Early-life predictors and risk factors of peanut allergy, and its association with asthma in later-life: Population-based birth cohort study

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Abstract

Background: Understanding risk factors for peanut allergy (PA) is essential to develop effective preventive measures.

Objective: The objective was to ascertain associates and predictors of PA, and the relationship between PA and asthma severity.

Methods: In a population-based birth cohort, we investigated the association between objectively confirmed PA with early-life environmental exposures, filaggrin (FLG)-loss-of-function mutations and other atopic disease. We then examined the association of PA with longitudinal trajectories of sensitization, wheeze and allergic comorbidities, which were previously derived using machine learning. Finally, we ascertained the relationship between PA and asthma severity.

Results: PA was confirmed in 30/959 participants with evaluable data. In the multivariate analysis, eczema in infancy (OR = 4.4, 95% CI 1.5–13.2, p = 0.007), egg sensitization at age 3 years (OR = 9.7, 95% CI 3.3–29.9, p < 0.001) and early-life cat ownership (OR = 3.0, 95% CI 1.1–8.4, p = 0.04) were independent associates of PA.

In the stratified analysis among 700 participants with genetic information, in children with early-life eczema there was no difference in FLG mutations between children with and without PA (3/18 [16.7%] vs. 42/220 [19.1%, p = 1.00). In contrast, among children without eczema, those with PA were almost eight times more likely to have FLG mutations (2/6 [33.3%] vs. 27/456 [5.9%, p = 0.049). We observed associations between PA and multiple allergic sensitization profiles derived using machine learning, with ~60-fold increase in risk among individuals assigned to multiple early sensitization. PA was significantly associated with persistent wheeze (but not other wheeze phenotypes), and with trajectories of atopic disease characterized by co-morbid persistent eczema and wheeze (but not with transient phenotypes). Children with PA were more likely to have asthma, but among asthmatics we found no evidence of an association between PA and asthma severity.

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**Conclusions:** Peanut allergy is associated with multiple IgE sensitization and early-onset persistent eczema and wheeze. FLG loss-of-function mutations were associated with peanut allergy in children without eczema.

**Keywords:** asthma, atopic dermatitis, epidemiology, filagrin, food allergy, genetics, peanut

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**GRAPhICAL ABSTRACT**

Peanut allergy is associated with multiple IgE sensitization and early-onset persistent eczema and wheeze. FLG loss-of-function mutations were associated with peanut allergy in children without eczema.

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**1 | INTRODUCTION**

Peanut allergy is among the most common food allergies, affecting ~2% of children and 0.5% of adults in the UK, \(^1\) \(^3\) and ~2% of <18-year-olds in the United States. \(^4\) Peanut allergy tends to start in early life and has generally been considered to be lifelong, \(^5\) although some studies suggest that >20% of children may outgrow it. \(^6\) Data from the United States suggest that prevalence of peanut allergy has increased in the first decade of 21st century, \(^7\) and studies looking at nationwide UK records between 2001 and 2005 revealed similar trends. \(^8\) Reactions in peanut-allergic individuals can be unpredictable and severe, and although death remains rare, peanut allergy is among the most common causes for food-related fatal anaphylaxis. \(^9\), \(^10\) In patients with food allergy, a history of asthma and previous asthma exacerbations are risk factors for fatal anaphylaxis. \(^11\), \(^12\) Among asthmatic patients, the presence of peanut allergy is often considered to be associated with more severe asthma, \(^13\) but the data about this relationship are sparse. \(^14\)

The mainstay of management is strict avoidance and carrying of adrenaline auto-injectors for emergency use. \(^15\) Avoidance, however, can be difficult, \(^16\) and accidental reactions are relatively common. \(^17\) This creates anxiety among patients and their families, leading to restrictions in eating habits and social activities. \(^18\) Peanut oral immunotherapy offers promise for treatment, but this approach focuses on mitigating the risk of reactions due to accidental exposure rather than providing a cure. \(^19\), \(^20\) Measures aimed at primary and secondary prevention remain the preferred option for addressing this growing problem, \(^21\) highlighting the importance of understanding the risk factors and predictors of peanut allergy.

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**Key Messages**

- Peanut Allergy is associated with longitudinal trajectories characterized by early-onset and persistent eczema and wheeze.
- Among children without eczema, FLG mutations are significantly associated with peanut allergy.
- Peanut-allergic children are more likely to have asthma, but among asthmatics, peanut allergy is not associated with more severe asthma.
Methods

2.1 Study design, setting and participants

Manchester Asthma and Allergy Study is a population-based birth cohort. Detailed description is provided in the Supplementary Appendix. Briefly, participants were recruited prenatally and followed prospectively, attending review clinics at ages 1, 3, 5, 8 and 11 years. The study received approval by the local ethics committee, and informed consent was obtained in all cases.

2.2 Data sources

2.2.1 Questionnaires

At each visit, interviewer-administered validated questionnaires were used to collect information on environmental exposures, parent-reported symptoms, physician-diagnosed diseases and treatments received. These were enriched with additional questions on food allergy and diet.

2.2.2 Allergic sensitization

We completed skin prick tests (SPTs) and sIgE measurement (ImmunoCAP™, Phadia) to common food (milk, egg and peanut) and aero-allergens (house dust mite-HDM, cat, dog, moulds, grass and birch pollen) at all time-points.

Component resolved diagnostics (CRD) to peanut components Ara h 1–3 was performed by ImmunoCAP (age 8 years). Further CRD data were obtained through multiplex Immuno Solid-Phase Allergen Chip (ISAC).40

2.2.3 Primary care medical records

We transcribed data from primary healthcare records for the first 10 years of life (details in Supplementary Appendix). This included information on asthma medication and oral corticosteroid prescriptions, wheeze episode presentations to the GP, and asthma/wheeze related emergency department attendances and hospital admissions.

2.2.4 Genotyping

Filaggrin (FLG) genotyping was performed as previously described to ascertain the presence of six FLG loss-of-function mutations (R501X, S3247X, R2447X, 2282del4, 3673delC and 3702delG).

2.3 Definitions of outcomes and key variables

2.3.1 Peanut sensitization

Skin prick test mean wheal diameter (MWD) to peanut extract of 3 mm or greater than the negative control and/or sIgE to whole peanut extract >0.35 kU/L.
2.3.2 | Peanut allergy

All cohort children with evidence of peanut sensitization at ages 5 and/or 8 years (SPT response ≥3 mm or sIgE level ≥0.2 kUa/L), or history of immediate reaction upon exposure, were offered an OFC to confirm peanut allergy.2,29,30 To enrich peanut-allergic group, we recruited 12 children (6 boys) with confirmed peanut allergy from a tertiary referral local allergy clinic (reaction on exposure to peanut and sIgE ≥ 15 kUa/L and/or SPT ≥ 8 mm); these children had longitudinally collected data to facilitate studies on peanut allergy and did not undergo OFC. Detailed description of OFC protocol is provided in the Supplementary Appendix. Briefly, open OFCs were carried out among children who had a history of tolerating peanut on consumption; all other children underwent a double-blind, placebo-controlled food challenge (DBPCFC). Two or more objective signs were required to constitute a positive challenge.2,30

Non-sensitized children with no history of a previous reaction who were consuming peanuts were a priori classified as non-peanut allergic. Children with negative peanut OFC were also classified as peanut non-allergic.

2.3.3 | FLG loss-of-function mutations

Children carrying any one or more of the six mutations were defined as carriers.30,42

Definitions of all other variables (including previously derived data-driven longitudinal patterns of allergic sensitization,33,43 wheeze phenotypes32 and atopic multimorbidity clusters34,44) are presented in the Supplemental appendix.

2.4 | Statistical analysis

All evaluable data were used in the analysis. Differences between groups were assessed using unpaired t-test for normally distributed continuous data, Mann–Whitney for skewed continuous data and Pearson’s chi-square and Fisher’s exact test for categorical binary data. Univariate logistic regression analysis was carried out to assess the unadjusted odds ratio (OR) of each independent variable to the outcome. Multivariate logistic regression models were then used to examine the association of each independent variable with peanut allergy; results are reported as ORs and 95% confidence intervals (CI). Variables for the multivariate analysis were selected based on the findings in the univariate analyses and the results of previous studies. We used STATA 14.2 for all analyses.

3 | RESULTS

We included 959 children in this analysis (514 [53.6%] boys and 895 [93.3%] White-Caucasian). Demographic characteristics of the study population and comparisons between included and excluded participants are presented in Table S2. In the included group, we observed higher breastfeeding rates (71.7% vs. 61.9%; p = 0.007) and day-care attendance (70.0% vs. 59.6%; p = 0.005), and lower proportion of older siblings (53.6% vs. 71.5%; p < 0.001), maternal smoking (13.5% vs. 20.2%, p = 0.012) and non-working parents (2.6% vs. 8.9%; p = 0.004).

3.1 | Peanut allergy and tolerance in the study population

Figure 1 shows the participant flow. Of 1029 children who attended follow-up at age 8 years, 864 were classified as not allergic to peanut (no peanut sensitization at ages 5 and/or 8, eating peanuts, no reactions); 924/1029 had either SPT or sIgE at age 8 years, of whom 101 fulfilled criteria for further study to confirm/refute peanut allergy (100 peanut-sensitized, one not sensitized, but reported reaction upon exposure) and were offered OFC, of whom 5 declined. Of the 96 participants who agreed to take part, 2 withdrew the consent for OFC and were subsequently classified as peanut allergic based on positive sIgE to Ara h 2 (>0.35 kuA/L measured by ImmunoCAP and >0.3 ISU measured by ISAC chip at age 11 years). Of 94 children who underwent OFC (40 DBPCFC, 54 open), 14 had positive OFC, 65 passed OFC, and 15 had inconclusive OFC (of those, 2 were classified as peanut allergic based on IgE sensitization to Ara h 2, and 13 were excluded). Detailed information on 4 children who were diagnosed as peanut allergic based on sIgE to Ara h 2 is presented in Supplementary Appendix. Children (n = 12) recruited from local allergy clinic with severe reaction upon exposure, SPT ≥ 8 mm and/or IgE ≥ 15 kuA/L were a priori classified as peanut allergic. Thereby, in total, 30 children in this analysis had confirmed peanut allergy, and 929 were not allergic to peanut (864 not sensitized and eating peanuts, and 65 who were sensitized, but had negative OFC).

3.2 | Characteristics of peanut-allergic children and those not allergic to peanut

Table 1 shows the demographic and early-life characteristics of peanut-allergic and non-allergic children. Peanut allergy was significantly associated with parental atopy, parental asthma and cat ownership during pregnancy, but these differences did not reach statistical significance. Similarly, small differences between the groups were noted in the rate of reported wheeze in infancy and rhinitis at age 3 years. Peanut-allergic children were almost 2 times more likely to have FLG mutations (20% vs. 10.4%), but this difference was not statically significant due to issues related to sample size.
**FIGURE 1** Participant flow

1184 children born into study

1029 children reviewed at age 8 years follow up

924 children had either SPT or sIgE at age 8 years

832 children not sensitised at age 8 years

- 3 excluded; (2 sensitised at age 11; 1 missing data)
- 7 included in sensitised group; sensitised at age 5 years & not eating peanut

821 children non-sensitised at 8 age years; eating peanut

- 43: Negative SPT/sIgE at age 11 years; eating peanut

864 children assigned as NOT Peanut Allergic

54 Open OFC

- 8 inconclusive OFCs Excluded

44 negative challenges; NOT Peanut Allergic

65 NOT Peanut Allergic (passed OFC; 44 open, 21 DBPCFC)

40 DBPCFC

- 7 inconclusive OFC: 5 excluded

- 2 PA confirmed, 11 years positive Ara h 2 sIgE

- 12 positive challenges NOT Peanut Allergic

- 30 children with PA

14 positive OFC, 4 diagnosis confirmed at age 11 years, 12 confirmed peanut allergy
3.2.1 | Multivariate analysis

We performed multivariate analyses accounting for gender, cat ownership, parental atopy, eczema in infancy and egg sensitization at age 3 years; results are shown in Table 2. Eczema in the first year of life (OR = 4.4, 95% CI 1.5–13.2, \( p = 0.007 \)) and egg sensitization at age 3 years (OR = 9.7, 95% CI 3.3–28.9, \( p < 0.001 \)) were independent associates of peanut allergy. Cat ownership during pregnancy/early life was also associated with an increased risk (OR = 3.0, 95% CI 1.1–8.4, \( p = 0.04 \)).

We also performed multivariate models which included maternal peanut consumption during breastfeeding (among breastfed infants) (Table S3). The only significant associate of peanut allergy in this model was early-life eczema.

3.3 | FLG loss-of-function mutations and peanut allergy in children with and without eczema

We further explored the association between FLG mutations, eczema and peanut allergy among 700 Caucasian participants with complete data by stratifying the population according to whether the child had eczema in the first year of life. Among 238 children with early-life eczema, there was no difference in the frequency of FLG mutations carriers between peanut-allergic children and those not allergic (16.7% vs. 19.1%, \( p = 1.00 \)) (Table 3). In contrast, among 462 children without eczema, those who carried FLG mutations were almost 8 times more likely to have peanut allergy compared to those with FLG wild-type (OR 7.9, 95% CI 1.4–45.3, \( p = 0.02 \)). However, since peanut allergy was rare in children without early-life eczema (6/462), these results need to be interpreted with caution.

3.4 | Longitudinal profiles of sensitization and allergic diseases in children with peanut allergy

There was a steady rise in the point prevalence of allergic sensitization among peanut-allergic children and those not allergic to peanut over time (Figure S1), with the prevalence of sensitization being consistently and significantly higher in peanut-allergic children at all time-points (Figure S1a). Despite the overall increase in sensitization, there was a gradual reduction in the proportion of children sensitized to egg, and the association of egg sensitization with peanut allergy weakened substantially with increasing age (Figure S1b). In contrast, associations of sensitization to inhalant allergens with peanut allergy strengthened with increasing age (Figure S1c–f).

We observed significantly higher rates of eczema to age of 8 years (Figure S2a), and rhinitis and wheeze throughout childhood (Figures S2, S3), in peanut-allergic children compared to those not allergic to peanut. Peanut-allergic children were more likely to have unscheduled visit to GPs and emergency departments with wheeze (Figure S3bc) and to have a doctor-diagnosed asthma and receive asthma medication (Figure S4).

3.5 | Association between peanut allergy and data-driven phenotypes

We previously described longitudinal sensitization clusters derived using machine learning.\(^{33}\) Using this classification, peanut allergy was associated with the multiple early and multiple late sensitization, but not to other sensitization clusters (Table 4). This association was strikingly strong for multiple early sensitization (OR 59.1, 95% CI 13.4–260).

Differences were also noted in relation to wheeze phenotypes,\(^{32}\) in that peanut allergy was strongly associated with persistent wheeze (OR 6.9, 95% CI 2.5–18.8, \( p < 0.001 \)), but not any other wheeze phenotype (Table 4).

Associations also differed for different developmental profiles of allergic diseases.\(^{34}\) Peanut allergy was strongly associated with the multimorbidity phenotype (eczema + wheeze + rhinitis, OR = 27.7, 95% CI 7.35–104.6, \( p < 0.001 \)). There was also an association with other comorbidity clusters (persistent eczema and rhinitis, OR = 13.1, 95% CI 3.3–52.1, \( p < 0.001 \); persistent eczema and wheeze, OR = 8.1, 95% CI 1.6–41.5, \( p = 0.012 \)), but not with the eczema only class (Table 4).

3.6 | Peanut allergy and asthma severity in school age

Peanut-allergic children were more likely to have asthma diagnosis at age 11 years (OR 4.0, 95% CI 1.9–8.5, \( p < 0.001 \)) (Table S4). Association between peanut allergy and asthma severity is shown in Table 5. Among asthmatics, those with peanut allergy were numerically more likely to receive oral corticosteroid prescription, have severe exacerbations and hospital admissions for asthma exacerbation, but none of these reached statistical significance. Peanut-allergic asthmatics were three times more likely to have multiple (≥4) exacerbations compared to those not allergic to peanut (OR = 2.9, 95% CI 0.9–9.3, \( p = 0.07 \)), but this difference was not statistically significant.

4 | DISCUSSION

In a population-based birth cohort which included food challenges to diagnose peanut allergy, we confirmed that eczema in the first year of life and egg sensitization in the first three years are associated with peanut allergy in school age. Among children with eczema, there was no association between peanut allergy and FLG genotype. In contrast, among those without eczema, carriers of FLG loss-of-function mutations were almost 8 times more likely to have peanut allergy compared to children without FLG mutations. However, given the low frequency of peanut allergy in children without infantile eczema, caution is needed when interpreting these results.

Cat ownership in pregnancy and early life was associated with almost threefold increased risk of peanut allergy. Peanut allergy was...
| Variables: Categorical (proportions, %) | Study population (n = 959) | No peanut allergy (n = 929) | Peanut allergy (n = 30) | p-Value | Odds ratio (95% CI) | Mean differences (95% CI) |
|--------------------------------------|-----------------------------|-----------------------------|-------------------------|---------|---------------------|--------------------------|
| Sex (Boys)                           | 514 (53.6%)                 | 494 (53.2%)                 | 20 (66.7%)              | p = 0.15 | 1.76 (0.82, 3.80)   |                           |
| Ethnicity (% Caucasian)              | 895 (95.3%)                 | 867 (95.4%)                 | 28 (93.3%)              | *p = 0.65 | 1.47 (0.34, 6.40)   |                           |
| Maternal age at birth (years)        | 30.6 years (30.3–30.9)      | 30.6 years                  | 31.7 years              | p = 0.24 | Diff −1.09 (−2.91, 0.73) |                           |
| Gestational age at birth (weeks)     | 39.9 weeks (39.8–40.0)      | 39.9 weeks                  | 39.5 weeks              | p = 0.16 | Diff 0.44 (−1.76, 1.05) |                           |

**Socioeconomic class**

| Managerial                          | 402 (61.6%)                 | 392 (61.6%)                 | 10 (58.8%)              | *p = 0.24 | *Excluded due to empty cells |                           |
| Intermediate                        | 151 (23.1%)                 | 144 (22.6%)                 | 7 (41.2%)               |           | 1.47 (0.34, 6.40)   |                           |
| Routine                             | 78 (11.9%)                  | 78 (12.3%)                  | 0 (0%)                  |           | 0.54 (0.13, 2.30)   |                           |
| Not working                         | 17 (2.6%)                   | 17 (2.7%)                   | 0 (0%)                  |           | 0.49 (0.19, 1.30)   |                           |

**Smoking during pregnancy (Y)**

| Maternal                            | 109 (11.5%)                 | 107 (11.7%)                 | 2 (6.7%)                | *p = 0.56 | 0.98 (0.34, 2.87)   |                           |
| Paternal                            | 270 (28.6%)                 | 265 (29.0%)                 | 5 (16.7%)               | p = 0.14 | 0.56 (0.21, 1.47)   |                           |

**Smoking at child’s age 1 year (Y)**

| Maternal                            | 129 (13.5%)                 | 125 (13.5%)                 | 4 (13.3%)               | *p = 1.00 | 0.56 (0.21, 1.47)   |                           |
| Paternal                            | 250 (26.1%)                 | 245 (26.4%)                 | 5 (16.7%)               | p = 0.23 | 0.98 (0.34, 2.87)   |                           |
| Breastfeeding (Y)                   | 660 (71.7%)                 | 640 (71.6%)                 | 20 (74.1%)              | p = 0.78 | 1.13 (0.47, 2.71)   |                           |

**Peanut consumption (Y)**

| Before pregnancy                    | 88 (91.7%)                  | 62 (92.5%)                  | 26 (89.7%)              | *p = 0.69 | 0.98 (0.34, 2.87)   |                           |
| In pregnancy                        | 78 (81.2%)                  | 55 (82.1%)                  | 23 (79.3%)              | p = 0.75 | 0.84 (0.28, 2.50)   |                           |
| During breastfeeding (in BF only)   | 49 (76.6%)                  | 34 (77.3%)                  | 15 (75%)                | p = 0.84 | 0.88 (0.26, 3.03)   |                           |

**Pet ownership (Y)**

| Cat ownership in pregnancy and early life | 193 (20.6%)                  | 183 (20.1%)                 | 10 (33.3%)              | *p = 0.078 | 1.98 (0.99, 4.31)   |                           |
| Dog ownership in pregnancy and early life | 154 (16.4%)                  | 150 (16.5%)                 | 4 (13.3%)               | *p = 0.81 | 0.78 (0.27, 2.26)   |                           |

**Older sibling (Y)**

| 511 (53.6%)                  | 496 (53.7%)                 | 15 (50%)                  | p = 0.69 | 0.86 (0.42, 1.78)   |                           |

**Day-care attendance (Y)**

| 629 (70.0%)                  | 610 (69.9%)                 | 19 (73.1%)                | p = 0.73 | 1.17 (0.49, 2.82)   |                           |

**Parental atopy (Y)**

| 771 (82.7%)                  | 745 (82.3%)                 | 26 (96.3%)                | p = 0.07 | 5.58 (0.75, 41.4)   |                           |
| Maternal                       | 542 (58.3%)                 | 525 (58.2%)                | 17 (63.0%)              | p = 0.62 | 1.22 (0.55, 2.70)   |                           |
| Paternal                       | 588 (63.8%)                 | 566 (63.2%)                | 22 (81.5%)              | p = 0.052 | 2.56 (0.96, 6.82)   |                           |

**Parental asthma (Y)**

| 291 (30.3%)                  | 278 (29.9%)                 | 13 (43.3%)                | p = 0.12 | 1.79 (0.86, 3.74)   |                           |
| Maternal                       | 187 (19.5%)                 | 179 (19.3%)                | 8 (26.7%)               | p = 0.31 | 1.52 (0.67, 3.48)   |                           |
| Paternal                       | 137 (14.3%)                 | 131 (14.1%)                | 6 (20%)                 | p = 0.37 | 1.52 (0.61, 3.79)   |                           |

**Eczema in the first years of life (Y)**

| 318 (35.1%)                  | 298 (33.9%)                 | 20 (74.1%)                | p < 0.001 | 5.56 (2.33, 13.3)   |                           |

**Eczema scoring at age 1 year**

| No eczema                       | 344 (82.7%)                 | 340 (84.4%)                | 4 (30.8%)               | Ref Variable |                           |                           |
| Mild                             | 54 (13.0%)                  | 50 (12.4%)                 | 4 (30.8%)               | 6.8 (1.65, 28.1)   |                           |                           |
| Mod-severe                       | 18 (4.3%)                   | 13 (3.2%)                  | 5 (30.5%)               | 32.7 (7.8, 136.0)  |                           |                           |

**FLG loss-of-function mutations (Caucasian only)**

| Any of the 6 mutations           | 79 (10.7%)                  | 74 (10.4%)                 | 5 (20%)                 | p = 0.13 | 2.16 (0.79, 5.92)   |                           |
markedly more common among children with persistent wheezing, but not any other wheeze phenotype, with approximately sevenfold increase in risk. Also of note is a near-exclusive association between peanut allergy and multiple allergic sensitization classes (both early and late), with almost 60-fold increase in risk among individuals assigned to multiple early sensitization. When we investigated the association between peanut allergy and machine-learning derived developmental profiles of eczema, wheeze and rhinitis, we observed consistent association for all profiles characterized by persistent eczema and multimorbidity, but there was no association with class characterized by eczema only, with no atopic comorbidities. Finally, although peanut-allergic children were more likely to have asthma diagnosis, among children with asthma, there was no convincing evidence of a strong association between peanut allergy and asthma severity.

A key limitation of our study is relatively small number of peanut-allergic children available for the analysis, but this is inevitable when studying a relatively uncommon outcome in an unselected birth cohort. Therefore, our results need to be interpreted with caution. To increase the size of peanut-allergic group, we recruited 12 children from a tertiary referral allergy clinic with confirmed peanut allergy who had longitudinal data to enable our analyses; exclusion of these children did not materially alter our findings (data available on request).

We acknowledge that not all children classified as peanut allergic underwent OFC. Four participants who declined OFC (n = 2) or had equivocal OFC (n = 2) were classified as peanut allergic based on clinical information and Ara-h-2 sIgE consistent with allergy.

Another limitation of our study is that the population is not ethnically diverse, and the results are therefore not directly transferable to other ethnic groups. Furthermore, we could not ascertain with certainty which of the associates of peanut allergy are shared risk factors for atopy/sensitization in general. To address this important question, we need large case-control studies comparing patients with OFC-confirmed peanut allergy with individuals who are peanut-sensitized but tolerant (who in our analysis outnumber those with true peanut allergy by the factor 3:1).

### TABLE 1

(Continued)

| Variables: | Study population (n = 959) | No peanut allergy (n = 929) | Peanut allergy (n = 30) | Odds ratio (95% CI) |
|------------|--------------------------|---------------------------|------------------------|-------------------|
| Allergic sensitization (SPT) | | | | |
| Sensitized (any allergen), age 1 year | 46 (11.2%) | 37 (9.3%) | 9 (69.2%) | *p < 0.001 21.9 (6.43, 74.6) |
| Sensitized (any allergen), age 3 years | 190 (22.8%) | 172 (21.3%) | 18 (72%) | *p < 0.001 9.49 (3.90, 23.1) |
| Egg sensitization (by SPT/sIgE) | | | | |
| Sensitized, age 1 year | 43 (10.6%) | 34 (8.7%) | 9 (69.2%) | *p < 0.001 23.7 (6.93, 81.0) |
| Sensitized, age 3 years | 46 (5.7%) | 38 (4.9%) | 8 (33.3%) | *p < 0.001 9.79 (3.94, 24.3) |
| Parentally reported wheeze | | | | |
| In the first year of life | 251 (27.4%) | 241 (27.1%) | 10 (37.0%) | p = 0.26 1.58 (0.71, 3.50) |
| Parentally reported rhinitis | | | | |
| In the first 3 years of life | 39 (4.3%) | 36 (4.1%) | 3 (11.1%) | *p = 0.11 2.92 (0.84, 10.1) |

*Denotes when p-value is provided by Fisher’s exact test, Bold font denotes p-values with statistical (or near statistical) significance, Ref Variable = reference variable.

### TABLE 2

Multivariate logistic regression analysis models of associates for peanut allergy

| Variables | Model 1 | | Model 2 | |
|-----------|---------|----------------|---------|----------------|
|           | aOR | 95% CI | p-Value | aOR | 95% CI | p-Value |
| Sex (Male) | 1.64 | 0.61–4.43 | 0.32 | 1.66 | 0.67–4.11 | 0.27 |
| Cat ownership in pregnancy and early life | 2.96 | 1.05–8.35 | 0.04 | 2.83 | 1.11–7.21 | 0.03 |
| Parental atopy | 2.78 | 0.33–23.4 | 0.35 | 3.23 | 0.41–25.1 | 0.26 |
| Eczema in the first year of life | 4.43 | 1.49–13.2 | 0.007 | 4.03 | 1.51–10.7 | 0.005 |
| Egg sensitization at age 3 years | 9.71 | 3.27–28.9 | <0.001 | 6.54 | 2.36–18.1 | <0.001 |
| FLG loss-of-function mutations | 1.35 | 0.42–4.33 | 0.61 | n/a | n/a | n/a |

Note: Model 1: FLG loss-of-function mutations included. Model 2: FLG loss-of-function mutations excluded.
studies are likely to require multi-cohort and multi-study collaborations to ensure adequate sample size.

One of the strengths is that our birth cohort incorporated OFC to diagnose peanut allergy. Most studies to date relied on clinical history and/or IgE sensitization to define for food allergy, which may overestimate prevalence.\(^{35}\) Another strength is the unselected design, with longitudinal phenotyping from birth and a high follow-up rate, thereby minimizing recall bias. Our data will be valuable for comparison with population-based studies in children with objective food allergy outcomes (e.g. HealthNuts).\(^{46}\)

Importantly, our previous work allowed longitudinal phenotyping of participants into data-driven clusters of sensitization, wheeze and allergic multimorbidity,\(^{32-34}\) thereby enabling us to gain invaluable insight into the relationship between peanut allergy and developmental trajectories of atopic diseases. A strong association between early-life eczema and development of food

### TABLE 3

| Variables: | Study population (n = 700) | No peanut allergy (n = 676) | Peanut allergy (n = 24) | p-Value | Odds ratio (95% CI) | p-value |
|------------|---------------------------|-----------------------------|------------------------|---------|---------------------|---------|
| Eczema in the first year of life | | | | | | |
| FLG Mutations (n = 238) | | | | | | |
| No (%) | 193 (81.1%) | 178 (80.9%) | 15 (83.3%) | *p = 1.00 | 0.85 (0.23, 3.06) | |
| Yes (%) | 45 (18.9%) | 42 (19.1%) | 3 (16.7%) | | | |
| No Eczema in the first year of life | | | | | | |
| FLG Mutations (n = 462) | | | | | | |
| No (%) | 433 (93.7%) | 429 (94.1%) | 4 (66.7%) | *p = 0.049 | 7.94 (1.39, 45.3) | |
| Yes (%) | 29 (6.3%) | 27 (5.9%) | 2 (33.3%) | | | |

*Denotes when p-value is provided by Fisher's exact test, Bold font denotes p-values with statistical (or near statistical) significance.

### TABLE 4

Association of peanut allergy with different wheeze phenotypes\(^{32}\) and longitudinal trajectories of sensitization and developmental profiles of allergic diseases determined using data-driven methods

| Variable | Study population (n = 959) | No peanut allergy (n = 929) | Peanut allergy (N = 30) | Odds ratio (95% CI) | p-Value |
|----------|---------------------------|-----------------------------|------------------------|---------------------|---------|
| Wheeze phenotypes\(^{32}\) | | | | | |
| Never wheezed | 410 (43.3%) | 404 (44.1%) | 6 (20%) | Ref Variable | Ref Var |
| Transient wheeze | 239 (25.2%) | 232 (25.3%) | 7 (23.3%) | 2.03 (0.67, 6.12) | p = 0.21 |
| Intermittent wheeze | 114 (12.0%) | 112 (12.8%) | 2 (6.7%) | 1.20 (0.24, 6.04) | p = 0.82 |
| Late-onset wheeze | 55 (5.8%) | 52 (12.8%) | 3 (10%) | 3.88 (0.94, 16.0) | p = 0.06 |
| Persistent wheeze | 129 (13.6%) | 117 (12.8%) | 12 (40%) | 6.91 (2.54, 18.8) | p < 0.001 |

| Clusters of allergic sensitization\(^{33}\) | | | | | |
| 1. No atopic vulnerability | 468 (55.2%) | 466 (56.7%) | 2 (7.7%) | Ref Variable | Ref Var |
| 2. Predominantly non-HDM | 97 (11.4%) | 97 (11.8%) | 0 (0%) | Omitted as empty | OMITTED |
| 3. Predominantly HDM | 47 (5.5%) | 47 (5.7%) | 0 (0%) | Omitted as empty | OMITTED |
| 4. Multiple late | 147 (17.3%) | 141 (17.2%) | 6 (23.1%) | 9.91 (1.98, 49.7) | p = 0.005 |
| 5. Multiple early | 89 (10.5%) | 71 (8.6%) | 18 (69.2%) | 59.1 (13.4, 260) | p < 0.001 |

| Developmental profiles of allergic diseases\(^{34}\) | | | | | |
| 1. No disease | 369 (38.5%) | 366 (39.4%) | 3 (10.0%) | Ref Variable | Ref Var |
| 2. Persistent eczema & Late-onset Rhinitis | 72 (7.5%) | 65 (7.0%) | 7 (23.3%) | 13.1 (3.31, 52.1) | p < 0.001 |
| 3. Eczema only | 156 (16.3%) | 155 (16.7%) | 1 (3.3%) | 0.79 (0.08, 7.63) | p = 0.84 |
| 4. Transient wheeze | 62 (6.5%) | 60 (6.5%) | 2 (6.7%) | 4.07 (0.67, 7.63) | p = 0.13 |
| 5. Persistent wheeze & late-onset rhinitis | 84 (8.8%) | 82 (8.8%) | 2 (6.7%) | 2.98 (0.49, 18.1) | p = 0.24 |
| 6. Persistent eczema & wheeze | 48 (5.0%) | 45 (4.9%) | 3 (10.0%) | 8.13 (1.59, 41.5) | p = 0.012 |
| 7. Rhinitis only | 114 (11.9%) | 112 (12.1%) | 2 (6.7%) | 2.18 (0.36, 13.2) | p = 0.40 |
| 8. Atopic March | 54 (5.6%) | 44 (4.7%) | 10 (33.3%) | 27.7 (7.35, 104.6) | p < 0.001 |

Abbreviation: HDM, house dust mite; Ref Variable, reference variable.
allergy is well recognized, with the risk being higher in children with earlier onset and more severe skin disease.\textsuperscript{26-47} We have extended these findings to demonstrate that peanut allergy is associated with all developmental patterns of childhood allergic diseases which include persistent eczema with allergic comorbidities (persistent wheeze and rhinitis), but there was no association with eczema or wheeze presenting as single diseases (particularly transient). We observed strong associations between peanut allergy and atopic multimorbidity and multiple sensitization clusters. We acknowledge that these observation do not imply any specific causal relationships and that the results are predominantly hypothesis-generating.

Our findings provide further evidence for the importance of a disrupted skin barrier in early life for the development of peanut allergy. We have shown that among children with eczema (and thereby disrupted skin barrier), FLG mutations did not further increase the risk. In contrast, in those without eczema, FLG mutations (which result in skin barrier dysfunction\textsuperscript{48}) were associated with almost eightfold increased risk. These findings are consistent with the dual allergen exposure hypothesis,\textsuperscript{27} which describes the paradigm where low-dose allergen exposure through an impaired skin leads to development of sensitization and allergy, whereas a higher-dose oral exposure and antigen presentation to the gut immune system induces immune tolerance.

Sharing a home with a cat during pregnancy and early life was associated with a threefold increase in the risk of subsequent peanut allergy. We propose that this effect may be mediated via the associated with a threefold increase in the risk of subsequent pea-

It has been proposed that asthmatic children with peanut allergy have more severe asthma than asthmatics without peanut allergy.\textsuperscript{13} However, although our analysis revealed that peanut-allergic children were more likely to have a diagnosis of asthma, we found no consistent evidence that among asthmatic children, peanut allergy was associated with any markers of increased asthma severity. However, this warrants further investigation in larger studies.

In conclusion, our data suggest that peanut allergy is strongly associated with atopic disease trajectories characterized by early-onset and persistent eczema and wheeze, but not with transient eczema or wheeze. Among children without eczema, carriers of FLG loss-of-function mutations were more likely to have peanut allergy, but in those with eczema, there was no association between peanut allergy and FLG genotype.

**CONFLICT OF INTEREST**

Dr. Custovic reports personal fees from Novartis, personal fees from Regeneron / Sanofi, personal fees from Thermo Fisher Scientific, personal fees from Boehringer Ingelheim, personal fees from Novartis and personal fees from Philips, outside the submitted work. AS reports lecture fees from Thermo Fisher Scientific. Other authors have no competing interests to declare.

**AUTHOR CONTRIBUTIONS**

AC, CK, AS and CSM conceived and planned the study; NN and GK completed all OFCs; CK and SH analysed the data; CK, AC and PJT wrote the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.
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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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