**Dog ownership at three months of age is associated with protection against food allergy**

T. Marrs1,2 \*, K. Logan1, J. Craven1, S. Radulovic1, W.H.A. Irwin McLean3, G. Lack1,2, C. Flohr4 & & M.R. Perkin5 & on behalf of the EAT Study Team

& - joint last authorship

1 Paediatric Allergy Department, Women and Children’s Health, King’s College London, UK

2 Children’s Allergies Department, Evelina London, Guy’s and St Thomas’ NHS Foundation Trust, St Thomas’ Hospital, Westminster Bridge Road, Lambeth, SE1 7EH

3 Centre for Dermatology and Genetic Medicine, Division of Molecular Medicine, University of Dundee, Dundee, UK.

4 Unit for Population-Based Dermatology Research, St John’s Institute of Dermatology, King’s College London and Guy’s & St Thomas’ Hospital NHS Foundation Trust, London, UK

5 Population Health Research Institute, St George’s, University of London, Cranmer Terrace, London, SW17 0RE

**Corresponding author:**

Dr Tom Marrs, Consultant & Honorary Senior Lecturer in Paediatric Allergy

Paediatric Allergy Department, Women and Children’s Health, King’s College London.

Email: Thomas.Marrs@kcl.ac.uk

Phone: +44 207188 7188 ext 84877

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**Members of the EAT Study Team include:**

**Nursing Staff:** Louise Young, RN Children, Victoria Offord, BSc Nursing, Mary DeSousa, BSc Nursing, Jason Cullen, BSc Nursing, Katherine Taylor, MRes. **Dietitians:** Anna Tseng, MPH Nutrition, Bunmi Raji, MSc Nutrition, Sarah Byrom, BSc Human Nutrition and Dietetics, Gillian Regis, BSc Human Nutrition and Dietetics, Charlie Bigwood BSc, Charlotte Stedman, PG Dip Dietetics. **Study management and administration:** Sharon Tonner, PhD, Emily Banks, Yasmin Kahnum, Rachel Babic, BA, Ben Stockwell, BSc, Erin Thompson, BSc, Lorna Wheatley, BSc. **Phlebotomist:** Devi Patkunam. **Laboratory projects:** Kerry Richards, MSc Medicine, Ewa Pietraszewicz, MSc, Alick Stephens, PhD, Asha Sudra, MSc, and Victor Turcanu, PhD.

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**ABSTRACT**

**Background:**

The prevention of food allergy is a key priority for reducing the burden of allergic disease. Environmental exposures modulate the risk of developing food allergy and some of this may be mediated by the infants’ developing microbiome. However, the role of potentially protective environmental exposures, such as pet ownership, are largely un-investigated with respect to food allergy.

**Methods:**

We performed a secondary cohort analysis in the Enquiring About Tolerance (EAT) study, which enrolled 1,303 three-month infants onto a randomised trial to prevent food allergy. A survey elicited domestic animal ownership and participants were examined for atopic dermatitis (AD) at enrolment. Sensitisation to foods and aeroallergens were elicited by skin and serum testing at three, 12 and 36 months. Food allergy status was determined by double-blind placebo-controlled food challenges between one and three years.

**Results:**

Food allergy was diagnosed among 6.1% (68/1124) of participants with complete data. No significant relationships were demonstrated between food allergy and caesarean delivery, infections or antibiotic exposure in early life. After adjusting for familial atopic disease, maternal dog/cat sensitisation and participant AD, living with dogs was associated with a 90% reduction in the odds of infants developing food allergy (adjusted Odds Ratio (aOR) 0.10 (Confidence Interval (CI) 0.01-0.71), p=0.02). None of the 49 infants living with at least two dogs developed food allergy, suggesting a dose response relationship (each dog owned aOR 0.12 (CI 0.02–0.81), p=0.03). No relationship was demonstrated between owning dogs or cats and the development of AD.

**Conclusion:**

Dog ownership in infancy may prevent food allergy.

**Keywords:** Dogs, domestic pets, food allergy, microbiome, prevention

**Abbreviations**

AD Atopic dermatitis

aOR Adjusted odds ratio

CI Confidence interval

cOR Crude odds ratio

EAT Study Enquiring About Tolerance randomised trial

*FLG*  Filaggrin loss-of-function mutation

sIgE Specific IgE sensitisation

SPT Skin prick test

TEWL Transepidermal water loss

**INTRODUCTION**

Food allergy now affects between 6 and 10% of young children in developed countries.[1 2] The microbiome is felt to play an important role in determining the likelihood of developing allergic conditions such as atopic dermatitis (AD), atopy and wheezing.[3 4] For instance, both delivery by Caesarean section and antibiotic treatment influence infants’ developing microbiome and have been associated with increased risk of developing allergic disease. In contrast, other environmental factors may prevent the development of allergic disease potentially through augmentation of the microbiome, such as owning pets, growing up on a farm,[5 6] having more siblings and using communal day care facilities.[7 8] Pet ownership may also influence the development of allergic disease through allergen specific immune pathways, although both positive and inverse relationships have been described in relation to cat ownership.[9-12] Considerable work has investigated how environmental exposures relate with AD and respiratory allergic disease.[13-15] It is unknown whether pet ownership may protect against food allergy.[16]

Whilst the number of children growing up on farm is less than 1%,(insert reference) domestic pet ownership remains common with dog ownership estimated to be between 17.9 and 24.0%.[McBride EuroPrevall Survey 2012 PAI, Westgarth BMC Veterinary Research 2007] Only two birth cohorts have published associations between pet ownership and food allergy. In this journal, the Australian ‘Healthnuts’ cohort reported that dog ownership was associated with a reduction in egg allergy.[17] However, the EuroPrevall cohort screening 823 young children from Hampshire, UK, found an insignificant increase in food allergy.[18] Studies investigating the association between pet ownership and allergy developing in children are subject to potential reverse causality. It has already been established that dog and cat ownership amongst families with a baby is less common if parents also report that they have a history of atopic disorders.[19] Preceding studies have assessed parental pet allergy status via questionnaire rather than objective measures of parental pet sensitisation status such as skin prick testing or specific IgE measurement.

In this paper we assess whether pet ownership and other environmental exposures with the capacity to influence the infant microbiome are associated with the development of food allergy, sensitisation and allergic disease within the interventional Enquiring About Tolerance (EAT) Study.[1]

**METHODS**

**Participants, recruitment and study design**

Three-month-old, healthy and exclusively breastfed infants were enrolled from the general population across England and Wales on a randomised trial investigating whether the early dietary introduction of six allergenic solids (egg, peanut, milk, wheat, cod and sesame) reduced the prevalence of food allergy diagnosed from 12 to 36 months of age.[1 20] The investigation of pet ownership was planned from the study’s inception. Our study was approved by the Research Ethics Committee of Guy’s & St Thomas’ Hospitals Foundation Trust (REC reference 08/H0802/93), and the study was registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN 14254740).

**Exposure and outcome definitions**

The primary exposure was pet ownership elicited from participants’ enrolment survey responses. The size and atopic history of the participant's families as well as mode of delivery, childcare, infectious illnesses and antibiotic usage were also ascertained. Monthly questionnaires were completed through the remaining nine months of infancy, eliciting infants’ symptoms of suspected food induced allergic reactions, infections and completed courses of antibiotics.

Mothers underwent SPT to cat and dog dander allergens (a positive response determined by any wheal ≥3mm) and were asked whether their family had avoided pet ownership owing to a preceding history of atopic disease.

The primary outcome was food allergy to any of the six study foods as defined by the EAT Study protocol.[1] Food sensitisation was assessed through serum specific IgE (sIgE) assay and SPT with Stallergenesextracts for cow’s milk, egg white, cod, peanut, sesame and wheat at the three, 12 and 36 month visits. Aeroallergen sensitisation was assessed using Stallergenes SPT solutions for D*ermatophagoides pteronyssinus*, cat, dog, grass and tree pollen mixes at 12 and 36 month visits. A validated tool was used to elicit parents’ report of their baby’s wheezing and rhinitis, and whether they had a cold or flu at the time.[21]

Infants were examined for AD at their enrolment visit at three months, and skin barrier function assessed by measuring trans-epidermal water loss (TEWL) using the Biox Aquaflux AF200 (Biox, London, UK) closed condenser chamber device.[22 23] DNA was extracted from venous blood samples using the TaqMan allelic discrimination assay (Applied Biosystems, ABI 7900 HT, Foster City, CA) to screen for the six most common *FLG* loss-of-function variants detected amongst European populations.[24]

**Statistical analysis**

Univariate and multivariate analyses were undertaken using logistic regression using Stata (version 14.0). Dose response variables for pet ownership were constructed: increasing number of pets (none versus one versus at least two pets); and degree of shared living space (comparing no pets versus owning a pet not allowed in bedroom versus allowing the pet into the infants’ bedroom). Low levels of sensitisation have been associated with clinical food allergy among young children.[2 25 26] We therefore report if sensitisation to any one of the EAT study food allergens breached thresholds at ≥0.10kU/l or ≥0.35kU/l at three months, and SPT ≥1mm, ≥3mm or ≥0.35kU/l at 12 and 36 months. Unless otherwise stated, sensitisation levels reported in the manuscript text refer to the ≥3mm or ≥0.35kU/l cut-off values. *A priori* adjustment was made for the number of parents reporting an allergic disease (including any AD, food allergy, rhinitis or asthma), avoidance of pet ownership and maternal pet dander sensitisation. Exposures found to have a significant relationship with the primary exposure were progressively introduced into the multivariate model and retained if the effect size for the main exposure altered by more than 10% to reduce confounding.

**RESULTS**

**Participant sample**

Among included participants, 15.7% of families owned dogs and 23.3% cats. Multiple pet ownership was less common: 4.3% two or more dogs, 10.9% two or more cats and 3.7% at least one of each.

**Characteristics of participants with food allergy**

Sixty-eight participants (6.1%; 68/1124) were diagnosed with food allergy. Participants of non-white or mixed ethnicity were more likely to be diagnosed with food allergy (cOR 2.46 (95% CI 1.39-4.34), p<0.01). Food allergy was associated with: enrolment AD (cOR 5.74 (3.44-9.56), p<0.001), skin barrier impairment (raised TEWL; cOR 5.62 (3.28–9.63), p<0.001) and having an older sibling affected by allergic disease (cOR 2.60 (1.58–4.30), p<0.001; Supp. Table B).

Parental factors included: parental allergy (one parent cOR 3.55 (1.07–11.7), p=0.04; both parents cOR 4.83 (1.46–15.95), p=0.01); maternal pet dander sensitisation (cOR 1.89 (1.11–3.22), p=0.02), and families reporting pet avoidance (cOR 2.96 (1.78–4.94), p<0.001). *FLG* mutation inheritance was not significantly associated with food allergy (cOR 1.71 (0.89–3.29), p=0.11).

**Crude associations between environmental exposures and food allergy**

Significant protective univariate associations were demonstrated amongst infants living with any furred pet (including cats, dogs, rodents or rabbits; cOR 0.33 (0.18-0.63), p=0.001) and with either dogs or cats (cOR 0.26 (0.13–0.54), p<0.001) (Table 1). Living with dogs was strongly associated with protection from developing food allergy (cOR 0.08 (0.01–0.54), p=0.01) as was cat ownership (cOR 0.42 (0.20–0.89), p=0.02). None of the participants living with more than one dog, or living with at least one dog and at least one cat developed food allergy.

Mode of delivery was not associated with food allergy in univariate analysis (cOR 0.82 (0.45–1.48), p=0.51; Table 1). The presence of at least one sibling was positively associated with food allergy in univariate analysis (cOR 2.58 (1.41–4.70), p<0.01), however a dose response effect with an increasing number of siblings was not evident (data not shown). The univariate associations between other microbiome-related exposures and food allergy are discussed in more detail in the Supplementary Appendix, as is the potential for confounding of the relationship between pet ownership and food allergy (Supplementary Table D).

**Adjusted analyses of pet ownership and food allergy**

Living with dogs was associated with a 90% reduction in the odds of developing food allergy (aOR 0.10 (0.01–0.71), p=0.02; Table 2 and Figure 1), after adjusting for *a priori* variables living in a rural area, spending time with pet owners and visiting homes with pets did not alter the effect size by 10% and were not included in the model. Cat ownership was no longer significant when tested alongside dog ownership (aOR 0.59 (0.26–1.30), p=0.19).

These associations remained when adjusted for skin barrier impairment and *FLG* inheritance (dog ownership aOR 0.12 (0.02-0.87), p=0.04; cat ownership aOR 0.59 (0.26-1.34), p=0.21). None of the participants in families who owned a dog developed either egg or peanut allergy. A dose response effect was apparent for owning an increasing number of dogs (aOR 0.12 (0.02-0.81), p=0.03), but not cats (aOR 0.69 (0.40-1.18), p=0.18). No participants developed food allergy if they lived with two dogs, or if they cohabited with at least one dog and at least one cat.

Living with a dog that did not frequent the infants’ bedroom was associated with a significant level of protection (aOR 0.12 (0.02–0.89), p=0.04). No participants developed any food allergies amongst the 54 families who allowed their dog to frequent their child’s bedroom. Closer co-habitation between dogs and respective infants’ bedroom areas demonstrated a dose response effect across these categories (aOR 0.11 (0.02–0.79), p=0.03).

A sensitivity analysis examined whether the results retained statistical significance after incorporating randomisation group into the logistic regression model, and this did not appreciably alter the risk estimate (aOR 0.09 (0.01–0.67), p=0.02). There was no interaction between dog ownership and AD on the likelihood of developing food allergy (p=0.78).**Atopic sensitisation and secondary outcomes**

At 12 months, SPT food sensitisation (10.4% (112/1074)) was more common than SPT aeroallergen sensitisation (3.1% (33/1065)) and 20 participants were sensitised to both food and aeroallergens. By 36 months, SPT food sensitisation had fallen to 6.7% (77/1144) whilst SPT positivity to aeroallergens was almost twice as prevalent at 11.7% (129/1100) and 43 participants were sensitised to both foods and aeroallergens.

Inverse associations were demonstrated between owning dogs and food and aeroallergen sensitisation (Table 3 & Figure 1). Owning dogs was associated with significantly less food SPT sensitisation at 12 (aOR 0.17 (0.05-0.54), p<0.01) and 36 months (aOR 0.35 (0.12-0.99), p=0.05). Similar inverse relationships were shown with serum food sensitisation at 12 months although the effect appeared to be less strong (aOR 0.53 (0.28–0.97), p=0.04).

Infants of participants who owned dogs were less likely to develop aeroallergen sensitisation at 36 months (aOR 0.51 (0.26-0.997), p=0.05) and this appeared to be driven by a 66% reduction in house dust mite sensitisation (aOR 0.34 (0.13-0.87), p=0.02; Table 3). There was a low prevalence of dog and cat dander sensitisation, however owning a cat was positively associated with increased likelihood of cat sensitisation at 36 months (aOR 3.13 (1.41-6.95), p<0.01). No relationship was demonstrated between dog or cat ownership and visible AD at three months, parent reported non-viral induced rhinitis or wheeze at 36 months.

**DISCUSSION**

Living with dogs was associated with a 90% reduction in the odds of developing challenge-proven food allergy, with a dose-response relationship found for the number of dogs owned and closer co-habitation. Dog ownership was inversely related to both food and house dust mite sensitisation. No association was found between dog or cat ownership and the development of AD. There was no relationship between antibiotic usage, caesarean delivery, number of siblings or communal childcare exposure and the development of food allergy. The inverse univariate relationship between cat ownership and food allergy became nonsignificant on adjustment.

Strengths of this analysis include the prospective evaluation of environmental exposures and double-blind placebo-controlled food challenges to confirm food allergy. We assessed whether participating families were consciously choosing to avoid pet ownership and investigated mothers’ pet dander sensitisation to reduce the risk of reverse causality. We considered a wide range of direct and indirect pet exposures.[27] Dose response effects were reported for owning an increasing number of dogs and closer co-habitation with a dog. Parallel inverse associations were demonstrated across a range of secondary food sensitisation outcomes, supporting biological plausibility of this relationship. The data also suggests that the inverse association between food sensitisation and dog ownership starts to emerge by three months of age. Prenatal exposure to animals has been inversely associated with allergic disease which raises the possibility of immunological modulation *in utero,*[28 29] however unfortunately these data were unavailable within the EAT study. The Australian Healthnuts study found that living with a dog was inversely related to egg allergy amongst one year olds,[17] however the analysis was not adjusted for parents’ conscious avoidance of pets or objective parental pet sensitisation.

An inverse association was demonstrated between dog ownership and house dust mite sensitisation at three years of age. Sensitisation to house dust mite in early childhood has been associated with the later development of asthma, with and without co-morbid rhinitis.[30] This inverse relationship suggests that dog exposure may reduce the likelihood of developing allergic airways disease, in addition to food allergy. By contrast, owning cats was associated with significantly increased cat dander sensitisation, which is consistent with the Manchester Allergy Study data.[12] Associations between cat ownership and clinical outcomes may also be dependent upon the regional prevalence of cat ownership [Svanes et Burney JACI 2003; Konradsen JACI 2005] . Associations between dog ownership, food, aeroallergen, house dust mite sensitisation and respiratory disease will be monitored through the ongoing EAT-On follow up study.

Ownership of dogs and cats influences the pattern of environmental bacteria found inside homes. *Prevotella, Porphyromonas, Morazella* and *Bacteroides* genera are common oral and gut commensals amongst dogs and cats.[31] The presence of these bacterial phylotypes in the home have been shown to be sufficiently specific to allow prediction of dog and cat ownership with 92% and 83% accuracy respectively.[32] Pyrosequencing studies have identified that diversity and evenness of environmental microbiota are related to dog rather than cat ownership.[32] The exposure of children to diverse environmental microbiota amongst household dust has been associated with protection from developing atopy and asthma.[5] This protection is likely to start early in infancy or even through maternal exposure at the time of pregnancy. Alternatively, dog ownership may bring family members into closer contact with their local vegetative environment.

In eastern Finland, the use of land surrounding childrens’ homes was significantly associated with the prevalence of atopy. Children living amongst forests and agricultural areas showed the least atopy. An association was found with the generic diversity of Proteobacteria on the skin and the local type of environmental land use.[33] Recent studies have shown that raising murine models on soil increases the anti-inflammatory mediator expression from the gut.[34]

Replication studies are now required to assess whether the inverse relationship between dog ownership and food allergy is robust between populations, and to explore how such putative protection may be conferred.

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**Table 1.** Univariate associations between microbiome-related environmental exposures and food allergy.

**Table 2.** Two adjusted models to examine associations between owning domestic dogs, cats and food allergy.

**Table 3**. Prevalence of secondary clinical outcomes and their adjusted associations with dog and cat ownership.

**Legend for Figure 1.** Bar chart showing adjusted odds ratios for the likelihood of clinical outcomes given ownership of at least one dog at three months of age.

*Food sensitisation was fulfilled if any one of the completed set of food assays (peanut, egg, cow’s milk, sesame, cod fish or sesame) were positive at the threshold level and time point outlined. Aeroallergen sensitisation was fulfilled if any one of skin prick testing to house dust mite, cat, dog, tree or grass mix pollen allergen extracts were ≥3mm.*

**Supplementary Appendix**

**Supplementary results**

**Supplementary Table A.** Comparison of demographics, skin barrier characteristics, family history and microbiome-related exposure prevalence between excluded and included participants.

**Supplementary Table B**. Univariate associations assessing demographic, skin barrier and familial atopic disease in relation to food allergy.

**Supplementary Table C.** Univariate associations assessing ancillary direct and indirect animal exposures, vaccination, infection and antibiotics in relation to food allergy.

**Supplementary Table D**. Univariate associations assessing demographic, skin barrier function, AD, familial atopic status, trial randomisation and microbiome-related exposures in relation to dog or cat ownership.

Table 1. Univariate associations between microbiome-related environmental exposures and food allergy.

|  |  | **Exposure prevalence** | **Challenge-proven food allergy (12 to 36 months); 6.1% (68/1124)** |
| --- | --- | --- | --- |
|  | % (n/N) | Food allergy % (n/N) | Crude Odds Ratio (95% CI) | p |
|  |  |  |  |  |
| **Delivery** |  |  |  |  |
| Mode of delivery | Caesarean-delivery | 25.4% (286/1124) | 5.2% (15/286) | 0.82 (0.45 – 1.48) | 0.51 |
|  |  |  |  |  |  |
| **Sibling / peer exposure** |  |  |  |  |  |
| Any siblings | Yes | 61.1% (687/1124) | 7.9% (54/687) | 2.58 (1.41 – 4.70) | < 0.01 |
| Communal childcare at three months of age | Childminder or nursery | 2.8% (31/1124) | 3.2% (1/31) | 0.51 (0.07 – 3.80) | 0.51 |
|  |  |  |  |  |  |
| **Direct animal exposure at three months of age** |  |  |  |  |
| Own any furred pet |  Ownership of dogs, cats, rodents or rabbits | 37.9% (426/1124) | 2.8% (12/426) | **0.33 (0.18 – 0.63)** | **0.001** |
| Own dog(s) or cat(s) | Yes | 35.2% (396/1124) | 2.3% (9/396) | **0.26 (0.13 – 0.54)** | **< 0.001** |
| Pet owned | Owning dog(s) | 15.7% (176/1124) | 0.6% (1/176) | **0.08 (0.01 – 0.54)** | **0.01** |
|  | Owning cat(s) | 23.3% (262/1124) | 3.1% (8/262) | **0.42 (0.20 – 0.89)** | **0.02** |
|  | Owning rodent(s) | 3.7% (41/1124) | 4.9% (2/41) | 0.79 (0.19 – 3.34) | 0.75 |
|  | Owning rabbit(s) | 2.4% (27/1124) | 3.7% (1/27) | 0.59 (0.05 – 4.42) | 0.61 |

Abbreviations: CI – confidence interval

**Table 2.** Two adjusted models to examine associations between owning domestic dogs, cats and food allergy.

|  |  |  |
| --- | --- | --- |
|  | **Prevalence** | **EAT Study food allergy (from 12m to 36m); 6.1% (68/1124)** |
| % (n/N) | Food allergy % (n/N) | Adjusted OR (95% CI) | p  |
| **Model 1**  |  |  |  |  |
| Owning dogs | Any dogs | 15.7% (176/1124) | 0.6% (1/176) | **0.10 (0.01 – 0.71)** | **0.02** |
| Owning cats | Any cats | 23.3% (262/1124) | 3.1% (8/262) | 0.59 (0.26 – 1.30) | 0.19 |
|  |  |  |  |  |  |
| **Model 2**  |  |  |  |  |
| Owning domestic pets | None | 64.8% (728/1124) | 8.1% (59/728) |  |  |
|  | Only dogs | 11.9% (134/1124) | 0.8% (1/134) | **0.12 (0.02 – 0.86)** | **0.04** |
|  | Only cats | 19.6% (220/1124) | 3.6% (8/220) | 0.60 (0.27 – 1.34) | 0.21 |
|  | Both dog(s) and cat(s) | 3.7% (42/1124) | 0% (0/42) | *-* |  |

Adjusted for non-white ethnicity, AD at 3 months, number of parents with atopic disease, maternal pet sensitisation, pet avoidance, sibling atopic disease & having siblings. Abbreviations: AD – atopic dermatitis, CI – confidence interval, OR – odds ratio, SPT – skin prick testing

**Table 3.** Prevalence of secondary clinical outcomes and their adjusted associations with dog and cat ownership.

|  |  |  |
| --- | --- | --- |
|  | **Prevalence of clinical outcome** | **Mutually adjusted associations for dog and cat ownership** |
|  | **Prevalence among included participants** | **Prevalence among dog owners** | **Prevalence among cat owners** | **Adjusted OR with dog ownership amongst included participants** | **Adjusted OR with cat ownership amongst included participants** |
|  | **% (n/N)** | **% (n/N)** | **% (n/N)** | **Adjusted OR (95% CI)**  | **p** | **Adjusted OR (95% CI)** | **p** |
|  |  |  |  |  |  |  |  |
| AD at 3m | 24.6% (282/1148) | 21.0% (38/181) | 20.6% (55/267) | 0.97 (0.64 – 1.46) **ˠ** | 0.89 | 0.81 (0.56 – 1.16) **ˠ** | 0.24 |
|  |  |  |  |  |  |  |  |
| **Food sensitisation** |  |  |  |  |  |  |
| sIgE at 3m \* | 17.3% (175/1014) | 9.9% (16/162) | 12.2% (29/237) | 0.56 (0.32 – 0.99) | < 0.05 | 0.70 (0.45 – 1.11) | 0.13 |
| sIgE at 3m | 5.9% (60/1014) | 2.5% (4/162) | 4.2% (10/237) | 0.54 (0.18 – 1.57) | 0.26 | 0.94 (0.44 – 2.01) | 0.87 |
| SPT at 12m $ | 16.3% (175/1074) | 5.4% (9/166) | 12.1% (30/248) | **0.31 (0.15 – 0.64)** | **0.001** | 0.78 (0.50 – 1.24) | 0.30 |
| SPT at 12m | 10.4% (112/1074) | 1.8%(3/166) | 7.7% (19/248) | **0.17 (0.05 – 0.54)** | **< 0.01** | 0.81 (0.47 – 1.41) | 0.46 |
| sIgE at 12m | 17.5% (165/944) | 9.1% (13/143) | 11.8% (26/220) | **0.53 (0.28 – 0.97)** | **0.04** | 0.67 (0.42 – 1.09) | 0.11 |
| SPT at 36m $ | 9.4% (107/1144) | 2.8% (5/180) | **6.0% (16/265)** | **0.31 (0.12 – 0.78)** | **0.01** | 0.74 (0.41 – 1.34) | 0.32 |
| SPT at 36m | 6.7% (77/1144) | 2.2% (4/180) | **4.2% (11/265)** | **0.35 (0.12 – 0.99)** | **0.05** | 0.71 (0.35 – 1.42) | 0.33 |
| sIgE at 36m | 17.8% (183/1030) | 11.6% (19/164) | 13.5% (32/237) | 0.66 (0.39 – 1.11) | 0.11 | 0.73 (0.47 – 1.13) | 0.16 |
|  |  |  |  |  |  |  |  |
| **Aeroallergen SPT sensitisation** |  |  |  |  |  |  |
| SPT at 12m | 3.1% (33/1065) | 0.6% (1/163) | 4.5% (11/246) | 0.16 (0.02 – 1.21) | 0.08 | 1.87 (0.85 – 4.09) | 0.12 |
| SPT at 36m | 11.7% (129/1100) | 6.4% (11/171) | **9.7% (25/258)** | **0.51 (0.26 – 0.997)** | **0.05** | 0.87 (0.53 – 1.42) | 0.58 |
| SPT HDM 36m | 7.7% (85/1107) | 2.9% (5/173) | **5.0% (13/260)** | **0.34 (0.13 – 0.87)** | **0.02** | 0.63 (0.33 – 11.18) | 0.15 |
| SPT dog 36m | 2.2% (24/1106) | 2.3% (4/171) | 1.6% (4/258) | 1.18 (0.37 – 3.73) | 0.78 | 0.74 (0.23 – 2.35) | 0.61 |
| SPT cat 36m | 3.0% (33/1105) | 1.2% (2/173) | 5.0% (13/258) | 0.39 (0.09 – 1.73) | 0.22 | **3.13 (1.41 – 6.95)** | **< 0.01** |
|  |  |  |  |  |  |  |  |
| Non-viral rhinitis last year | 15.6% (179/1146) | 11.1% (20/180) | 14.3% (38/265) | 0.76 (0.44 – 1.22) | 0.24 | 1.08 (0.72 – 1.62) | 0.73 |
| Non-viral wheeze last year | 4.8% (55/1149) | 3.9% (7/180) | 3.8% (10/265) | 0.83 (0.36 – 1.91) | 0.67 | 0.86 (0.41 – 1.78) | 0.68 |

The prevalence of each clinical outcome is reported among dog and cat owning families. Specific IgE data reports binary variable for any food (comprising milk, egg, wheat, sesame, cod and peanut) sensitisation sIgE ≥0.35kU/l, except where \* indicates using ≥0.1 kU/l cut-off. SPT data reports binary variable for any allergen wheal ≥3mm for food allergens (comprising milk, egg, wheat, sesame, cod and peanut) and aeroallergens (comprising house dust mite, tree pollen mix, grass pollen mix, cat dander and dog dander), except where $ indicates using ≥1mm cut-off . Multivariate models are adjusted for non-white ethnicity, AD at 3 months, number of parents with atopic disease, maternal pet dander sensitisation, pet avoidance, any sibling atopic disease and having siblings.

HDM – House dust mite; SPT – Skin prick testing; ˠ Adjusted model for examined AD at three months includes skin barrier impairment TEWL ≥ 15 g/m\*h.

**Supplementary Appendix**

Supplementary Results

Growing up in a rural environment was not related to food allergy (cOR 0.51 (0.25–1.04), p=0.06). No significant relationships were demonstrated between food allergy and any use of (or number of hours attending) communal childcare, history of upper respiratory tract infections or diarrhoea at three months (Supplementary Table C). Neither were there any significant relationships with bronchiolitis, lower or upper respiratory tract infections or frequency of diarrhoeal episodes from three until 12 months of age (data not shown). Exposure to any antibiotics, frequency of antibiotics, individual vaccinations and completion of routine childhood vaccination programmes through infancy were not associated with food sensitisation or food allergy (data not shown).

Assessment for confounding

The potential for confounding of the association between pet ownership and food allergy was explored (Supplementary table D). Male infants were more likely to live in a house that owned pets (cOR 1.32 (1.03–1.69), p=0.03), whilst those of non-white ethnicity were significantly less likely to own cats or dogs (cOR 0.42 (0.28–0.64), p<0.001). Raised TEWL (cOR 0.73 (0.56–0.96), p=0.02), visible AD at three months (cOR 0.73 (0.54–0.98), p=0.04) and maternal pet sensitisation (cOR 0.66 (0.48–0.91), p=0.01) were less likely amongst pet owners. Randomisation to the early introduction group was un-related to dog or cat ownership (cOR 0.89 (0.69 – 1.13), p=0.33).

A strong inverse relationship was demonstrated between parents reporting that they chose not to own pets due to allergic disease in the family and having a dog or cat at home (cOR 0.16 (0.10–0.25), p<0.001). Owning domestic pets was positively associated with rural lifestyle (non-farm cOR 2.27 (1.68-3.06), p<0.001; farming cOR 4.83 (2.16–10.81), p<0.001), time spent visiting places with pets (increasing time across categories cOR 1.77 (1.51–2.08), p<0.001) and time spent with pet owners (cOR 1.63 (1.42–1.88), p<0.001). Having an older sibling, sharing communal childcare, infections and exposure to antibiotics by three months demonstrated no associations with pet ownership.

**Supplementary table A**. Comparison of demographics, skin barrier characteristics, family history and microbiome-related exposure prevalence between excluded and included participants.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total cohort****exposure prevalence** | **Exposure prevalence** |  |
| Amongst included | Amongst excluded | p |
|  |  | % (n/N) | % (n/N) | % (n/N) |  |
| **Demography** |  |  |  |  |  |
| Sex | Male | 50.1% (653/1303) | 50.8% (571/1124) | 45.8% (82/179) | 0.22 |
| Maternal age (75th centile) \* | Greater than 36 years | 24.9% (324/1302) | 25.5% (287/1124) | 20.8% (37/178) | 0.17 |
| Birth weight (75th centile) \* | Greater than 3.86kg | 24.6% (320/1302) | 24.4% (274/1124) | 25.8% (46/178) | 0.67 |
| Ethnicity | Non-white / mixed | 15.3% (199/1303) | 13.6% (153/1124) | 25.7% (46/179) | < 0.001 |
|  |  |  |  |  |  |
| **Skin barrier exposures** |  |  |  |  |  |
| Carrying a *FLG* mutation\* | Yes | 11.9% (143/1206) | 12.1% (126/1039) | 10.2% (17/167) | 0.47 |
| Skin barrier impairment \* | TEWL ≥ 15 g/m\*h | 32.3% (420/1300) | 32.4% (363/1121) | 31.8% (57/179) | 0.89 |
| Atopic dermatitis at 3 months \* | Yes | 24.4% (317/1302) | 24.4% (274/1124) | 24.2% (43/178) | 0.95 |
|  |  |  |  |  |  |
| **Familial atopic status** |  |  |  |  |  |
| Number of parents with atopic disease \* | Neither | 16.1% (209/1301) | 15.2% (171/1124) | 21.5% (38/177) | kruskaL-wallis;0.25 |
|  | One parent | 47.0% (611/1301) | 47.8% (537/1124) | 41.8% (74/177) |
|  | Both parents | 37.0% (481/1301) | 37.0% (416/1124) | 36.7% (65/177) |
| Maternal pet SPT sensitisation \* | Dog or cat ≥ 3mm | 20.9% (241/1152) | 20.9% (235/1124) | 21.4% (6/28) | 0.95 |
| Avoidance of pet ownership \* | Avoiding | 19.3% (251/1301) | 19.5% (219/1124) | 18.1% (32/177) | 0.66 |
|  |  |  |  |  |  |
| **Microbiome-related exposures** |  |  |  |  |  |
| Mode of delivery | Caesarean | 25.2% (328/1303) | 25.4% (286/1124) | 23.5% (42/179) | 0.57 |
| Any siblings | Yes | 62.3% (812/1303) | 61.1% (687/1124) | 69.8% (125/179) | 0.03 |
| Owning dogs \* | Any dogs | 16.5% (214/1301) | 15.7% (176/1124) | 21.5% (38/177) | 0.05 |
| Owning cats \* | Any cats | 23.0% (299/1301) | 23.3% (262/1124) | 20.9% (37/177) | 0.48 |

AD – atopic dermatitis, *FLG – Filaggrin* gene mutation, SPT – skin prick testing; \* - incomplete data

**Supplementary Table B.** Univariate associations assessing demographic, skin barrier and familial atopic disease in respect to food allergy.

|  |  |  |
| --- | --- | --- |
|  | **Exposure prevalence** | **EAT Study primary outcome of food allergy (12 to 36 months); 6.1% (68/1124)** |
| % (n/N) | Food allergy % (n/N) | Crude Odds Ratio (95% CI) | p |
|  |  |  |  |  |  |
| **Demography** |  |  |  |  |  |
| Sex | Male | 50.8% (571/1124) | 6.3% (36/571) | 1.10 (0.67 - 1.79) | 0.72 |
| Maternal age (75th centile) | Greater than 36 years | 25.5% (287/1124) | 8.0% (23/287) | 1.53 (0.91 – 2.58) | 0.11 |
| Birth weight (75th centile) | Greater than 3.86kg | 24.4% (274/1124) | 4.7% (13/274) | 0.72 (0.39 – 1.34) | 0.30 |
| Ethnicity | Non-white / mixed | 13.6% (153/1124) | 11.8% (18/153) | 2.46 (1.39 – 4.34) | < 0.01 |
|  |  |  |  |  |  |
| **Skin barrier exposures** |  |  |  |  |  |
| Carrying a *FLG* mutation\* | Yes | 12.1% (126/1039) | 9.5% (12/126) | 1.71 (0.89 – 3.29) | 0.11 |
| Skin barrier impairment \* | TEWL ≥ 15 g/m\*h | 32.4% (363/1121) | 13.2% (48/363) | 5.62 (3.28 – 9.63) | < 0.001 |
| Visible atopic dermatitis at 3 months | Yes | 24.4% (274/1124) | 15.3% (42/274) | 5.74 (3.44 – 9.56) | < 0.001 |
|  |  |  |  |  |  |
| **Familial atopic status** |  |  |  |  |  |
| Number of parents with atopic disease | Neither | 15.2% (171/1124) | 4.4% (3/171) | - |  |
|  | One parent | 47.8% (537/1124) | 6.0% (32/537) | 3.55 (1.07 – 11.7) | 0.04 |
|  | Both parents | 37.0% (416/1124) | 7.9% (33/416) | 4.83 (1.46 – 15.95) | 0.01 |
| Any sibling with atopic disease | Has atopic sibling | 38.3% (430/1124) | 9.5% (41/430) | 2.60 (1.58 – 4.30) | < 0.001 |
| Maternal pet SPT sensitisation | Dog or cat ≥ 3mm | 20.9% (235/1124) | 9.4% (22/235) | 1.89 (1.11 – 3.22) | 0.02 |
| Avoidance of pet ownership | Avoiding | 19.5% (219/1124) | 12.3% (27/219) | 2.96 (1.78 – 4.94) | < 0.001 |
|  |  |  |  |  |  |
| **Intervention arm** |  |  |  |  |  |
| Randomisation to early introduction group | Yes | 48.9% (550/1124) | 4.9% (27/550) | 0.67 (0.41 – 1.11) | 0.12 |

Abbreviations: CI – confidence interval, *FLG* – filaggrin, SPT – skin prick testing, TEWL - transepidermal water loss at 3 months, \* - data unavailable on minority

**Supplementary table C.** Univariate associations assessing ancillary direct and indirect animal exposures, infection and antibiotics in relation to food allergy.

|  |  | **Exposure prevalence** | **Challenge-proven food allergy (12 to 36 months); 6.1% (68/1124)** |
| --- | --- | --- | --- |
|  | % (n/N) | Food allergy % (n/N) | Crude Odds Ratio (95% CI) | p |
| **Rural setting** |  |  |  |  |
| Living in rural setting | Yes | 22.5% (253/1124) | 3.6% (9/253) | 0.51 (0.25 – 1.04) | 0.06 |
| Type of rural setting | Rural; non-farming lifestyle | 20.0% (225/1124) | 3.6% (8/225) | 0.51 (0.24 – 1.08) | 0.08 |
|  | Rural farming lifestyle | 2.5% (28/1124) | 3.6% (1/28) | 0.51 (0.07 – 3.82) | 0.51 |
|  |  |  |  |  |
| **Direct animal exposure at three months of age (furred pets, dogs, cats, rodents and rabbits in Table 2)** |  |  |
| Other pets owned | Owning horse(s) / pony(ies) | 1.4% (16/1124) | 0% (0/16) | *-* |  |
|  | Owning chicken(s) / bird(s) | 2.8% (31/1124) | 3.2% (1/31) | 0.51 (0.07 – 3.80) | 0.51 |
|  | Owning reptile(s) | 1.8% (20/1124) | 5.0% (1/20) | 0.81 (0.11 – 6.18) | 0.84 |
|  |  |  |  |  |  |
| **Pet exposure through visiting places with any pets** |  |  |  |
| Visiting places with pets (dog, cat, rodent, rabbit or any of the above) | Yes | 47.2% (530/1124) | 5.1% (27/530) | 0.72 (0.44 – 1.19) | 0.21 |
| Categorical time spent in places with pets | None | 52.9% (594/1124) | 6.9% (41/594) | - |  |
|  | 1-2 hours per week | 28.1% (316/1124) | 6.0% (19/316) | 0.86 (0.49 – 1.51) | 0.61 |
|  | At least three hours per week | 19.0% (214/1124) | 3.7% (8/214) | 0.52 (0.24 – 1.14) | 0.10 |
|  | Across categories for time visiting pet households |  |  | 0.76 (0.54 – 1.06) | 0.11 |
|  |  |  |  |  |  |
| **Indirect animal exposure by three months** |  |  |  |  |
| Any contact with pet owners | Yes | 50.4% (566/1124) | 5.5% (31/566) | 0.82 (0.50 – 1.33) | 0.42 |
|  |  | **Exposure prevalence** | **Challenge-proven food allergy (12 to 36 months); 6.1% (68/1124)** |
|  | % (n/N) | Food allergy % (n/N) | Crude Odds Ratio (95% CI) | P |
|  |  |  |  |  |
| Categorical time with pet owners | None | 49.6% (558/1124) | 6.6% (37/558) | - |  |
|  | 1-2 hours per week | 17.4% (196/1124) | 4.6% (9/196) | 0.68 (0.32 – 1.43) | 0.31 |
|  | At least three hours per week | 32.9% (370/1124) | 6.0% (22/370) | 0.89 (0.52 – 1.53) | 0.68 |
|  | Across categories for time in contact with pet owners |  |  | 0.93 (0.71 – 1.23) | 0.61 |
|  |  |  |  |  |  |
| **Infections and antibiotic exposure by three months** |  |  |  |  |  |
| Any days of diarrhoea \* | Yes | 15.0% (159/1063) | 8.8% (14/159) | 1.58 (0.85 – 2.93) | 0.14 |
| Any upper respiratory tract infections \* | Yes | 51.7% (550/1064) | 6.9% (38/550) | 1.29 (0.78 – 2.13) | 0.32 |
| Received any courses of antibiotics \* | Yes | 13.5% (144/1064) | 6.3% (9/144) | 1.01 (0.49 – 2.09) | 0.98 |

Abbreviations: CI – confidence interval, \* restricted sample due to missing data

**Supplementary table D.** Univariate associations assessing demographic, skin barrier function, AD, familial atopic status, trial randomisation and microbiome-related exposures in relation to dog or cat ownership.

|  |  | **Exposure prevalence** | **Owning dog or cat at three months; 35.2% (396/1124)** |
| --- | --- | --- | --- |
|  | % (n/N) | Food allergy % (n/n) | Crude Odds Ratio (95% CI) | p |
| **Demographic exposures** |  |  |  |  |
| Sex | Male | 50.8% (571/1124) | 38.4% (219/571) | 1.32 (1.03 – 1.69) | 0.03 |
| Maternal age | Greater than 36 years | 25.5% (287/1124) | 32.4% (93/287) | 0.84 (0.64 – 1.12) | 0.25 |
| Birth weight | Greater than 3.86kg | 24.4% (274/1124) | 38.3% (105/274) | 1.19 (0.90 – 1.58) | 0.22 |
| Ethnicity | Non-white / mixed | 13.6% (153/1124) | 20.3% (31/153) | 0.42 (0.28 – 0.64) | < 0.001 |
|  |  |  |  |  |
| **Skin barrier exposures** |  |  |  |  |
| Carrying a *FLG* mutation\* | Yes | 12.1% (126/1039) | 37.3% (47/126) | 1.11 (0.76 – 1.64) | 0.59 |
| Skin barrier impairment \* | TEWL ≥ 15 g/m\*h | 32.4% (363/1121) | 30.6% (111/363) | 0.73 (0.56 – 0.96) | 0.02 |
| Atopic dermatitis at 3 months | Yes | 24.4% (274/1124) | 29.9% (82/274) | 0.73 (0.54 – 0.98) | 0.04 |
|  |  |  |  |  |
| **Familial atopic status** |  |  |  |  |
| Number of parents with atopic disease | Neither | 15.2% (171/1124) | 39.2% (67/171) | - |  |
|  | One | 47.8% (537/1124) | 35.4% (190/537) | 0.85 (0.60 – 1.21) | 0.36 |
|  | Both | 37.0% (416/1124) | 33.4% (139/416) | 0.78 (0.54 – 1.13) | 0.18 |
| Any sibling with atopic disease | Sibling with atopic disease | 38.3% (430/1124) | 38.3% (145/430) | 0.90 (0.70 – 1.16) | 0.40 |
| Maternal pet sensitisation | Dog or cat SPT ≥ 3mm | 20.9% (235/1124) | 28.1% (66/235) | 0.66 (0.48 – 0.91) | 0.01 |
| Avoidance of family pet ownership | Avoiding | 19.5% (219/1124) | 10.1% (22/219) | 0.16 (0.10 – 0.25) | < 0.001 |
|  |  |  |  |  |  |
| **Intervention arm** |  |  |  |  |  |
| Randomisation to the early introduction group | Yes | 48.9% (550/1124) | 33.8% (186/550) | 0.89 (0.69 – 1.13) | 0.33 |
|  |  |  |  |  |  |

|  |  | **Exposure prevalence** | **Owning cat or dog at three months; 35.2% (396/1124)** |
| --- | --- | --- | --- |
|  | % (n/N) | Food allergy % (n/n) | Crude Odds Ratio (95% CI) | p |
| **Microbiome related exposures** |  |  |  |  |  |
| Mode of delivery | Caesarean-delivery | 25.4% (286/1124) | 32.5% (93/286) | 0.85 (0.64 – 1.13) | 0.27 |
| Living in rural setting | Yes | 22.5% (253/1124) | 51.8% (131/253) | 2.46 (1.85 – 3.27) | < 0.001 |
| Type of rural setting | Rural; non-farming lifestyle | 20.0% (225/1124) | 49.8% (112/225) | 2.27 (1.68 - 3.06) | < 0.001 |
|  | Rural farming lifestyle | 2.5% (28/1124) | 67.9% (19/28) | 4.83 (2.16 – 10.81) | < 0.001 |
|  |  |  |  |  |
| Visiting places with pets | Yes | 47.2% (530/1124) | 44.9% (238/530) | 2.25 (1.75 – 2.89) | < 0.001 |
| Time in places with pets | None | 52.9% (594/1124) | 26.6% (158/594) | - |  |
|  | 1-2 hours per week | 28.1% (316/1124) | 39.2% (124/316) | 1.78 (1.33 – 2.38) | < 0.001 |
|  | At least three hours per week | 19.0% (214/1124) | 53.3% (114/214) | 3.15 (2.27 – 4.35) | < 0.001 |
|  | Across categories for time visiting pet households |  |  | 1.77 (1.51 – 2.08) | < 0.001 |
| Any contact with pet owners at 3m | Yes | 50.4% (566/1124) | 44.9% (254/566) | 2.38 (1.85 – 3.07) | < 0.001 |
| Time spent with pet owners at 3m | None | 49.6% (558/1124) | 25.5% (142/558) | - |  |
|  | 1-2 hours per week | 17.4% ((196/1124) | 39.8% (78/196) | 1.94 (1.37 – 2.73) | < 0.001 |
|  | At least three hours per week | 32.9% (370/1124) | 47.6% (176/370) | 2.66 (2.01 – 3.51) | < 0.001 |
|  | Across categories for time in contact with pet owners |  |  | 1.63 (1.42 – 1.88) | < 0.001 |
|  |  |  |  |  |  |
| **Siblings and communal childcare by three months of age** |  |  |  |  |
| Any siblings | Yes | 61.1% (687/1124) | 35.5% (244/687) | 1.03 (0.80 – 1.33) | 0.80 |
| Communal childcare at 3 months | Childminder or nursery | 2.8% (31/1124) | 45.2% (14/31) | 1.53 (0.75 – 3.14) | 0.24 |
|  |  |  |  |  |  |
| **Infections and antibiotic courses by three months of age** |  |  |  |  |  |
| Any diarrhoea before 3m\* | Yes | 15.0% (159/1063) | 37.7% (60/159) | 1.14 (0.80 – 1.61) | 0.47 |
| Any upper respiratory tract infections before 3m | Yes | 51.7% (550/1064) | 35.1% (193/550) | 1.00 (0.77 – 1.28) | 0.97 |
| Received any courses of antibiotics | Yes | 13.5% (144/1064) | 41.7% (60/144) | 1.38 (0.96 – 1.97) | 0.08 |

Abbreviations; AD – atopic dermatitis, *FLG* – filaggrin, TEWL – transepidermal water loss, 3m – three months