Clinical & Experimental Allergy
CEA-2017-0189 (Revised II manuscript; Clean manuscript)
Original Article/14112017

Coincidence of pollen season with the first fetal trimester together with early pet exposure is associated with sensitisation to cat and dog allergens in early childhood: a Finnish population-based study

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Word count: main text 3840 words, abstract 272 words

Short title: Season of the 11th fetal week and sensitisation to pets

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Abstract (Words 272)

Background: Children whose 11th fetal week falls in pollen season (spring) reportedly have an increased risk of sensitisation to food allergens. No such finding has been reported for pet allergens.

Objective: The aim of the study was to 1) evaluate the incidence of pet (dog and cat) sensitisation according to the season of the 11th fetal week and 2) whether the association between pet exposure and respective sensitisation is modified by the coincidence of the 11th fetal week with pollen season.

Methods: The study population comprised all children (born between 2001 and 2006) in the province of South Karelia, Finland (N=5920). Their data of IgE and skin prick tests to pet allergens (N=538) were collected from patient records and linked with questionnaire data on pet exposure.

Results: The seasonal incidence peak of cat sensitisation was observed in children whose 11th fetal week occurred in June (7.4%) and that of dog sensitisation in April (3.8%) and June (4.7%). The relative rate (RR) for cat sensitisation was 2.92 (95% CI 1.40-6.08) in children with cat exposure alone, 8.53 (4.07−17.86) in children with cat and fetal pollen exposures, and 0.61 (0.20−1.83) in children exposed to pollen alone, compared with children without these exposures. The respective RRs for dog sensitisation were 2.17 (1.13-4.19), 4.40 (2.19−8.83) and 1.65 (0.77−3.53).

Conclusions and clinical relevance: Coincidence of the first fetal trimester with pollen season strengthens the association between pet exposure and respective sensitisation. Pollen exposure at early pregnancy may deviate immune system towards Th2 type reactivity promoting development of specific allergy in case allergen exposure occurred. Therefore, primary prevention of allergic diseases may need to begin during early pregnancy.

Keywords: *cat, dog, epidemiology, season, sensitisation*

Abbreviations used

PIC:	personal identity code
RERI:	relative excess risk due to interaction
RR:	relative rate
SKARP:	South Karelian Allergy Research Project
sIgE:	specific Immunoglobulin E antibodies
SPT:	skin prick test

Introduction

Food and pet allergies are often considered as early atopic manifestations and risk factors for asthma. Allergic sensitisation reflects a nontolerogenic Th2 type immune reactivity against harmless environmental stimuli. It is essential to recognize the early determinants leading to this inappropriate deviation of the immune system, in order to prevent atopic sensitisation and clinical manifestations [1]. The crucial period for the development of sensitisation has remained a controversial issue [2-5]. The synthesis of immunoglobulin E-antibodies (IgE) may begin as early as during the 11th fetal week in the lung and liver [2,3,6], while allergen-specific responses have been detected from the 23rd fetal week onwards, especially in fetuses whose mothers were exposed to respective allergens during 20 to 28 gestational weeks [3,7,8].

The timing of the 11th fetal week at the spring season has been previously shown to be associated with sensitisation to milk and egg allergens during the first four years of life [9]. Some studies have linked pollen exposure during late pregnancy or at early postnatal period to atopic sensitisation and hospitalization for asthma [10-14]. Children born in late autumn may have an elevated risk for sensitisation to non-seasonal allergens like animal epithelium [15], especially dog dander [16,17], or some food items [9,17-19] compared with children born in spring or summer. However, no consensus exists on how seasonal exposures at different phases of pregnancy affect later sensitisation among the offspring [20-22].

The South Karelian Allergy Research Project (SKARP) is a population-based epidemiological study of allergic manifestations and hypersensitivities [9,23-25] among children living in South-East Finland and born during the period 2001-2006. Information on all allergy tests performed among the study population for diagnostic purposes were collected from the pertinent patient records and linked with an independent questionnaire survey conducted on the same population. We have previously shown that in this population, the coincidence of vernal pollen season with the first trimester of pregnancy is associated with sensitisation to food

allergens [9], possibly due to maternal pollen exposure. As this might indicate early overall deviation of the immune system towards Th2 type reactivity and IgE sensitisation, similar associations might exist for other non-seasonal allergens as well. This paper therefore set out to examine whether the coincidence of the pollen season with early pregnancy is also associated with sensitisation of the offspring to dog and cat allergens. We also looked whether this coincidence modifies the previously reported association between pet exposure and respective sensitisation [26-30].

Methods

Data collection

A postal survey was conducted among all 5973 children born between April 2001 and March 2006 who were residents of the province of South Karelia in south-east Finland at the time of the survey. The children were identified and their demographic details obtained from the Finnish Population Register Centre.

The survey was conducted in close co-operation with local child health clinics between March 2005 and September 2006 [24]. All children in Finland are scheduled to visit the child health clinics regularly during their early childhood. In the clinics, allergy symptoms are identified by public health nurses, appropriate allergy tests are ordered by a physician, and paediatricians are consulted if necessary. The questionnaire (English translation available at www.oulu.fi/terveystieteet/node/29090) included questions on the duration of pregnancy, exposure to pets (dog or cat) at home during the first year of the child's life (categorised as: none/dog only/cat only/both pets) [26] and parental animal allergy (Fig 1). The questionnaire was returned by parents of 3952 children.

Information of all the allergy tests performed on the target population (children born between April 2001 and March 2006) were collected from all the healthcare units in the area concurrently with but independently of the questionnaire survey, with the intention of covering the entire population, including non-respondents. All tests had been performed for diagnostic purposes between April 2001 and September 2006. The age range of the study population at the end of September 2006 was 0.5 to 5.5 years. The child's personal identity code (PIC; http://vrk.fi/en/personal-identity-code1) was used for the data linkage. Since parents of 53 children refused the use of PIC, their data were excluded. The final analyses included data on 5920 children [9].

Ethics and permissions

The protocol was reviewed by the Ethical Committee of the Northern Ostrobothnia Hospital District (95/2003). The test data were collected with the permission of the Finnish Ministry of Social Affairs and Health. All eleven health care centres in the region consented to co-operate. In the questionnaires, the parents were asked permission to use their child's PIC for the data linkage.

Outcomes

Sensitisation to pet allergens was indicated by skin prick tests (SPT) and/or specific immunoglobulin E antibodies (sIgE) for pet allergens. The occurrence of either the first allergy test or the first positive result from any of these tests for pet (dog and/or cat) allergens were considered separately as longitudinal outcomes. The cut-off point for a positive sIgE was 0.35kU/l with RAST-CAP FEIA and Phadiatop Combi. In one child, sIgE for dog was measured by Magic Lite with the cut-off point 1.43 standardised units per ml (the result was negative). The cut-off point for SPTs was defined as the mean of two orthogonal diameters of the urticarial weal of 3 mm. Both positive (histamine) and negative controls had been used and those with negative control equal or above 3mm were considered as negative. Test values equal or above the cutoff point were considered as positive.

Explanatory variables

A detailed description of all explanatory variables is given elsewhere [9,23-26]. Shortly, the month of birth was obtained from the PIC. The PIC of the child and his/her siblings were compared, whereby the birth order of the child was defined as 'firstborn' or 'not firstborn'.

Parents were advised to check the duration of pregnancy from the maternity card and mark it to the questionnaire. In more than 90% of pregnancies in the area, gestational age was ascertained

with ultrasound scan during the 11th to 22nd fetal weeks [9]. The calendar month of the 11th fetal week was calculated by using the date of birth and the estimated duration of pregnancy. Year of birth and the year of the 11th fetal week were used as markers for potential pollen exposure based on local measurements of annual pollen concentrations during 2001 to 2005 (Fig S1) [9]. After the 2001 pollen season, the sampler was moved from a higher (136 metres above sea level) to a lower roof (119 metres above sea level), which explain partly the slightly different patterns of pollen concentrations in 2001 and 2002-5. However, the same criteria to define pollen season were used in all years.

In the area concerned the concentration of leaf tree (alder and birch) pollen is normally highest in April-May and that of grass and mugwort pollen in July-August. Pollen counts (daily mean counts of pollen grains per cubic meter of air) were measured throughout the pollen seasons on the roof levels in the town of Joutseno in the middle of the study area. Annual pollen seasons were based on these measurements (the R script as a Supplementary file).

Statistical methods

The outcome event was either the first test performed or the first positive test result indicating IgE medicated sensitisation for pet allergens, as appropriate. The risk time began on the date of birth and ended at the time of the test event (i.e. the child's age on the date of that event), given that such an event occurred. Among children without the outcome event in question, the risk time ended on the closing date of data collection (30 September, 2006).

The cumulative incidences of each outcome by age were computed by Kaplan-Meier-method [31] (`survival` package of the R). The computations were performed by the calendar month at the end of the 11th fetal week and at birth. Kaplan-Meier-method was also used to describe the incidences of the first positive test result separately among children exposed and not-

exposed to pets and those with and without parental animal allergy, stratifying according to whether the child's 11th fetal week, birth or neither of these fell on a pollen season.

To catch any seasonal patterns in sensitisation, Cox analysis (`coxph` function of `survival` package) was used to regress the outcome events on harmonic terms of the month of the 11th fetal week and the month of birth [32]. The significance of successive terms of length 12 months, 6 months, 4 months and 3 months was tested by likelihood ratio test (Table S1). The results from Cox analyses were expressed as relative rates (RR) adjusted for gender, birth order and the year of the 11th fetal week or the year of birth, and separate analyses were conducted using the respective pet exposure and animal allergy among biologic parents as explanatory factors. Potential interactions between pet exposure and pollen exposure period were examined by entering respective interaction terms to the models (Table S2) and also reporting the relative excess risk due to interaction in additive (RERI) and the RR-ratio in multiplicative scales [33]. The 95% confidence intervals (CI) for the RERIs were calculated as (1) the 2.5th and 97.5th percentiles of bootstrapped distributions based on 1000 replications (`boot.ci` function of the `boot` package of the R) [34] and (2) the delta method (`epi.interaction` function of `epiR` package, modified as applicable to `coxph` function).

Information on the date of birth was available for the entire population, but the duration of pregnancy was reported by the parents of 3595 children (92% of the survey participants and 61% of the whole population). Among 90% of children the duration of pregnancy was 38 weeks to 43 weeks, with mean duration of 278.2 days. In the Kaplan-Meier-analyses, the missing data on the duration of pregnancy (2325 children) were replaced by conditional means of values provided [9]. In Cox regressions using harmonic terms, the missing values on the duration of pregnancy were compensated by multiple imputation [35], as previously described [9]. Monthly incidence ratios based on complete cases and those complemented by mean and imputed values showed no marked differences (Table S3).

Circular data were described to exclude potential bias due to the season of the testing time. The circular correlations [36,37] between the calendar time of the first test and that of the 11th fetal week or the date of birth were computed by using `circular` package available in the R software (Fig S2).

The release 3.3.0 of the R environment was used in all data analyses (http://www.r-project.org/).

Results

Out of all 5920 children, 538 had been tested for cat or dog allergens (most of the tested and survey participants had also reported a symptom of an atopic manifestation [26]), 258 being based on sIgE and 346 on SPT (Fig 1). The medians of positive IgE values for pet, dog and cat were 3.90, 2.11 and 5.50 kU/l (Table S4), respectively. The medians for urticarial weal sizes of positive SPTs were 4.5, 4.0 and 5.0 mm, respectively. Among the entire study population, the calendar time of the 11th fetal week, birthday, conducting the first test for pet allergens as well as their positive test results showed little seasonal variation (Fig S2). Among the tested children, the circular correlations indicated no association between the testing season and the season of birth (r=0.07) or that of the 11th fetal week (r=0.08).

By the age of 4 years, the cumulative incidence of children tested for the pet allergy varied from 9% (March) to 16% (December) according to the month of birth, and from 10% (September) to 16% (June) according to the month of the 11th fetal week (Table 1). The seasonal variation in the RRs of pet allergy testing was negligible compared to that of the positive tests (Fig 2).

Coincidence of pollen season with early pregnancy and sensitisation to dog and cat

The seasonal pattern of positive dog allergy tests was bimodal, the RRs being highest among children whose 11th fetal week fell in April or July and lowest among children who had it in late autumn (Fig 2). The respective pattern for cat allergens was unimodal with the peak in early summer and the trough in mid-winter. The bimodality seen in dog allergens was repeated in the RRs for both pets combined. The respective analyses conducted by the month of birth gave similar patterns shifted forwards by approximately 7 months, the peaks locating November and January-February and the troughs in June-July. In the analyses based on complete data, the seasonal patterns remained practically unchanged, although statistical precision of the model parameters was weaker, as reflected by their wider confidence intervals (Fig S3).

The incidences of sensitisation to dog and cat allergens, both separately and combined, were consistently higher among children whose 11th fetal week occurred in a pollen season compared with those who had it in a non-pollen season (Fig 3). The finding is repeated in Table 2 in form of Cox regressions which show consistently high RRs for children who had their 11th fetal week in the pollen season.

Interactions and subgroup analyses

Table 3 summarises the Cox regressions of sensitisation on pollen season and pet exposure, together with interactions and cumulative incidences. The RR for cat sensitisation was 2.92 (95%CI 1.40-6.08) in children with cat exposure alone, 8.53 (4.07−17.86) in children who had both early exposure to cat and experienced their 11th fetal week in the pollen season, and 0.61 (0.20−1.83) in children whose 11th fetal week fell in pollen season but were not exposed to cat, compared to children with neither of these early exposures. The respective RRs for dog sensitisation were 2.17 (1.13-4.19), 4.40 (2.19−8.83) and 1.65 (0.77−3.53).

Table 3 also shows that added effect of interaction between pollen season and cat exposure is statistically significant (RERI 6.01; 1.47-15.2 in additive and ratio of RRs 4.82; 1.42-31.9 in multiplicative scale), but remains insignificant between pollen season and dog. Tables S**5**-S**7** show the interaction analysis in the format recommended by Knol et al [33].

All interactions were accentuated when further adjustments were done for parents' animal allergy (Table 3). The incidences of sensitisation to pet allergens were consistently higher in the offspring of parents with than without animal allergy and higher in children exposed than in those unexposed to pet allergens, depending on the season at which they had ended their first fetal trimester (Fig S4 and S5).

Discussion

The present study is the first to observe that the occurrence of the 11th fetal week in the pollen season is a risk factor for subsequent IgE-mediated sensitisation to dog and cat allergens in early childhood. We also provide evidence that the occurrence of the 11th fetal week in the pollen season strengthens the association between early cat exposure and sensitisation to cat allergens, while the respective effect modification was weaker regarding dog exposure and subsequent sensitisation to dog allergens. While dog or cat exposure is a prerequisite to the subsequent sensitisation to respective pets, the occurrence of the 11th fetal week on the pollen season as such is not associated with pet sensitisation.

Our results suggest that pollen exposure or exposure to high concentration of any allergen at early pregnancy might deviate the immune system towards Th2 type reactivity. This would promote the development of sensitisation to a specific allergen in case exposure to the respective allergen occurs. Based on growing evidence in the literature, the potential underlying mechanism would most probably be epigenetic modification of immunoregulatory genes. Epigenetic modification (e.g. DNA metylation) regulates T cell differentiation and the balance between various T helper cell subsets [38,39]. It has been proposed that maternal exposure to environmental pollutants and allergens in a period of early immune development may result in epigenetic programming towards Th2 type reactivity and allergic phenotype [38,39]. The synthesis of raw immunoglobulin E-antibodies (IgE) has been reported as early as in the 11th fetal week [2,3,6] and allergen-specific IgEs in the 23rd fetal week [3,7,8]. We propose here that the occurrence of pollen season in the 11th fetal week (a marker of early pollen exposure) potentially deviates immune response towards Th2 type reactivity, although allergen exposure (here pets) is a prerequisite for a subsequent sensitisation to the respective allergen.

It is also possible that maternal specific IgEs against pollen and pet allergens are directly transported through the placenta [40,41] or the fetus begins independent synthesis of IgEs due to the genetic inheritage from both parents. We focused on sensitisation to cat and dog allergens as the only outcomes, since sensitisation to the group of different pollen allergens as outcomes require a longer follow-up and therefore it should be elaborated in a separate paper. Information on more detailed biological mechanisms of immune development cannot be obtained without tissue or serum samples of fetus and his/her parents. We also presented the incidences of positive tests according to parental animal allergy, stratified by the time of potential pollen exposure (Fig S5). The effect of parental animal allergy seemed to be consistent with but a slightly stronger than that of parental atopy, maternal or parental pollen allergy or separately maternal animal allergy (data not shown).

Our findings are consistent with the current understanding about the prenatal immunologic development of IgE-mediated sensitisation [2,5] and with the previous reports on the seasonal variation of sensitisation to food allergens [9,19,42]. Our findings are also in line with previous studies from Finland and Germany according to which the lowest risk for animal allergies and the lowest occurrence of positive SPTs for cat allergens, respectively, were found in children born in July [15,20]. They are also in accordance with a Dutch study [16], which comprised serum samples of nearly 45 000 patients and reported the lowest frequency of positive IgE test results for cat and dog allergens among children born in June. A bimodal seasonal pattern for sensitisation to animal epithelia quite similar to what we found here, was previously reported from Finland [15], with the peaks in children born in March-May and September-November.

We cannot rule out the possibility that other seasonal factors such as viral infections could explain the seasonal variation in the occurrence of pet allergies. It is possible that pollen exposure at the age of six months (the same calendar month as that of the 11^{th} fetal week) would contribute to the occurrence of pet allergy, too. However, a recent meta-analysis found

that children born in a winter season had higher concentrations of IgEs in the cord blood than others [43]. If this were specifically true for pet allergens among the children born in late autumn - winter season (as found here), then the exposure factors like pollen should have rather occurred in the prenatal than postnatal period.

The main strength of this work is the longitudinal real-life study design which covers the entire child population in a geographically defined area. Due to its four seasons, Finland provides an ideal setting for a natural experiment to assess the association of seasonal exposures with subsequent morbidity.

A further strength of our study is the unique database of allergy test results which covered the entire study population [9,24,25,44] and could be individually linked with a large questionnaire survey conducted on the same population. Our data included the exact dates of both allergy testing and their results, which enabled us to display the incidences of these outcomes using advanced methods of survival analysis. The precision of the analyses was improved by imputation of missing data [9,35]. The findings among the complete cases were well in line with the results obtained in the entire population. Differences in clinical expertise of physicians in the area may have introduced variations in their testing practices and thereby some heterogeneity into the data [26]. In our study setting, most children who had been tested were tested by either IgE or SPT only, rarely by both methods, depending on which methods were available in the health care unit they visited. However, any variations of testing practices or selecting children for testing are unlikely to be selective with respect to the seasons at which different phases of pregnancy fall.

The main weakness of our study may be considered to be the pollen exposure data, which was based on measurements of one sampler in the area, not on individual measurements. In a large population like this, regional measurements have been considered adequate [9,11,14,18].

Individual measurements of exposures to pollen allergens were unfeasible, also because not all parents would have been motivated to follow the study protocol with regular measurements. The pollen seasons occur simultaneously throughout the study area, because mixed forests grow relatively homogenously. The individual pollen exposure has been considered to agree well with regional pollen concentrations measured by one sampler in the middle of the area [9,45-47]. The clinical importance of the spring season is based on the high concentrations of leaf tree pollen and their wider spreading in the environment, which makes them more difficult to avoid than pollen from other plants. However, pollen grains of lower growing plants like grass and mugwort are carried by furry pets in their furs [45], which increases their indoor concentration and exposure to these allergens.

Another shortcoming of the present study is our pet exposure data, which were based on questionnaires and pet keeping during the child's first year of life only. Although we asked only postnatal, not prenatal pet keeping in the questionnaire, parents rarely take a new pet to their home while having children younger than one year. Therefore, when the child's family reported having had a cat or dog indoors at home during the child's first year of life, the mother had most likely been exposed to the same pet during the pregnancy. Since we did not have information on the maternal allergies to specific pollen allergens, we could not evaluate their associations with maternal exposure to these same allergens and the occurrence of positive test result for these same allergens in the offspring.

Our results are also limited by the relatively short follow-up time. The future follow-up of the present study will obviously yield a higher number of cases and narrower confidence intervals for the outcomes. We did not have individual exposure data either on viral infections or sunlight (related to serum concentrations of vitamin D), both of which have seasonal variation and could potentially affect the prenatal immune regulation [48,49]. These factors might have introduced unknown bias but could not be controlled for in lack of relevant data.

In conclusion, the present study provides novel evidence that the coincidence of pollen season with the 11th fetal week is associated with an elevated incidence of positive test results for dog and cat allergens. Pollen exposure at the stage of early immune programming also strengthens the association between cat exposure and sensitisation to cat allergens, and a similar effect is possible for dog exposure and sensitisation, too. The likely explanation for these findings might be epigenetic modification(s) due to maternal exposure to high pollen concentrations. These modifications might deviate the fetal immune reactivity towards atopic phenotype and promote the development of sensitisation to pet allergens in case respective pet exposure occurs. Although our findings are population-based**,** their generalisability should be evaluated by replication studies conducted in other population-based cohorts.

Author contributions: KP designed the original study protocol and the questionnaires in cooperation with SN. KP organized the data collection, was responsible for the data management and performed the data analyses. All the authors contributed to the interpretation of the data and to the preparation of the manuscript by reviewing, commenting, critically revising the text were applicable, and approving the final submission.

Acknowledgements The authors thank all the nurses in the child health clinics of South Karelia for their co-operation, the staff of the various health care units for their assistance and co-operation in collecting the test data and Mr Markku Koiranen for his skilful technical assistance with the data management. The authors also thank the South Karelia Allergy and Environmental Institute and especially its head, Adjunct Professor Kimmo Saarinen, for providing the data on daily pollen concentrations in the area 2001-5.

Funding: The data collection was mainly funded by the Social Insurance Institution of Finland and partly by EVO grants from the hospital districts of South Karelia, Northern Ostrobothnia and Pirkanmaa, by Lappeenranta City Council and personal grants to the principal investigator from the Finnish Cultural Foundation, South Karelia Regional fund, the Viipuri Tuberculosis Foundation, the Väinö and Laina Kivi Foundation, the Tyyni Tani Foundation, Kymenlaakson Terveyden Turva ry, the Allergy Foundation, and the Medical Society of South Karelia. None of these organisations was involved in the design or execution of the study. The work of the principal investigator (KP) was funded in years 2012 to 2014 by University of Oulu and

Lappeenranta University of Technology and in 2016 to 2017 by the Finnish Cultural Foundation, South Karelia Regional fund and by the Finnish Cultural Foundation/Pekka and Jukka-Pekka Lylykari's Fund. The work of the second author (PK) was supported by the research grants from the Alma and K.A. Snellman Foundation, the Finnish Medical Association, the Allergy Research Foundation and the Finnish Pediatric Research Foundation. The University of Oulu has provided working facilities for the study. None of the funding organisations was involved in the design or execution of the study.

Conflicts of interest: none.

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Figure legends

Figure 1. Flow diagram showing the study population, complete cases, data sources and data linkages of the South Karelia Allergy Research Project (the SKARP).

Figure 2. Relative rates (RR) of testing for pet allergy and positive test results among the entire study population (N=5920) by the month of the 11th fetal week and the month of birth. The points indicate monthly RRs from the Cox regression adjusted for gender, birth order and year at the end of the first fetal trimester or birth, and the vertical bars show their 95% confidence intervals. Continuous lines are RRs smoothed by adjusted harmonic models (periodicities of 12 and 3 months for both pets; 12, 6 and 3 months for dog; 12 months for cat), shaded areas representing their 95% confidence bands. Pollen seasons (average weekly pollen concentrations >10 grains/m^3 in years 2001-5) are indicated by green (alder & birch) and yellow (grass & mugwort).

Figure 3. Kaplan-Meier curves showing the cumulative incidences of positive results in dog or cat allergy tests during the first four years of life, classified according to whether the 11th gestational week, the date of birth or neither of these, were located during the pollen season (Fig S1 and R-script as a supplement file). The positive allergy tests included specific immunoglobulin E antibodies (sIgE) and/or skin prick tests (SPT) for dog and/or cat allergens.

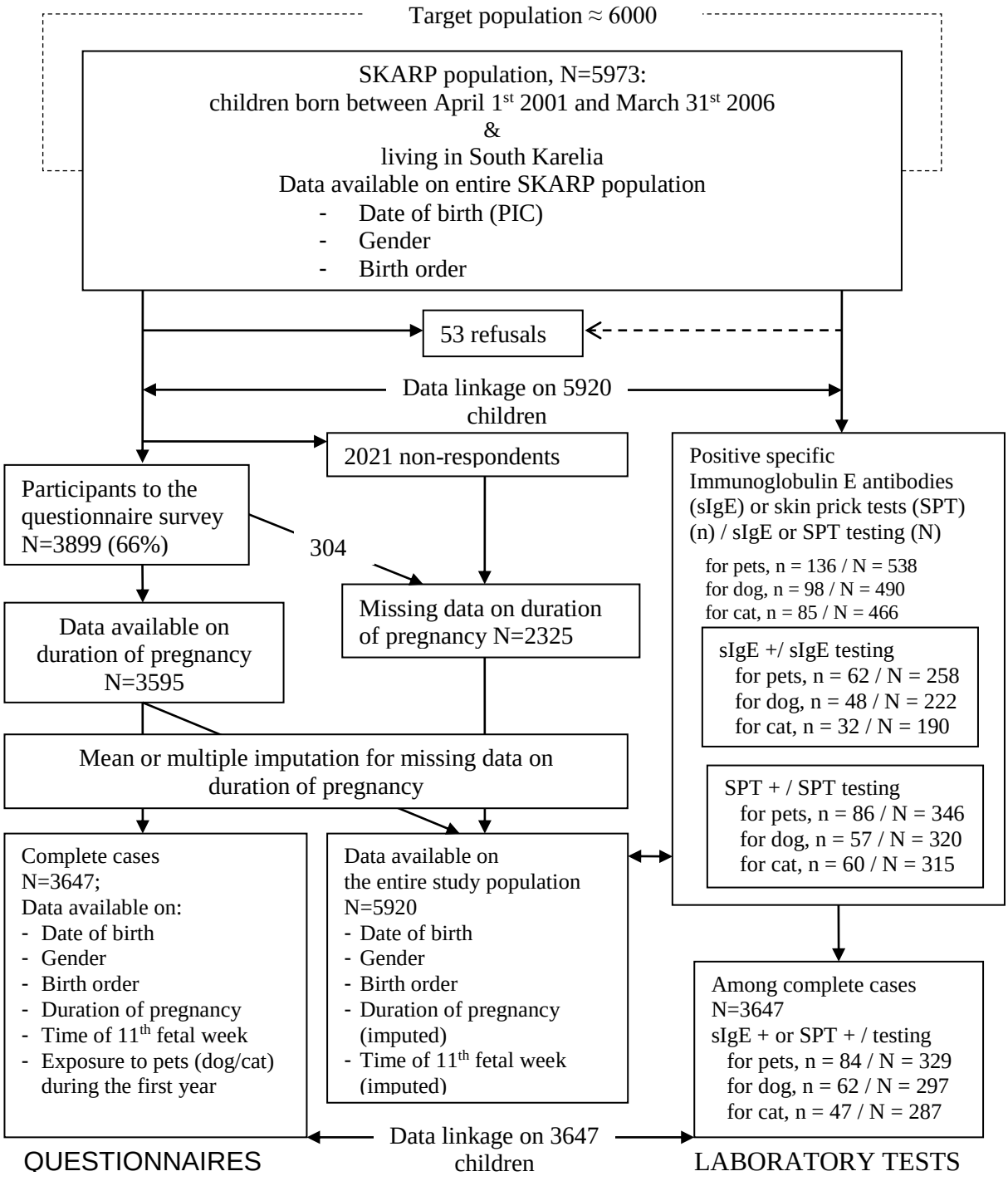
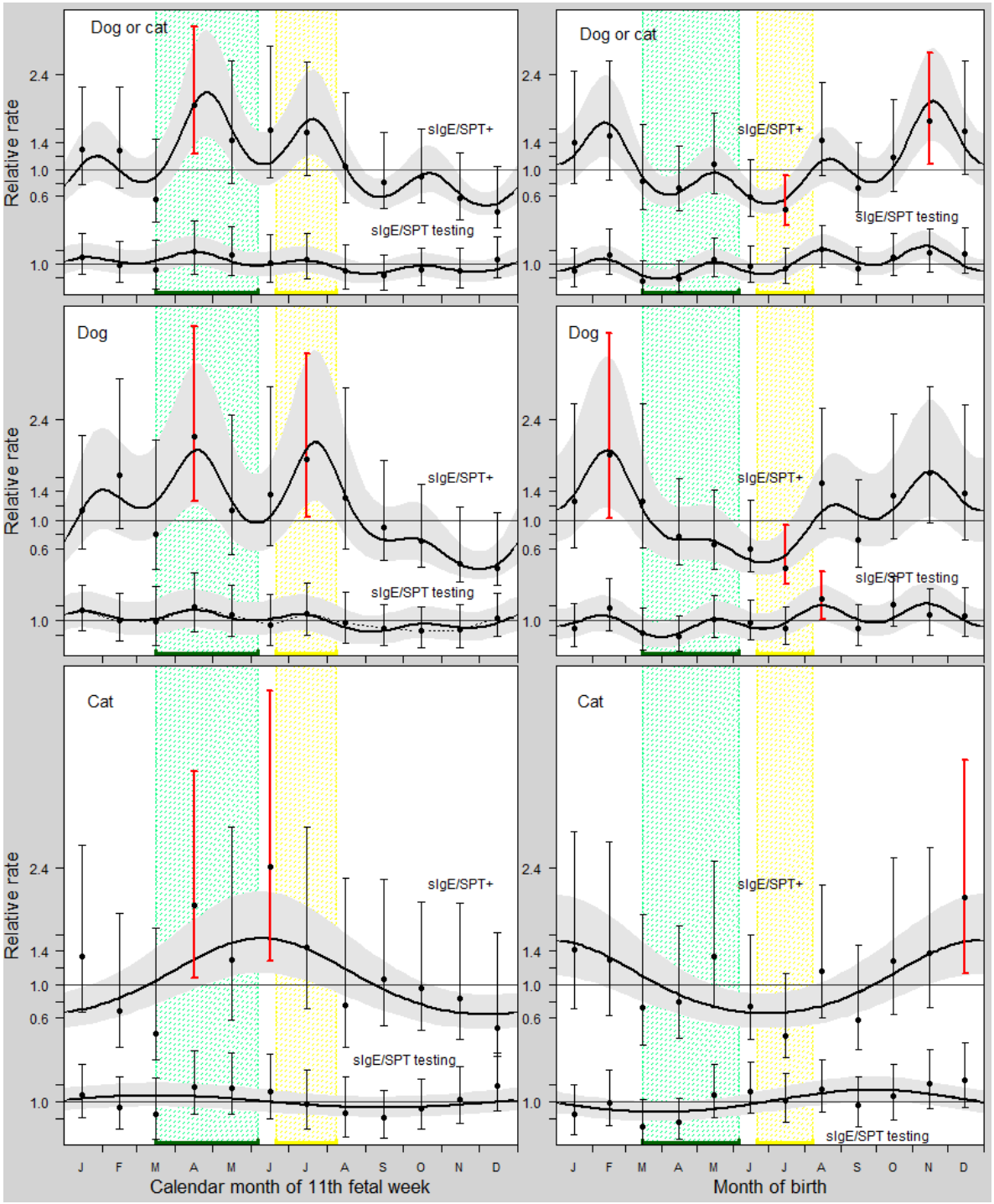


Figure 1. Flow diagram showing the study population, complete cases, data sources and data linkages of the South Karelia Allergy Research Project (the SKARP).



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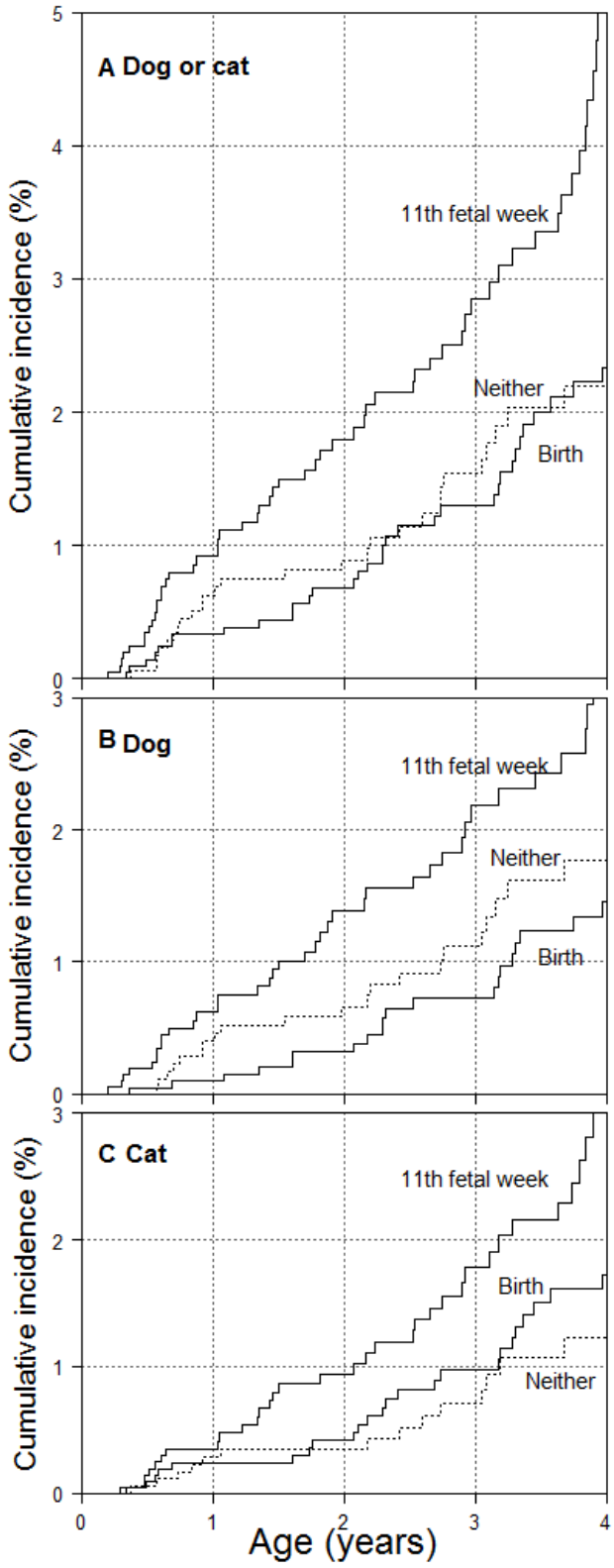

Figure 3. Kaplan-Meier curves showing the cumulative incidences of positive results in dog or cat allergy tests during the first four years of life, classified according to whether the 11th gestational week, the date of birth or neither of these, were located during the pollen season (Fig S1 and R-script as a supplement file). The positive allergy tests included specific immunoglobulin E antibodies (sIgE) and/or skin prick tests (SPT) for dog and/or cat allergens.

Table 1 Numbers of subjects tested for dog or cat sensitisation and those with a positive result in these tests and cumulative incidences (%) of testing and positive test results up to 4 years of age by month in which the 11th fetal week[1] occurred and the month of birth.

		Dog or cat		Dog		Cat	
Calendar month of	**N**	Testing % (n)	First positive result % (n)	Testing % (n)	First positive result % (n)	Testing % (n)	First positive result % (n)
11th fetal week[1]							
Jan	539	14 (58)	3.7 (16)	13 (54)	2.2 (10)	12 (50)	2.4 (10)
Feb	519	11 (48)	2.0 (14)	10 (44)	1.9 (12)	9 (39)	1.1 (5)
Mar	457	11 (35)	1.2 (5)	11 (34)	1.2 (5)	10 (29)	0.3 (3)
Apr	515	14 (53)	4.6 (19)	13 (49)	3.8 (16)	12 (45)	2.9 (10)
May	484	15 (45)	4.4 (13)	12 (38)	1.6 (6)	13 (39)	3.2 (8)
Jun	461	16 (40)	6.2 (14)	14 (33)	4.7 (8)	16 (38)	7.4 (13)
Jul	512	15 (45)	4.0 (13)	14 (42)	3.0 (11)	12 (35)	2.2 (7)
Aug	468	11 (33)	4.5 (10)	11 (32)	4.0 (9)	9 (27)	2.4 (5)
Sep	490	10 (37)	2.9 (9)	10 (36)	2.4 (7)	9 (31)	2.7 (7)
Oct	473	11 (45)	2.4 (12)	9 (39)	1.3 (7)	10 (39)	1.6 (8)
Nov	484	12 (43)	1.6 (6)	11 (39)	0.9 (3)	12 (41)	1.4 (5)
Dec	518	15 (56)	1.2 (5)	13 (50)	1.1 (4)	14 (53)	0.9 (4)
Overall	5920	13 (538)	3.1 (136)	12 (490)	2.2 (98)	11 (466)	2.1 (85)
Birth							
Jan	487	13 (37)	3.6 (12)	12 (33)	1.8 (7)	11 (31)	3.7 (8)
Feb	445	15 (42)	3.5 (12)	14 (39)	3.1 (10)	12 (33)	2.5 (7)
Mar	480	9 (29)	3.6 (7)	9 (29)	3.6 (7)	9 (24)	2.2 (4)
Apr	488	10 (40)	2.4 (9)	9 (37)	1.9 (7)	9 (34)	2.2 (6)
May	463	13 (50)	2.7 (13)	12 (44)	1.3 (6)	11 (44)	1.9 (10)
Jun	509	14 (50)	2.5 (8)	13 (46)	1.9 (6)	14 (49)	2.0 (6)
Jul	537	11 (48)	0.4 (5)	10 (42)	0.0 (3)	10 (44)	0.4 (3)
Aug	540	15 (61)	4.5 (18)	14 (59)	3.2 (14)	12 (49)	2.6 (9)
Sep	490	10 (42)	1.8 (8)	9 (37)	0.8 (6)	9 (37)	0.5 (4)
Oct	499	14 (46)	3.0 (12)	14 (46)	2.3 (10)	12 (38)	1.8 (8)
Nov	519	14 (50)	5.0 (18)	11 (42)	3.1 (13)	13 (44)	3.1 (9)
Dec	463	16 (43)	6.7 (14)	15 (36)	5.1 (9)	15 (39)	5.8 (11)
Overall	5920	13 (538)	3.1 (136)	12 (490)	2.2 (98)	11 (466)	2.1 (85)

[1] Missing data on the duration of pregnancy were replaced by the mean duration calculated from the answers given in the questionnaire survey, 278.2 days.

Table 2. Cumulative incidences (%, from Kaplan-Meier analyses) of subjects with a positive dog or cat allergy test up to the age of 4 years and relative rates (RR) from Cox regression models according to whether the end of the 11th fetal week occurred in pollen or non-pollen season. (N= group size, n= number of cases)

Positive test for dog/cat	Model I[1] Entire population N=5920		Model II[1] Participants N=3647		Model III[1] Participants N=3288	
Season of the 11th fetal week	% (n)	RR (CI 95%)[2]	% (n)	RR (CI 95%)[3]	% (n)	RR (CI 95%)[4]
Dog or cat						
Pollen	5.0 (60)	1.97 (1.40−2.79)	4.9 (35)	1.82 (1.16−2.84)	5.5 (35)	2.26 (1.41−3.61)
Non-pollen	2.4 (76)	1	2.3 (49)	1	2.0 (39)	1
Dog						
Pollen	3.4 (43)	2.09 (1.39−3.14)	3.2 (26)	1.86 (1.11−3.12)	3.6 (26)	2.36 (1.36−4.08)
Non-pollen	1.7 (55)	1	1.7 (36)	1	1.4 (28)	1
Cat						
Pollen	3.5 (37)	1.92 (1.24−2.98)	2.9 (18)	1.60 (0.87−2.94)	3.3 (18)	1.97 (1.04−3.72)
Non-pollen	1.6 (48)	1	1.5 (29)	1	1.2 (23)	1

[1] Number of subjects whose 11th fetal week occurred in pollen and non-pollen season were 2041 and 3879 in Model I, 1225 and 2422 in Model II, and 1107 and 2181 in Model III, respectively.
[2] Adjusted for sex, birth order and the year of the 11th fetal week.
[3] Additionally adjusted for exposure to respective pet.
[4] Additionally adjusted for animal allergy in biological parents.

Table 3. Regression of positive pet allergy test on the occurrence of the 11th fetal week in a pollen season and respective pet exposure and their interactions. Relative rates (RR) obtained from Cox regression models, with their interactions also expressed on additive scale as relative excess risk due to interaction (RERI) and on multiplicative scale (ratio of RRs). Cumulative incidences (%, from Kaplan-Meier analyses) of positive test results up to the age of 4 years are also shown by exposure category (N= group size, n= number of cases)

Positive test for dog/cat	Model II[1] Participants N=3647			Model III[2] Participants N=3288		
Pollen season/ pet exposure	N	% (n)	RR (CI 95%)	N	% (n)	RR (CI 95%)
Dog or cat						
No pollen season, no dog/cat	1312	1.6 (21)	1	1169	1.1 (16)	1
Pollen season	647	2.9 (9)	1.10 (0.50−2.41)	585	3.2 (9)	1.35 (0.59−3.07)
Dog or cat	1110	3.1 (28)	1.60 (0.91−2.82)	1012	2.9 (23)	1.94 (1.01−3.70)
Pollen season and dog or cat	578	7.1 (26)	3.71 (2.06−6.68)	522	8.0 (26)	5.54 (2.90−10.6)
Additive scale: RERI			2.01 (0.29−4.29)[3]			3.25 (0.69−7.83)[3]
			2.01 (0.22−3.80)[4]			3.25 (0.48−6.03)[4]
Multiplicative scale: ratio of RRs			2.11 (0.82−6.68)[3]			2.12 (0.82−7.09)[3]
Dog						
No pollen season, no dog	1639	1.1 (18)	1	1466	0.8 (14)	1
Pollen season	816	1.9 (11)	1.65 (0.77−3.53)	736	2.2 (11)	2.01 (0.90−4.47)
Dog	783	2.9 (18)	2.17 (1.13−4.18)	715	2.6 (14)	2.32 (1.10−4.90)
Pollen season and dog	409	5.6 (15)	4.40 (2.19−8.83)	371	6.2 (15)	5.98 (2.83−12.7)
Additive scale: RERI			1.57 (-1.00−4.84)[3]			2.66 (-0.72−8.07)[3]
			1.57 (-1.09−4.23)[4]			2.66 (-0.99−6.30)[4]
Multiplicative scale: ratio of RRs			1.23 (0.44−3.93)[3]			1.28 (0.44−3.94)[3]
Cat						
No pollen season, no cat	1879	1.1 (16)	1	1689	0.7 (12)	1
Pollen season	965	1.4 (4)	0.61 (0.20−1.83)	876	1.6 (4)	0.76 (0.24−2.36)
Cat	543	2.9 (13)	2.92 (1.40−6.08)	492	2.8 (11)	3.70 (1.62−8.48)
Pollen season and cat	260	8.7 (14)	8.53 (4.07−17.86)	231	7.9 (14)	12.8 (5.74−28.6)
Additive scale: RERI			6.01 (1.47−15.2)[3]			9.34 (2.46−27.0)[3]
			6.01 (0.46−11.6)[4]			9.34 (0.44−18.2)[4]
Multiplicative scale: ratio of RRs			4.82 (1.42−31.9)[3]			4.56 (1.25−31.1)[3]

[1] Adjusted for sex, birth order, the year of the 11th fetal week.
[2] Additionally adjusted for animal allergy in biological parents.
[3] Confidence intervals calculated by the bootstrap method with 1000 replications
[4] Confidence intervals calculated by delta-method

Supplementary material

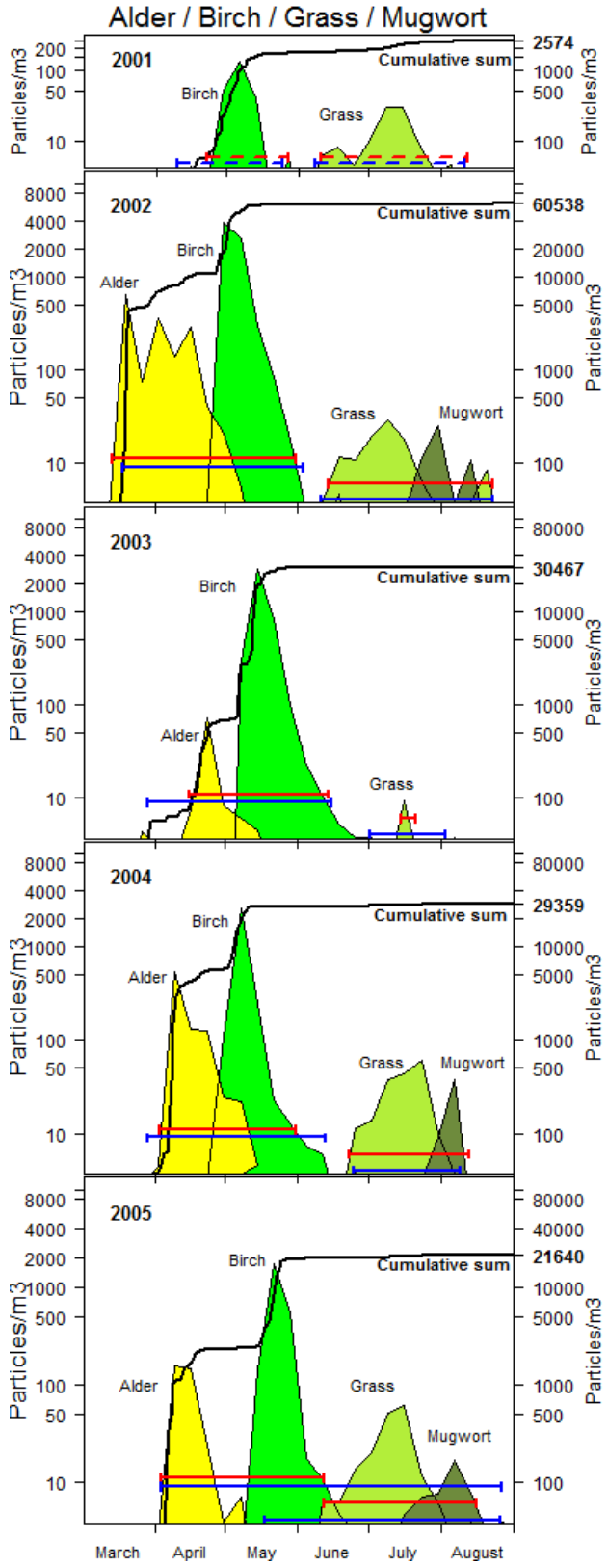

Figure S1. Concentrations of pollen (grains per cubic meter of air) shown (in locarithmic scale) as cumulative sums (black curves, scale on the right hand axis) and average weekly concentrations (coloured areas, scale on the left hand axis). Each pollen season began when overall pollen concentrations exceeded 10 pollen grains/m^3 and ended on the date when it fell below this threshold for at least one week. Daily concentrations of pollen grains are shown by blue and average weekly concentrations by red line segments in each plot. Since the location of the sampler was moved after the 2001 pollen season, the pollen concentrations in 2001 and 2001-5 are not directly comparable. However, the criteria for pollen season were the same in all years.

Supplementary file: R-script for calculation of pollen season

The limits of the annual pollen seasons were defined in terms of daily concentrations of pollen grains (>10particles/m^3) and shown as blue segments in Figure S1). The coincidence of the end of the 11th fetal week and the pollen season defined as follows (the `Epi` package of R was used to achieve operations with dates):

1) The calendar time at the end of the 11th fetal week was determined by subtraction of the calendar time of birth (in numeric format) and the gestational age, plus 77 days as follows:

```
BIRTH <-as.Date(ISOdate(BIRTHyear, BIRTHmonth, BIRTHday))
d11week<-as.numeric(BIRTH)- DURATIONGESTATION + 77
```

2) The calendar time at the end of the 11th fetal week was converted into decimal format as follows:

```
date11wk <- as.Date(d11wk, origin="1970-01-01")
11.FETAL_WEEK <- cal.yr(date11wk)
```

3) A variable indicating the coincidence of the pollen season and the end of the 11th fetal week was defined as follows:

```
POLLEN.EXP.11week<-1*((2001.269 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2001.392)|
                      (2001.431 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2001.606)|
                      (2002.205 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2002.416)|
                      (2002.438 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2002.638)|
                      (2003.235 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2003.448)|
                      (2003.495 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2003.582)|
                      (2004.237 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2004.445)|
                      (2004.478 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2004.601)|
                      (2005.253 < 11.FETAL_WEEK & 11.FETAL_WEEK < 2005.65))


POLLEN.EXP.11week. <-factor(POLLEN.EXP.11week, levels=0:1, labels=c("No","Yes"))
```

4) The calendar time of the birthday was at first converted into decimal format as follows:

```
dateBIRTH <- as.Date(BIRTH, origin="1970-01-01")
BIRTHDAY  <- cal.yr(dateBIRTH)
```

5) A variable indicating the coincidence of the pollen season and birth was defined as follows:

```
POLLEN.EXP.BIRTH <-1*((2001.269 < BIRTHDAY & BIRTHDAY < 2001.392)|
                      (2001.431 < BIRTHDAY & BIRTHDAY < 2001.606)|
                      (2002.205 < BIRTHDAY & BIRTHDAY < 2002.416)|
                      (2002.438 < BIRTHDAY & BIRTHDAY < 2002.638)|
                      (2003.235 < BIRTHDAY & BIRTHDAY < 2003.448)|
                      (2003.495 < BIRTHDAY & BIRTHDAY < 2003.582)|
                      (2004.237 < BIRTHDAY & BIRTHDAY < 2004.445)|
                      (2004.478 < BIRTHDAY & BIRTHDAY < 2004.601)|
                      (2005.253 < BIRTHDAY & BIRTHDAY < 2005.65))

POLLEN.EXP.BIRTH.<-factor(POLLEN.EXP.BIRTH,levels=0:1,labels=c("No","Yes"))
```

6) Coincidence of the pollen season with different phases of pregnancy was defined as follows:

```
COINC.Pollen.Pregn <-   1*(POLLEN.EXP.BIRTH==1 & POLLEN.EXP.11week==0) +
                        2*(POLLEN.EXP.BIRTH==0 & POLLEN.EXP.11week==1) +
                        3*(POLLEN.EXP.BIRTH==0 & POLLEN.EXP.11week==0) +
                        4*(POLLEN.EXP.BIRTH==1 & POLLEN.EXP.11week==1)

COINC.Pollen.Pregn. <- factor(COINC.Pollen.Pregn, levels=1:4,
                           labels=c("Birth","11th   week", "Neither","Both"))
```

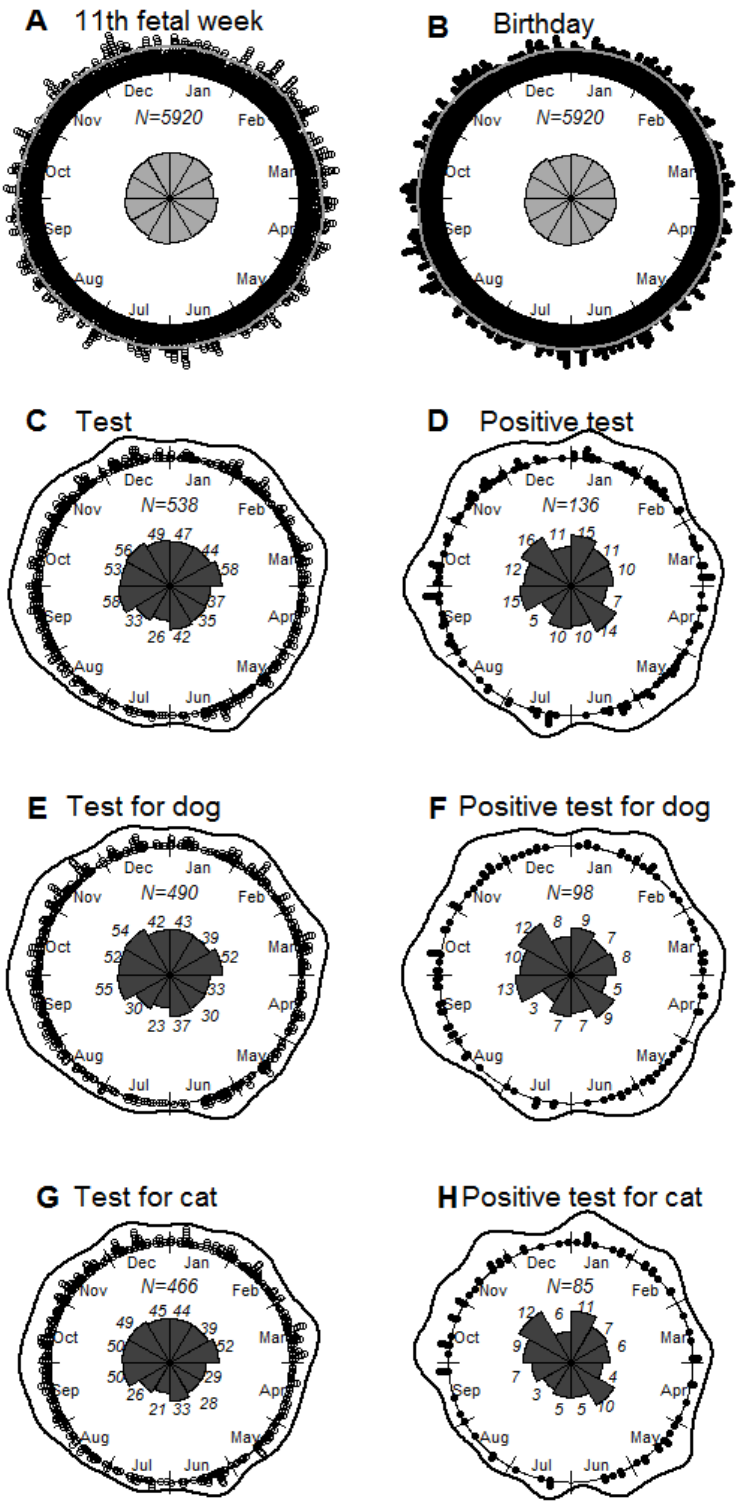

Figure S2. Circular figures showing the the calendar time of the 11th fetal week (A), the birth (B), the first test (C, E, G) and the first positive test result (D, F, H) for pet allergens. Smoothed density for each of these outcomes is shown by grey (A and B) and black (C, D, E, F, G, H) circular lines (Kernel density estimates of circular outcomes with bandwidth of 75 [37]). The sectors of the rose diagram represent the relative frequencies of events among respective subpopulations; subjects experienced the 11th fetal week per each calendar month (A), born per each month (B), tested (C,E G) and test positives (D, F, H) among population undergoing respective tests or children with positive test results per each month.

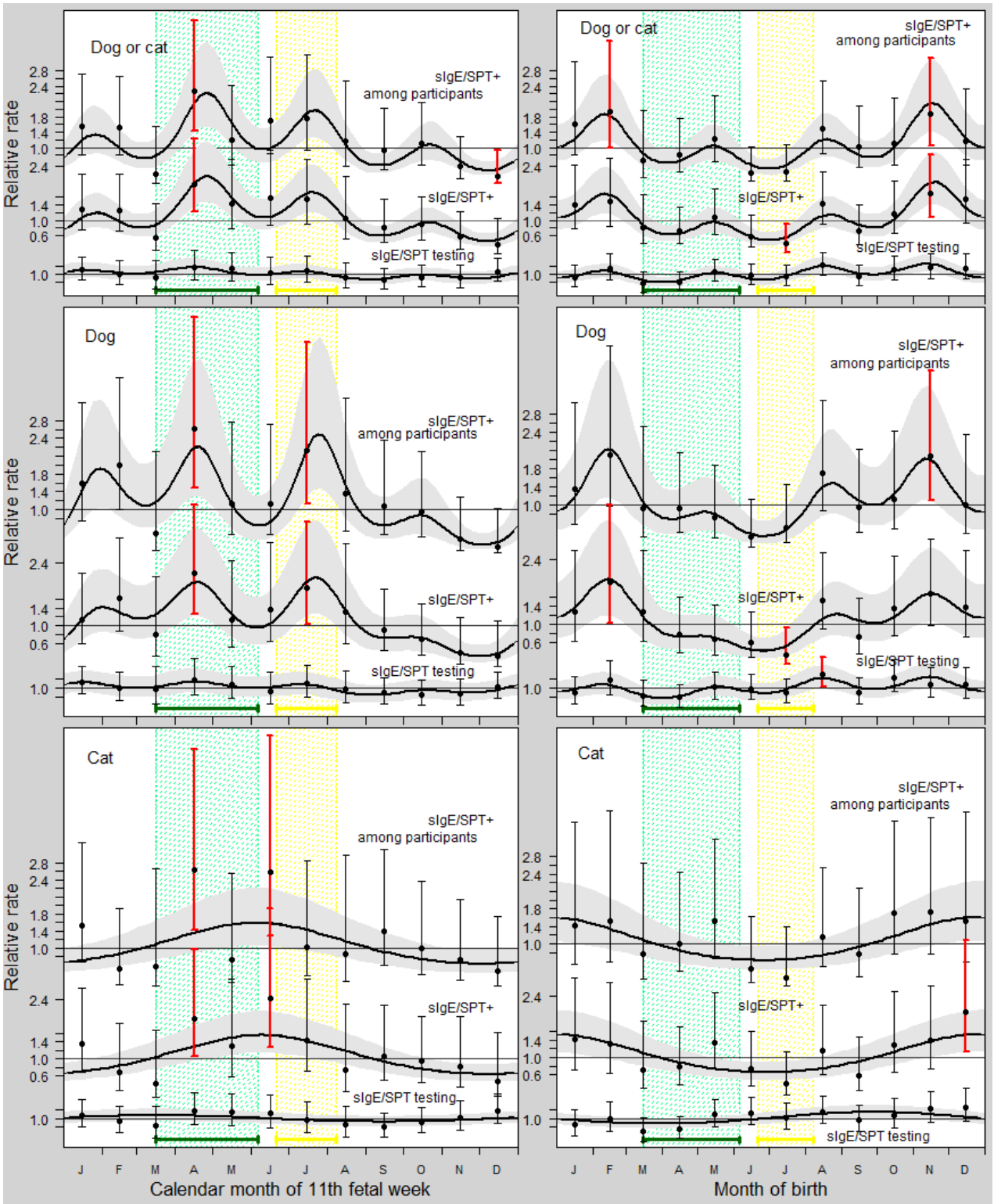

Figure S3. Relative rates (RR) of testing for pet allergy and positive test results among the entire study population (N=5920) and among participants of a questionnaire survey (N=3647) by the month of the 11th fetal week and the month of birth. The points indicate monthly RRs from the Cox regression adjusted for gender, birth order, year at the end of the first fetal trimester or year of birth as appropriate and also for pet exposure among participants, vertical bars showing their 95% confidence intervals. Continuous lines are RRs smoothed by adjusted harmonic models (periodicities 12 and 3 months for both pets; 12, 6 and 3 months for dog; 12 months for cat) shaded areas representing their 95% confidence bands. Pollen seasons (average weekly pollen concentrations >10 grains/m^3 in years 2001-5) are indicated by green (alder & birch) and yellow (grass & mugwort).

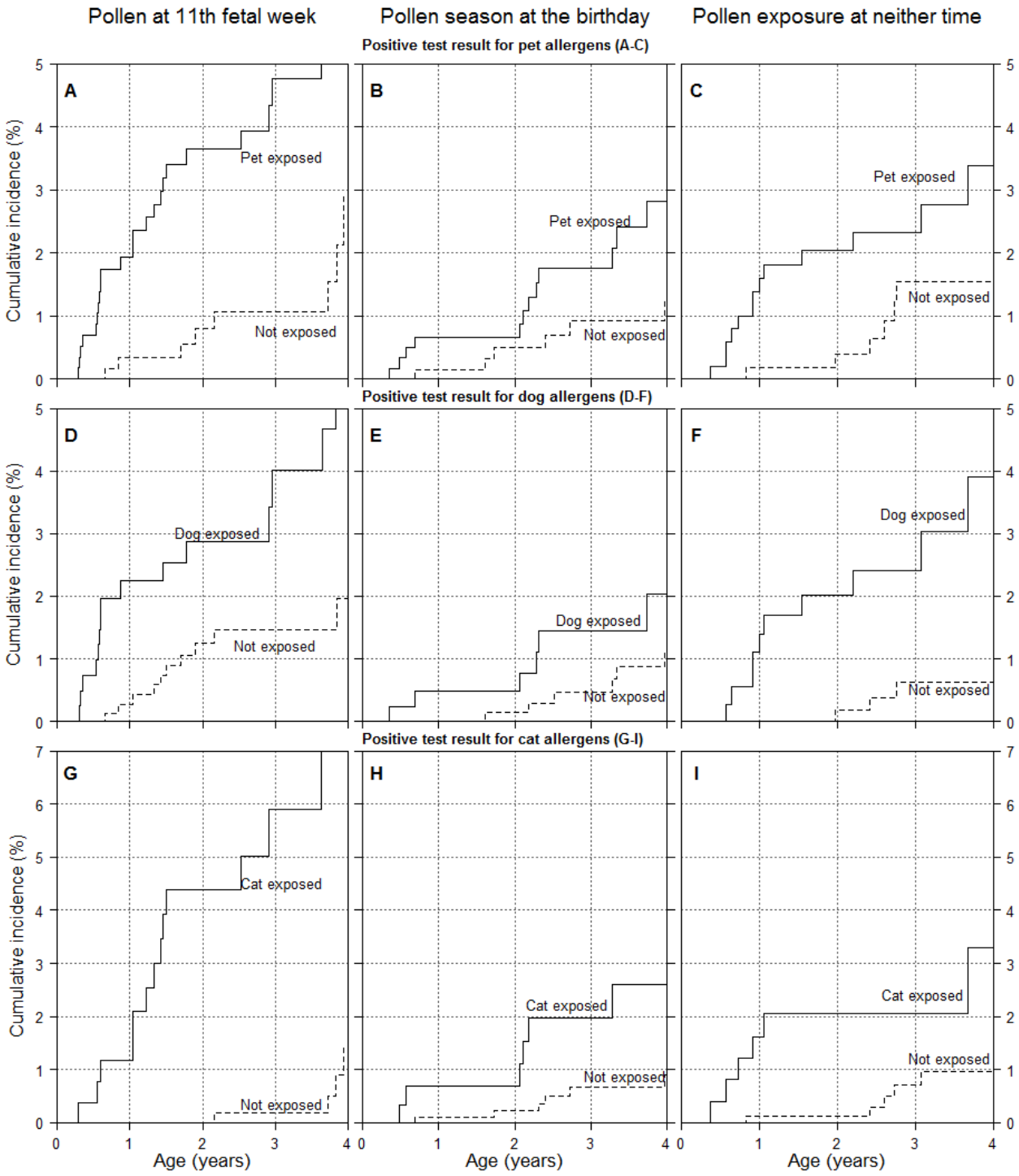

Figure S4. Kaplan-Meier curves showing cumulative incidences of children with positive test results for pet (the plots of the above row), dog (the plots of the middle row) and cat (the plots of the below row) allergens classified whether the 11th fetal week, the date of birth or neither of these were located during pollen season and separately for children exposed and non-exposed to respective pets.

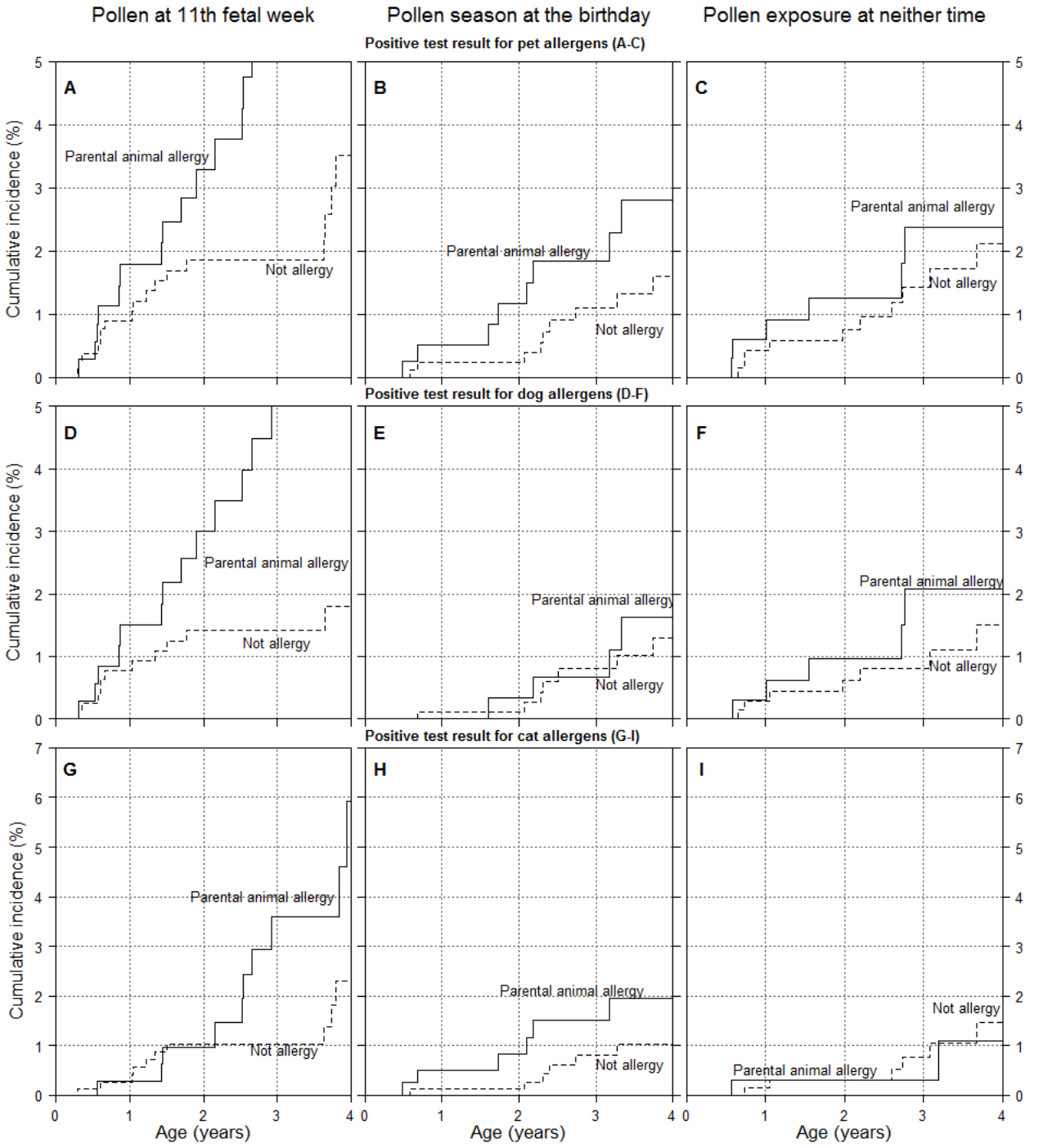

Figure S5. Kaplan-Meier curves showing cumulative incidences of children with positive test results for pet (the plots of the above row), dog (the plots of the middle row) and cat (the plots of the below row) allergens classified whether the 11th fetal week, the date of birth or neither of these were located during pollen season and separately for children who had parents with and without animal allergy.

Table S1 Comparison between harmonic models with different periodicities:

s1 = sin(1*2π*date11week[1]), c1 = cos(1*2π*date11week) (12 months)
s2 = sin(2*2π*date11week), c2 = cos(2*2π*date11week) (6 months)
s3 = sin(3*2π*date11week), c3 = cos(3*2π*date11week) (4 months)
s4 = sin(4*2π*date11week), c4 = cos(4*2π*date11week) (3 months)

Comparison between models I and II by anova		Participants to the survey N=3647[2]		Entire study population N=5920[3]	
Model I	Model II	χ^2	p~	χ^2	p~
Dog or cat					
M0: ~ cov.	M1: ~ c1 + s1 + cov.	8.854	0.012	13.788	0.001
M1: ~ c1 + s1 + cov.	M2: ~ c1 + s1 + c2 + s2 + cov.	1.858	0.395	0.391	0.823
M1: ~ c1 + s1 + cov.	M3: ~ c1 + s1 + c3 + s3 + cov.	0.257	0.880	0.658	0.720
M1: ~ c1 + s1 + cov.	**M4: ~ c1 + s1 + c4 + s4 + cov.**	9.130	0.010	7.900	0.019
M0: ~ cov.	**M4: ~ c1 + s1 + c4 + s4 + cov.**	17.985	0.001	21.688	<0.001
M0: ~ cov.	M4.2: ~ c1 + s1 + c2 + s2 + c4 + s4 + cov.	19.936	0.003	22.114	0.001
Dog					
M0: ~ cov.	M1: ~ c1 + s1 + cov.	8.045	0.018	13.659	0.001
M1: ~ c1 + s1 + cov.	M2: ~ c1 + s1 + c2 + s2 + cov.	5.312	0.070	4.544	0.103
M1: ~ c1 + s1 + cov.	M3: ~ c1 + s1 + c3 + s3 + cov.	0.122	0.941	0.437	0.804
M1: ~ c1 + s1 + cov.	M4: ~ c1 + s1 + c4 + s4 + cov.	7.898	0.019	4.064	0.131
M4.2: ~ c1 + s1 + c2 + s2 + c4 + s4 + cov.	M4: ~ c1 + s1 + c4 + s4 + cov.	5.696	0.058	4.764	0.092
M0: ~ cov.	M4: ~ c1 + s1 + c4 + s4 + cov.	15.942	0.003	17.723	0.001
M0: ~ cov.	**M4.2: ~ c1 + s1 + c2 + s2 + c4 + s4 + cov.**	21.638	0.001	22.487	<0.001
Cat					
M0: ~ cov.	**M1: ~ c1 + s1 + cov.**	4.833	0.089	8.143	0.017
M1: ~ c1 + s1 + cov.	M2: ~ c1 + s1 + c2 + s2 + cov.	0.396	0.820	0.806	0.669
M1: ~ c1 + s1 + cov.	M3: ~ c1 + s1 + c3 + s3 + cov.	0.055	0.973	0.655	0.721
M1: ~ c1 + s1 + cov.	M4: ~ c1 + s1 + c4 + s4 + cov.	1.422	0.491	0.802	0.670

[1] `date11week` corresponds to the date at the end of the 11th fetal week in decimal format

[2] cov. includes following covariates: year of the 11th fetal week + sex + birth order + pet exposure

[3] cov. includes following covariates: year of the 11th fetal week + sex + birth order

Table S2. Relative rates (RR) from Cox regressions of positive dog and/or cat allergy test on the occurrence of the 11th fetal week in the pollen season, dog/cat exposure and their interaction.

Positive test for dog/cat 11th week on pollen season/ pet exposure	Crude models RR (95% CI)	Adjusted main effects model[1] RR (95% CI)	Adjusted interaction model[1] RR (95% CI)
Dog or cat			
Pollen season	1.73 (1.12−2.67)	1.79 (1.15−2.80)	1.10 (0.50−2.41)
Dog or cat	2.19 (1.40−3.42)	2.14 (1.36−3.35)	1.60 (0.91−2.82)
Pollen season : Dog or cat			2.11 (0.82−5.44)
Dog			
Pollen season	1.78 (1.07−2.96)	1.84 (1.10−3.09)	1.65 (0.77−3.53)
Dog	2.42 (1.47−3.99)	2.36 (1.43−3.90)	2.17 (1.13−4.18)
Pollen season : Dog			1.23 (0.44−3.39)
Cat			
Pollen season	1.49 (0.83−2.69)	1.60 (0.87−2.92)	0.61 (0.20−1.83)
Cat	5.00 (2.80−8.91)	5.06 (2.83−9.05)	2.92 (1.40−6.08)
Pollen season : Cat			4.82 (1.27−18.28)

[1] From Cox models adjusted for sex, birth order and the year of the 11th fetal week.

Table S3 Relative rates (RR) for positive pet allergy tests according to the month of the 11th fetal week in the entire study population (complete cases) after replacing the missing values of duration of pregnancy by mean duration given in the questionnaire (278.2) and after replacing missing values by multiple imputation.

	Complete cases RR (95%CI)	Mean imputation RR (95%CI)	Multiple imputation RR (95%CI)
Pet			
Jan	1.31 (0.69−2.50)	1.39 (0.86−2.27)	1.30 (0.77−2.21)
Feb	1.53 (0.84−2.77)	1.23 (0.73−2.05)	1.27 (0.73−2.22)
Mar	0.38 (0.10−1.37)	0.58 (0.25−1.31)	0.56 (0.21−1.44)
Apr	2.46 (1.45−4.15)	1.85 (1.18−2.91)	1.95 (1.22−3.11)
May	1.06 (0.49−2.29)	1.47 (0.86−2.49)	1.43 (0.79−2.60)
Jun	1.55 (0.79−3.06)	1.64 (0.98−2.75)	1.58 (0.88−2.81)
Jul	1.84 (0.99−3.41)	1.41 (0.83−2.40)	1.54 (0.92−2.59)
Aug	1.08 (0.47−2.49)	1.23 (0.68−2.23)	1.04 (0.51−2.13)
Sep	0.92 (0.45−1.88)	0.77 (0.41−1.44)	0.81 (0.43−1.55)
Oct	1.09 (0.57−2.09)	0.96 (0.55−1.66)	0.90 (0.50−1.60)
Nov	0.47 (0.19−1.20)	0.47 (0.22−1.00)	0.57 (0.26−1.24)
Dec	0.35 (0.12−1.01)	0.38 (0.17−0.87)	0.37 (0.13−1.05)
Dog			
Jan	1.40 (0.67−2.93)	1.25 (0.68−2.30)	1.14 (0.59−2.18)
Feb	1.90 (1.01−3.59)	1.52 (0.86−2.67)	1.62 (0.89−2.96)
Mar	0.54 (0.15−1.96)	0.84 (0.37−1.93)	0.81 (0.31−2.11)
Apr	2.67 (1.48−4.83)	2.27 (1.37−3.74)	2.17 (1.27−3.70)
May	0.97 (0.38−2.49)	0.97 (0.45−2.09)	1.13 (0.52−2.47)
Jun	1.05 (0.41−2.69)	1.36 (0.69−2.66)	1.35 (0.64−2.86)
Jul	2.29 (1.18−4.44)	1.73 (0.97−3.11)	1.85 (1.03−3.32)
Aug	1.18 (0.46−3.01)	1.58 (0.83−2.98)	1.31 (0.60−2.84)
Sep	1.04 (0.47−2.28)	0.82 (0.40−1.66)	0.89 (0.44−1.82)
Oct	0.96 (0.44−2.12)	0.74 (0.36−1.52)	0.71 (0.34−1.50)
Nov	0.31 (0.08−1.14)	0.31 (0.11−0.89)	0.40 (0.13−1.19)
Dec	0.31 (0.08−1.12)	0.41 (0.16−1.03)	0.33 (0.10−1.11)
Cat			
Jan	1.35 (0.56−3.22)	1.37 (0.74−2.53)	1.34 (0.68−2.66)
Feb	0.75 (0.25−2.22)	0.67 (0.29−1.55)	0.68 (0.25−1.85)
Mar	0.35 (0.06−2.17)	0.54 (0.19−1.57)	0.41 (0.10−1.67)
Apr	3.08 (1.59−5.97)	1.52 (0.82−2.81)	1.95 (1.07−3.55)
May	0.66 (0.18−2.43)	1.44 (0.73−2.82)	1.29 (0.58−2.88)
Jun	2.56 (1.20−5.45)	2.46 (1.42−4.26)	2.41 (1.29−4.51)
Jul	1.37 (0.53−3.57)	1.22 (0.59−2.49)	1.44 (0.72−2.88)
Aug	0.82 (0.22−3.04)	1.00 (0.43−2.29)	0.75 (0.25−2.28)
Sep	1.50 (0.67−3.36)	0.97 (0.47−1.98)	1.07 (0.50−2.26)
Oct	1.13 (0.47−2.71)	1.02 (0.52−2.01)	0.95 (0.46−1.99)
Nov	0.67 (0.23−2.01)	0.64 (0.28−1.47)	0.83 (0.35−1.98)
Dec	0.43 (0.12−1.59)	0.49 (0.19−1.24)	0.48 (0.14−1.62)

Table S4 Cumulative incidences (%) of subjects tested by Skin prick test (SPT) or IgE and their positive results up to the age of 4 years for either pet allergens (dog/cat) and separately for cat and dog allergens according to selected background variables among entire SKARP population (N=5920). Among positive test results, medians of IgE values and sizes of urticarial weal are shown with the range between minimum and maximum values and the values of the 1st and 3rd quartiles.

			SPT			IGE		
			Tested	Positive result		Tested	Positive result	
Test	Background variable	N	% (n)	% (n)	**median** (range; 1st Qu, 3rd Qu)	% (n)	% (n)	**median** (range; 1st Qu, 3rd Qu)
PET	Date of birth							
(dog/cat)	Apr 1, 2005- March 31, 2006	1187	3 (22)	1 (6)	**3.50** (3.00–5.00; 3.00, 4.75)	2 (16)	0 (1)	**3.23**
	Apr 1, 2004- March 31, 2005	1151	5 (43)	1 (7)	**3.00** (3.00–5.00; 3.00, 4.00)	4 (46)	0 (4)	**4.11** (0.56–21.20; 0.81, 10.80)
	Apr 1, 2003- March 31, 2004	1176	6 (65)	1 (10)	**5.00** (3.00–8.00; 4.25, 5.00)	3 (38)	1 (8)	**1.61** (0.42–27.40; 0.71, 2.09)
	Apr 1, 2002- March 31, 2003	1165	9 (104)	2 (27)	**5.00** (3.00–7.00; 4.00, 6.00)	6 (71)	1 (18)	**6.14** (0.52–73.90; 1.07, 29.9)
	Apr 1, 2001- March 31, 2002	1241	7 (112)	2 (36)	**4.00** (3.00–10.00;3.00, 6.00)	6 (87)	2 (31)	**4.20** (0.38–73.90; 1.91, 17.10)
	Gender							
	Boy	3025	10 (208)	3 (63)	**4.00** (3.00–10.00; 3.50, 5.00)	6 (146)	2 (37)	**5.03** (0.38–73.90; 1.91, 17.10)
	Girl	2895	7 (138)	1 (23)	**5.00** (3.00–8.00; 3.00, 6.00)	5 (112)	1 (25)	**1.37** (0.38–79.40; 0.67, 6.59)
	Birth order							
	Firstborn	2635	9 (161)	3 (50)	**5.00** (3.00–10.0; 4.00, 5.00)	7 (142)	2 (46)	**3.42** (0.38–79.40; 0.89, 24.83)
	Not firstborn	3285	8 (185)	2 (36)	**4.00** (3.00–8.00; 3.00, 5.25)	4 (116)	1 (16)	**5.40** (0.38–48.30; 0.67, 12.65)
	Year of 11th week							
	2000-1	1613	7 (153)	1 (46)	**5.00** (3.00–10.0; 3.00, 6.00)	6 (104)	2 (34)	**4.39** (0.38–79.40; 0.88, 16.40)
	2002	1159	8 (86)	2 (21)	**5.00** (3.00–8.00; 3.00, 5.00)	6 (68)	1 (17)	**6.02** (0.52–73.90; 1.56, 30.20)
	2003-5	3148	8 (107)	2 (19)	**4.00** (3.00–5.00; 3.00, 5.00)	4 (86)	0 (11)	**1.29** (0.42–21.20; 0.66, 2.63)
	Parental animal allergy							
	No	2539	6 (118)	2 (31)	**4.00** (3.00–8.00; 3.00, 5.00)	5 (96)	1 (25)	**3.23** (0.42–79.40; 0.68, 21.20)
	Yes	1180	12 (93)	3 (22)	**5.00** (3.00–7.00; 3.00, 5.00)	7 (69)	2 (18)	**4.62** (0.38–72.00; 0.89, 14.00)
	Missing	2201	9 (135)	2 (33)	**4.00** (3.00–10.0; 3.00, 6.00)	6 (93)	1 (19)	**4.58** (0.52–56.00; 1.47, 15.00)
	Overall	5920	8 (346)	2 (86)	**4.50** (3.00–10.00; 3.00, 5.00)	6 (258)	1 (62)	**3.90** (0.38–79.40; 0.88, 16.40)
DOG	Date of birth							
	Apr 1, 2005- March 31, 2006	1187	2 (15)	0 (2)	**3.00** (3.00–5.00; 3.00, 3.00)	1 (13)	0 (0)	–
	Apr 1, 2004- March 31, 2005	1151	5 (38)	1 (5)	**3.00** (3.00–4.00; 3.00, 3.00)	3 (35)	0 (4)	**4.11** (0.56–21.20; 0.81, 10.80)
	Apr 1, 2003- March 31, 2004	1176	5 (59)	0 (3)	**3.00** (3.00–5.00; 3.00, 3.00)	2 (30)	0 (4)	**1.03** (0.42–1.92; 0.68, 1.45)
	Apr 1, 2002- March 31, 2003	1165	9 (100)	2 (16)	**3.00** (3.00–7.00; 3.00, 4.00)	5 (66)	1 (16)	**6.49** (0.54–73.90; 1.22, 16.60)
	Apr 1, 2001- March 31, 2002	1241	6 (108)	2 (31)	**3.00** (3.00–6.00; 3.00, 4.00)	5 (78)	1 (24)	**2.18** (0.38–79.40; 0.82, 10.76)
	Gender							
	Boy	3025	9 (194)	2 (45)	**3.00** (3.00–7.00; 3.00, 5.00)	5 (127)	1 (27)	**3.80** (0.54–73.90; 1.62, 11.15)
	Girl	2895	6 (126)	1 (12)	**3.00** (3.00–6.00; 3.00, 3.00)	4 (95)	1 (21)	**0.88** (0.38–79.40; 0.56, 6.26)
	Birth order							
	Firstborn	2635	8 (146)	2 (32)	**3.00** (3.00–7.00; 3.00, 4.00)	6 (123)	2 (36)	**3.07** (0.89–79.40; 0.89, 12.15)
	Not firstborn	3285	8 (174)	1 (25)	**3.00** (3.00–6.00; 3.00, 4.00)	4 (99)	0 (12)	**1.37** (0.41–48.30; 0.67, 8.59)
	Year of 11th week							
	2000-1	1613	8 (148)	0 (38)	**3.00** (3.00–7.00; 3.00, 5.00)	5 (94)	1 (27)	**2.44** (0.38–79.40; 0.76, 11.15)
	2002	1159	7 (80)	2 (10)	**3.00** (3.00–5.00; 3.00, 3.00)	5 (58)	1 (13)	**6.26** (0.67–73.90; 1.33, 23.50)
	2003-5	3148	8 (92)	1 (9)	**3.00** (3.00–5.00; 3.00, 3.00)	3 (70)	0 (8)	**1.09** (0.42–21.20; 0.72, 3.27)
	Parental animal allergy							
	No	2539	6 (110)	1 (21)	**3.00** (3.00–6.00; 3.00, 3.25)	4 (79)	1 (21)	**1.91** (0.40–79.40; 0.68, 6.72)
	Yes	1180	11 (85)	2 (16)	**3.00** (3.00–7.00; 3.00, 3.25)	6 (61)	2 (15)	**4.20** (0.38–72.00; 1.10, 12.35)
	Missing	2201	8 (125)	1 (20)	**3.00** (3.00–6.00; 3.00, 4.00)	5 (82)	1 (12)	**4.19** (0.41–56.00; 1.19, 12.15)
	Overall	5920	8 (320)	1 (57)	**4.00** (3.00–7.00; 3.00, 7.00)	5 (222)	1 (48)	**2.11** (0.38–79.40; 0.85, 10.78)
CAT	Date of birth							
	Apr 1, 2005- March 31, 2006	1187	2 (18)	0 (4)	**3.00** (3.00–3.00; 3.00, 5.00)	1 (12)	0 (1)	**3.23**
	Apr 1, 2004- March 31, 2005	1151	5 (40)	0 (4)	**3.00** (3.00–5.00; 3.00, 3.00)	3 (35)	0 (1)	**9.17**
	Apr 1, 2003- March 31, 2004	1176	5 (59)	1 (7)	**3.00** (3.00–8.00; 3.00, 3.50)	2 (24)	0 (4)	**2.16** (0.51–27.40; 1.64, 8.58)
	Apr 1, 2002- March 31, 2003	1165	8 (95)	2 (23)	**3.00** (3.00–7.00; 3.00, 5.25)	5 (58)	1 (10)	**5.42** (0.52–58.00; 1.74, 29.90)
	Apr 1, 2001- March 31, 2002	1241	6 (103)	1 (22)	**4.00** (3.00–10.00; 3.00, 5.00)	4 (61)	1 (16)	**7.54** (0.38–60.60; 0.88, 18.83)
	Gender							
	Boy	3025	9 (189)	2 (42)	**4.00** (3.00–10.00; 3.00, 5.00)	5 (110)	1 (24)	**7.15** (0.38–58.00; 1.39, 27.80)
	Girl	2895	6 (126)	1 (18)	**3.00** (3.00–8.00; 3.00, 5.25)	4 (80)	0 (8)	**4.20** (0.57–60.60; 1.92, 10.94)
	Birth order							
	Firstborn	2635	8 (144)	2 (37)	**4.00** (3.00–10.00; 3.00, 5.00)	5 (102)	1 (23)	**5.03** (0.52–60.60; 1.79, 28.20)
	Not firstborn	3285	7 (171)	1 (23)	**3.00** (3.00–8.00; 3.00, 5.00)	3 (88)	0 (9)	**8.49** (0.38–30.70; 0.89, 12.50)
	Year of 11th week							
	2000-1	1613	7 (142)	1 (31)	**4.00** (3.00–10.00; 3.00, 6.00)	4 (75)	1 (18)	**7.54** (0.38–60.60; 0.87, 22.28)
	2002	1159	7 (79)	2 (17)	**3.00** (3.00–8.00; 3.00. 5.00)	5 (56)	1 (10)	**5.42** (0.52–58.00; 2.27, 29.50)
	2003-5	3148	8 (94)	1 (12)	**3.00** (3.00–5.00; 3.00, 4.00)	2 (59)	0 (4)	**2.63** (0.51–9.17; 1.64, 4.72)
	Parental animal allergy							
	No	2539	6 (107)	1 (20)	**3.00** (3.00–8.00; 3.00, 5.00)	3 (70)	1 (11)	**9.17** (0.51–60.60; 4.22, 29.60)
	Yes	1180	11 (85)	2 (14)	**3.00** (3.00–6.00; 3.00, 5.00)	6 (51)	1 (9)	**5.03** (0.38–58.00; 0.86, 24.00)
	Missing	2201	11 (123)	2 (26)	**4.00** (3.00–10.00; 3.00, 5.25)	4 (69)	1 (12)	**2.75** (0.52–45.60;1.39, 9.22)
	Overall	5920	8 (315)	2 (60)	**5.00** (3.00–10.00; 3.00, 6.00)	4 (190)	1 (32)	**5.50** (0.38–60.60; 1.39, 24.85)

Table S4 *(Continued)* Cumulative incidences (%) of subjects tested by Skin prick test (SPT) or IgE and their positive results up to the age of 4 years for either pet allergens (dog/cat) and separately for cat and dog allergens according to selected background variables among entire SKARP population (N=5920). Among positive test results, medians of IgE values and sizes of urticarial weal are shown with the range between minimum and maximum values and the values of the 1st and 3rd quartiles.

			SPT			IGE		
			Tested	Positive result		Tested	Positive result	
Test	Background variable	N	% (n)	% (n)	**median** (range; 1st Qu, 3rd Qu)	% (n)	% (n)	**median** (range; 1st Qu, 3rd Qu)
PET (dog/cat)	Month of birth							
	Mar-May	1431	8 (79)	2 (18)	**4.50** (3.00–8.00; 3.00, 6.00)	5 (55)	1 (13)	**2.30** (0.54–48.30, 0.68, 14.30)
	Jun-Apr	1586	9 (103)	2 (23)	**5.00** (3.00–10.00; 3.00, 5.50)	6 (79)	1 (12)	**1.33** (0.38–29.00; 0.57, 3.34)
	Sep-Nov	1508	8 (85)	2 (20)	**4.00** (3.00–8.00; 3.00, 5.00)	6 (69)	2 (22)	**17.05** (0.53–79.40; 3.57, 53.40)
	Dec-Feb	1395	10 (79)	4 (25)	**5.00** (3.00–7.00; 4.00, 5.00)	6 (55)	2 (15)	**3.19** (0.38–13.10; 0.83, 6.43)
	Month of 11th fetal week							
	Mar-May	1456	9 (84)	2 (21)	**4.00** (3.00–8.00; 3.00, 5.00)	2 (64)	2 (21)	**7.98** (0.52–79.40; 1.92, 33.00)
	Jun-Apr	1441	9 (75)	3 (21)	**5.00** (3.00–6.00; 4.00, 5.00)	4 (53)	2 (16)	**3.40** (0.38–30.70; 0.67, 6.34)
	Sep-Nov	1447	8 (88)	2 (21)	**5.00** (3.00–8.00; 3.00, 8.00)	3 (55)	1 (10)	**5.40** (0.54–48.30; 1.01, 24.13)
	Dec-Feb	1576	8 (99)	2 (23)	**4.00** (3.00–10.00; 3.00, 5.00)	6 (86)	1 (15)	**2.02** (0.38–73.90; 0.57, 9.46)
DOG	Month of birth							
	Mar-May	1431	8 (75)	1 (12)	**3.00** (3.00–7.00; 3.00, 3.00)	4 (46)	1 (10)	**1.17** (0.40–48.30; 0.65, 11.68)
	Jun-Apr	1586	8 (96)	1 (16)	**3.00** (3.00–6.00; 3.00, 3.00)	5 (69)	1 (9)	**1.37** (0.56–10.20; 0.67, 2.44)
	Sep-Nov	1508	8 (80)	1 (14)	**3.00** (3.00–6.00; 3.00, 3.00)	5 (59)	1 (18)	**9.31** (0.53–79.40; 1.91, 30.63)
	Dec-Feb	1395	9 (69)	2 (15)	**3.00** (3.00–6.00; 3.00, 3.00)	6 (48)	1 (11)	**3.60** (0.38–10.40; 0.60, 6.80)
	Month of 11th fetal week							
	Mar-May	1456	8 (78)	1 (12)	**3.00** (3.00–6.00; 3.00, 3.00)	5 (56)	1 (17)	**6.72** (0.77–23.50; 1.91, 23.50)
	Jun-Apr	1441	8 (66)	2 (14)	**3.00** (3.00–6.00; 3.00, 3.00)	6 (49)	2 (14)	**2.25** (0.38–30.70; 0.48, 5.75)
	Sep-Nov	1447	8 (83)	1 (13)	**3.00** (3.00–7.00; 3.00, 3.00)	3 (44)	1 (7)	**1.44** (0.54–48.30; 1.13, 12.25)
	Dec-Feb	1576	8 (93)	1 (18)	**3.00** (3.00–5.00; 3.00, 3.00)	5 (73)	0 (10)	**1.54** (0.53–73.90; 0.60, 5.13)
CAT	Month of birth							
	Mar-May	1431	7 (72)	1 (14)	**3.00** (3.00–8.00; 3.00, 4.40)	3 (39)	1 (7)	**2.30** (0.57–27.40; 0.83, 7.15)
	Jun-Apr	1586	8 (95)	2 (16)	**3.00** (3.00–10.00; 3.00, 5.00)	4 (60)	0 (5)	**2.02** (0.38–29.00; 0.51, 17.10)
	Sep-Nov	1508	7 (78)	1 (9)	**3.00** (3.00–8.00; 3.00, 3.00)	4 (48)	1 (13)	**24.00** (0.79–60.60; 5.20, 45.60)
	Dec-Feb	1395	9 (70)	3 (21)	**3.50** (3.00–7.00; 3.00, 5.00)	5 (43)	1 (7)	**2.26** (0.52–13.10; 1.23, 4.89)
	Month of 11th fetal week							
	Mar-May	1456	8 (78)	1 (13)	**3.00** (3.00–8.00; 3.00, 4.00)	4 (43)	1 (11)	**12.50** (0.52–58.00; 5.12, 30.45)
	Jun-Apr	1441	8 (66)	3 (18)	**3.00** (3.00–6.00; 3.00, 5.00)	5 (42)	1 (7)	**3.19** (0.57–13.10; 1.58, 6.20)
	Sep-Nov	1447	8 (82)	2 (16)	**3.00** (3.00–8.00; 3.00, 5.00)	3 (39)	0 (6)	**5.40** (0.80–29.00; 1.22, 22.67)
	Dec-Feb	1576	8 (89)	1 (13)	**3.00** (3.00–10.00; 3.00, 5.00)	5 (66)	0 (8)	**2.63** (0.38–60.60; 0.72, 22.53)

Table S5 Modification of the association between pet (dog and/or cat) exposure and respective sensitisation by the occurrence of the 11th fetal week in pollen season, shown in format recommended by Knol et al [33].

Season of the 11th fetal week	Pet exposure				RR[2] (95% CI) for pet exposure within pollen season strata
	No		Yes		
	n/N[1]	RR[2] (95% CI)	n/N[1]	RR[2] (95% CI)	
Non-pollen season	21/1291	1.0 (Reference)	28/1082	1.60 (0.91−2.82); p=0.104	1.65 (0.93−2.92); p=0.084
Pollen season	9/638	1.10 (0.50−2.41); p=0.816	26/552	3.71 (2.06−6.68); p<0.001	3.19 (1.49−6.86); p=0.002

Measure of effect modification on additive scale, RERI (95% CI) : 2.01 (0.29−4.29 by bootstrap); 2.01 (0.22−3.80 by delta method)
Measure of effect modification on multiplicative scale, ratio of RRs (95% CI) : 2.11 (0.82−6.68)
[1] n=number of children with a dog and/or cat test positive; N=number of children with no positive dog and/or cat test
[2] RRs are adjusted for sex, birth order and the year of 11th fetal week

Table S6 Modification of the association between dog exposure and respective sensitisation by the occurrence of the 11th fetal week in pollen season, shown in format recommended by Knol et al [33].

Season of the 11th fetal week	Dog exposure				RR[2] (95% CI) for dog exposure within pollen season strata
	No		Yes		
	n/N[1]	RR[2] (95% CI)	n/N[1]	RR[2] (95% CI)	
Non-pollen season	18/1621	1.0 (Reference)	18/765	2.17 (1.13−4.18); p=0.020	2.24 (1.16−4.32); p=0.016
Pollen season	11/805	1.65 (0.77−3.53); p=0.196	15/394	4.40 (2.19−8.83); p<0.001	2.55 (1.16−5.56); p=0.019

Measure of effect modification on additive scale, RERI (95% CI) : 1.57 (-1.00−4.84 by bootstrap); 1.57 (-1.09−4.23 by delta method)
Measure of effect modification on multiplicative scale, ratio of RRs (95% CI) : 1.23 (0.44−3.93)
[1] n=number of children with a dog test positive; N=number of children no positive dog test
[2] RRs are adjusted for sex, birth order and the year of 11th fetal week

Table S7 Modification of the association between cat exposure and respective sensitisation by the occurrence of the 11th fetal week in pollen season, shown in format recommended by Knol et al [33].

Season of the 11th fetal week	Cat exposure				RR[2] (95% CI) for cat exposure within pollen season strata
	No		Yes		
	n/N[1]	RR[2] (95% CI)	n/N[1]	RR[2] (95% CI)	
Non-pollen season	16/1863	1.0 (Reference)	13/530	2.92 (1.40−6.08); p=0.004	2.93 (1.40−6.12); p=0.004
Pollen season	4/961	0.61 (0.20−1.83); p=0.374	14/246	8.53 (4.07−17.86); p<0.001	13.76 (4.51−42.04); p<0.001

Measure of effect modification on additive scale, RERI (95% CI) : 6.01 (1.47−15.2 by bootstrap); 6.01 (0.46−11.6 by delta method)
Measure of effect modification on multiplicative scale, ratio of RRs (95% CI) : 4.82 (1.42−31.9)
[1] n=number of children with a cat test positive; N=number of children no positive cat test
[2] RRs are adjusted for sex, birth order and the year of 11th fetal week