

ORIGINAL ARTICLE Epidemiology of Allergic Disease

Pets at birth do not increase allergic disease in at-risk children

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Summary

Background The literature is contradictory concerning pet exposure and risk of allergic disease in childhood especially among those with a family history of allergy.

Objective To investigate the relationship between cat and dog exposure at birth and allergic outcomes over the first 12 years in a birth cohort selected for familial allergy.

Methods A prospective birth cohort of 620 infants with a family history of allergic diseases was recruited. Data on pet keeping, family demographics and cord blood samples were collected at birth. Information on childhood wheeze, eczema and hay fever was collected 18 times in the first 2 years, at 7 years and at 12 years. Skin prick tests were conducted at 2, 7 and 12 years, and in parents. Regression analyses were used to investigate the relevant associations while adjusting for potential confounders.

Results Exposure to cats or dogs at birth showed a moderate reduction in risk of wheeze (aOR = 0.76; 95% CI 0.53, 1.09) and hay fever (aOR = 0.71; 0.49, 1.02) after 7 years of age. Protective effects were stronger in children of non-sensitized fathers (aOR wheeze 0.55; 0.31, 0.98; aOR hay fever 0.33; 0.15, 0.77 on exposure to cats alone, or cats or dogs at birth). Pet keeping was not related to cord blood IgE or sensitization from 2 to 12 years.

Conclusions and Clinical Relevance Pets at birth either decreased or had no effect on allergic disease up to age 12. We found no evidence that exposure to cats or dogs at birth increases the risk of allergic disease in high-risk children.

Keywords asthma, birth cohort, cats, dogs, hay fever, pets, sensitization

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Introduction

Although pets are known to exacerbate asthma and allergic disease in sensitized individuals [1], controversy remains as to whether pet exposure in early life influences the development of allergic disease. Increased cat allergen levels, cat keeping and cat exposure have all been found to increase, decrease or have no effect on sensitization to cat and other aeroallergens, and allergic disease outcomes in children and adults. Similar inconsistencies have been found for keeping dogs.

Attempts to elucidate these relationships using systematic reviews [2–5] and meta-analysis [6] have drawn disparate conclusions. These inconsistencies may relate

to various factors, including pooling different study designs. Our recent systematic review [7], which selected birth cohort studies that examined exposure to cats and dogs during the perinatal period, concluded that pets, especially dogs, may reduce the development of allergic disease in those without a family history of allergy. However, the relationship in allergic families was not clear. Consequently, current national and international guidelines [8–11] all agree there is insufficient evidence to provide recommendations in relation to pet keeping in early life and development of asthma. A major methodological issue when investigating this relationship is managing confounding from pet-keeping choices made by families with allergic disease [12–14].

In addition, we have shown that selective avoidance of cats by those with allergies may be partly responsible for an apparent protective effect of childhood cats on asthma and allergy [15].

The aim of this study was to investigate the relationship between pet keeping at birth and risk of sensitization, wheeze, hay fever and eczema up to 12 years of age in high-risk children, whilst accounting for factors which influenced pet-keeping behaviour. A secondary aim was to investigate if parental sensitization modified these associations.

Methods

Study population

The Melbourne Atopy Cohort study (MACS), a longitudinal, birth cohort, initially started as a randomized controlled trial to investigate the effect of three infant formulas at weaning on subsequent allergies [16]. Six hundred and twenty babies were enrolled by recruiting pregnant women living in Melbourne, Australia, between 24 March 1990 and 1 November 1994. Eligible babies had at least one first-degree family member with a history of eczema and/or asthma and/or allergic rhinitis and/or severe food allergy. The recruitment process has been described [17]. The study was approved by the Mercy Maternity Hospital Ethics Committee and all mothers provided written informed consent.

Data collection

An allergy-trained research nurse conducted telephone surveys with babies' mothers 4 weekly from birth to 15 months, at 18 months, at 2 years, at 7 years and at 12 years.

Detailed demographic, environmental and familial allergy information was obtained at birth. Follow-up interviews included questions concerning the development of allergic/atopic diseases and symptoms, other infant illnesses or conditions, contact with health care professionals and medications used. The 12-year survey included validated asthma questions from the International Study of Asthma & Allergies in Childhood (ISAAC) [18].

Cord blood IgE and IgA

Cord blood ($n = 436$) was collected from the umbilical vein after placental delivery. Alternatively, a 1 mL capillary sample ($n = 55$) was collected on day 2–3. Serum was separated by centrifugation (2500 rpm for 5 min) and samples stored at -20°C . To exclude maternal contamination, serum IgA was measured using low-level IgA radial diffusion plates (Behring AG, Germany).

Samples with IgA levels $> 32\mu\text{g/mL}$ ($n = 52$) were assumed contaminated [19]. Serum IgE was determined using solid-phase radio-immunoassay based on a sandwich technique, RIA Ultra kit (Pharmacia, Uppsala, Sweden). IgE levels were considered continuous log transformed and also dichotomized at a detection limit of 0.5 ku/L. A child was considered to have raised IgE if ≥ 0.5 ku/L [20] providing the IgA level was $< 32\mu\text{g/mL}$ [19]. The remaining 391 cord blood and 48 peripheral blood samples were included.

Skin prick testing

Allergy-trained nurses performed skin prick testing (SPT) using standardized technique [21] at ages 2, 7 and 12 years. Parents were tested within 2 years of their child's birth. Allergens used were cow's milk, egg white, peanut, house dust mite (HDM), rye grass and cat dander (Bayer, Spokane, WA, USA). Details of methods have been published [22]. In accordance with other studies [23], positive SPT was defined as mean weal diameter $\geq 2\text{mm}$ in children aged 2 years. In participants over 2 years, including parents, positive SPT was defined as a mean weal diameter $\geq 3\text{mm}$.

Cat and dog keeping

The presence of a cat or dog was prospectively defined by questionnaire responses at birth and 7 and 12 years of age.

Wheeze

Wheeze at 2 years was defined by questionnaire responses of at least one episode of doctor diagnosed asthma, wheezy bronchitis, bronchitis or bronchiolitis by 2 years of age (further details in Online Supplement). Wheeze at 7 years was defined by a positive response to the question 'Has your child had any episodes of asthma in the past 12 months?'

At 12-year follow-up, wheeze was defined by a positive response to the ISAAC question 'Has your child ever had wheezing or whistling in the chest in the past 12 months?' [18].

Hay fever

Hay fever at 7 and 12 years was defined as any reported episodes of hay fever in the past 12 months on questionnaire.

Eczema

Eczema at 2 years was defined as doctor's consultation for eczema, or any rash which had been treated with

steroid creams (excluding rashes on the scalp and nappy area) by age 2 years.

Other variables

Parental smoking, carpets in the house, number of siblings, parental history of ever asthma, hay fever and eczema were defined by responses to baseline questionnaire [mean age 14 days prior to birth (IQR 26 days prior to birth until 2 days post)]. Socio-economic status was defined as receiving social security benefits at baseline by one or both parents. Intervention formula was assessed by intention to treat at baseline allocation. All these variables were considered potential confounders.

Statistical analysis

Two-sample comparison tests were used to assess potential differential loss to follow-up. Multiple logistic regression was used to investigate associations between pet keeping at birth and sensitization at birth, 2, 7 and 12 years and between pet keeping at birth and allergic disease at 2, 7 and 12 years while adjusting for confounders. Multiple logistic regression was also used to assess allergic outcomes at all times of follow-up by combining sensitization, wheeze, eczema and hay fever outcomes into one variable with three times of measurement (2, 7 and 12 years), clustering by ID numbers and using robust standard errors. Hay fever and wheeze measured at 2 years were omitted from these models due to concerns about misclassification of these conditions at this age. In all models, the exposure variables were the presence of cat controlled for dog and *vice versa*, or either a cat or dog at birth. Confounders were assessed for inclusion according to causal modelling theory [24]. Each variable had an appropriate temporal relationship with the exposure and outcome variables and was a plausible confounder of this relationship. Pet ownership at 7 and 12 years was not included as confounders on the relationship of pet at birth and subsequent allergic disease. Confounders were included in final models if there was a change of 10% or more from the crude odds ratio. Interactions were tested for parental cat dander and aeroallergen sensitization. Stratified associations were reported if the *P* for interaction was ≤ 0.05 . Stata (release 11.0, Stata Corporation, College Station, TX, USA) was used for all analyses.

Results

As previously reported [17], the MACS cohort was predominantly well-educated (~60% of parents attended university), Australian born (85%) and of high socio-economic status (3–4% parents were receiving social security benefits at baseline). Approximately half (51%)

the children were male. All children had at least one immediate family member with 'allergic disease', while 74% had two or more affected family members (Supporting Information Table S1).

Of the 620 participants, 618 provided information on cats and 605 on dogs at birth. Data on skin prick testing were available for 459 (74%) children at 2 years of age, 183 (30%) at 7 years and 366 (59%) at 12 years. At 12 years, 370 (60%) children provided information on current wheeze, eczema and hay fever (40 participants withdrew from the study and 210 were unable to be contacted). The relatively low proportion of children able to be contacted at 7 years was due to funding restrictions. Further funding became available in later years.

Baseline characteristics (including pet ownership, family history of allergic disease, parental smoking, parental sensitization, prior SPT results and early life wheeze) were not different between those who participated at each time point and those who did not (Supporting Information Table S2) except for dog ownership at 7 years which was less in those missing. Also those missing surveys at 2 years had younger parents with less educated mothers at baseline, 28% of families kept cats and 31% kept dogs. Two thirds (66%) of those who had a cat at baseline, still had a cat at the 12-year follow-up; 71% of those who had a dog at baseline, still kept a dog at the 12-year follow-up. Conversely of those who had no cat at baseline, 80% still had no cat at the 12-year follow-up. Interestingly, 45% of families without a dog at baseline had acquired one by the 12-year follow-up (Supporting Information Table S3).

In the first 2 years after birth, 511(82%) mothers and 399 (64%) fathers were skin prick tested. Of the 370 children with data at 12 years, skin prick test results were available for 357 (96%) mothers and 296 (80%) fathers. These prevalences did not differ for the subset of children with data at age 12 (Supporting Information Figs S1 and S2).

Predictors of cat and dog keeping at birth

Families were more likely to have cats if they were smokers or their house was carpeted (Table 1). They were less likely to have cats if fathers had hay fever and less likely to have dogs if fathers had asthma. Parental sensitization (≥ 3 mm) to cat dander was not associated with cat keeping, but families where either parent was highly sensitized to cat dander at a threshold of 7 mm were less likely to keep cats or dogs. This high sensitization threshold was decided upon after reviewing each cut-off (by mm) and their relationship with cat keeping (Supporting Information Table S4).

Table 1. Predictors of cat and dog keeping at birth

		Cat at birth		Dog at birth	
		%(n/N)	aOR (95% CI)	%(n/N)	aOR (95% CI)
Parental smoking	No	27 (130/491)	1	28 (138/491)	1
	Yes	35 (45/127)	1.52 (1.01, 2.31)	43 (55/127)	1.21 (0.70, 2.07)
Carpets in bed or living room	No	15 (7/46)	1	28 (13/46)	1
	Yes	30 (164/556)	3.64 (1.26, 10.5)	32 (175/556)	1.48 (0.61, 3.61)
Maternal asthma	No	28 (99/349)	1	30 (105/349)	1
	Yes	28 (76/268)	1.22 (0.78, 1.91)	33 (88/268)	0.98 (0.64, 1.51)
Paternal asthma	No	30 (135/455)	1	31 (141/455)	1
	Yes	25 (40/158)	0.75 (0.43, 1.33)	32 (51/158)	0.58 (0.34, 0.99)
Maternal hay fever	No	27 (66/243)	1	31 (76/243)	1
	Yes	29 (109/374)	1.17 (0.72, 1.88)	31 (117/374)	0.89 (0.58, 1.36)
Paternal hay fever	No	32 (105/331)	1	31 (101/331)	1
	Yes	25 (70/282)	0.55 (0.35, 0.88)	32 (91/282)	1.06 (0.67, 1.68)
Maternal cat sensitization (≥ 3 mm)	No	30 (108/365)	1	34 (125/365)	1
	Yes	29 (42/144)	1.11 (0.69, 1.79)	29 (42/144)	0.71 (0.44, 1.15)
Paternal cat sensitization (≥ 3 mm)	No	30 (93/311)	1	34 (105/311)	1
	Yes	31 (27/86)	1.38 (0.75, 2.52)	30 (26/86)	0.95 (0.55, 1.63)
Maternal aeroallergen sensitization ≥ 3 mm	No	28 (63/227)	1	34 (77/227)	1
	Yes	31 (87/282)	1.38 (0.90, 2.11)	32 (90/282)	0.81 (0.52, 1.27)
Paternal aeroallergen sensitization ≥ 3 mm	No	35 (67/193)	1	29 (56/193)	1
	Yes	26 (53/204)	0.83 (0.51, 1.36)	37 (75/204)	1.48 (0.92, 2.40)
Paternal or maternal cat sensitization ≥ 7 mm	No	18 (13/73)	1	34 (149/436)	1
	Yes	31 (137/436)	0.47 (0.25, 0.89)	25% (18/73)	0.55 (0.29, 1.05)

Confounders considered included parental asthma, eczema, hay fever, atopy and smoking, household carpets, and whether the parents were receiving government assistance, and gender of the child.

Cat or dog at birth and allergic disease at, 2, 7 and 12 years

There was no strong relationship observed between pet keeping at birth and allergic disease outcomes at the three time points (Table 2). It appeared, however, that as the cohort aged, there was a non-significant trend to reduction in the risk of allergic disease in those pet exposed at birth for both hay fever and wheeze. In the combined ages of outcome model (Supporting Information Table S5), there was a modest reduction in the risk of hay fever (OR 0.71; 95%CI 0.49, 1.02) and wheeze (OR 0.76; 0.53, 1.09) among those children exposed to cats or dogs at birth.

Cat or dog at birth and sensitization at birth, 2, 7 and 12 years

Pet exposure at birth was not related to neonatal blood IgE (Supporting Information Table S6). The results were unchanged when blood from sites other than cord were excluded. In both the combined ages of outcome model (Table 3), and sensitization models stratified by ages of outcome (Supporting Information Table S7), there was no clear relationship between sensitization and pet ownership.

The effect of current pet ownership on the association between cat and dog at birth and allergic disease at, 2, 7 and 12 years

Controlling for current pet ownership produced a further reduction in the risk of allergic disease. This was mediated through a negative association between current pet ownership and allergic disease at 12 years (crude OR for wheeze 0.70; 95% CI 0.42–1.16) and was consistent for all models (Supporting Information Table S8). Furthermore, those children who kept pets at birth but not at 12 years were more likely to be sensitized to any allergen by the age of 1 year than those who kept pets at both times (aOR 3.11; 95% CI 1.19–8.13). Similar trends were seen at 7 years where these children were more likely to have asthma or hay fever. Therefore, we observed that pet keeping was not maintained in children who developed sensitization or allergic disease.

Modification in the association between pet keeping and allergic disease in the child by parental sensitization

Children of non-sensitized fathers had less risk of wheeze or hay fever if exposed to cats, or cats/dogs at birth (Table 4). Children of sensitized fathers were at a

Table 2. Allergic disease outcomes at 2, 7 and 12 years by pet keeping at birth

	Age(years)	Wheeze% (n/N)	aOR (95% CI)	Hay fever % (n/N)	aOR (95% CI)	Eczema % (n/N)	aOR (95% CI)
Cat at birth							
No	2	39 (160/413)	1			42 (185/442)	1
Yes	2	42 (69/164)	1.14 (0.80, 1.66)	21 (73/356)	1	47 (82/174)	1.48 (0.95, 2.29)
No	7	26 (93/356)	1	17 (23/138)	0.78 (0.46, 1.30)	21 (76/354)	1
Yes	7	25 (35/138)	0.96 (0.61, 1.51)	40 (102/258)	1	25 (35/138)	1.39 (0.82, 2.39)
No	12	30 (81/267)	1	32 (32/101)	0.71 (0.44, 1.16)	24 (61/258)	1
Yes	12	23 (23/102)	0.67 (0.39, 1.14)			24 (24/101)	1.01 (0.59, 1.73)
Dog at birth							
No	2	39 (154/392)	1			44 (185/423)	1
Yes	2	40 (75/185)	1.05 (0.74, 1.51)	22 (72/333)	1	42 (82/193)	0.78 (0.51, 1.20)
No	7	28 (93/333)	1	15 (24/161)	0.72 (0.43, 1.20)	25 (83/332)	1
Yes	7	22 (35/161)	0.72 (0.46, 1.12)	39 (93/236)	1	18 (28/160)	0.70 (0.41, 1.22)
No	12	30 (73/244)	1	33 (41/123)	0.77 (0.49, 1.21)	23 (55/236)	1
Yes	12	25 (31/125)	0.66 (0.37, 1.86)			24 (30/123)	1.43 (0.70, 2.89)
Cat or dog at birth							
No	2	34 (103/305)	1			42 (130/312)	1
Yes	2	35 (104/295)	1.07 (0.76, 1.50)	22 (54/245)	1	45 (137/304)	1.15 (0.83, 1.58)
No	7	29 (70/245)	1	17 (42/249)	0.83 (0.49, 1.39)	23 (56/244)	1
Yes	7	23 (58/249)	0.84 (0.52, 1.36)	42 (72/173)	1	22 (55/248)	1.06 (0.65, 1.75)
No	12	31 (56/180)	1	33 (62/186)	0.70 (0.46, 1.08)	22 (38/173)	1
Yes	12	25 (48/189)	0.75 (0.48, 1.19)			25 (47/186)	1.36 (0.79, 2.36)

*Current pet ownership not included in models.

Confounders considered included parental asthma, eczema, hay fever, atopy and smoking, household carpets, and whether the parents were receiving government assistance, and gender of the child. After consideration all models included between 0 and 3 confounders.

Table 3. Relationship of pets at birth and the risk of sensitization aged 2–12 years

Allergen	Cat	aOR (95%CI)	Dog	aOR (95%CI)	Cat or dog	aOR (95%CI)
Cat dander	No	1	No	1	No	1
	Yes	1.15 (0.61, 2.16)	Yes	0.93 (0.52, 1.68)	Yes	1.27 (0.74, 2.16)
Dust mite	No	1	No	1	No	1
	Yes	0.88 (0.57, 1.36)	Yes	0.78 (0.51, 1.21)	Yes	0.83 (0.56, 1.23)
Rye grass	No	1	No	1	No	1
	Yes	1.03 (0.64, 1.65)	Yes	0.82 (0.52, 1.29)	Yes	1.01 (0.66, 1.55)

*Maternal and paternal cat sensitization (3 mm) included in cat dander model, only paternal cat sensitization included in dust mite and rye grass models.

moderately increased risk of wheeze if exposed to cats at birth, but not at increased or decreased risk of hay fever when exposed to cats, or cats/dogs. The sensitization status of fathers was an effect modifier for wheeze and hay fever, but not eczema. The sensitized status of mothers was not an effect modifier for any of the allergic outcomes. The interactions with paternal sensitization were important for cat, or cat/dog exposure, but not for dog exposure alone.

Discussion

This is the first birth cohort study of high-risk children to investigate pet exposure at birth and subsequent allergic outcomes up to age 12. We found cat or dog exposure at birth moderately reduced the risk of current

wheeze and hay fever from ages 7 to 12 years. This protective effect was stronger among children of non-sensitized fathers. In contrast, children of cat-sensitized fathers were at increased risk of wheeze when cat exposed at birth. Cord blood IgE was not affected by prenatal pet exposure.

Investigating perinatal pet exposure is important as this is a critical time for immune system maturation [25]. A number of birth cohort studies have examined the effect of post-perinatal pet keeping [14, 26–33] with discrepant findings. Also, over half of early childhood wheeze is transient [34], so considering allergic outcomes such as asthma beyond 5 years is important to avoid misclassification related to transient wheeze phenotypes. Two perinatal pet studies which reported short-term outcomes [35, 36] have also found

Table 4. Interaction of paternal sensitization with pet at birth on allergic outcomes in children

				Adjusted OR for allergic disease in child
Pet at birth	Sensitization in father	<i>P</i> for interaction	Father +ve	
Current wheeze in child 7–12 years				
Cat	Cat Dander 3 mm	0.011	No	0.55 (0.31–0.98)
			Yes	1.89 (0.98–3.66)
Current hay fever in child 7–12 years				
Cat	Any 3 mm	0.016	No	0.33 (0.15–0.77)
			Yes	1.16 (0.66–2.02)
	Aero 3 mm	0.011	No	0.32 (0.14–0.74)
			Yes	1.18 (0.68–2.06)
	Cat dander 3 mm	0.022	No	0.58 (0.34–1.02)
			Yes	2.10 (0.83–5.34)
Cat or dog	Any 3 mm	0.029	No	0.39 (0.18–0.82)
			Yes	1.06 (0.65–1.74)

Confounders considered included parental asthma, eczema, hay fever, atopy and smoking, household carpets, and whether the parents were receiving government assistance, and gender of the child.

a protective effect of pet keeping. In addition, the Tucson Children's Respiratory Study (TCRS) measured perinatal pet exposure and reported allergic outcomes beyond the age of 5 years [37]. In agreement with the current study, they reported protective effects from pets at birth, finding a reduced risk of frequent wheeze in dog-exposed children aged 1–13 years.

In contrast, however, they studied an unselected population. A major reason for the gap in knowledge concerning pet exposure and subsequent allergies in high-risk children is the lack of birth cohort studies of high-risk families which have been followed into early adolescence when all childhood allergies are fully expressed.

Although our entire cohort had a family history of allergic disease, in non-sensitized fathers we found a stronger protective effect of pet exposure. In contrast, in pet-exposed children of sensitized fathers, there was a modestly increased risk of wheeze. As this was found only in fathers and involved small numbers, these observations need to be interpreted with caution and in light of the results from other studies. Nevertheless, three birth cohorts found similar interactions with parental allergic status. Celedon *et al.* [31] studied wheeze in cat-exposed children up to age 5, finding children of non-asthmatic mothers were protected, whilst those with asthmatic mothers were at increased risk. Polk *et al.* [28] found maternal asthma increased the risk of wheeze in cat exposed 3-year olds. Remes *et al.* [37] found the protective effect of dogs at birth was stronger in families without parental asthma. In two of these studies, the interaction was seen with maternal but not paternal asthma, in the third study with parental asthma. Due to the high-risk nature of

our cohort, where mothers were the initial contact, our mothers may have been too similar in their allergy backgrounds (despite the SPT results) to show an interaction by sensitization. Indeed 84% of mothers had some form of allergy compared with 61% of fathers. This may help explain effect modification by paternal but not maternal sensitization. Conversely, one birth cohort [12] reported less risk of wheeze in pet-exposed children with asthmatic mothers, and yet others have found no interaction [14, 27, 38, 39]. Discrepant results between studies may be due to differences in measurement of familial allergic disease or lack of statistical power. Different variables are used to represent familial allergy, most commonly parental history of asthma which may be prone to recall bias, and may also be an insensitive measure of pet allergy and pet-keeping behaviour. Asthma is a heterogeneous disease related to myriad causes, attributed to sensitization in just over half of all cases [40]. Even when dealing with atopic asthma, pet allergy is implicated in only a proportion. Most people with asthma do not have pet allergy, and this may not influence their pet-keeping choices.

In agreement with our findings, other birth cohort studies have found no relationship between cat exposure and cat sensitization [14, 41, 42]. In contrast, however, some birth cohort studies have reported increased cat sensitization with cat exposure [26, 27, 32, 38, 43], although none of these measured sensitization beyond the age of 6 years. In addition, Wegienka *et al.* [44] reported half the odds of sensitization for 18-year olds who were cat exposed or 18-year old males who were dog exposed during the first year of life.

Two theories have been proposed to explain why animal exposure may reduce allergic disease. First, that the developing immune system requires a variety of microbial stimuli to develop normal responses [45]. Dogs, which thrive in microbe-rich environments, may be different to cats in the number and diversity of microbes they introduce to the home, although we did not observe strong evidence that there was a difference in the effect of dog and cat keeping at birth on risk of allergic disease. Whether pet ownership in the urban environment is associated with increased microbial load is not clear. One study found increased endotoxin levels associated with pets in urban settings [46]; however, a recent publication found no difference [47]. The second theory is that pet keeping may induce antigenic tolerance [13]. Children exposed to high cat allergen levels appear to develop tolerance to cat [48], producing an IgG antibody response without sensitization [47, 49]. Whether this is limited to children of non-allergic heredity is not known. The ability to mount a 'tolerance' response may be mediated by genetic contributions from parents and, in the current study, may help to explain the differing risks of current wheeze in the

pet-exposed children of sensitized and non-sensitized fathers. Linneberg et al. [50] proposed that children with strong allergic predisposition may require greater levels of allergens to induce tolerance. Relatively low levels in the urban environment may therefore cause a differential response depending on genetic background. In our study, this may mean that children of sensitized fathers are at increased risk and may require greater allergen exposure to induce tolerance.

A major strength of the study is the detailed prospective information collected from birth to 12 years. Another strength is the parental SPT data, providing an objective measure of 'sensitization' as a possible determinant of pet-keeping behaviour, and a potential effect modifier. A third area is the length of follow-up, allowing outcome measurement at 12 years when wheeze is far more likely to represent 'asthma' than in early life. A final strength is the serial assessment of pet keeping allowing us to demonstrate that pets were not maintained in families where children became sensitized or developed allergic disease. It should be noted, however, that it was not known whether sensitization occurred before or after removal of the pet. We also showed that current pet keeping was related to less risk of current wheeze. Furthermore, we demonstrated that including current pet ownership within the statistical models resulted in an overestimation of the protective effect of early life pet keeping due to reverse causation. Removal of pets which occurs in allergic families, as we have previously shown [15], may have resulted in an overestimate of the protective effect of pet keeping in some studies. However, we have seen a modest protective effect of pet at birth on subsequent allergies even when not adjusted for current pet ownership.

The study has some limitations. This cohort had 60% retention at 12 years. Although this reduced the study power, we found no significant differences in baseline

characteristics, early wheeze or skin prick testing results among those lost to follow-up. We did not measure dog sensitization (Can f1) and have no measurements of Fel d1 or Can f1 in dust samples, so were unable to look for a 'dose-response' effect of pet exposure. In addition, we have no information on whether pets resided in or outside the house. In the process of investigating possible interaction by parental sensitization, we performed many different subgroup analyses, allowing the possibility that associations may be found by chance alone. Caution needs to be exercised in their interpretation. Finally, families in this cohort were predominantly well educated and of high socio-economic class, which limits generalizability of the findings.

Conclusion

In our high-risk cohort, we found keeping pets in early life did not increase children's risk of asthma or hay fever and may even protect from developing these conditions. We found no evidence to support exclusion of pets from the environment of high-risk babies.

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Declaration of conflict of interest

The funding bodies had no role in the study design, collection, analysis or interpretation of data, nor in writing this report or the decision to publish. The results, conclusions and opinions reported in the manuscript are those of the authors and are independent from the funding sources. None of the authors have conflicts of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Proportion of positive skin prick testing in all parents tested.

Figure S2. Proportion of positive skin prick testing in parents of children with data at 12 years.

Table S1. Numbers of first degree relatives with allergic disease.

Table S2. Demographics of participants at baseline, who attended or did not attend follow-ups.

Table S3. Cat and dog keeping over time.

Table S4. The relationship between parental sensitization to cat and cat keeping.

Table S5. Relationship of pets at birth and the risk of current wheeze or hay fever aged 7–12 years (eczema model also includes 2-year old eczema).

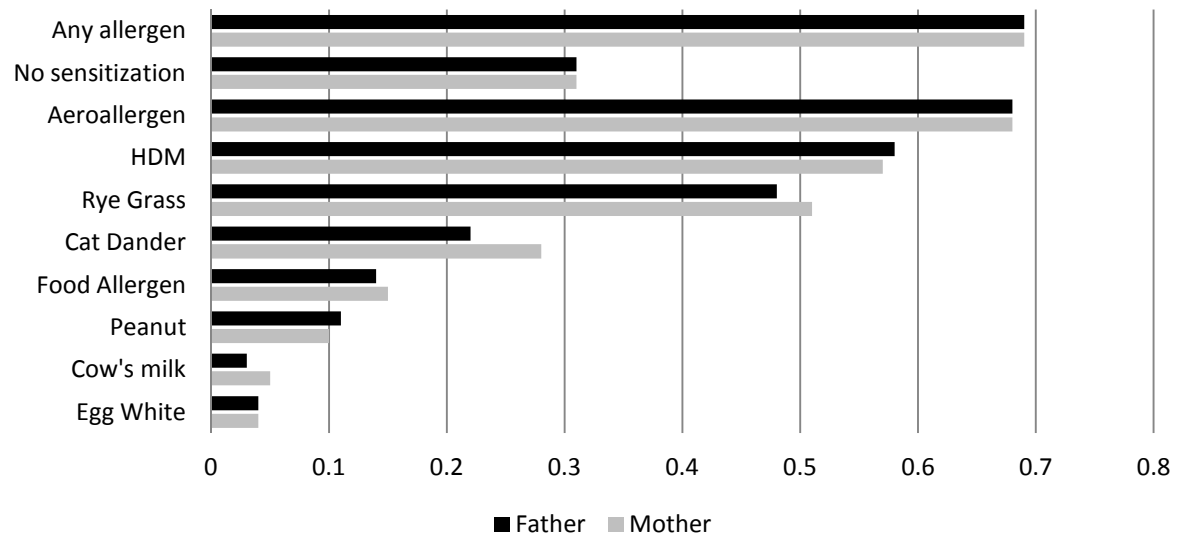
Table S6. IgE in cord blood (binary variable > 0.5 ku/L.) by pet keeping at baseline.

Table S7. Odds of sensitization to aeroallergens at 2, 7 or 12 years if exposed to pets at birth.

Table S8. Pets at birth and odds of wheeze at 12 years with and without 12-year pet ownership.

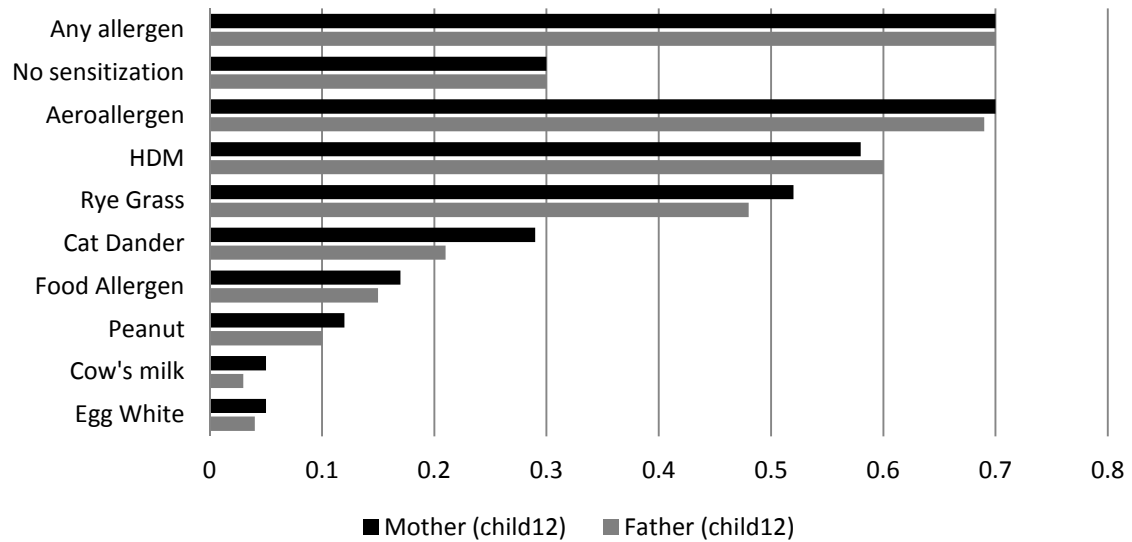
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Proportion of parents sensitized (511 mothers and 399 fathers tested)



Proportion sensitized parents of 12 year old children

(Mother n=357, Father n=296)



Supporting Information

Pets at birth do not increase allergic disease in at-risk children.

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Table S1. Numbers of first degree relatives with allergic disease

First degree relatives with allergy at Baseline	% affected (n)	% affected (n)
	Whole cohort (N=620)	12yr sub-group (N=370)
Mother only	18% (109)	16% (60)
Father only	5% (30)	5% (18)
One or more siblings only	3% (21)	3% (12)
Mother & Father	24% (147)	24% (89)
Mother & one or more siblings	19% (115)	18% (68)
Father & one or more siblings	9% (55)	10% (37)
Mother & Father & one or more siblings	23% (143)	23% (86)

Table S2 Demographics of participants at baseline, who attended or did not attend follow-ups.

Baseline		No miss					Miss				
		2yr	2yrSPT	7yr	7yrSPT	12yr	2yr	2yrSPT	7yr	7yrSPT	12yr
No. of participants	620	560	459	414	183	370	57	161	206	437	250
Gender %(male/female)	51/49	51/49	52/48	50/50	57/43	53/47	51/49	48/52	53/47	49/51	49/51
Mothers age (mean yrs)	31	*31	32	32	32	32	*29	30	30	31	30
Fathers age (mean yrs)	33	*34	34	34	34	34	*31	32	32	33	32
Mothers University educated (%)	59	*61	63	62	61	63	*40	46	52	58	52
Fathers University educated (%)	61	62	63	63	60	61	55	60	57	61	61
Mothers with eczema ever (%)	39	40	39	39	37	42	33	38	39	40	35
Fathers with eczema ever (%)	20	20	22	20	24	20	21	18	20	19	21
Mothers with asthma ever (%)	43	43	43	43	42	44	46	45	44	44	42
Fathers with asthma ever (%)	26	25	26	26	26	27	34	24	24	26	23
Mothers with hayfever ever (%)	61	59	60	62	61	59	72	63	58	60	63
Fathers with hayfever ever (%)	46	46	45	47	45	48	50	49	49	44	44
Any pos SPT Mother(3mm) (%)	69	69	69	70	70	70	68	65	66	68	66
Any pos SPT Father (3mm) (%)	69	69	70	69	72	70	76	64	70	67	66
Cat keeping(%)	28	29	29	30	31	27	25	28	26	27	30
Dog Keeping(%)	31	32	33	*34	36	34	21	28	*25	29	28

There are so few missing from the 12yearSPT compared with the 12year survey data (370 vs 366) that this column was not completed.

*Pairs with significant differences at the 0.05 level

Table S3 – Cat and Dog keeping over time.

Cat keeping at birth					
	% (n/N)			% (n/N)	
Yes	28% (175/618)		No	72% (443/618)	
	Number of those still keeping cat at:			Number of those still without cat at :	
	3-5yrs	77% (97/126)		3-5yrs	87% (267/307)
	6-7yrs	68% (79/116)		6-7yrs	85% (243/285)
	12yrs	66% (61/93)		12yrs	80% (204/256)
Dog keeping at birth					
	% (n/N)			% (n/N)	
Yes	31% (189/605)		No	69% (416/605)	
	Number of those still keeping dog at:			Number of those still without dog at:	
	3-5yrs	79% (115/146)		3-5yrs	78% (225/287)
	6-7yrs	74% (101/137)		6-7yrs	73% (192/264)
	12yrs	71% (84/118)		12yrs	55% (126/231)

Table S4. The relationship between parental sensitization to cat and cat keeping

Maternal or paternal cat dander sensitization threshold	% cat ownership when sensitized to this threshold	% cat ownership when not sensitized to this threshold	The odds of keeping a cat if sensitized to this threshold Odds Ratio (95% CI)
3mm	29.4% (62/211)	29.5% (88/298)	0.99 (0.67,1.46)
4mm	26.8% (33/123)	30.3% (117/386)	0.84 (0.54,1.33)
5mm	26.3% (25/95)	30.2%(125/414)	0.83 (0.50,1.36)
6mm	23.0%(17/74)	30.6%(133/435)	0.68 (0.38,1.21)
7mm	17.8 %(13/73)	31.5%(137/436)	0.47 (0.25,0.89)

Table S5. Relationship of pets at birth and the risk of current wheeze or hay fever aged 7 to 12 years
(eczema model also includes 2 year old eczema)

	Cat	aOR (95%CI)	Dog	aOR (95%CI)	Cat or dog	aOR (95%CI)
Current Wheeze	No	1	No	1	No	1
	Yes	0.83 (0.55,1.26)	Yes	0.75(0.50, 1.11)	Yes	0.76 (0.53, 1.09)
Current Hay fever	No	1	No	1	No	1
	Yes	0.75 (0.50, 1.13)	Yes	0.71 (0.48, 1.05)	Yes	0.71 (0.49, 1.02)
Current Eczema	No	1	No	1	No	1
	Yes	1.31 (0.93, 1.86)	Yes	0.85 (0.59, 1.21)	Yes	1.11 (0.85, 1.45)

Paternal aeroallergen sensitization was included in the eczema models, Pet status at birth only included

Table S6. IgE in cord blood (binary variable >0.5 ku/l.) by pet keeping at baseline.

Cat at birth			Dog at birth		Cat or dog at birth	
IgE>0.5	% (n/N)	aOR(95% CI), p	% (n/N)	aOR(95% CI), p	% (n/N)	aOR(95% CI), p
No	19% (57/305)	1	16% (47/288)	1	16% (35/215)	1
Yes	17% (20/117)	0.61 (0.29, 1.31), 0.209	22% (30/134)	1.63 (0.83, 3.20), 0.157	20% (42/207)	1.12 (0.58, 2.16), 0.741

Paternal and maternal aeroallergen sensitization were included as confounders.

The dichotomized results are presented here, however they are similar to the results found with the log transformed IgE.

Table S7 Odds of sensitization to aeroallergens at 2, 7 or 12 years if exposed to pets at birth.

	Age in yrs	Cat Dander % (n/N)	aOR (95% CI), p	HDM % (n/N)	aOR (95% CI), p	Rye Grass % (n/N)	aOR (95% CI), p
	Age in		aOR(95% CI), p	HDM	aOR (95% CI), p	Rye Grass	aOR (95% CI), p
Cat at Birth							
No	2	7% (22/327)	1	23% (76/327)	1	9% (31/327)	1
Yes	2	9% (12/131)	1.40 (0.67, 2.91)	21% (28/131)	1.06 (0.61, 1.84)	10% (13/131)	1.16 (0.54, 2.51)
No	7	12%(15/126)	1	41% (52/126)	1	28% (35/126)	1
Yes	7	14%(8/57)	1.71 (0.63 – 4.69)	33% (19/57)	0.80 (0.38, 1.68)	28% (16/57)	1.21 (0.55, 2.66)
No	12	21%(55/262)	1	49%	1	36% (95/266)	1
Yes	12	19%(19/98)	0.87 (0.45, 1.66)	(130/266) 43% (43/99)	0.91(0.56, 1.46)	31% (31/99)	0.94 (0.54,1.64)
Dog at birth							
No	2	8% (25/309)	1	24% (74/309)	1	11% (33/309)	1
Yes	2	6% (9/149)	0.92 (0.38, 2.19)	20% (30/149)	0.80 (0.50, 1.29)	7% (11/149)	0.57 (0.25, 1.31)
No	7	13%(15/118)	1	42% (50/118)	1	31% (36/118)	1
Yes	7	12% (8/65)	0.91 (0.32, 2.58)	32% (21/65)	0.80 (0.39,1.65)	23% (15/65)	0.83 (0.38 ,1.80)
No	12	21%(51/244)	1	50% (122/244)	1	35%(85/244)	1
Yes	12	21%(26/121)	0.92(0.50,1.68)	42% (51/121)	0.73(0.47,1.13)	34%(41/121)	0.88 (0.53, 1.49)
Cat or Dog at Birth							
No	2	7% (16/225)	1	25% (56/225)	1	10% (23/225)	1
Yes	2	8% (18/233)	1.48 (0.65, 3.40)	21% (48/233)	0.78 (0.51, 1.21)	9% (21/233)	0.78 (0.38, 1.58)
No	7	10% (8/81)	1	44% (36/81)	1	30% (24/81)	1
Yes	7	15%(15/102)	1.55(0.62, 3.88)	34% (35/102)	0.76 (0.38, 1.52)	26% (27/102)	1.17(0.55, 2.50)
No	12	21%(38/178)	1	51% (92/181)	1	35% (64/181)	1
Yes	12	20%(36/182)	0.98 (0.55, 1.74)	44% (81/184)	0.76 (0.50, 1.15)	34% (62/184)	1.05 (0.64, 1.72)

Confounders considered included parental asthma, eczema, hayfever, atopy and smoking, household

carpets, and whether the parents were receiving government assistance, and gender of the child

Table S8. Pets at birth & odds of wheeze at 12 years with and without 12 year pet ownership

	Wheeze% (n/N)	Adjusted OR (without 12 year pet ownership)	Adjusted OR (with 12 year pet ownership)
Cat at birth			
No	30% (81/267)	1	1
Yes	23% (23/102)	0.67 (0.39 ,1.14)	0.51 (0.26 ,1.00)
Dog at birth			
No	30% (73/244)	1	1
Yes	25% (31/125)	0.66 (0.37, 1.86)	0.53 (0.26, 1.09)
Cat or Dog at birth			
No	31% (56/180)	1	1
Yes	25% (48/189)	0.75 (0.48, 1.19)	0.56 (0.30, 1.05)

Confounders considered included parental asthma, eczema, hayfever, atopy and smoking, household carpets, and whether the parents were receiving government assistance, and gender of the child

Methods Continued – definition of wheeze at 2 years.

The definition of wheeze at 2 years is based on a positive answer to either of two different questions in the early life questionnaires:

1. Has your child visited the doctor for asthma in the past 4 weeks?
2. Has your child been diagnosed as suffering from asthma, wheezing or wheezy bronchitis, bronchitis or bronchiolitis in the past 4 weeks?