complete follow-up to age 26 found that although there were smaller numbers and slight discrepancies in the age 26 study population, the overall findings were largely intact. Similarly, the lack of routine skin prick testing before age 4 years also resulted in a smaller sample size and possible selection bias.

Our findings have several potential clinical implications. Children with FA/FAS should have increased surveillance to detect the early development of asthma and subsequently instigate early treatment, which has been shown to improve asthma outcomes (38). This is crucial as FA is

well described to be associated with poor asthma outcomes, whereby confirmed FA is a risk factor of asthma-related death (7,8). These findings may be of additional importance to children transitioning to the adult clinic, as they may not yet fully understand their disease, may struggle to take responsibility for self-management and are perceived to be a challenging group to manage(39). Additionally, further studies will be required to investigate the immunologic pathways linking FA/FAS and AAD. Furthermore, primary and secondary preventive strategies have been described to reduce the incidence of food allergy (40,41). Given our findings, it would be valuable to follow up those study participants to ascertain whether these strategies have any long-term impact on AAD.

## Conclusion

In conclusion, childhood FA and FAS appear to be significantly associated with adult asthma and to a lesser extent rhinitis. Additionally, this study has highlighted the differential associations of childhood FA and FAS on AAD in adulthood. Clinicians should be aware of this when looking after children with FA/FAS, especially as they transition into adulthood.

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## Author contributions

Wei Chern Gavin Fong: Formal Analysis (lead), Methodology (equal) Visualization (lead), Writing – Original Draft Preparation (equal), Writing – review and editing (equal). Adrian Chan: Formal Analysis (supporting), Methodology (equal), Writing – Original Draft Preparation (equal), Writing – review and editing (equal). Hongmei Zhang: Formal Analysis (supporting), Methodology (supporting), Supervision (supporting), Writing – review and editing (equal). John Holloway: Writing – review and editing (equal). Graham Roberts: Writing – review and editing (equal). Ramesh Kurukulaarachy: Formal Analysis (supporting), Supervision (supporting), Methodology (supporting), Writing – review and editing (equal). Hasan Arshad: Conceptualization (lead), Formal Analysis (supporting), Funding Acquisition (lead), Supervision (lead), Writing – review and editing (equal).

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## Tables

**Table 1. Clinical characteristics of the Isle of Wight birth cohort.**

| Clinical characteristics           | Cumulative % (N) |
|------------------------------------|------------------|
| <b>Food allergy</b>                |                  |
| Ages 1 or 2                        | 7.9% (105)       |
| Age 4                              | 5% (61)          |
| Age 10                             | 2.6% (35)        |
| <b>Food allergen sensitisation</b> |                  |
| Age 4                              | 3.2% (31)        |
| Age 10                             | 4.5% (47)        |
| <b>Asthma</b>                      |                  |
| Age 10                             | 14.7% (201)      |
| Age 18                             | 17.7% (231)      |
| Age 26                             | 15.5% (160)      |
| <b>Rhinitis</b>                    |                  |
| Age 10                             | 15.1% (205)      |
| Age 18                             | 35.8% (468)      |
| Age 26                             | 42.1% (435)      |
| <b>Atopic asthma</b>               |                  |
| Age 10                             | 9.7% (100)       |
| Age 18                             | 13.4% (114)      |
| Age 26                             | 12.8% (71)       |
| <b>Atopic rhinitis</b>             |                  |
| Age 10                             | 10.6% (110)      |
| Age 18                             | 15.2% (233)      |
| Age 26                             | 30% (167)        |
| <b>Persistent asthma</b>           |                  |
| Age 10 to 18                       | 9.9% (122)       |
| Age 18 to 26                       | 11.8% (115)      |
| <b>Aeroallergen sensitisation</b>  |                  |
| Age 10                             | 26.7% (276)      |
| Age 18                             | 40.3% (343)      |
| Age 26                             | 45.1% (251)      |

**Table 2: The associations between Food allergy/ Food allergen sensitisation and Asthma**

|                                                   | Asthma at 18 years                                                                                               |                                       | Asthma at 26 years                                         |                                       |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------------|---------------------------------------|
|                                                   | aOR [95% CI]                                                                                                     | Number of cases included in the model | aOR [95% CI]                                               | Number of cases included in the model |
| <b>FA at 1 or 2 years</b>                         | 1.56 (0.94-2.58)<br>P=0.084                                                                                      | 1166                                  | <b>2.00 (1.14-3.49)</b><br><b>P=0.015</b>                  | 931                                   |
| <b>FA at 4 years</b>                              | <b>2.75 (1.53-4.92)</b><br><b>P=0.001</b>                                                                        | 1096                                  | <b>2.62 (1.32-5.20)</b><br><b>P=0.006</b>                  | 864                                   |
| <b>FA at 10 years</b>                             | 0.86 (0.29-2.53)<br>P=0.780                                                                                      | 1086                                  | 0.51 (0.12-2.20)<br>P=0.365                                | 858                                   |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | <b>4.35 (1.74-10.87)</b><br><b>P=0.002</b>                                                                       | 133                                   | <b>3.07 (1.18-7.98)</b><br><b>P=0.021</b>                  | 104                                   |
| <b>FAS at 4 years</b>                             | <b>5.69 (2.45-13.20)</b><br><b>P&lt;0.001</b>                                                                    | 895                                   | <b>4.95 (1.95 – 12.57)</b><br><b>P=0.001</b>               | 721                                   |
| <b>FAS at 10 years</b>                            | <b>5.25 (2.73-10.08)</b><br><b>P&lt;0.001</b>                                                                    | 953                                   | <b>3.33 (1.59-6.96)</b><br><b>P=0.001</b>                  | 780                                   |
| <b>Co-variables included in the model</b>         | Family history of asthma, Family history of rhinitis, Family history of eczema, Sex, Eczema at corresponding age |                                       | Family history of asthma, Sex, Eczema at corresponding age |                                       |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI: adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

Table 3: The associations between Food allergy/ Food allergen sensitisation and Rhinitis

|                                                   | Rhinitis at 18 years                                              |                                       | Rhinitis at 26 years                      |                                       |
|---------------------------------------------------|-------------------------------------------------------------------|---------------------------------------|-------------------------------------------|---------------------------------------|
|                                                   | (aOR [95% CI])                                                    | Number of cases included in the model | (aOR [95% CI])                            | Number of cases included in the model |
| <b>FA at 1 or 2 years</b>                         | 0.97 (0.59-1.59)<br>P=0.893                                       | 899                                   | 1.06 (0.67-1.70)<br>P=0.795               | 935                                   |
| <b>FA at 4 years</b>                              | 0.77 (0.40-1.47)<br>P=0.425                                       | 962                                   | 1.02 (0.55-1.87)<br>P=0.956               | 870                                   |
| <b>FA at 10 years</b>                             | 0.59 (0.21-1.66)<br>P=0.317                                       | 822                                   | 0.67 (0.30-1.50)<br>P=0.325               | 916                                   |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | 1.59 (0.70-3.60)<br>P=0.269                                       | 108                                   | 1.47 (0.67-3.26)<br>P=0.339               | 104                                   |
| <b>FAS at 4 years</b>                             | <b>3.93 (1.58-9.78)</b><br><b>P=0.003</b>                         | 790                                   | 1.83 (0.76-4.39)<br>P=0.179               | 724                                   |
| <b>FAS at 10 years</b>                            | <b>13.26 (4.60-38.25)</b><br><b>P&lt;0.001</b>                    | 754                                   | <b>2.59 (1.26-5.30)</b><br><b>P=0.009</b> | 783                                   |
| <b>Co-variables included in the model</b>         | Family history of rhinitis, Cord IgE, Eczema at corresponding age |                                       | Family history of food allergy            |                                       |

FA: Food allergy, FAS: Food allergen sensitisation, aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Table 4- The associations between Food allergy (FA) and Food allergen sensitisation (FAS) with asthma persistence**

|                                                   | Persistence of asthma between 10-18 years                  |                                       | Persistence of asthma between 18-26 years                |                                       |
|---------------------------------------------------|------------------------------------------------------------|---------------------------------------|----------------------------------------------------------|---------------------------------------|
|                                                   | (aOR [95% CI])                                             | Number of cases included in the model | (aOR [95% CI])                                           | Number of cases included in the model |
| <b>FA at 1 or 2 years</b>                         | 1.51 (0.58-3.92)<br>P=0.395                                | 153                                   | 1.60 (0.59-4.37)<br>P=0.360                              | 162                                   |
| <b>FA at 4 years</b>                              | 3.28 (0.90-11.95)<br>P=0.071                               | 158                                   | 1.10 (0.40-3.01)<br>P=0.851                              | 150                                   |
| <b>FA at 10 years</b>                             | 0.68 (0.10-4.71)<br>P=0.692*                               | 165                                   | 1.42 (0.13-16.10)<br>P=0.777                             | 156                                   |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | 2.61 (0.57-11.91)<br>P=0.215                               | 35                                    | 2.17 (0.40-11.74)<br>P=0.370                             | 27                                    |
| <b>FAS at 4 years</b>                             | 4.32 (0.90-20.84)<br>P=0.069                               | 133                                   | 5.05 (0.60-42.52)<br>P=0.136                             | 130                                   |
| <b>FAS at 10 years</b>                            | 7.19 (0.88-58.61)<br>P=0.065*                              | 150                                   | 1.90 (0.58-6.26)<br>P=0.291                              | 150                                   |
| <b>Co-variables included in the model</b>         | Sex<br>*Eczema at age 10 was also included in these models |                                       | Eczema at the corresponding age (apart from ages 1 OR 2) |                                       |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Table 5- The associations between Food allergy and Food allergen sensitisation with subsequent aeroallergen sensitisation.**

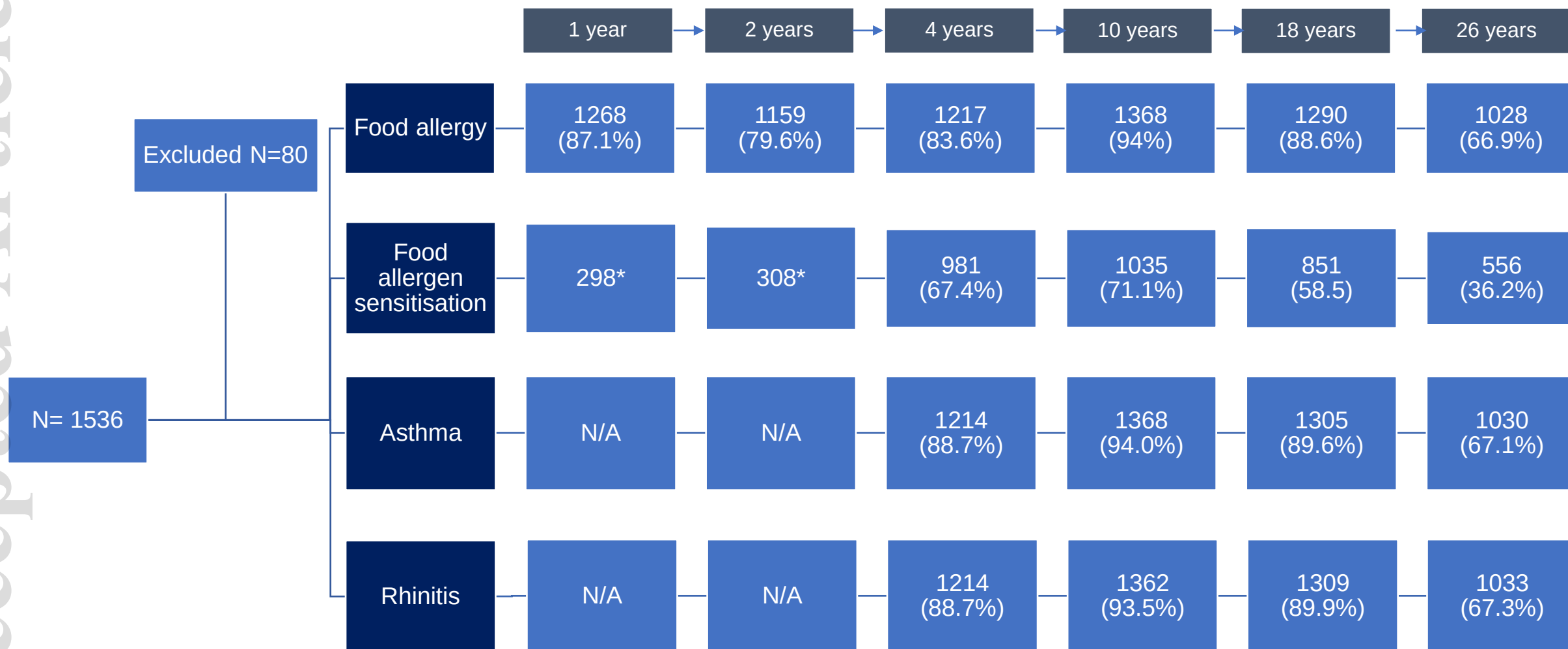
|                                                   | Aeroallergen sensitisation at 18 years                                                                                                                                                                     |                                       | Aeroallergen sensitisation at 26 years            |                                       |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------|---------------------------------------|
|                                                   | (aOR [95% CI])                                                                                                                                                                                             | Number of cases included in the model | (aOR [95% CI])                                    | Number of cases included in the model |
| <b>FA at 1 or 2 years</b>                         | 1.45 (0.85-2.46)<br>P=0.174                                                                                                                                                                                | 768                                   | <b>2.44 (1.13-5.26)</b><br><b>P=0.023</b>         | 409                                   |
| <b>FA at 4 years</b>                              | 1.12 (0.56-2.24)<br>P=0.743                                                                                                                                                                                | 762                                   | 0.92 (0.37-2.32)<br>P=0.865                       | 428                                   |
| <b>FA at 10 years</b>                             | 0.54 (0.19-1.55)<br>P=0.252                                                                                                                                                                                | 723                                   | 0.31 (0.08-1.25)<br>P=0.100                       | 377                                   |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | <b>2.67 (1.15-7.66)</b><br><b>P=0.024</b>                                                                                                                                                                  | 92                                    | <b>5.48 (1.22-24.71)</b><br><b>P=0.027</b>        | 51                                    |
| <b>FAS at 4 years</b>                             | <b>8.59 (1.90-38.80)</b><br><b>P=0.005</b>                                                                                                                                                                 | 671                                   | <b>5.24 (1.08-25.39)</b><br><b>P=0.040</b>        | 377                                   |
| <b>FAS at 10 years</b>                            | <b>28.67 (6.79-121.09)</b><br><b>P&lt;0.001</b>                                                                                                                                                            | 741                                   | <b>45.60 (6.16-5819.68)</b><br><b>P&lt;0.001*</b> | 383                                   |
| <b>Co-variables included in the model</b>         | Sex, Cord IgE, Maternal smoking<br>Sex, family social status cluster, Family history of rhinitis, Family history of Asthma, Eczema at corresponding age<br>(except age 10 as P>0.1 in univariate analysis) |                                       |                                                   |                                       |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Family social status cluster is a measure of socioeconomic status. Please see definition in methods. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses. \*Due to 0's in counts a penalised logistic regression was performed.

## Figure legends

Figure 1. Participation data availability at ages 1, 2, 4, 10, 18 and 26 years in the Isle of Wight birth cohort (Consort diagram) for Food allergy, Food allergen sensitisation, Asthma and Rhinitis.

\*At ages 1 and 2, skin prick tests were only conducted when clinically indicated.



## **Online Repository material**

**Online Repository Table E1: Overlap between aeroallergen sensitisation, food allergy and food allergen sensitisation**

|                                            | No Aeroallergen sensitisation at age 4 (N=810)  | Aeroallergen sensitisation at age 4 (N=170)  | <b>P value</b> |
|--------------------------------------------|-------------------------------------------------|----------------------------------------------|----------------|
| Food allergen sensitisation at age 1 or 2* | 20% (13/65)                                     | 65.1% (28/43)                                | <0.001         |
| Food allergen sensitisation at age 4       | 0.2% (2/810)                                    | 17.1% (29/170)                               | <0.001         |
| Food allergy at age 1 or 2                 | 6.2% (48/772)                                   | 19.8% (32/162)                               | <0.001         |
| Food allergy at age 4                      | 4.1% (33/809)                                   | 14.1% (24/170)                               | <0.001         |
|                                            |                                                 |                                              |                |
|                                            | No Aeroallergen sensitisation at age 10 (N=759) | Aeroallergen sensitisation at age 10 (N=276) | <b>P value</b> |
| Food allergen sensitisation at age 1 or 2* | 23% (14/61)                                     | 55.8% (29/52)                                | <0.001         |
| Food allergen sensitisation at age 4       | 0.7% (4/596)                                    | 10.6% (24/226)                               | <0.001         |
| Food allergen sensitisation at age 10      | 0.3% (2/759)                                    | 16.3% (45/276)                               | <0.001         |
| Food allergy at age 1 or 2                 | 6.5% (46/707)                                   | 14.6% (37/254)                               | <0.001         |
| Food allergy at age 4                      | 4.3% (29/681)                                   | 10.2% (26/254)                               | 0.001          |
| Food allergy at age 10                     | 2.7% (18/676)                                   | 2.9% (7/244)                                 | 0.855          |

Chi-squared tests or Fishers exact tests were performed to assess for associations. \*SPT was only performed at ages 1 or 2 when clinically indicated.

**Online Repository Table E2- The associations between food allergy/food allergen sensitisation and Atopic asthma**

|                                                   | Atopic asthma at 18 years                                                                                                        |                                   | Atopic asthma at 26 years                              |                                   |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------|-----------------------------------|
|                                                   | aOR [95% CI]                                                                                                                     | Number of cases included in model | aOR [95% CI]                                           | Number of cases included in model |
| <b>FA at 1 or 2 years</b>                         | <b>1.51 (0.73-3.13)</b><br>P=0.268                                                                                               | 601                               | <b>2.41 (1.14-5.08)</b><br>P=0.021                     | 496                               |
| <b>FA at 4 years</b>                              | <b>1.92 (0.72-5.11)</b><br>P=0.193                                                                                               | 633                               | <b>3.45 (1.02-8.43)</b><br>P=0.007                     | 474                               |
| <b>FA at 10 years</b>                             | <b>1.41 (0.38-5.21)</b><br>P=0.604                                                                                               | 545                               | <b>1.08 (0.23-5.00)</b><br>P=0.921                     | 446                               |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | <b>5.02 (1.23-20.52)</b><br>P=0.025                                                                                              | 72                                | <b>5.28 (1.47-18.61)</b><br>P=0.011                    | 60                                |
| <b>FAS at 4 years</b>                             | <b>5.69 (1.84-17.56)</b><br>P=0.002                                                                                              | 559                               | <b>6.03 (1.86-19.59)</b><br>P=0.003                    | 421                               |
| <b>FAS at 10 years</b>                            | <b>6.83 (3.10-15.05)</b><br>P<0.001                                                                                              | 567                               | <b>7.35 (3.00-17.97)</b><br>P<0.001                    | 460                               |
| <b>Co-variates included in the model</b>          | Family history of asthma, Family history of rhinitis, Family history of eczema, Cord IgE, eczema at corresponding age time point |                                   | Family history of asthma , eczema at corresponding age |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Atopic asthma were defined as meeting study criteria for asthma alongside positive aeroallergen sensitisation at the time-point of diagnosis. Logistic regression modelling was performed and co-variates were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E3- The associations between food allergy/food allergen sensitisation and Atopic rhinitis**

|                                                   | Atopic rhinitis at 18 years                                                                 |                                   | Atopic rhinitis at 26 years                                                                                    |                                   |
|---------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------|
|                                                   | aOR [95% CI]                                                                                | Number of cases included in model | aOR [95% CI]                                                                                                   | Number of cases included in model |
| <b>FA at 1 or 2 years</b>                         | 0.92 (0.48-1.74)<br>P=0.787                                                                 | 564                               | 1.32 (0.69-2.55)<br>P=0.404                                                                                    | 435                               |
| <b>FA at 4 years</b>                              | 0.67 (0.27-1.66)<br>P=0.384                                                                 | 594                               | 0.99 (0.42-2.31)<br>P=0.972                                                                                    | 405                               |
| <b>FA at 10 years</b>                             | 0.88 (0.30-2.58)<br>P=0.813                                                                 | 513                               | 0.70 (0.22-2.28)<br>P=0.556                                                                                    | 407                               |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | 1.66 (0.57-4.87)<br>P=0.353                                                                 | 69                                | 1.57 (0.48-5.14)<br>P=0.457                                                                                    | 53                                |
| <b>FAS at 4 years</b>                             | <b>5.21 (1.59-17.08)</b><br><b>P=0.006</b>                                                  | 522                               | <b>3.25 (1.04-10.17)</b><br><b>P=0.043</b>                                                                     | 367                               |
| <b>FAS at 10 years</b>                            | <b>21.92 (6.50-73.87)</b><br><b>P&lt;0.001</b>                                              | 534                               | <b>4.27 (1.71-10.70)</b><br><b>P=0.002</b>                                                                     | 403                               |
| <b>Co-variables included in the model</b>         | Family history of asthma, Family history of rhinitis, Cord IgE, eczema at corresponding age |                                   | Family history of asthma, Family history of rhinitis, Family history of eczema, Family history of food allergy |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Atopic rhinitis was defined as meeting study criteria for rhinitis alongside positive aeroallergen sensitisation at the time-point of diagnosis. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E4- The associations between food allergy/food allergen sensitisation and Non-atopic asthma (univariate)**

|                                                               | <b>Non-atopic asthma at<br/>18 years<br/>(OR [95% CI])</b> | <b>Non-atopic asthma at<br/>26 years<br/>(OR [95% CI])</b> |
|---------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| <b>FA at 1 or 2 years</b>                                     | 2.27 (0.96-5.36)<br>P=0.080                                | 0.54 (0.07-4.16)<br>P=1.000                                |
| <b>FA at 4 years</b>                                          | <b>6.42 (2.53-16.25)<br/>P=0.001</b>                       | 1.18 (0.15-9.31)<br>P=0.594                                |
| <b>FA at 10 years</b>                                         | 0.40 (0.02-6.78)<br>P=0.526                                | 0.51 (0.03-8.78)<br>P=0.643*                               |
| <b>FAS in<br/>symptomatic<br/>infants at 1 or 2<br/>years</b> | 2.73 (0.56-13.33)<br>P=0.232*                              | 0.75 (0.03-19.70)<br>P=0.865*                              |
| <b>FAS at 4 years</b>                                         | 0.90 (0.05-15.89)<br>P=0.942*                              | 1.91 (0.10-35.60)<br>P=0.664*                              |
| <b>FAS at 10 years</b>                                        | 0.36 (0.02-6.10)<br>P=0.480*                               | 0.79 (0.05-13.78)<br>P=0.869*                              |

FA: Food allergy, FAS: Food allergen sensitisation. OR;95 CI= odds ratio (95% confidence interval). Non-atopic asthma was defined as meeting study criteria for asthma in the absence of allergen sensitisation at the time. Chi-squared or Fisher's exact tests were used to assess the associations. \*Where zeros cause problems with computation of the odds ratio, the Haldane-Anscombe correction was applied.

**Online Repository Table E5- The associations between food allergy/food allergen sensitisation and Non-atopic rhinitis (Univariate)**

|                                                               | Non-atopic rhinitis at<br>18 years<br>(OR [95% CI]) | Non-atopic rhinitis at 26<br>years<br>(OR [95% CI]) |
|---------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| <b>FA at 1 or 2 years</b>                                     | 1.20 (0.56-2.56)<br>P=0.642                         | 0.68 (0.25-1.84)<br>P=0.444                         |
| <b>FA at 4 years</b>                                          | 0.96 (0.32-2.85)<br>P=1.000                         | 0.58 (0.17-2.05)<br>P=0.581                         |
| <b>FA at 10 years</b>                                         | 0.17 (0.01-2.91)<br>P=0.223*                        | 0.58 (0.13-2.68)<br>P=0.740                         |
| <b>FAS in<br/>symptomatic<br/>infants at 1 or 2<br/>years</b> | 1.22 (0.31-4.90)<br>P=1.000                         | 0.53 (0.09-3.06)<br>P=0.686                         |
| <b>FAS at 4 years</b>                                         | 0.38 (0.02 – 6.88)<br>P=0.515*                      | 0.30 (0.02-5.51)<br>P=0.418*                        |
| <b>FAS at 10 years</b>                                        | 0.48 (0.03-8.67)<br>P=0.616*                        | 0.21 (0.01-3.66)<br>P=0.282*                        |

FA: Food allergy, FAS: Food allergen sensitisation. OR;95 CI= odds ratio (95% confidence interval). Non-atopic rhinitis was defined as meeting study criteria for rhinitis in the absence of allergen sensitisation at the time. Chi-squared or Fisher's exact tests were used to assess the associations. \*Where zeros cause problems with computation of the odds ratio, the Haldane-Anscombe correction was applied.

**Online Repository Table E6: Subgroup analysis of subjects seen at age 26 vs not-seen at age 26**

|                                                              | <b>Not seen at age 26<br/>N=503</b> | <b>Seen at age 26<br/>N=1033</b> | <b>P value</b> |
|--------------------------------------------------------------|-------------------------------------|----------------------------------|----------------|
| Sex, Female                                                  | 37.6% (189/503)                     | 54.2% (560/1033)                 | <0.001         |
| Eczema at 1 or 2                                             | 12.9% (54/417)                      | 14.8% (142/960)                  | 0.369          |
| Eczema at 4                                                  | 11.4% (39/343)                      | 12.4% (108/871)                  | 0.621          |
| Eczema at 10                                                 | 11.2% (43/385)                      | 14.7% (143/973)                  | 0.088          |
| Asthma at 4                                                  | 14.9% (51/343)                      | 15.0% (15/871)                   | 0.940          |
| Asthma at 10                                                 | 14.8% (58/393)                      | 14.7% (143/975)                  | 0.965          |
| Asthma at 18                                                 | 13.8% (45/326)                      | 19.0% (186/979)                  | 0.033          |
| Rhinitis at 4                                                | 4.1% (14/343)                       | 6.0% (52/871)                    | 0.191          |
| Rhinitis at 10                                               | 13.3% (52/392)                      | 15.8% (153/970)                  | 0.241          |
| Rhinitis at 18                                               | 33.8% (111/328)                     | 36.4% (357/981)                  | 0.404          |
| Food Allergy at 1 or 2                                       | 6.9% (27/394)                       | 8.3% (78/938)                    | 0.366          |
| Food Allergy at 4                                            | 4.7% (16/343)                       | 5.1% (45/874)                    | 0.728          |
| Food Allergy at 10                                           | 1.8% (8/447)                        | 2.9% (29/921)                    | 0.210          |
| Food allergen sensitisation in symptomatic infants at 1 or 2 | 25% (10/40)                         | 41.3% (43/104)                   | 0.068          |
| Food allergen sensitisation at 4                             | 4% (10/253)                         | 2.9% (21/727)                    | 0.405          |
| Food allergen sensitisation at 10                            | 4.8% (12/249)                       | 4.5% (35/786)                    | 0.809          |
| Aeroallergen sensitisation at 4                              | 18.2% (46/253)                      | 17.1% (124/727)                  | 0.684          |
| Aeroallergen sensitisation at 10                             | 24.5% (61/249)                      | 27.4% (215/787)                  | 0.375          |
| Aeroallergen sensitisation at 18                             | 38.8% (54/139)                      | 40.6% (289/712)                  | 0.702          |

Chi-squared tests or Fishers exact tests were performed to assess for associations. SPT was only performed at ages 1 or 2 when clinically indicated.

**Online Repository Table E7: Sensitivity analysis of subjects with complete follow-up up to age 26 questionnaires**

|                                                   | Asthma at 18 years                                                                                               |                                   | Rhinitis at 18 years                                              |                                   |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------|-----------------------------------|
|                                                   | aOR [95% CI]                                                                                                     | Number of cases included in model | aOR [95% CI]                                                      | Number of cases included in model |
| <b>FA at 1 or 2 years</b>                         | 1.56 (0.89-2.76)<br>P=0.124                                                                                      | 886                               | 0.86 (0.49-1.51)<br>P=0.588                                       | 681                               |
| <b>FA at 4 years</b>                              | <b>3.59 (1.90-6.78)</b><br><b>P&lt;0.001</b>                                                                     | 831                               | 0.75 (0.35-1.60)<br>P=0.462                                       | 721                               |
| <b>FA at 10 years</b>                             | 0.68 (0.20-2.31)<br>P=0.532                                                                                      | 825                               | 0.49 (0.16-1.54)<br>P=0.223                                       | 627                               |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | <b>5.13 (1.68-15.63)</b><br><b>P=0.004</b>                                                                       | 100                               | 1.56 (0.61-3.98)<br>P=0.352                                       | 82                                |
| <b>FAS at 4 years</b>                             | <b>5.02 (1.89-13.33)</b><br><b>P=0.001</b>                                                                       | 698                               | <b>3.21 (1.17-8.80)</b><br><b>P=0.023</b>                         | 609                               |
| <b>FAS at 10 years</b>                            | <b>4.21 (2.03-8.71)</b><br><b>P&lt;0.001</b>                                                                     | 754                               | <b>9.76 (3.31-28.76)</b><br><b>P&lt;0.001</b>                     | 594                               |
| <b>Co-variables included in the model</b>         | Family history of asthma, Family history of rhinitis, Family history of eczema, Sex, Eczema at corresponding age |                                   | Family history of rhinitis, Cord IgE, Eczema at corresponding age |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E8: Sensitivity analysis of subjects with complete follow-up up to age 26 skin prick test**

|                                            | Asthma at 18 years                                                                                               |                                   | Rhinitis at 18 years                                              |                                   |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------|-----------------------------------|
|                                            | (aOR [95% CI])                                                                                                   | Number of cases included in model | (aOR [95% CI])                                                    | Number of cases included in model |
| FA at 1 or 2 years                         | 1.62 (0.80-3.26)<br>P=0.178                                                                                      | 507                               | 0.84 (0.39-1.77)<br>P=0.638                                       | 401                               |
| FA at 4 years                              | <b>3.94 (1.75-8.87)</b><br><b>P=0.001</b>                                                                        | 480                               | 0.62 (0.24-1.60)<br>P=0.321                                       | 418                               |
| FA at 10 years                             | 0.63 (0.14-2.92)<br>P=0.558                                                                                      | 458                               | 0.69 (0.17-2.80)<br>P=0.603                                       | 363                               |
| FAS in symptomatic infants at 1 or 2 years | <b>4.22 (1.16-15.45)</b><br><b>P=0.029</b>                                                                       | 59                                | 2.58 (0.71-9.41)<br>P=0.151                                       | 49                                |
| FAS at 4 years                             | <b>5.86 (1.72-19.94)</b><br><b>P=0.005</b>                                                                       | 425                               | 3.25 (0.94-11.26)<br>P=0.063                                      | 372                               |
| FAS at 10 years                            | <b>6.66 (2.71-16.17)</b><br><b>P&lt;0.001</b>                                                                    | 471                               | <b>35.56 (4.67-270.98)</b><br><b>P=0.001</b>                      | 377                               |
| <b>Co-variates included in the model</b>   | Family history of asthma, Family history of rhinitis, Family history of eczema, Sex, Eczema at corresponding age |                                   | Family history of rhinitis, Cord IgE, Eczema at corresponding age |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variates were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E9: Sensitivity analysis of subjects with complete follow-up up to age 26**

|                                                   | Atopic Asthma at 18 years                                                                                                        |                                   | Atopic Rhinitis at 18 years                                                                            |                                   |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|
|                                                   | (aOR [95% CI])                                                                                                                   | Number of cases included in model | (aOR [95% CI])                                                                                         | Number of cases included in model |
| <b>FA at 1 or 2 years</b>                         | 1.16 (0.52-2.60)<br>P=0.712                                                                                                      | 508                               | 0.82 (0.41-1.64)<br>P=0.577                                                                            | 481                               |
| <b>FA at 4 years</b>                              | 2.61 (0.93-7.35)<br>P=0.069                                                                                                      | 530                               | 0.66 (0.25-1.76)<br>P=0.406                                                                            | 501                               |
| <b>FA at 10 years</b>                             | 0.96 (0.20-4.55)<br>P=0.959                                                                                                      | 461                               | 0.76 (0.23-2.50)<br>P=0.651                                                                            | 437                               |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | 4.24 (0.82-21.89)<br>P=0.085                                                                                                     | 64                                | 1.31 (0.40-4.31)<br>P=0.657                                                                            | 61                                |
| <b>FAS at 4 years</b>                             | <b>5.93 (1.60-21.94)</b><br><b>P=0.008</b>                                                                                       | 472                               | 3.26 (0.91-11.72)<br>P=0.070                                                                           | 445                               |
| <b>FAS at 10 years</b>                            | <b>6.76 (2.85-16.04)</b><br><b>P&lt;0.001</b>                                                                                    | 479                               | <b>16.86 (4.91-57.93)</b><br><b>P&lt;0.001</b>                                                         | 455                               |
| <b>Co-variables included in the model</b>         | Family history of asthma, Family history of rhinitis, Family history of eczema, Cord IgE, eczema at corresponding age time point |                                   | Family history of asthma, Family history of rhinitis, Cord IgE, eczema at corresponding age time point |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E10: Sensitivity analysis of subjects with complete follow-up up to age 26 skin prick test**

|                                                   | Atopic Asthma at 18 years                                                                                                        |                                   | Atopic Rhinitis at 18 years                                                                            |                                   |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|
|                                                   | (aOR [95% CI])                                                                                                                   | Number of cases included in model | (aOR [95% CI])                                                                                         | Number of cases included in model |
| <b>FA at 1 or 2 years</b>                         | 1.28 (0.48-3.44)<br>P=0.627                                                                                                      | 340                               | 0.78 (0.32-1.91)<br>P=0.582                                                                            | 324                               |
| <b>FA at 4 years</b>                              | 1.37 (0.37-5.10)<br>P=0.637                                                                                                      | 353                               | 0.36 (0.10-1.28)<br>P=0.114                                                                            | 335                               |
| <b>FA at 10 years</b>                             | 1.43 (0.28-7.46)<br>P=0.671                                                                                                      | 310                               | 0.93 (0.22-3.87)<br>P=0.918                                                                            | 295                               |
| <b>FAS in symptomatic infants at 1 or 2 years</b> | 2.66 (0.39-18.09)<br>P=0.317                                                                                                     | 41                                | 2.77 (0.58-13.38)<br>P=0.203                                                                           | 41                                |
| <b>FAS at 4 years</b>                             | <b>7.54 (1.56-36.54)</b><br><b>P=0.012</b>                                                                                       | 323                               | 3.34 (0.76-14.67)<br>P=0.110                                                                           | 306                               |
| <b>FAS at 10 years</b>                            | <b>10.17 (3.63-28.52)</b><br><b>P&lt;0.001</b>                                                                                   | 328                               | <b>49.33 (6.33-384.15)</b><br><b>P&lt;0.001</b>                                                        | 313                               |
| <b>Co-variables included in the model</b>         | Family history of asthma, Family history of rhinitis, Family history of eczema, Cord IgE, eczema at corresponding age time point |                                   | Family history of asthma, Family history of rhinitis, Cord IgE, eczema at corresponding age time point |                                   |

FA: Food allergy, FAS: Food allergen sensitisation. aOR;95 CI= adjusted odds ratio (95% confidence interval). Family history: Paternal, Maternal or Sibling history of disease. Cord IgE= Cord immunoglobulin E, a dichotomous variable based on a cut-off of  $\geq 0.5$  kU/L. Eczema at corresponding age: met the study definition of eczema at the corresponding age time point. Logistic regression modelling was performed and co-variables were selected based on a significance level of 0.1 at univariate analyses.

**Online Repository Table E11- Example Crosstabulation between Food allergen sensitisation and Aeroallergen sensitisation**

|                           | <b>No aeroallergen<br/>sensitisation at 26<br/>years</b> | <b>Aeroallergen<br/>sensitisation at 26<br/>years</b> |
|---------------------------|----------------------------------------------------------|-------------------------------------------------------|
| <b>No FAS at 10 years</b> | <b>262/461</b>                                           | <b>199/461</b>                                        |
| <b>FAS at 10 years</b>    | <b>0</b>                                                 | <b>23/23</b>                                          |

FA: Food allergy, FAS: Food allergen sensitisation, OR;95 CI= odds ratio (95% confidence interval). Chi-squared or Fisher's exact tests were used to assess the associations.