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Cat ownership, cat allergen exposure, and trajectories of sensitization and asthma throughout childhood

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Word count: 1100

28 **SUMMARY**

29 Exposure to cat and/or cat allergens can confer either an increase in risk, or protection, or will
30 have no effect, depending on the age of the assessment, study design and the choice of study
31 population.

To the Editor

For almost two decades, cat exposure has been linked to a number of different and often contradictory outcomes. Several birth cohorts reported increased risk of cat-specific sensitization in pre-school children with increasing early-life cat allergen exposure.¹⁻³ In contrast, a protective effect of high allergen exposure on cat sensitization, with a bell-shaped dose-response relationship, has been reported in cross-sectional studies in older children and adults.^{4,5} Similar inconsistencies have been reported on the association between cat ownership and cat-specific sensitization.^{1,6,7} We hypothesized that the effect of early-life cat exposure on sensitization differs: (1) over time, rendering the generalisation of effects from cross-sectional analyses at specific age points potentially misleading; (2) for different allergenic proteins from cat; and (3) between children with different risk of allergy.

To address our hypotheses, we investigated the effect of cat exposure in the first year of life on longitudinal trajectories of sensitization and asthma throughout childhood in a population-based birth cohort in which skin prick tests (SPT) and IgE to cat allergens Fel d 1, 2, and 4 (ImmunoCAP[®] ISAC) were available at six time points (ages 1, 3, 5, 8, 11 and 16 years). We defined SPT sensitization as a wheal diameter ≥ 3 mm; for component-resolved diagnostics (IgE/CRD), we considered a child being sensitized if IgE was >0.3 ISU to at least one component. We ascertained cat ownership in infancy using questionnaires, and quantitated Fel d 1 in dust samples collected in homes within the first year of life using enzyme-linked immunoassay ($\mu\text{g/g}$). We carried out longitudinal analyses using generalized estimation equations (GEE). We generated prototypical trajectories of sensitization from infancy to adolescence based on mean predicted values of the multivariate GEE model, with an interaction between cat ownership and time.

We analysed data for 1004/1051 children in the observational cohort who had confirmed exposure in infancy, and at least one valid sensitization measurement. Table E1 shows the demographic and clinical characteristics of study participants (Online Repository at www.jacionline.org). In cross-sectional analyses, cat ownership in infancy was associated with a significantly higher risk of cat sensitization in preschool age, but not thereafter (Figure E1). In the multivariable longitudinal model (Figure 1, Table E2), early-life cat ownership significantly increased the risk of sensitization to cat (OR [95% CI]: SPT, 2.50 [1.37-4.55], $P=0.003$; IgE/CRD, 3.13 [1.62-6.07], $P=0.001$). However, there was a significant interaction between early-life cat ownership and time, in that compared to cat owners, among children without a cat the annual increase in the rate of SPT sensitization from 1 one to 16 years was 6% higher (95% CI [1-11%], $P=0.02$), and for IgE/CRD sensitization 8% higher ([2-14%], $P=0.005$). Most children with a cat in home who developed cat sensitization during childhood, did so by age 1 year. After age 1, sensitization rate amongst cat owners either increased very slowly (SPT, Figure 1A), or remained unchanged (IgE/CRD, Figure 1B). In contrast, for children without a cat, the pre-school sensitization rate was low, but their trajectory over time was markedly different, with a significantly higher increase in sensitization with increasing age. By adolescence, there was no difference in the point prevalence of cat sensitization between cat owners and those not owning a cat (Figure 1).

Cat ownership significantly increased the risk of sensitization to Fel d 1 and Fel d 4, but not Fel d 2, with a significant interaction between cat ownership and time in relation to the development of IgE to Fel d 1 ($P=0.008$), marginal for Fel d 4 ($P=0.06$), but not for Fel d 2 ($P=0.39$) (Figure 1C).

We measured Fel d 1 in 939 homes. In cross-sectional analyses, an increase in Fel d 1 exposure in infancy significantly increased the likelihood of sensitization in pre-school age, but not thereafter (Table E3). In the multivariable GEE model, there was a significant association between early-life Fel d 1 exposure and the development of sensitization to cat (Table E4); the increase in risk per logarithmic unit increase in Fel d 1 concentration was 15% for SPT (95% CI [4-28%], $P=0.008$), and 22% for IgE/CRD ([10-36%], $P<0.001$). However, as with cat ownership, we observed a significant interaction between Fel d 1 exposure and time, in that the effect of early-life exposure significantly decreased with increasing age (SPT: OR [95% CI], 0.99 [0.98-1.00], $P=0.04$; IgE/CRD: 0.98 [0.98-0.99], $P<0.001$).

Sensitization rates were consistently higher among high-risk children of atopic parents, but the rate of change over time in relation to cat ownership or allergen exposure did not significantly differ between the high- and low-risk children (Figure 2, Tables E2-4). Finally, there was no effect of cat ownership on sensitization to allergens other than cat, and no significant effect on asthma (Figure E2). Fel d 1 exposure in infancy was not significantly associated with the development of asthma (0.98 [0.89-1.07], $P=0.61$). The absence of any association between cat exposure and asthma is consistent with a pooled analysis of 11 European birth-cohorts,⁶ and suggests that early-life exposure to cat exerts cat-allergen specific immune responses.

In our population, 18% of cat owners removed their cat between pregnancy and the first birthday of their child. When we adjusted our analyses for contemporaneous exposure, there was very little difference in the results. Limitations of our study are discussed in the Online Supplement.

Our findings highlight the changing nature of the association between early-life cat exposure and specific sensitization during childhood, and the key role of the time of the assessment of outcomes. These results can explain most inconsistencies in the previous literature. For example,

most reports from birth-cohort studies have assessed sensitization in pre-school age, and have identified cat ownership as a risk factor, along with a linear dose-response relationship between cat allergen exposure and specific sensitization.^{1-3,8} Cross-sectional and case-control studies in older children and adults have found either no association or a protective effect of cat exposure.^{4,5,9} This is entirely consistent with our sensitization trajectories. The sensitization rate at age 16 years in our study was numerically lower among children who had a cat in early life, but this difference was not statistically significant. We propose that if we extrapolate our data to adulthood, with projected sensitization rates of 25-30%, a significant protective effect of cat ownership would be seen. Thus, exposure to cat can confer either an increase in risk, or protection, or will have no effect, depending on the age of the assessment, study design and the choice of study population. Therefore, the fact that the findings of previous studies are apparently contradictory does not make them incorrect, but is a consequence of markedly different trajectories of cat sensitization through life-course between early-life cat owners compared to individuals without a cat.

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LEGEND FOR FIGURES

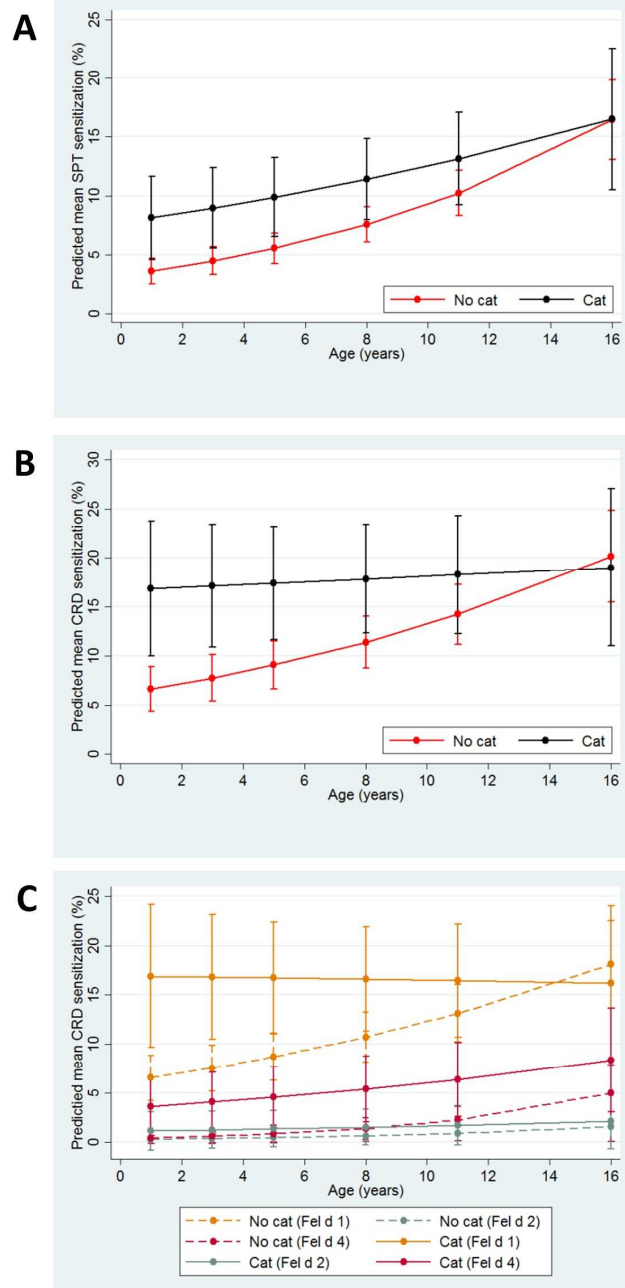
FIGURE 1. Longitudinal trajectories of cat sensitization among children who lived in a home with a cat in early life cat and those who did not. Predicted value of mean response is shown in graphical format along with 95% confidence intervals.

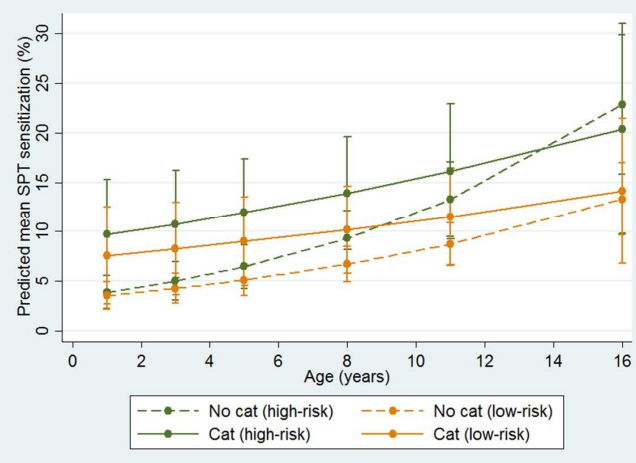
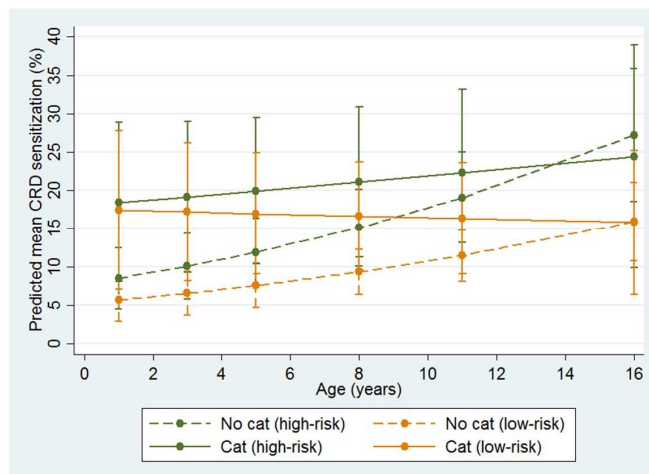
A, SPT sensitization; **B,** CRD sensitization to cat; **C,** CRD components.

FIGURE 2. Longitudinal trajectories of cat sensitization among high and low-risk children who lived in a home with a cat in early life cat and those who did not. Predicted value of mean response is shown in graphical format along with 95% confidence intervals.

High-risk group: Both biological parents with at least one positive skin prick test at recruitment

A, SPT sensitization; **B,** IgE/CRD sensitization



A**B**

ONLINE REPOSITORY

**Cat ownership, cat allergen exposure and trajectories of sensitization and
asthma throughout childhood**

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Table E1: Demographic and clinical characteristics of the study population

	Age 1 N (%)	Age 3 N (%)	Age 5 N (%)	Age 8 N (%)	Age 11 N (%)	Age 16 N (%)
Sex (Male)	482/878 (54.9)	489/908 (53.9)	508/932 (54.5)	483/879 (55.0)	429/791 (54.2)	346/648 (53.4)
Cat owner	196/878 (22.3)	197/908 (21.7)	209/932 (22.4)	207/879 (23.6)	209/791 (26.4)	175/648 (27.0)
High risk	266/853 (31.2)	289/890 (32.5)	285/907 (31.4)	266/854 (31.1)	240/776 (30.9)	202/631 (32.0)
Maternal asthma	111/877 (12.7)	118/907 (13.0)	125/931 (13.4)	111/878 (12.6)	99/790 (12.5)	80/648 (12.3)
Maternal smoking	118/878 (13.4)	166/907 (18.3)	176/929 (19.0)	148/878 (16.9)	116/790 (14.7)	80/646 (12.4)
Allergic sensitization	35/318 (11.0)	166/821 (20.2)	226/814 (27.8)	249/798 (31.2)	234/694 (33.7)	272/492 (55.3)
Asthma	N/A	121/766 (15.8)	191/787 (24.3)	148/743 (19.9)	153/675 (22.7)	108/521 (20.7)
Current wheeze	233/836 (27.9)	194/889 (21.8)	195/892 (21.9)	152/876 (17.4)	138/789 (17.5)	101/633 (16.0)
Cat SPT sensitized	7/318 (2.2)	43/816 (5.3)	76/812 (9.4)	83/798 (10.4)	70/694 (10.1)	95/545 (17.4)
CRD sensitized	10/144 (6.9)	18/175 (10.3)	62/494 (12.6)	56/466 (12.0)	69/397 (17.4)	69/310 (22.3)
Fel d 1 sensitized	9/144 (6.3)	17/175 (9.7)	60/494 (12.2)	52/466 (11.2)	62/397 (15.6)	62/310 (20.0)
Fel d 2 sensitized	0/144	1/175 (0.6)	5/494 (1.0)	1/466 (0.2)	9/397 (2.3)	6/310 (1.9)
Fel d 4 sensitized	3/144 (2.1)	4/175 (2.3)	10/494 (2.0)	7/466 (1.5)	17/397 (4.3)	18/310 (5.8)

Table E2: Association between cat ownership in early life and the development of sensitization to cat; longitudinal GEE model

Predictors of sensitization	Odds ratio	95% Confidence Interval	P value
SPT - whole population			
Gender (Male)	1.77	1.22-2.58	0.003
Maternal age at birth (years)	1.05	1.01-1.09	0.008
Cat ownership in early life	2.50	1.37-4.55	0.003
Time (Years)	1.12	1.09-1.15	<0.001
Interaction - Cat ownership and time	1.06	1.01-1.11	0.02
SPT – high-risk			
Gender (Male)	1.40	0.81-2.41	0.23
Maternal age at birth (years)	1.03	0.98-1.08	0.23
Cat ownership in early life	2.86	1.25-6.56	0.01
Time (Years)	1.14	1.10-1.19	<0.001
Interaction - Cat ownership and time	1.08	1.01-1.15	0.03
SPT – low-risk			
Gender (Male)	2.09	1.25-3.50	0.005
Maternal age at birth (years)	1.06	1.01-1.11	0.01
Cat ownership in early life	2.37	0.99-5.65	0.05
Time (Years)	1.10	1.07-1.14	<0.001
Interaction - Cat ownership and time	1.05	0.98-1.13	0.16
CRD - whole population			
Gender (Male)	1.37	0.88-2.13	0.16
Maternal age at birth (years)	1.06	1.01-1.10	0.009
Cat ownership in early life	3.13	1.62-6.07	0.001
Time (Years)	1.09	1.06-1.12	<0.001
Interaction - Cat ownership and time	1.08	1.02-1.14	0.005
CRD – high-risk			
Gender (Male)	0.79	0.41-1.52	0.48

Maternal age at birth (years)	1.05	0.99-1.12	0.10
Cat ownership in early life	2.63	1.06-6.52	0.04
Time (Years)	1.10	1.06-1.14	<0.001
Interaction - Cat ownership and time	1.07	1.00-1.15	0.06
CRD – low-risk			
Gender (Male)	2.14	1.17-3.92	0.01
Maternal age at birth (years)	1.06	1.00-1.12	0.04
Cat ownership in early life	3.92	1.48-10.35	0.006
Time (Years)	1.08	1.04-1.13	<0.001
Interaction - Cat ownership and time	1.09	1.01-1.18	0.04
Fel d 1			
Gender (Male)	1.42	0.91-2.22	0.13
Maternal age at birth (years)	1.06	1.01-1.11	0.009
Cat ownership in early life	3.20	1.60-6.37	0.001
Time (Years)	1.08	1.05-1.11	<0.001
Interaction - Cat ownership and time	1.08	1.02-1.15	0.008
Fel d 2			
Gender (Male)	0.83	0.21-3.23	0.79
Maternal age at birth (years)	1.06	0.95-1.19	0.31
Cat ownership in early life	4.39	0.42-45.69	0.22
Time (Years)	1.12	1.00-1.25	0.04
Interaction - Cat ownership and time	1.08	0.91-1.27	0.39
Fel d 4			
Gender (Male)	0.92	0.39-2.18	0.84
Maternal age at birth (years)	0.98	0.89-1.08	0.70
Cat ownership in early life	9.54	1.76-51.78	0.009
Time (Years)	1.18	1.07-1.30	0.001
Interaction - Cat ownership and time	1.11	1.00-1.24	0.06

Table E3: Cross-sectional analysis: The association between early life Fel d 1 exposure and sensitization

	Odds ratio	95% confidence intervals	P value
SPT – whole population			
Age 1	1.71	1.20-2.45	0.003
Age 3	1.17	1.04-1.32	0.009
Age 5	1.04	0.94-1.15	0.50
Age 8	1.01	0.91-1.12	0.90
Age 11	0.98	0.88-1.10	0.79
Age 16	1.03	0.93-1.13	0.59
SPT – high-risk			
Age 1	1.71	1.20-2.45	0.003
Age 3	1.11	0.92-1.33	0.28
Age 5	1.01	0.86-1.18	0.90
Age 8	0.93	0.79-1.10	0.42
Age 11	0.89	0.72-1.10	0.29
Age 16	0.95	0.81-1.11	0.50
SPT – low-risk			
Age 1	-	-	-
Age 3	1.22	1.05-1.43	0.01
Age 5	1.06	0.93-1.21	0.41
Age 8	1.07	0.93-1.21	0.35
Age 11	1.03	0.90-1.19	0.63
Age 16	1.09	0.96-1.23	0.19
CRD – whole population			
Age 1	1.32	1.03-1.70	0.03
Age 3	1.07	0.87-1.32	0.53
Age 5	1.15	1.03-1.28	0.01
Age 8	0.99	0.88-1.12	0.93
Age 11	1.05	0.93-1.18	0.45
Age 16	1.00	0.89-1.12	0.98
CRD – high-risk			
Age 1	1.32	1.03-1.70	0.03
Age 3	1.08	0.88-1.34	0.46

Age 5	1.20	1.00-1.44	0.05
Age 8	0.89	0.71-1.10	0.28
Age 11	0.97	0.81-1.17	0.74
Age 16	0.85	0.70-1.04	0.12
CRD – low-risk			
Age 1	-	-	-
Age 3	0.79	0.13-4.59	0.79
Age 5	1.13	0.98-1.31	0.08
Age 8	1.05	0.91-1.22	0.51
Age 11	1.12	0.95-1.31	0.17
Age 16	1.11	0.96-1.28	0.17
Fel d 1 – whole population			
Age 1	1.29	0.99-1.67	0.06
Age 3	1.08	0.87-1.34	0.48
Age 5	1.12	1.00-1.25	0.05
Age 8	0.98	0.87-1.12	0.81
Age 11	1.05	0.93-1.18	0.44
Age 16	0.99	0.88-1.12	0.87
Fel d 1 – high-risk			
Age 1	1.29	0.99-1.67	0.06
Age 3	1.10	0.88-1.36	0.41
Age 5	1.16	0.96-1.39	0.12
Age 8	0.92	0.74-1.15	0.47
Age 11	0.96	0.79-1.16	0.67
Age 16	0.85	0.70-1.05	0.13
Fel d 1 – low-risk			
Age 1	-	-	-
Age 3	0.79	0.13-4.59	0.79
Age 5	1.11	0.96-1.28	0.17
Age 8	1.02	0.87-1.19	0.85
Age 11	1.13	0.96-1.33	0.13
Age 16	1.10	0.95-1.29	0.21

Table E4: The association between early life Fel d 1 exposure and the longitudinal trajectory of sensitization to cat (longitudinal GEE model)

Predictors of sensitization	Odds ratio	95% Confidence Interval	P value
SPT - whole population			
Gender (Male)	1.73	1.17-2.56	0.006
Maternal age at birth	1.05	1.01-1.09	0.01
Fel d 1 exposure	1.15	1.04-1.28	0.008
Time (Age)	1.11	1.08-1.13	<0.001
Interaction - Fel d 1 exposure and time	0.99	0.98-1.00	0.04
SPT – high-risk			
Gender (Male)	1.46	0.82-2.58	0.20
Maternal age at birth	1.04	0.99-1.10	0.14
Fel d 1 exposure	1.19	1.02-1.38	0.03
Time (Age)	1.13	1.10-1.17	<0.001
Interaction - Fel d 1 exposure and time	0.98	0.97-1.00	0.02
SPT – low-risk			
Gender (Male)	1.97	1.15-3.37	0.01
Maternal age at birth	1.06	1.00-1.11	0.04
Fel d 1 exposure	1.14	0.99-1.31	0.08
Time (Age)	1.09	1.05-1.12	<0.001
Interaction - Fel d 1 exposure and time	1.00	0.99-1.00	0.39
CRD - whole population			
Gender (Male)	1.28	0.81-2.02	0.30
Maternal age at birth	1.06	1.02-1.11	0.006
Fel d 1 exposure	1.22	1.10-1.36	<0.001
Time (Age)	1.08	1.05-1.11	<0.001
Interaction - Fel d 1 exposure and time	0.98	0.98-0.99	<0.001
CRD – high-risk			
Gender (Male)	0.79	0.40-1.57	0.50

Maternal age at birth	1.07	1.00-1.14	0.06
Fel d 1 exposure	1.22	1.04-1.43	0.02
Time (Age)	1.09	1.05-1.13	<0.001
Interaction - Fel d 1 exposure and time	0.98	0.97-0.99	0.003
CRD – low-risk			
Gender (Male)	1.93	1.04-3.61	0.04
Maternal age at birth	1.06	1.00-1.13	0.04
Fel d 1 exposure	1.22	1.06-1.41	0.007
Time (Age)	1.06	1.02-1.10	0.003
Interaction - Fel d 1 exposure and time	0.99	0.98-1.00	0.05
Fel d 1 IgE – whole population			
Gender (Male)	1.33	0.83-2.12	0.23
Maternal age at birth	1.07	1.02-1.12	0.005
Fel d 1 exposure	1.21	1.09-1.35	<0.001
Time (Age)	1.07	1.04-1.10	<0.001
Interaction - Fel d 1 exposure and time	0.98	0.98-0.99	0.001
Fel d 1 IgE – high-risk			
Gender (Male)	0.77	0.39-1.53	0.46
Maternal age at birth	1.08	1.00-1.15	0.04
Fel d 1 exposure	1.24	1.05-1.46	0.01
Time (Age)	1.09	1.04-1.13	<0.001
Interaction - Fel d 1 exposure and time	0.98	0.97-0.99	0.005
Fel d 1 IgE – low-risk			
Gender (Male)	2.19	1.14-4.20	0.02
Maternal age at birth	1.06	1.00-1.13	0.05
Fel d 1 exposure	1.19	1.03-1.38	0.02
Time (Age)	1.04	1.01-1.08	0.02
Interaction - Fel d 1 exposure and time	0.99	0.98-1.00	0.10

DISCUSSION

Limitations

There were some differences between children included and excluded from our analysis (e.g. at age 11 years, children who were excluded were more likely to be sensitized). However, none of these differences were consistent across different ages and outcomes. Although this is unlikely to have influenced the results, we cannot unequivocally exclude this possibility.

We reviewed only a subgroup of children at age 1 year for practical reasons. We focussed our follow-up on infants with both atopic parents, and those whose two parents were non-atopic. The data was not missing at random, and we cannot exclude the possibility that this may have introduced bias in our analyses. However, exclusion of age one data from the longitudinal analysis did not make any material difference to sensitization trajectories (data not shown, available on request). We believe that presenting the age one data is important, as these results suggest that among high-risk children who live in a home with a cat, most of those who develop sensitization to cat do so by age one year.

The nature of the data collection makes it difficult to differentiate between the effect of exposure to allergen to that of the exposure to animal. The finding that significant effects of cat ownership and cat allergen exposure were almost identical and confined to cat allergen-specific sensitization (but not sensitization to other allergens or asthma), suggests that the observed effects are related to allergen exposure, rather than other factors potentially related to cat ownership (e.g. exposure to endotoxin). The absence of any association between cat ownership and asthma suggests that early-life exposure to cat exerts cat allergen specific immune responses.

When assessing allergen exposure, the relative importance of the choice of sampling site is unknown, and there has been little uniformity between studies. There is a possibility that living

room floor Fel d 1 concentration may not be the best index of allergen exposure. However, as correlation between allergen levels measured in different reservoirs is high, it is unlikely that the use of other indices of exposure would materially alter our findings.

We could not differentiate between the effect of exposure during pregnancy, from that in early life. However, most families who keep cats in home during pregnancy remain cat owners after the birth of their child. In our population, 18% of cat owners removed their cat between pregnancy and the first birthday of their child. When we adjusted our analyses for contemporaneous exposure, there was very little difference in the results (data not shown, available on request).

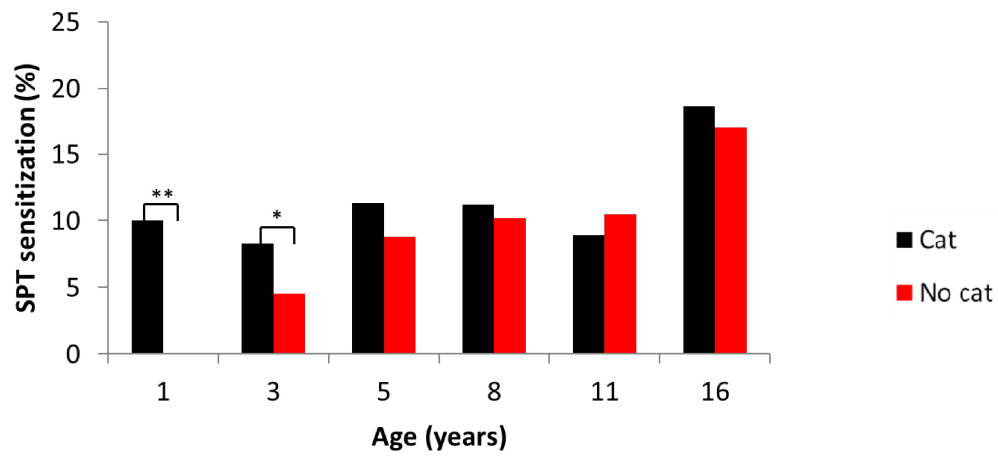
LEGEND FOR SUPPLEMENTARY FIGURES

Figure E 1: Cross-sectional association between cat ownership status during pregnancy and cat-specific sensitization (SPT, sIgE, CRD) during childhood.

A, SPT sensitization. B, sIgE/CRD sensitization

* $P < 0.05$, ** $P < 0.001$

FIGURE E2. Prototypical longitudinal trajectory of asthma development among children who owned a cat and those who did not own a cat in early life. Predicted value of mean response is shown in graphical format along with 95% confidence intervals

A**B**