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Occurrence of pollen season at the end of the first trimester predicts clinical atopic diseases in the offspring: a Finnish population-based study

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Running head: Early pollen exposure and clinical atopy

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Abstract (Words 200)

Objective: To evaluate the association between potential exposure to different pollen concentrations at the 11th fetal week and subsequent clinical atopic diseases.

Study design and setting: Parents of 1- to 4-year-old children (N=3035) returned a questionnaire regarding physician-diagnosed atopic diseases. The children were born between 2001 and 2005 in the province of South Karelia, Finland. Results of allergy tests were collected from patient records in the area.

Results: The prevalence of atopic diseases with sensitisation was higher in children whose 11th fetal week occurred during pollen rather than non-pollen season: atopic eczema 6.3% vs. 4.3% (adjusted odds ratio, aOR 1.58, 95% CI 1.10─2.28), food allergy 5.7% vs. 3.9% (1.63; 1.12─2.38), respiratory allergy or asthma 3.7% vs. 2.2% (2.03; 1.24─3.33) and any atopic diseases 7.4% vs. 5.5% (1.48; 1.07─2.05), respectively. Respectively, the prevalence was higher in the children exposed to high rather than low tree pollen concentrations (>1000 vs. <10 particles/m^3) at the 11th fetal week: 12.1% vs. 4.4% (3.35; 1.89─5.95), 12.1% vs. 3.9% (3.77; 2.11─6.72), 4.7% vs. 2.5% (2.95; 1.21─7.20) and 14.0% vs. 5.7% (3.15; 1.86─5.35).

Conclusion: Coincidence of potential exposure to high tree pollen concentrations at the 11th fetal week is associated with subsequent clinical atopic diseases with sensitisation.

Keywords: *allergy; atopic sensitisation; atopy; child; pollen season; pollen exposure;*

Word count: main text 3683 words, abstract 200 words

Highlights

- Pollen season at the end of the first trimester may increase the occurrence of atopy

- Early prenatal exposure to high tree pollen concentrations is a risk factor to atopy

- Early prenatal pollen exposure may deviate immune response towards allergic phenotype

1. Introduction

Since the 1970s, several studies have found a variation of the occurrence of allergic sensitisation and atopic diseases depending on the season of birth (Aalberse et al., 1992, Kuzume and Kusu, 2007, Nilsson et al., 1997, Vassallo et al., 2010, Mullins and Camargo Jr, 2011). An association between the occurrence of the pollen season at the end of the first fetal trimester and subsequent sensitisation to food and pets (Pyrhönen et al., 2012, Pyrhönen et al., 2018) is in accordance with the findings of an elevated risk for sensitisation in children born in late autumn (Kuzume and Kusu, 2007, Pyrhönen et al., 2012, Mullins et al., 2011, de Groot et al., 1990, Björkstén and Suoniemi, 1976, Aalberse et al., 1992, Pyrhönen et al., 2018) and a higher concentration of detectable Immunoglobulin E (IgE) or total IgE in cord blood found in children born in winter than in summer (Susanto et al., 2017). On the contrary, children exposed to birch pollen during early infancy have been found to be at an elevated risk for sensitisation to seasonal allergens (Björkstén et al., 1980, Kihlström et al., 2002), and persistent grass pollen exposure before 6 months of age has previously been associated with subsequent hay fever and asthma (Erbas et al., 2013).

Early synthesis of IgE-antibodies has been detected on the 11th fetal week in the lung and liver (Miller et al., 1973, Hertz-Picciotto et al., 2008). Maternal exposure to environmental allergens in a period of early immune development may deviate immune programming towards Th2 type reactivity and allergic phenotype. The first cases of sensitisation to animal and food allergens appear soon after birth, and early incidence peaks occur before 6 months of age (Pyrhönen et al., 2019); thus, the time window for potential risk factors should precede these. However, clinical relevance of the seasonal variation of allergic sensitisation and its association with early pollen exposure is unclear.

The South Karelian Allergy Research Project (SKARP) included both questionnaire-based information on physician-diagnosed atopic diseases and independently collected results of allergy tests from patient records (Pyrhönen et al., 2012, Pyrhönen et al., 2011a, Pyrhönen et al., 2011b).

We evaluate here the associations between clinically relevant atopic diseases with allergic sensitisation as outcomes and the coincidence of the 11th fetal week with a) the calendar months; b) annual pollen seasons; and c) potential exposure to different concentrations of environmental pollen as potential risk factors.

2. Methods

2.1. Data collection

The entire SKARP population originally comprised all children (N=5973) born between April 2001 and March 2006 who resided in the province of South Karelia in South-East Finland one month before the time of the questionnaire survey. They were identified, and their demographic details obtained, from the Population Register of Finland. The youngest age class born between April 2005 and March 2006 (< 1 year old; recruited before 2 months of age) were excluded due to a short follow-up and a low occurrence of atopic diseases, and thus, the target study population comprised 4779 children aged 1 to 4 years (Fig. 1).

The questionnaire survey was carried out in the scheduled visits at local child health clinics between March 2005 and September 2006. The results of all allergy tests performed for diagnostic purposes (between April 2001 and September 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. The study protocol has been previously described in detail (Pyrhönen et al., 2012, Pyrhönen et al., 2011a, Pyrhönen et al., 2018, Pyrhönen et al., 2011b).

The protocol was reviewed by the Ethical Committee of the Northern Ostrobothnia Hospital District. 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 the permission to use their child's Personal Identification

Code (PIC) for the data linkage (to merge the individual test and questionnaire data). Forty-six parents did not consent to data linkage, and thus, data for these children were excluded from the present analyses. The study population was restricted to the children whose first residence was in the study area (based on the information of individual migration histories from the Population Register) (Fig. 1). The questionnaires were translated into English after the survey and are available at www.oulu.fi/ltk/node/29090.

2.2. Outcomes and explanatory variables

A positive result in skin prick tests (SPT) or specific immunoglobulin E (sIgE) indicates IgE-mediated *sensitisation* to specific allergens. The outcomes of the present paper included both the clinical diagnosis of atopic diseases, based on questionnaire data, and the immunological mechanism, IgE-mediated sensitisation to respective allergens, which were required for the positive outcome as follows (more detailed description in Appendix): *Atopic eczema with any sensitisation* (animal/pollen/any food item), *Respiratory allergy* (rhinoconjunctivitis/hay fever/pollen allergy/animal allergy) *with respective sensitisation* and *Asthma with any sensitisation* (animal/pollen/any food item). *Food allergy* was defined by using either a questionnaire-based, physician-diagnosed food allergy to cow's milk or cow's milk products, egg, fish or cereals (wheat/rye/barley), or a positive result in open food challenge (OFC) to the food items above and a positive result in an IgE test to respective food allergen(s). Then, *Respiratory allergy with sensitisation* and *Asthma with any sensitisation* were combined as *Respiratory allergy or asthma with sensitisation*, and all outcomes above were combined as *Any atopic disease with sensitisation*.

Our previous findings (Pyrhönen et al., 2018, Pyrhönen et al., 2012) were based only on the positive results of allergy tests (sIgE, SPT or OFC) neglecting allergic symptoms and diagnoses reported by the parents. Here, the test data were used as complementary information on physician diagnoses (OFC) and the detection of IgE-mediated immune mechanism. The cut-off point for a positive sIgE

was 0.35kU/l with RAST-CAP FEIA and Phadiatop Combi and 1.43 standardised units per ml with Magic Lite. A wheal diameter of 3mm or more was regarded as a positive SPT result. A positive result in OFC was based on the judgement marked in the patient records. Longitudinal outcomes included the age of the first positive result in sIgEs or SPTs, i.e. the *incidence of sensitisation and respective physician diagnosis of atopic disease* as described above.

The date of birth was based on the PIC. The PICs of the child and his/her siblings were compared, whereby the birth order of the child was defined as 'firstborn' or 'not firstborn'. The parents were advised to check the duration of pregnancy from the maternity card and mark it to the questionnaire. Gestational age is ascertained with ultrasound scan between the 11^{th} and 22^{nd} gestational weeks in more than 90% of pregnancies in the area (Pyrhönen et al., 2012). The calendar month of the respective fetal weeks was calculated by using the date of birth and the duration of pregnancy.

Daily mean counts of pollen grains per cubic metre of air were measured by a sampler on the roof level throughout the pollen seasons in the middle of the study area in the town of Joutseno. In the study area, 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. Measurements of daily pollen counts in the area have been previously reported in detail (Pyrhönen et al., 2018). The year of the 11^{th} fetal week was used as a crude indicator for variation of pollen concentrations measured in years 2001 to 2005 (Pyrhönen et al., 2012). Annual pollen seasons were defined to begin when the pollen concentrations (daily counts) exceeded the threshold concentration (alternatively 10 pollen or 50 tree pollen particles/m^3), and to end when the concentration remained below the threshold for at least a week.

2.3. Statistical methods

The prevalence of each outcome was at first calculated for calendar months falling at the end of the 11th fetal week and then for the coincidence of the date at the end of the 11th week and pollen season based on measurements of pollen concentrations in the area (Pyrhönen et al., 2018).

The prevalence odds ratios (OR) were calculated for different outcomes by calendar months of the 11th fetal week and by the coincidence of pollen season and the 11th week using logistic regression (function `glm` in R). The models were adjusted for gender, birth order, the year of the 11th fetal week as appropriate and the child's age at the time when the parents returned the questionnaire. The logistic regression was also used to regress the outcome events on harmonic terms (periodities of 12 and 6 months) of the time of the 11th fetal week (Pyrhönen et al., 2012). Additionally, the analysis was repeated with the longitudinal outcomes using the Cox models (function `coxph` in R). The R environment release 3.5.1 was used for all the analyses (www.r-project.org).

The calendar dates for the entire fetal period of each child were merged with the respective daily pollen counts. Thereafter, the maximum pollen concentration at the 11th fetal week was calculated, categorised and included into the logistic regression model as a potential exposure factor. The logistic regression models were adjusted for gender, birth order and the child's age at the time when the parents returned the questionnaire. The Kaplan-Meier method was used to describe the cumulative incidences of the outcomes according to potential exposure of different pollen concentration levels.

Sensitivity analysis was performed to comprise the coincidence of pollen season and alternatively the entire 11th fetal week (7 days) and partly three-week period between the 10th and 12th fetal weeks. Since the place of measuring the pollen concentrations was changed after the pollen season of the year 2001, the measurements of pollen concentrations between year 2001 and 2002 to 2005 are not necessarily comparable. Therefore, the cumulative incidences of longitudinal outcomes

according to different levels of potential pollen exposure at the 11th fetal week were repeated in the subpopulation of children born between April 2002 to March 2005.

The information on the date of birth was available for the entire population, and information on the duration of pregnancy was reported by most parents of the survey participants (91%) (Fig. 1). The missing information on the duration of pregnancy was compensated in 271 children by using the mean duration of pregnancy (278.2 days).

Potential effect modification by parental atopy (and maternal physician-diagnosed pollen allergy) was examined and reported by estimates (with 95% confidence intervals) of relative excess risk due to interaction (RERI) in additive and the RR-ratio in multiplicative scales (detailed description in Appendix) (Pyrhönen et al., 2018, Knol et al., 2012).

3. Results

Parents of 3035 children returned the questionnaire regarding the atopic diseases and allowed the data linkage between the questionnaire survey and allergy test data (Fig. 1). In our study population, 51% (1546/3035) of children were boys, 46% (1395/3035) firstborn, and 52% (1567/3035) had the first residence in the provincial capital, 25% (770/3035) in another urban area and 23% (698/3035) in a rural municipality in the area.

In our study population, 34% (38/113) of children with physician-diagnosed asthma, 27% (144/539) of children with atopic eczema, and 26% (186/724) of children with any atopic disease were sensitised to animal, pollen or any food allergens. Sensitisation to essential food allergens (cow's milk, hen's egg, cereals or fish) and respiratory allergens were found in 56% (133/257) of children with physician-diagnosed food allergy and 35% (57/161) with respiratory allergy, respectively.

3.1. Calendar month at the 11th fetal week and birth and clinical atopic diseases

Up to the age of the questionnaire survey, the prevalences of all atopic diseases with sensitisation were highest in children whose 11th fetal week occurred in April to June or July (Table 1 and A.1 and Fig. 2), except asthma with any sensitisation alone, in which the figure was more equivocal. Contrary to this, the children who had experienced the 11th fetal week in November or December, in non-pollen season, had consistently the lowest prevalences of all atopic diseases with sensitisation. These findings could be repeated by including longitudinal outcomes into the Cox models instead of respective cross-sectional outcomes into the logistic regression models (Fig. 2). Additionally, the cumulative incidences of atopic diseases with sensitisation according to the calendar month of birth and calendar month of the 11th fetal week are very well in line (Fig. A.1).

3.2. Potential pollen exposure at the 11th fetal week and clinical atopic diseases

The prevalences of atopic diseases with sensitisation were consistently higher in the children whose end of the 11th fetal week occurred in pollen rather than non-pollen season (Table 2). Regardless of whether we inspected the coincidence of pollen season and alternatively the entire 11th fetal week or a partly three-week period around the 11th fetal week, these findings remained (Table A.2-A.3). The association was stronger between pollen season at the 11th fetal week and each atopic disease with sensitisation when the pollen season was defined according to the threshold level of 50 tree pollen particles/m^3 instead of 10 pollen particles/m^3 (Table 2, A.2 and A.3).

The children potentially exposed to an extremely high concentration (maximum >1000 particles/m^3) of tree pollen at their 11th fetal week had a higher lifetime prevalence of atopic diseases with sensitisation than those with a very low exposure: atopic eczema 12.1% vs. 4.4% (adjusted Odds ratio, aOR 3.35, 95% CI 1.89─5.95), food allergy 12.1% vs. 3.9% (aOR 3.77, 95% CI 2.11─6.72), respiratory allergy 4.7% vs. 2.5% (aOR (2.95, 95% CI 1.21─7.20) and any atopic disease 14.0% vs. 5.7% (aOR 3.15, 95% CI 1.86─5.35) (Table A.4, Fig. 3). A similar pattern of associations could be

seen with respective levels of maximum pollen exposure at the three weeks period: from the beginning of the 10th to the end of 12th fetal week (Fig. A.2). A weaker association between grass and mugwort exposure than between tree pollen and the occurrence of atopic diseases might be explained by much lower annual concentrations of grass and mugwort than that of tree pollen in Finland (Fig. 3 and A.2).

The children potentially exposed to higher pollen concentrations at the 11th fetal week had also a higher cumulative incidence of sensitisation with clinical atopic diseases than children without exposure or exposure to low pollen concentrations at the 11th fetal week (Fig. 4 and A.3). Because of suspected incomparability of the pollen measurements between years, the same analysis was repeated in the subpopulation of 1- to 3-year-old children. One age class was excluded, and the findings remained (Fig. A.4).

Additionally, we included parental atopy into the models, but only a weak effect could be seen (Table 2, Table A.2., A.3. and A.5.). We found that the effect of the 11th fetal week at pollen season (although the threshold was either 10 or 50 pollen particles per m^3) was not modified by parental atopy or maternal pollen allergy (Table A.6., A.7 and A.8.).

4. Discussion

We found ~~a~~ strong population-based evidence that children whose 11th fetal week coincided with tree pollen season and that were potentially exposed to a high concentration of pollen in Finland had an increased risk to a subsequent clinical diagnosis of atopic disease with respective sensitisation.

In a period of early immune development, maternal exposure to environmental allergens has been proposed to lead towards Th2 type reactivity and allergic phenotype via epigenetic programming (DeVries and Vercelli, 2015, Sabounchi et al., 2015). Epigenetic programming is a chain reaction of epigenetic modifications of immunoregulatory genes, which are responsible for regulation of T cell

differentiation and the balance between various T helper cell subsets (DeVries and Vercelli, 2015, Sabounchi et al., 2015). The synthesis of IgE and allergen-specific IgE has been reported as early as in the 11th (Miller et al., 1973, Hertz-Picciotto et al., 2008) and from the 22nd fetal week (Warner et al., 1996, Jones et al., 1996), respectively. In these time windows, maternal exposure to high allergen concentrations may deviate the immune system of the offspring towards Th2 type reactivity and lead to allergic sensitisation and finally to clinical atopic diseases, which might explain the immunologic background of our findings. Exposure to the respective allergen may be prerequisite to the development of sensitisation to specific allergens (Pyrhönen et al., 2018). However, we did not have tissue or serum samples of the fetus and his/her mothers, and thus, we cannot provide more detailed evidence on biological mechanisms of immune development.

Vitamin D has been hypothesised to act as a regulator in the immune system adapting the balance between Th1 and Th2 (Bozzetto et al., 2012). Maternal 25-hydroxyvitamin D status may vary according to seasons (Morales et al., 2012, Lamberg-Allardt et al., 2001), and therefore, it is another potential risk factor and alternative explanation to the seasonal variations of the occurrences of IgE-mediated sensitization. Thus far, controversial or no associations have been reported between maternal vitamin D status and subsequent atopy (Litonjua et al., 2016, Wills et al., 2013) or sensitisation in offspring (Wills et al., 2013, Hennessy et al., 2018). Additionally, other variables with seasonal variation such as viral infections or postnatal pollen exposure may also have contribution or interaction with prenatal pollen exposure, but could not be evaluated further here.

Our findings on the lowest occurrence of respiratory allergy are in line with previous studies regarding the lowest occurrence of sensitisation to animal allergens in children born in July (Björkstén and Suoniemi, 1976, Schafer et al., 1993) and in June (corresponding to December at the 11th fetal week) (de Groot et al., 1990). Forty years ago, the highest risk for positive test results for animal epithelia was reported in Finnish children born in March-May and September-November (Björkstén and Suoniemi, 1976) (September-November and March-May at the 11th fetal week,

respectively). Our findings are also consistent with the previous findings on the seasonal variation of sensitisation to food allergens (Pyrhönen et al., 2012, Mullins et al., 2011, Keet et al., 2012). According to a recent meta-analysis, children born in winter had higher odds of elevated cord blood IgE (Susanto et al., 2017), although total-IgE does not necessarily associate with subsequent atopic diseases like sIgEs.

Cumulative exposure to grass pollen in the time window from birth to 3 and 6 months of age has previously been associated with subsequent sensitisation to aeroallergens and asthma (Erbas et al., 2013), respectively, but not with diagnosis of food allergies or atopic eczema with sensitization. In our study area, most children whose 11th fetal week coincided with tree pollen season (peak in May) are re-exposed to peak concentrations (threshold 50 particles per m^3) of tree pollen after 4 months of age and none before 3 months of age, respectively. Thus, pollen exposure at birth or in the first four months of age is a quite unlikely explanation to our findings. Due to a short follow-up (the questionnaire survey at 1 to 4 years of age), we could not rule out a possibility that repeated pollen exposure in later life might also contribute to the development process of asthma and sensitisation to pollen allergens, and in different countries, pollen of various species of plants may also have different effects on the immune response. However, in our population, the incidences of sensitisation to animal and food allergens and food allergy start to arise soon after birth and peaked before 6 months of age, and thus, the time window for their potential risk factors should precede these peaks (Pyrhönen et al., 2019).

The main strength of our study is the epidemiological study design, an observational longitudinal and population-based setting with participants born in four consecutive calendar years representing four age classes. Our real-world test data could be individually linked with a large questionnaire survey. The entire general population was well-represented among the participants regarding allergy tests and their positive results (Pyrhönen et al., 2011a, Pyrhönen et al., 2011b). In Finland, exposure to the environmental factors such as concentrations of pollen and sunlight clearly vary according to

four seasons, which enable estimations of seasonal variability to morbidity. Although our study is an observational study, it can be regarded as a natural experiment since the calendar time of pregnancy is probably independent of other risk factors related to atopic diseases.

The main weakness of our study is probably the questionnaire survey, which is often prone to a recall bias and selection of participants. However, our study population was under 5 years of age at the time of the questionnaire survey, and therefore, a recall bias is less likely. Moreover, a recall bias is obviously independent of the calendar time of any fetal phases. A selection of participants may potentially be related to a low participation rate of a questionnaire survey. However, the participation rate of our questionnaire survey regarding a general population was very high (Nwaru et al., 2014).

Another limitation of our results may be considered a potential misclassification of the outcomes for different reasons. In Finland, small children regularly visit child health clinics, where allergic symptoms are screened, and a physician consulted when needed. The children with allergic symptoms are likely to become tested by the public health care system for allergic sensitisation or food allergies (OFC), since the appropriate diagnosis is a prerequisite for the reimbursement of the costs due to consumption of medicines, creams or special cow's milk supplements. Ordering of tests for allergic sensitisation might depend on physicians and available tests in the health care centre. None of these potential reasons for misclassification of the outcomes should, however, be dependent on the seasons of different phases of pregnancy.

5. Conclusions

The present study provided a relatively strong association between the coincidence of pollen season (as well as potential exposure to high concentrations of tree pollen) and the time window of around the 11th fetal week and subsequent clinical atopic diseases with allergic sensitisation. Present

findings motivate further studies to replicate and confirm our findings in other populations. Further studies should inspect potential effects of pollen exposure at other possible time windows from preconception to early childhood, and the studies with a longer follow-up should focus on the seasonal, environmental and prenatal risk factors with seasonal variation through which morbidity and burden of these public health diseases might be effectively prevented in populations.

Conflicts of interest: None

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Appendix

Combination of the clinical atopy with allergic sensitisation as the outcomes:

The history of physician-diagnosed atopic diseases and a positive result in skin prick test (SPT) or specific immunoglobulin E (sIgE) i.e. *sensitisation* to respective allergens and positive open food challenges (OFC) were combined as follows:

1) ***Atopic eczema diagnosis*** (i.e. 'atopic rash' asked as 'infantile or atopic eczema') *with sensitisation to any allergens* (animal/pollen/any food item)

2) ***Food allergy*** (either physician-diagnosed food allergy to cow's milk or cow's milk products, egg, fish or cereals; wheat/rye/barley reported in the questionnaires or a positive OFC to these food items) *with sensitisation to respective food items: e.g. physician diagnosed cow's milk allergy* reported in the questionnaire or *a positive OFC to cow's milk* and *a positive SPT or sIgE to cow's milk.*

3) ***Respiratory allergy*** (physician-diagnosed rhinoconjunctivitis, hay fever, pollen allergy or allergic conjunctivitis i.e. 'allergic inflammation of the eyes', animal allergy i.e. allergy to dog, cat or other animal) *with sensitisation to respective allergens*

4) ***Asthma diagnosis*** *with sensitisation to any allergens* (animal/pollen/any food item).

Altogether 200 children had sensitisation to food, animal or pollen allergen(s), out of which 14 children had not been diagnosed respective atopic disease and were here classified as non-cases: 3 children had parental-perceived symptoms for respective food allergens, 6 children had sensitisation to food item(s) without any symptoms, one child with sensitisation to cow's milk had missing information on food allergy symptoms, one had sensitisation but had never tasted soya, two children had sensitisation to animal(s) without reported symptoms and one child had physician-diagnosed cow's milk allergy but sensitisation to dog allergens only. Altogether 6 children had food allergy to other food items alone, thus they were not considered here as having food allergy.

Effect modification

Potential effect modification by parental atopy (and maternal physician-diagnosed pollen allegy) was examined and reported by estimates of relative excess risk due to interaction (RERI) in additive and the RR-ratio in multiplicative scales [Pyrhönen et al 2018, Knol et al 2012]. The estimates of RERI and RR-ratio were calculated by entering Var1 for the main effect (the end of 11th fetal week at pollen season) and Var2 for the parent's atopy into the models as follows:

M1 = coxph(Surv(RiskTime, Outcome.status) ~ Var1 + Var2 + Var1:Var2)
est1 = coef(M1)[1]; est2 = coef(M1)[2]; est3 = coef(M1)[3];
Additive scale i.e. RERI = exp(est1 + est2 + est3) – est1 – est2 + 1
Multiplicative scale i.e. RR-ratio = exp(est1 + est2 + est3) / (exp(est1)*exp(est2))

The 95% confidence intervals (CI) for the both RERIs and the RR-ratios were calculated by the bootstrap using `boot.ci` function of the boot package of the R (1000 replications) [Pyrhönen et al 2018, Goldstein N 2016].

Figure legends

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

Figure 2. Prevalence Odds ratios (ORs on the left plots) and respective Hazard ratio (HRs on the right plots) of physician-diagnosed atopic manifestations with sensitisation (positive result in sIgE/SPT) shown by the calendar month of the 11th fetal week. The points indicate monthly ORs and HRs (vertical segments for 95% confidence intervals) from the logistic regression and Cox models, respectively, adjusted for gender, birth order and year at the end of the 11th fetal week. Continuous lines are ORs and HRs smoothed by adjusted harmonic models with periodicities of 12 and 6 months, shaded areas representing their 95% confidence bands. Pollen seasons (average weekly pollen concentrations >10 particles/m^3 in years 2001-5) are indicated by grey (alder & birch) and light grey areas (grass & mugwort) in the plots.

Figure 3. Prevalence odds ratios (with 95% confidence intervals) of physician-diagnosed atopic diseases with sensitisation according to the different categories of maximum pollen concentrations in environment at the 11th fetal weeks for grass and mugwort and for alder and birch pollen. Note the logarithmic scale of x- and y-axis.

Figure 4. Cumulative incidences of physician-diagnosed atopic diseases with sensitisation according to the maximum exposure of tree pollen concentrations at the 11th fetal week in the left plots. The plots on the right side indicate respective Hazard ratios (from adjusted Cox model; the reference category shown by grey lines of the left and points in the right side) of physician-diagnosed atopic diseases with sensitisation according to the respective categories of environmental tree pollen concentrations. Note the logarithmic scale of x- and y-axes on the plots of the right side.

Table 1. Prevalence (%) of children (number of children in the parentheses) with both physician-diagnosed atopic disease and sensitisation (positive test results to sIgE/SPT) to respective allergens according to calendar month for the end of the 11th fetal week.

Calendar month	Atopic eczema		Food * allergy		Respiratory allergy		Allergic asthma		Allergic asthma or respiratory allergy		Any atopic disease	
	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)	%	(n/N)
Jan	4.8	(12/252)	3.7	(10/269)	2.4	(6/253)	1.6	(4/257)	3.2	(8/252)	6.2	(17/273)
Feb	4.6	(12/261)	5.9	(16/269)	2.4	(6/252)	2.0	(5/255)	2.8	(7/250)	6.6	(18/273)
Mar	4.5	(10/223)	3.1	(7/225)	0.5	(1/219)	0.4	(1/223)	0.9	(2/219)	4.3	(10/230)
Apr	7.6	(19/241)	8.5	(21/258)	3.7	(9/242)	2.0	(5/247)	4.6	(11/240)	8.4	(22/261)
May	7.0	(16/230)	6.0	(14/232)	2.7	(6/222)	2.2	(5/226)	4.5	(10/221)	8.9	(21/235)
Jun	7.5	(16/213)	5.9	(13/222)	3.3	(7/212)	—	(0/214)	3.3	(7/210)	9.0	(20/223)
Jul	5.6	(14/248)	3.1	(8/257)	2.9	(7/239)	2.0	(5/251)	3.8	(9/239)	6.2	(16/259)
Aug	4.3	(9/210)	4.2	(9/215)	1.0	(2/207)	1.0	(2/209)	1.9	(4/206)	5.0	(11/218)
Sep	3.8	(10/263)	3.3	(9/273)	1.6	(4/254)	0.8	(2/262)	1.6	(4/254)	4.7	(13/275)
Oct	4.1	(10/241)	4.4	(11/248)	2.6	(6/233)	1.3	(3/236)	2.6	(6/231)	6.4	(16/251)
Nov	3.3	(8/246)	2.0	(5/253)	0.4	(1/235)	0.4	(1/243)	0.9	(2/235)	3.4	(9/261)
Dec	3.0	(8/266)	3.6	(10/275)	0.8	(2/252)	1.9	(5/264)	2.0	(5/252)	4.7	(13/276)
Total	5.0	(144/2902)	4.4	(133/2996)	2.0	(57/2820)	1.3	(38/2887)	2.7	(75/2809)	6.1	(186/3035)

N: group size; *n*: number of cases (in parentheses)

*Physician-diagnosed food allergy or positive open food challenge with respective allergic sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish

Table 2. Lifetime prevalence (%) and the prevalence Odds ratios (OR; non-pollen season, i.e. pollen concentration below the threshold at the end of the 11th fetal week as a reference category) of physician-diagnosed atopic diseases with sensitisation by the coincidence of pollen season and the end of the 11th fetal week.

			Coincidence of pollen season and the end of the 11th fetal week threshold 10 pollen particles/m3						threshold 50 tree pollen particles/m3					
			Yes N=982		No N=2053				Yes N=319		No N=2716			
Atopic disease	N	(n)	%	(n)	%	(n)	OR* OR†	95% CI 95% CI	%	(n)	%	(n)	OR* OR†	95% CI 95% CI
Atopic eczema	2902	(144)	6.3	(60)	4.3	(84)	1.58	[1.10, 2.28]	8.4	(26)	4.6	(118)	2.04	[1.28, 3.25]
with any sensitisation							1.54	[1.07, 2.22]					2.03	[1.27, 3.26]
Food allergy‡	2996	(133)	5.7	(55)	3.9	(78)	1.63	[1.12, 2.38]	8.0	(25)	4.0	(108)	2.32	[1.44, 3.75]
with respective sensitisation							1.58	[1.08, 2.31]					2.26	[1.40, 3.67]
Respiratory allergy	2820	(57)	2.9	(27)	1.6	(30)	2.27	[1.29, 3.97]	3.0	(9)	1.9	(48)	2.47	[1.13, 5.43]
with respective sensitisation							2.19	[1.25, 3.83]					2.49	[1.13, 5.50]
Allergic asthma	2887	(38)	1.5	(14)	1.2	(24)	1.55	[0.76, 3.16]	1.0	(3)	1.4	(35)	1.05	[0.31, 3.62]
with any sensitisation							1.46	[0.72, 2.99]					1.04	[0.30, 3.61]
Respiratory allergy or asthma &	2809	(75)	3.7	(34)	2.2	(41)	2.03	[1.24, 3.33]	3.7	(11)	2.5	(64)	1.97	[0.98, 3.97]
with respective sensitisation							1.96	[1.19, 3.21]					1.97	[0.98, 3.99]
Any atopic disease	3035	(186)	7.4	(73)	5.5	(113)	1.48	[1.07, 2.05]	9.4	(30)	5.7	(156)	1.88	[1.22, 2.90]
with any sensitisation							1.43	[1.03, 1.99]					1.85	[1.20, 2.87]

N: group size; n: number of cases (in parentheses); %: Prevalence of the outcome i.e. atopic disease with sensitisation

* Adjusted by sex, birth order, the year of the 11th fetal week and the child's age when the parents filled the questionnaire.

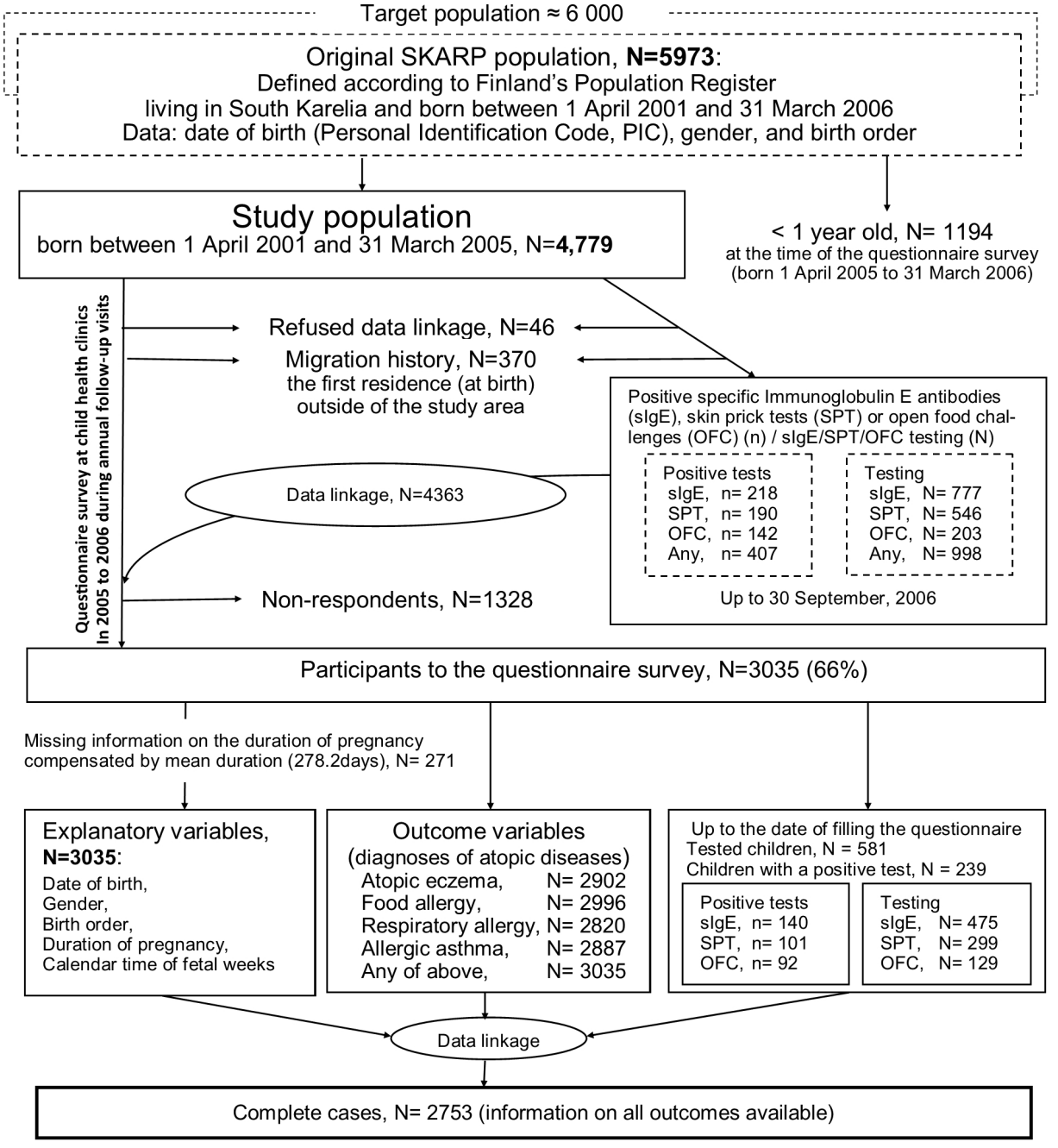
† Adjusted by above variables and additionally by parental atopy

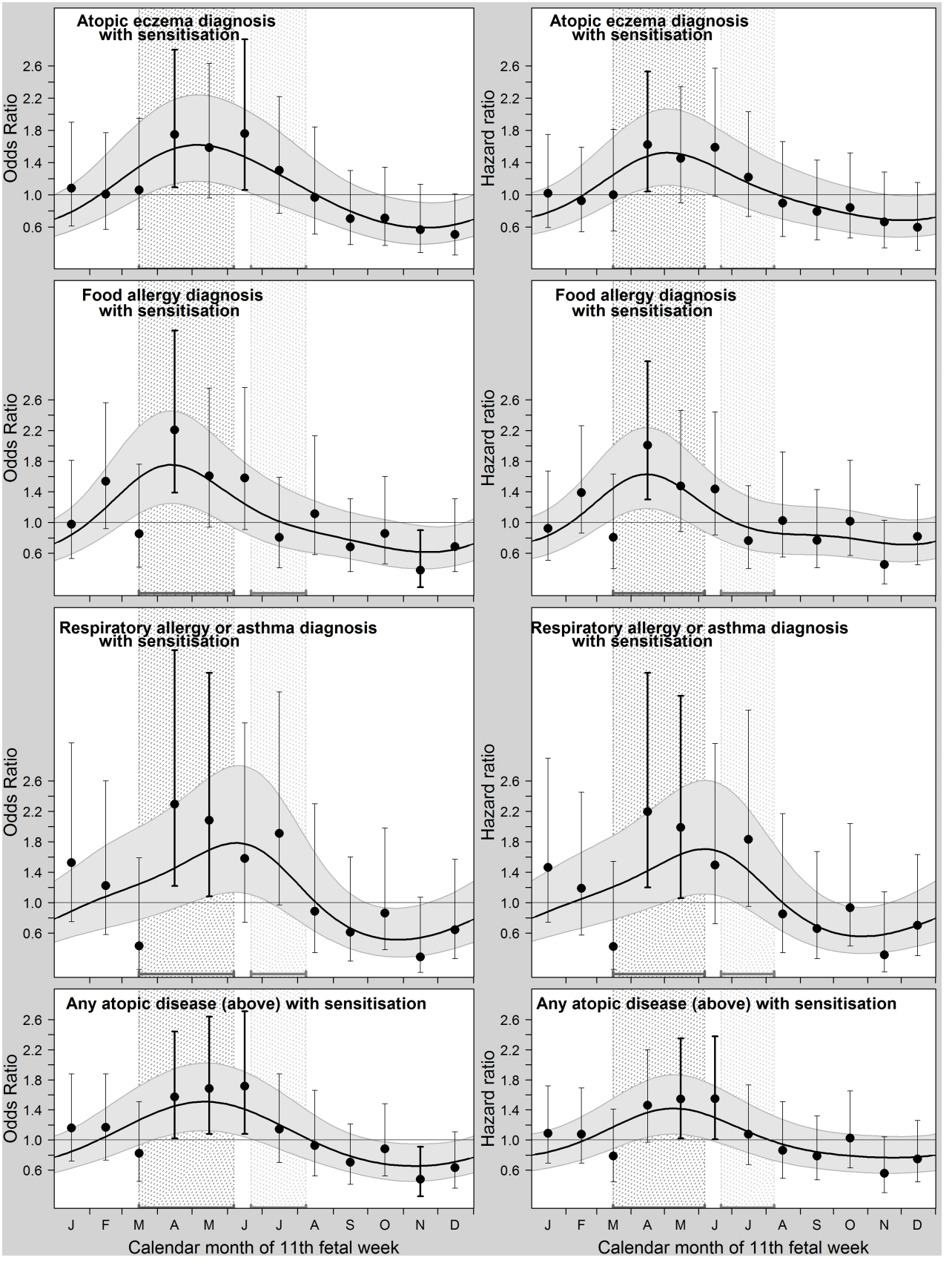
‡ Physician-diagnosed food allergy or positive open food challenge with respective allergic sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

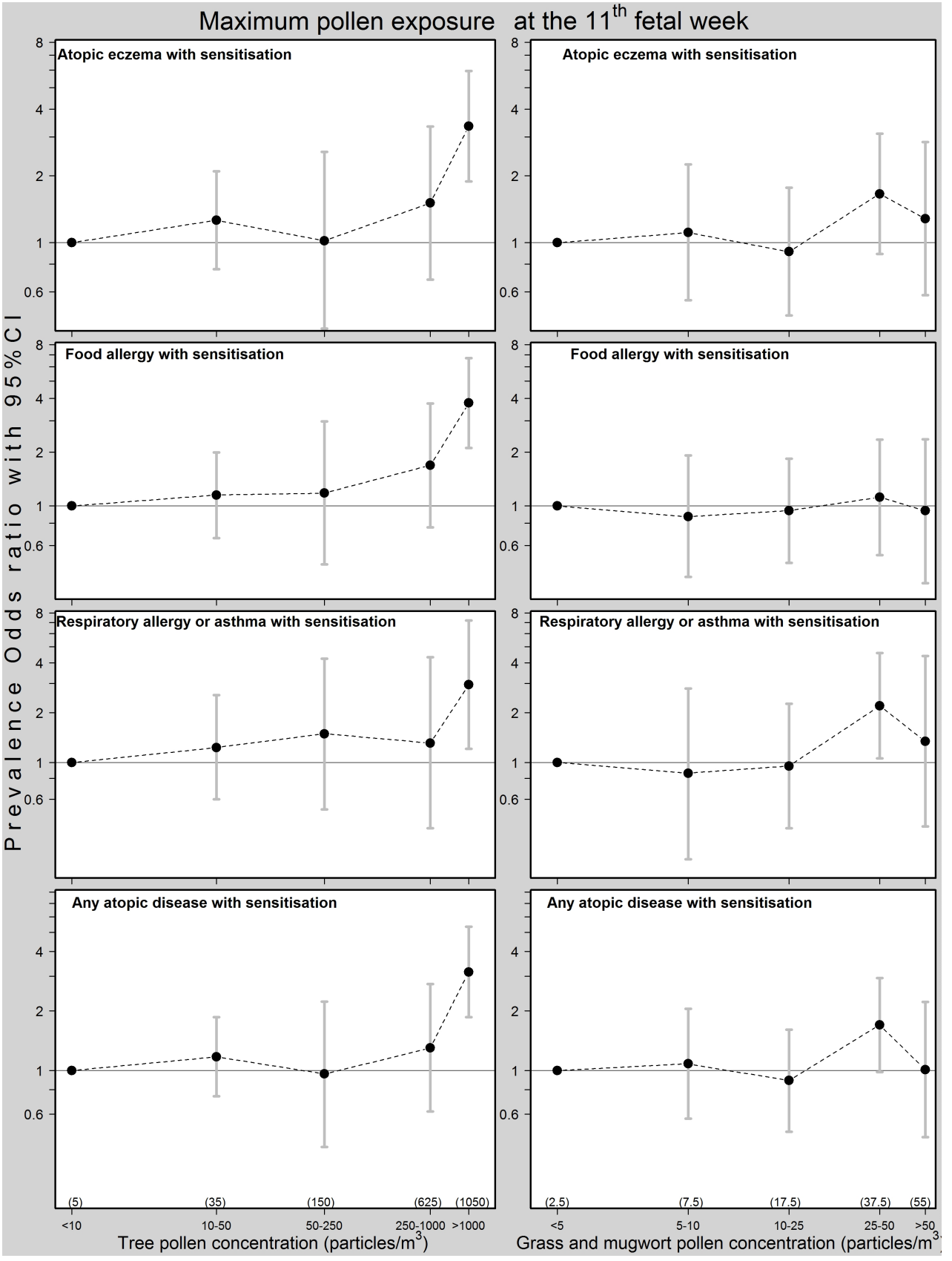
Table legends

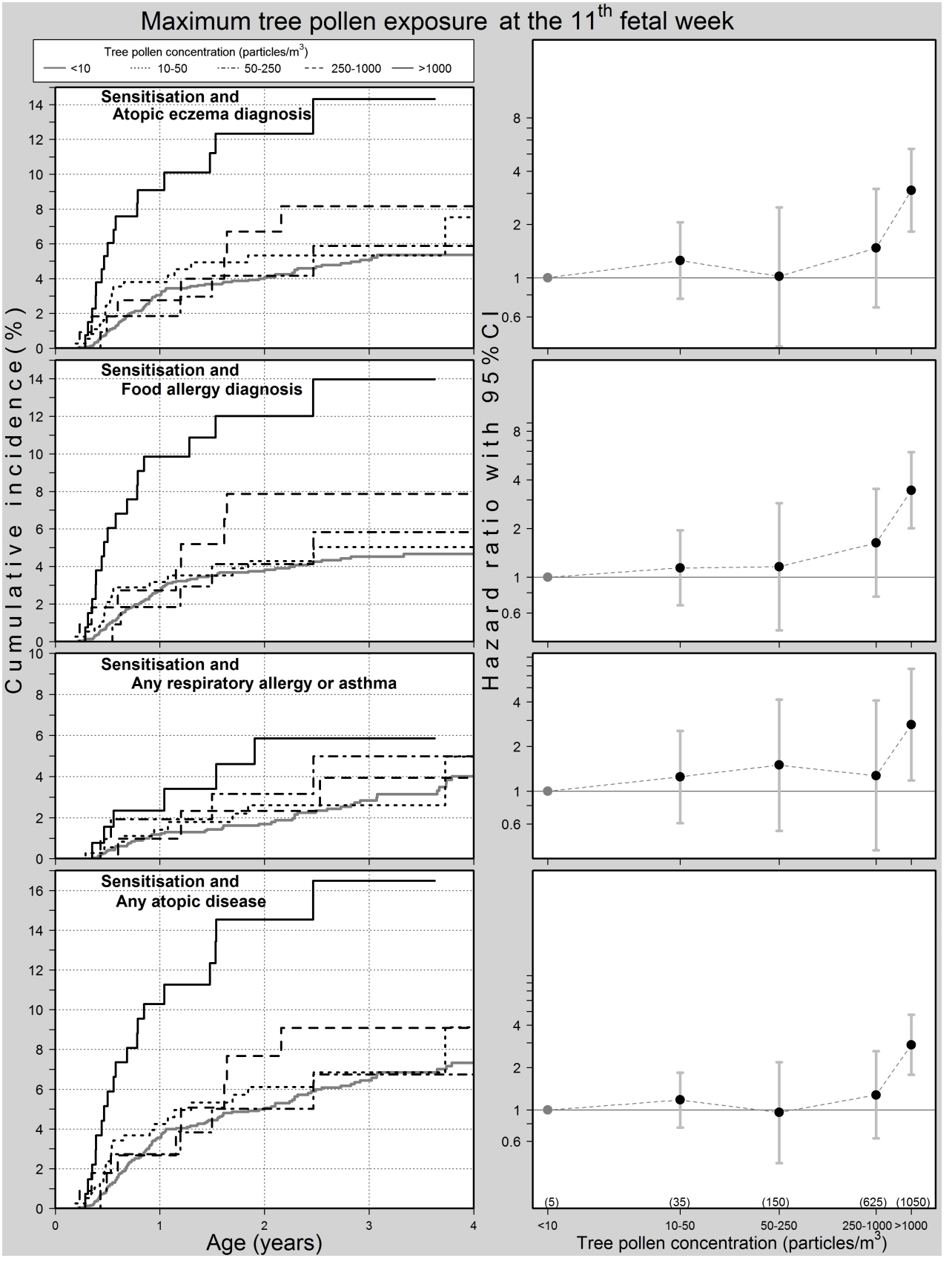
Table 1. Prevalence (%) of children (number of children in the parentheses) with both physician-diagnosed atopic disease and sensitisation (positive test results to sIgE/SPT) to respective allergens according to calendar month for the end of the 11th fetal week.

Table 2. Lifetime prevalence (%) and the prevalence Odds ratios (OR; non-pollen season, i.e. pollen concentration below the threshold at the end of the 11th fetal week as a reference category) of physician-diagnosed atopic diseases with sensitisation by the coincidence of pollen season and the end of the 11th fetal week.


Target population ≈ 6 000
Original SKARP population, N=5973:
Defined according to Finland's Population Register
living in South Karelia and born between 1 April 2001 and 31 March 2006
Data: date of birth (Personal Identification Code, PIC), gender, and birth order
Study population
born between 1 April 2001 and 31 March 2005, N=4,779
< 1 year old, N= 1194
at the time of the questionnaire survey
(born 1 April 2005 to 31 March 2006)
Questionnaire survey at child health clinics
In 2005 to 2006 during annual follow-up visits
Refused data linkage, N=46
Migration history, N=370
the first residence (at birth)
outside of the study area
Positive specific Immunoglobulin E antibodies (sIgE), skin prick tests (SPT) or open food challenges (OFC) (n) / sIgE/SPT/OFC testing (N)
Positive tests
sIgE, n= 218
SPT, n= 190
OFC, n= 142
Any, n= 407
Testing
sIgE, N= 777
SPT, N= 546
OFC, N= 203
Any, N= 998
Up to 30 September, 2006
Data linkage, N=4363
Non-respondents, N=1328
Participants to the questionnaire survey, N=3035 (66%)
Missing information on the duration of pregnancy
compensated by mean duration (278.2days), N= 271
Explanatory variables,
N=3035:
Date of birth,
Gender,
Birth order,
Duration of pregnancy,
Calendar time of fetal weeks
Outcome variables
(diagnoses of atopic diseases)
Atopic eczema, N= 2902
Food allergy, N= 2996
Respiratory allergy, N= 2820
Allergic asthma, N= 2887
Any of above, N= 3035
Up to the date of filling the questionnaire
Tested children, N = 581
Children with a positive test, N = 239
Positive tests
sIgE, n= 140
SPT, n= 101
OFC, n= 92
Testing
sIgE, N= 475
SPT, N= 299
OFC, N= 129
Data linkage
Complete cases, N= 2753 (information on all outcomes available)


Atopic eczema diagnosis with sensitisation
Odds Ratio
Hazard ratio
Food allergy diagnosis with sensitisation
Respiratory allergy or asthma diagnosis with sensitisation
Any atopic disease (above) with sensitisation
2.6
2.2
1.8
1.4
1.0
0.6
J F M A M J J A S O N D
Calendar month of 11th fetal week


Maximum pollen exposure at the 11th fetal week
Atopic eczema with sensitisation
Atopic eczema with sensitisation
Food allergy with sensitisation
Food allergy with sensitisation
Respiratory allergy or asthma with sensitisation
Respiratory allergy or asthma with sensitisation
Any atopic disease with sensitisation
Any atopic disease with sensitisation
Prevalence Odds ratio with 95% CI
8
4
2
1
0.6
(5)
(35)
(150)
(625)
(1050)
<10
10-50
50-250
250-1000
>1000
Tree pollen concentration (particles/m3)
(2.5)
(7.5)
(17.5)
(37.5)
(55)
<5
5-10
10-25
25-50
>50
Grass and mugwort pollen concentration (particles/m3)


Maximum tree pollen exposure at the 11th fetal week
Tree pollen concentration (particles/m3)
<10
10-50
50-250
250-1000
>1000
Sensitisation and
Atopic eczema diagnosis
Sensitisation and
Food allergy diagnosis
Sensitisation and
Any respiratory allergy or asthma
Sensitisation and
Any atopic disease
Cumulative incidence (%)
Hazard ratio with 95% CI
Age (years)
(5)
(35)
(150)
(625)
(1050)
<10
10-50
50-250
250-1000
>1000
Tree pollen concentration (particles/m3)

Pyrhönen K, Kulmala P

Occurrence of pollen season at the end of the first trimester predicts clinical atopic diseases in the offspring: a Finnish population-based study

Supplementary material
Tables A.1-A.8 and Figures A.1-A.4
16 December 2019

Table A.1. Prevalence odds ratios (OR) of children with physician-diagnosed atopic diseases together with sensitisation (a positive sIgE/SPT) by the calendar month at the end of the 11^{th} fetal week.

Calendar month of 11^{th} fetal week	**Atopic eczema**		**Food allergy***		**Allergic asthma or respiratory allergy**		**Any atopic disease**	
	OR	95% CI †	OR	95% CI †	OR	95% CI †	OR	95% CI †
Jan	1.08	0.61, 1.90	0.98	0.53, 1.80	1.53	0.75, 3.10	1.16	0.72, 1.88
Feb	1.00	0.57, 1.77	1.53	0.92, 2.55	1.23	0.58, 2.60	1.17	0.73, 1.88
Mar	1.06	0.57, 1.95	0.85	0.42, 1.75	0.43	0.12, 1.59	0.82	0.45, 1.51
Apr	1.75	1.09, 2.80	2.31	1.47, 3.63	2.29	1.22, 4.32	1.57	1.02, 2.44
May	1.58	0.96, 2.63	1.60	0.93, 2.74	2.08	1.08, 4.02	1.68	1.08, 2.64
Jun	1.76	1.06, 2.93	1.57	0.90, 2.74	1.58	0.74, 3.36	1.72	1.08, 2.71
Jul	1.30	0.77, 2.22	0.80	0.41, 1.58	1.91	0.97, 3.77	1.15	0.70, 1.88
Aug	0.97	0.51, 1.84	1.11	0.58, 2.12	0.88	0.34, 2.30	0.92	0.52, 1.66
Sep	0.70	0.38, 1.30	0.68	0.36, 1.30	0.61	0.23, 1.60	0.70	0.41, 1.21
Oct	0.71	0.37, 1.34	0.86	0.46, 1.59	0.86	0.38, 1.98	0.88	0.52, 1.48
Nov	0.56	0.28, 1.13	0.38	0.16, 0.89	0.29	0.08, 1.07	0.48	0.25, 0.91
Dec	0.51	0.25, 1.01	0.69	0.36, 1.30	0.64	0.26, 1.57	0.63	0.36, 1.11

*Physician-diagnosed food allergy or positive open food challenge with sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

†Adjusted by sex, birth order, the year of the 11^{th} fetal week and the child's age when the parents filled the questionnaire.

Table A.2. Prevalence (%) and prevalence odds ratio (OR; with 95% confidence intervals) of physician-diagnosed atopic diseases with sensitisation (sIgE/SPT) to respective allergens by the coincidence of pollen season with the 11^{th} fetal week (entire weeks of 7 days) and by at least partly coincidence of pollen season with the period from beginning of the 10^{th} to the end of the 12^{th} fetal week.

			Coincidence of pollen season									
			with the entire 11^{th} fetal week					**between the 10^{th} and 12^{th} fetal week**				
			Yes $N = 858$		No $N = 2177$			Yes $N = 1224$		No $N = 1811$		
Diagnosis	N	(n)	%	(n)	%	(n)	OR [95% CI] *	%	(n)	%	(n)	OR [95% CI] *
Atopic eczema with any sensitisation	2902	*(144)*	6.8	*(56)*	4.2	*(88)*	1.71 [1.19, 2.46] (1.68; 1.16, 2.43)	6.2	*(73)*	4.1	*(71)*	1.63 [1.13, 2.35] (1.60; 1.11, 2.30)
Food allergy† with respective sensitisation	2996	*(133)*	5.9	*(50)*	3.9	*(83)*	1.67 [1.14, 2.45] (1.63; 1.11, 2.39)	5.1	*(62)*	4.0	*(71)*	1.40 [0.96, 2.05] (1.36; 0.93, 1.98)
Respiratory allergy with respective sensitisation	2820	*(57)*	3.0	*(24)*	1.6	*(33)*	2.19 [1.24, 3.84] (2.14; 1.21, 3.76)	2.7	*(31)*	1.6	*(26)*	2.04 [1.16, 3.59] (1.96; 1.11, 3.45)
Allergic asthma with any sensitisation	2887	*(38)*	1.5	*(12)*	1.3	*(26)*	1.42 [0.69, 2.95] (1.36; 0.66, 2.83)	1.4	*(16)*	1.3	*(22)*	1.33 [0.66, 2.69] (1.26; 0.62, 2.55)
Respiratory allergy or asthma with respective sensitisation	2809	*(75)*	3.8	*(30)*	2.2	*(45)*	1.93 [1.17, 3.17] (1.88; 1.14, 3.10)	3.5	*(40)*	2.1	*(35)*	1.94 [1.17, 3.19] (1.87; 1.13, 3.08)
Any atopic disease with any sensitisation	3035	*(186)*	7.9	*(68)*	5.4	*(118)*	1.60 [1.15, 2.22] (1.56; 1.12, 2.17)	7.1	*(87)*	5.5	*(99)*	1.43 [1.03, 1.97] (1.38; 1.00, 1.91)

N:group size; n: number of cases (in parentheses); %: Prevalence of the outcome i.e. atopic disease with sensitisation

*Adjusted by sex, birth order, the year of the 11^{th} fetal week and the child's age when the parents filled the questionnaire (in the parentheses below the ORs with 95%CI from the models adjusted by the above variables and additionally by parental atopy .

†Include physician-diagnosed food allergy or positive open food challenge with sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

Table A.3. Physician-diagnosed atopic diseases with sensitisation (sIgE/SPT) to respective allergens by the coincidence of pollen season (daily pollen concentrations *exceeding 50 particles/m^3*) with the 11^{th} (entire week of 7 days).

			Coincidence of pollen season with the entire 11^{th} fetal week							
			Yes		No					
			$N = 260$		$N = 2775$					
Diagnosis	N	(n)	%	(n)	%	(n)	OR	95% CI *	OR	95% CI †
Atopic eczema with any sensitisation	2902	*(144)*	8.7	*(22)*	4.6	*(122)*	2.14	1.29, 3.55	2.20	1.32, 3.67
Food allergy‡ with respective sensitisation	2996	*(133)*	8.3	*(21)*	4.1	*(112)*	2.46	1.46, 4.14	2.46	1.46, 4.16
Respiratory allergy with respective sensitisation	2820	*(57)*	3.7	*(9)*	1.9	*(48)*	4.06	1.75, 9.39	4.18	1.79, 9.75
Allergic asthma with any sensitisation	2887	*(38)*	0.8	*(2)*	1.4	*(36)*	0.96	0.21, 4.32	0.97	0.22, 4.37
Respiratory allergy or asthma with respective sensitisation	2809	*(75)*	4.2	*(10)*	2.5	*(65)*	2.59	1.22, 5.50	2.64	1.24, 5.64
Any atopic disease with any sensitisation	3035	*(186)*	10.0	*(26)*	5.8	*(160)*	2.08	1.30, 3.31	2.12	1.32, 3.39

N:group size; n: number of cases (in parentheses); %: Prevalence of the outcome i.e. atopic disease with sensitisation
*Adjusted by sex, birth order, the year of the 11^{th} fetal week and the childs age when the parents filled the questionnaire.
†Adjusted by above variables and additionally by parental atopy.
‡Include physician-diagnosed food allergy or positive open food challenge with sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

Table A.4. Physician-diagnosed atopic diseases with sensitisation by the coincidence of maximum pollen concentrations in environment at the 11^{th} fetal week.

		Atopic eczema		Food * allergy		Respiratory allergy		Any atopic disease	
Concentrations		$N = 2902$		$N = 2996$		$N = 2809$		$N = 3035$	
(particles/m^3)	N	%	(n)	%	(n)	%	(n)	%	(n)
Tree pollen †									
< 10	2297	4.4	*(97)*	3.9	*(89)*	2.5	*(53)*	5.7	*(130)*
$10 - 50$	380	5.2	*(19)*	4.2	*(16)*	2.5	*(9)*	6.1	*(23)*
$50 - 250$	110	4.6	*(5)*	4.6	*(5)*	3.8	*(4)*	5.5	*(6)*
$250 - 1000$	112	6.4	*(7)*	6.4	*(7)*	2.9	*(3)*	7.1	*(8)*
> 1000	136	12.1	*(16)*	12.1	*(16)*	4.7	*(6)*	14.0	*(19)*
Grass pollen †									
< 5	2333	4.8	*(106)*	4.5	*(103)*	2.5	*(54)*	6.0	*(139)*
$5 - 10$	189	4.9	*(9)*	3.7	*(7)*	1.7	*(3)*	5.8	*(11)*
$10 - 25$	227	4.7	*(10)*	4.4	*(10)*	2.9	*(6)*	5.7	*(13)*
$25 - 50$	154	8.0	*(12)*	5.3	*(8)*	6.2	*(9)*	10.4	*(16)*
> 50	132	5.4	*(7)*	3.8	*(5)*	2.4	*(3)*	5.3	*(7)*

N:group size; n: number of cases (in parentheses);%: Prevalence of the outcome i.e. atopic disease with sensitisation

*Physician-diagnosed food allergy or positive open food challenge with sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

†Tree pollen for Alder or Birch and grass pollen for different Grasses or Mugwort.

Table A.5. Hazard ratios (HR) with 95% confidence intervals [95%CI] (from adjusted Cox models) for the associations between physician-diagnosed atopic diseases with sensitisation (outcomes) and potential exposure at the 11th fetal week to different levels of environmental tree pollen concentrations (<10 particles per m^3 as reference). Model I for each outcomes were adjusted by sex, birth order and the childs age when the parents filled the questionnaire and Model II by all variables above and additionally by parental atopy.

Outcomes of atopic diagnoses	**Model I**	**Model II**
Tree pollen concentration	HR [95% CI] *	HR [95% CI] *
Atopic eczema with any sensitisation		
<10	1.00	1.00
10–50	1.25 [0.76, 2.06]	1.22 [0.75, 2.01]
50–250	1.02 [0.41, 2.50]	1.03 [0.42, 2.52]
250–1000	1.47 [0.68, 3.17]	1.41 [0.66, 3.05]
>1000	3.12 [1.82, 5.34]	3.30 [1.93, 5.66]
Food allergy* with respective sensitisation		
<10	1.00	1.00
10–50	1.14 [0.67, 1.95]	1.10 [0.64, 1.87]
50–250	1.16 [0.47, 2.87]	1.13 [0.46, 2.79]
250–1000	1.63 [0.76, 3.52]	1.57 [0.73, 3.40]
>1000	3.45 [2.01, 5.92]	3.48 [2.03, 5.98]
Respiratory allergy with respective sensitisation		
<10	1.00	1.00
10–50	1.25 [0.61, 2.55]	1.20 [0.59, 2.45]
50–250	1.50 [0.54, 4.14]	1.52 [0.55, 4.21]
250–1000	1.27 [0.40, 4.09]	1.22 [0.38, 3.93]
>1000	2.81 [1.18, 6.68]	2.88 [1.21, 6.85]
Any atopic disease with any sensitisation		
<10	1.00	1.00
10–50	1.18 [0.75, 1.84]	1.13 [0.72, 1.76]
50–250	0.96 [0.42, 2.18]	0.94 [0.42, 2.14]
250–1000	1.28 [0.63, 2.62]	1.25 [0.61, 2.55]
>1000	2.90 [1.78, 4.74]	2.99 [1.83, 4.87]

*Include physician-diagnosed food allergy or positive open food challenge with sensitisation to cow's milk, hen's egg, cereals (wheat/rye/barley) or fish.

Table A.6 Modification of the association between the end of the 11th fetal week at pollen season: daily pollen concentrations *exceeding 10 particles/m*^{3} and atopic eczema diagnosis with sensitisation, food allergy diagnosis with respective sensitisation (IgE-mediated food allergy), respiratory allergy diagnosis with respective sensitisation and Any diagnosis of atopic disease with allergic sensitisation by parental atopy, shown by both Additive (relative excess risk due to interaction i.e. RERI) and Multiplicative scale (a ratio of HRs) estimates in format recommended by Knol et al [Int J Epidemiol 2012;41:514-520]. Additionally, additive and multiplicative scale estimates are shown in red colour for the respective cross-sectional outcomes from logistic regression model adjusted by the child's age when the parents filled in the questionnaire.

Outcome	**End of 11th fetal week at pollen season**				Pollen exp within strata of par. ato	RERI	HR-ratio
	No		**Yes**				
Parental atopy	n/N[1]	HR (95% CI)	n/N[1]	HR (95% CI)	HR (95% CI)	est.(95% CI)	est.(95% CI)
Atopic eczema diagnosis with any sensitisation							
Parental non-atopy	9/769	1.0 (Ref.)	15/355	3.67 (1.60, 8.38) p=0.002	3.61 (1.58, 8.24) p=0.002	-1.33 (-7.59, 1.76)[2]	0.33 (0.12, 0.83)[4]
						-1.33 (-4.80, 2.15)[3]	
Parental atopy	75/1090	5.93 (2.97, 11.9) p=0.305	45/525	7.28 (3.56, 14.9) p<0.001	1.22 (0.85, 1.77) p=0.282	-1.25 (-7.70, 2.07)[2]	0.33 (0.11, 0.85)[4]
Food allergy diagnosis with sensitisation to respective food items							
Parental non-atopy	13/768	1.0 (Ref.)	14/356	2.36 (1.11, 5.03) p=0.026	2.36 (1.11, 5.03) p=0.026	-0.33 (-3.30, 1.69)[2]	0.55 (0.23, 1.25)[4]
						-0.33 (-2.50, 1.83)[3]	
Parental atopy	65/1117	3.50 (1.93, 6.35) p=0.516	41/538	4.53 (2.43, 8.45) p<0.001	1.29 (0.87, 1.91) p=0.197	-0.30 (-3.34, 1.86)[2]	0.55 (0.23, 1.27)[4]
Respiratory allergy diagnosis with sensitisation to respective aeroallergens							
Parental non-atopy	5/7498	1.0 (Ref.)	9/350	4.07 (1.36, 12.2) p=0.012	4.11 (1.37, 12.3) p=0.012	-0.83 (-10.0, 5.38)[2]	0.35 (0.07, 1.16)[4]
						-0.83 (-5.43, 3.77)[3]	
Parental atopy	36/1095	5.24 (2.06, 13.4) p<0.001	25/522	7.48 (2.86, 19.5) p<0.001	1.43 (0.86, 2.38) p=0.171	-0.82 (-10.4, 6.14)[2]	0.34 (0.07, 1.14)[4]
Any allergy diagnosis with any sensitisation							
Parental non-atopy	18/776	1.0 (Ref.)	19/357	2.35 (1.24, 4.49) p=0.009	2.36 (1.24, 4.51) p=0.009	-0.72 (-3.31, 0.99)[2]	0.50 (0.22, 1.03)[4]
						-0.72 (-2.65,1.21)[3]	
Parental atopy	95/1100	3.79 (2.29, 6.27) p<0.001	54/529	4.42 (2.59, 7.53) p<0.001	1.17 (0.83, 1.63) p=0.370	-0.70 (-3.41, 1.21)[2]	0.49 (0.22, 1.04)[4]

[1] n=number of children with a positive test; N=number of children without positive test.
[2] Additive scale estimates calculated by bootstrap method)
[3] Additive scale estimates calculated by delta method)
[4] Multiplicative scale estimates calculated by bootstrap method

Table A.7. Modification of the association between **the end of the 11th fetal week at pollen season: daily pollen concentrations** *exceeding 50 particles/m*^{3} and atopic eczema diagnosis with sensitisation, food allergy diagnosis with respective sensitisation (IgE-mediated food allergy), respiratory allergy diagnosis with respective sensitisation and Any diagnosis of atopic disease with allergic sensitisation by parental atopy, shown by both Additive (relative excess risk due to interaction i.e. RERI) and Multiplicative scale (a ratio of HRs) estimates in format recommended by Knol et al [Int J Epidemiol 2012;41:514-520].

Outcome	**End of the 11th fetal week at pollen season**				Pollen exp within strata of par. ato	RERI	HR-ratio
	No		**Yes**				
Parental atopy	n/N[1]	HR (95% CI)	n/N[1]	HR (95% CI)	HR (95% CI)	est.(95% CI)	est.(95% CI)
Atopic eczema diagnosis with any sensitisation							
Parental non-atopy	17/1015	1.0 (Ref.)	7/109	3.80 (1.58, 9.17) p=0.003	3.74 (1.55, 9.03) p=0.003	-0.23 (-5.24, 4.89)[2]	0.43 (0.15, 1.33)[4]
Parental atopy	101/1444	4.16 (2.49, 6.96) p<0.001	19/171	6.74 (3.50, 13.0) p<0.001	1.63 (1.00, 2.66) p=0.052	-0.23 (-4.48, 4.03)[3]	
Food allergy diagnosis with sensitisation to respective food items							
Parental non-atopy	20/1020	1.0 (Ref.)	7/104	3.38 (1.43, 7.99) p=0.006	3.38 (1.43, 7.98) p=0.006	-0.14 (-4.10, 3.72)[2]	0.51 (0.18, 1.59)[4]
Parental atopy	88/1480	3.05 (1.88, 4.96) p<0.001	18/175	5.29 (2.80, 10.0) p<0.001	1.73 (1.04, 2.88) p=0.033	-0.14 (-3.73, 3.45)[3]	
Respiratory allergy diagnosis with sensitisation to respective aeroallergens							
Parental non-atopy	10/993	1.0 (Ref.)	4/106	4.06 (1.27, 12.9) p=0.018	4.20 (1.31, 13.5) p=0.016	-2.31 (-10.9, 3.34)[2]	0.29 (0.06, 2.33)[4]
Parental atopy	54/1441	3.85 (1.96, 7.55) p<0.001	7/176	4.60 (1.75, 12.1) p=0.002	1.19 (0.54, 2.62) p=0.668	-2.31 (-8.02, 3.41)[3]	
Any allergy diagnosis with any sensitisation							
Parental non-atopy	29/1024	1.0 (Ref.)	8/109	2.62 (1.20, 5.74) p=0.016	2.67 (1.22, 5.85) p=0.014	0.00 (-2.88, 3.14)[2]	0.58 (0.23, 1.59)[4]
Parental atopy	127/1458	3.08 (2.06, 4.62) p<0.001	22/171	4.71 (2.71, 8.20) p<0.001	1.52 (0.97, 2.40) p=0.069	0.00 (-2.76, 2.76)[3]	

[1] n=number of children with a positive test; N=number of children without positive test.
[2] Additive scale estimates calculated by bootstrap method)
[3] Additive scale estimates calculated by delta method)
[4] Multiplicative scale estimates calculated by bootstrap method

Table A.8. Modification of the association between **the end of the 11th fetal week at pollen season: daily pollen concentrations** *exceeding 10 particles/m*^{3} and atopic eczema diagnosis with sensitisation, food allergy diagnosis with respective sensitisation (IgE-mediated food allergy), respiratory allergy diagnosis with respective sensitisation and Any diagnosis of atopic disease with allergic sensitisation by maternal pollen allergy (physician-diagnosed), shown by both Additive (relative excess risk due to interaction i.e. RERI) and Multiplicative scale (a ratio of HRs) estimates in format recommended by Knol et al [Int J Epidemiol 2012;41:514-520].

Outcome	**End of the 11th fetal week at pollen season**				Pollen exp within strata of Maternal allergy	RERI	HR-ratio
	No		**Yes**				
Maternal pollen allergy	n/N[1]	HR (95% CI)	n/N[1]	HR (95% CI)	HR (95% CI)	est.(95% CI)	est.(95% CI)
Atopic eczema diagnosis with any sensitisation							
Maternal non-allergy	49/1321	1.0 (Ref.)	38/657	1.58 (1.03, 2.41) p=0.035	1.58 (1.03, 2.41) p=0.003	0.51 (-0.91, 2.03)[2]	1.08 (0.49, 2.29)[4]
Maternal allergy	27/484	1.54 (0.96, 2.46) p=0.073	19/192	2.63 (1.55, 4.46) p<0.001	1.75 (0.97, 3.15) p=0.063	0.51 (-0.90, 1.93)[3]	
Food allergy diagnosis with sensitisation to respective food items							
Maternal non-allergy	46/1331	1.0 (Ref.)	38/662	1.68 (1.09, 2.57) p=0.019	1.68 (1.09, 2.58) p=0.018	-0.28 (-1.87, 1.11)[2]	0.73 (0.33, 1.62)[4]
Maternal allergy	29/489	1.75 (1.10, 2.78) p=0.019	15/202	2.14 (1.19, 3.83) p=0.011	1.23 (0.66, 2.29) p=0.516	-0.28 (-1.70, 1.13)[3]	
Respiratory allergy diagnosis with sensitisation to respective aeroallergens							
Maternal non-allergy	24/1304	1.0 (Ref.)	24/645	2.07 (1.17, 3.64) p=0.012	2.07 (1.17, 3.64) p=0.012	0.06 (-2.52, 2.26)[2]	0.87 (0.26, 2.58)[4]
Maternal allergy	12/484	1.40 (0.70, 2.81) p=0.336	9/199	2.53 (1.18, 5.46) p=0.017	1.90 (0.79, 4.53) p=0.150	0.06 (-1.99, 2.11)[3]	
Any allergy diagnosis with any sensitisation							
Maternal non-allergy	67/1328	1.0 (Ref.)	46/661	1.41 (0.97, 2.05) p=0.075	1.40 (0.96, 2.04) p=0.076	0.49 (-0.69, 1.71)[2]	1.13 (0.54, 2.17)[4]
Maternal allergy	37/488	1.54 (1.03, 2.29) p=0.036	24/193	2.43 (1.52, 3.87) p<0.001	1.61 (0.96, 2.70) p=0.069	0.49 (-0.68, 1.66)[3]	

[1] n=number of children with a positive test; N=number of children without positive test.
[2] Additive scale estimates calculated by bootstrap method)
[3] Additive scale estimates calculated by delta method)
[4] Multiplicative scale estimates calculated by bootstrap method

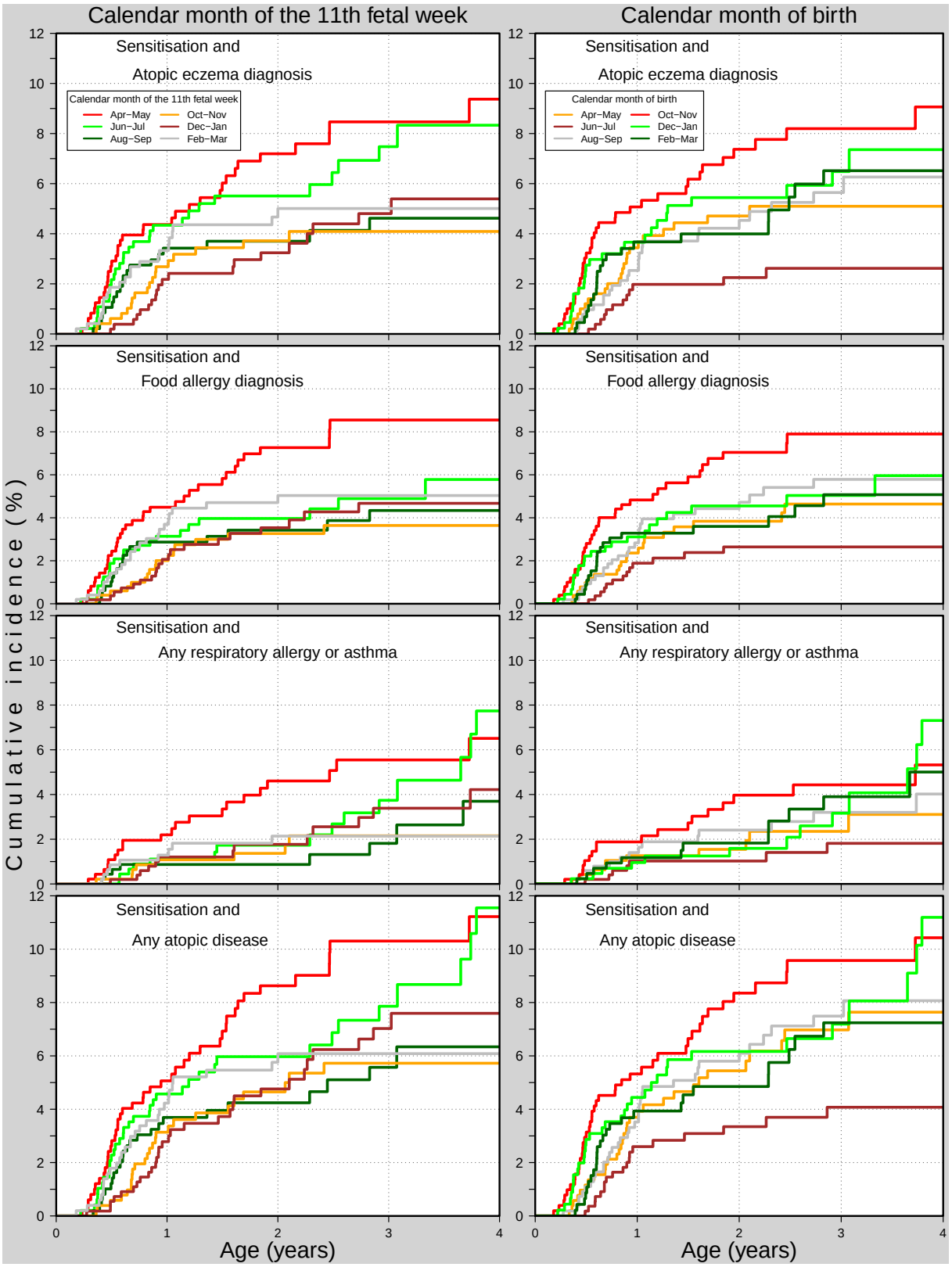


Figure A.1. Cumulative incidences of sensitisation with respective physician-diagnosed atopic disease by the calendar month (bi-monthly) of the 11th fetal week (plots on the left) and birth (plots on the right side).

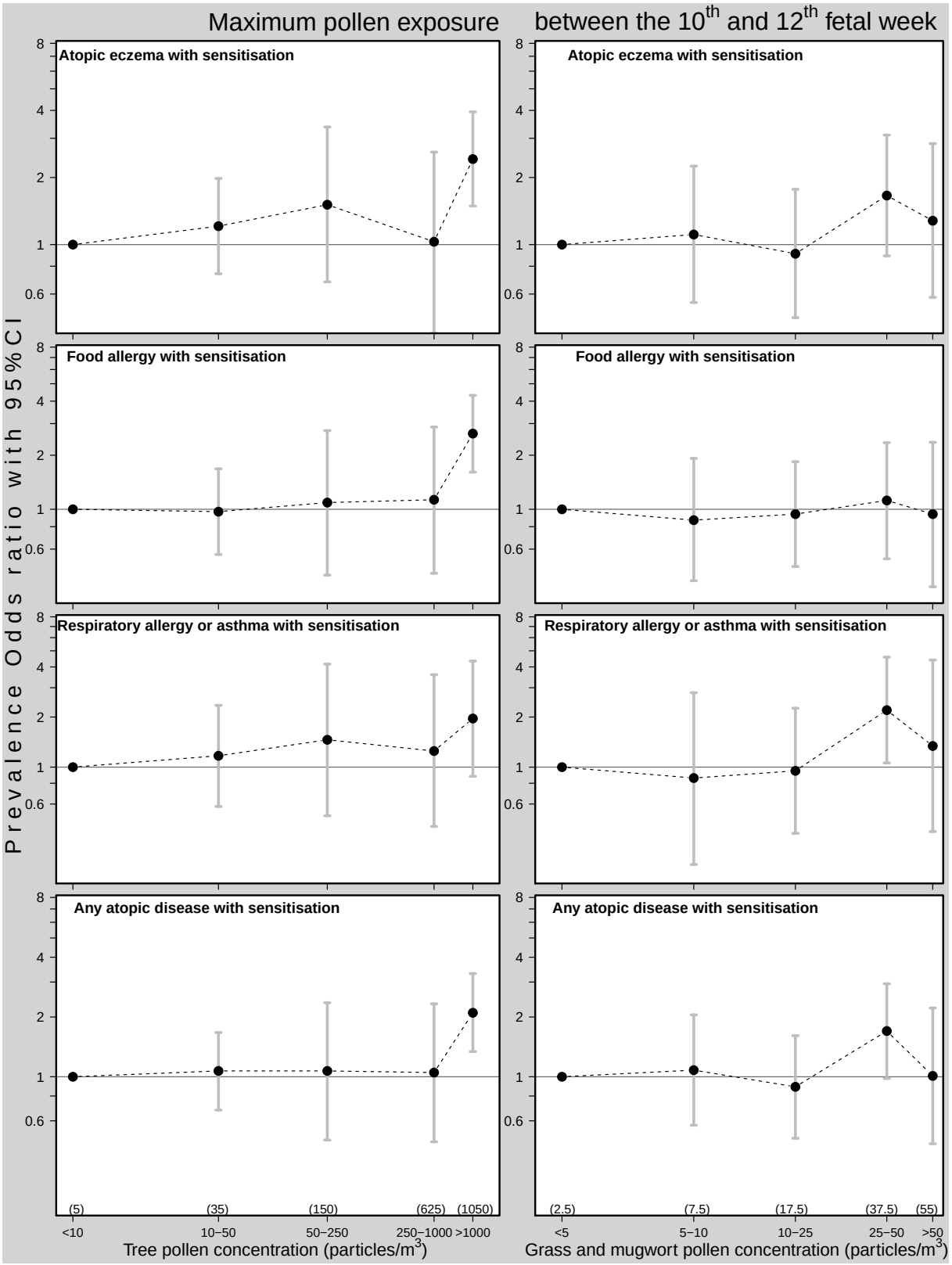


Figure A.2. Prevalence odds ratios (with 95% confidence intervals) of physician-diagnosed atopic manifestations with sensitisation by the coincidence of different pollen concentrations between the 10^{th} and 12^{th} fetal week for alder and birch pollen i.e. tree pollen (plots on the left) and for grass and mugwort pollen (plots on the right side). Note the logarithmic scale of x-and y-axes.

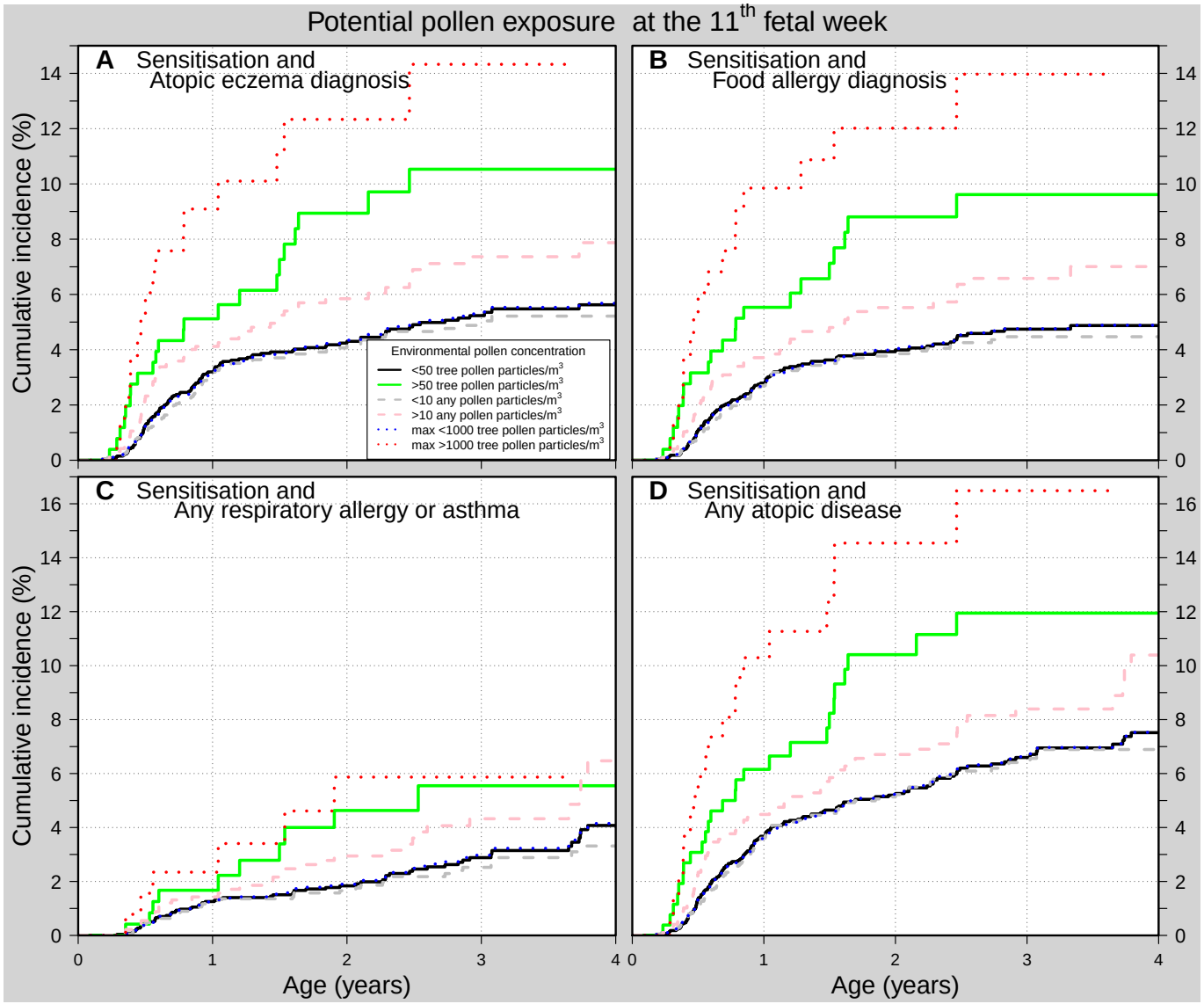


Figure A.3. Cumulative incidences of physician-diagnosed atopic diseases with sensitisation (A-D) according to the different categories of environmental pollen concentrations (shown in the legend of the plot A; < 10 vs. > 10 particles/m^3, < 50 vs. > 50 particles/m^3 and maximum < 1000 vs. > 1000 particles/m^3) at the 11^{th} fetal week.

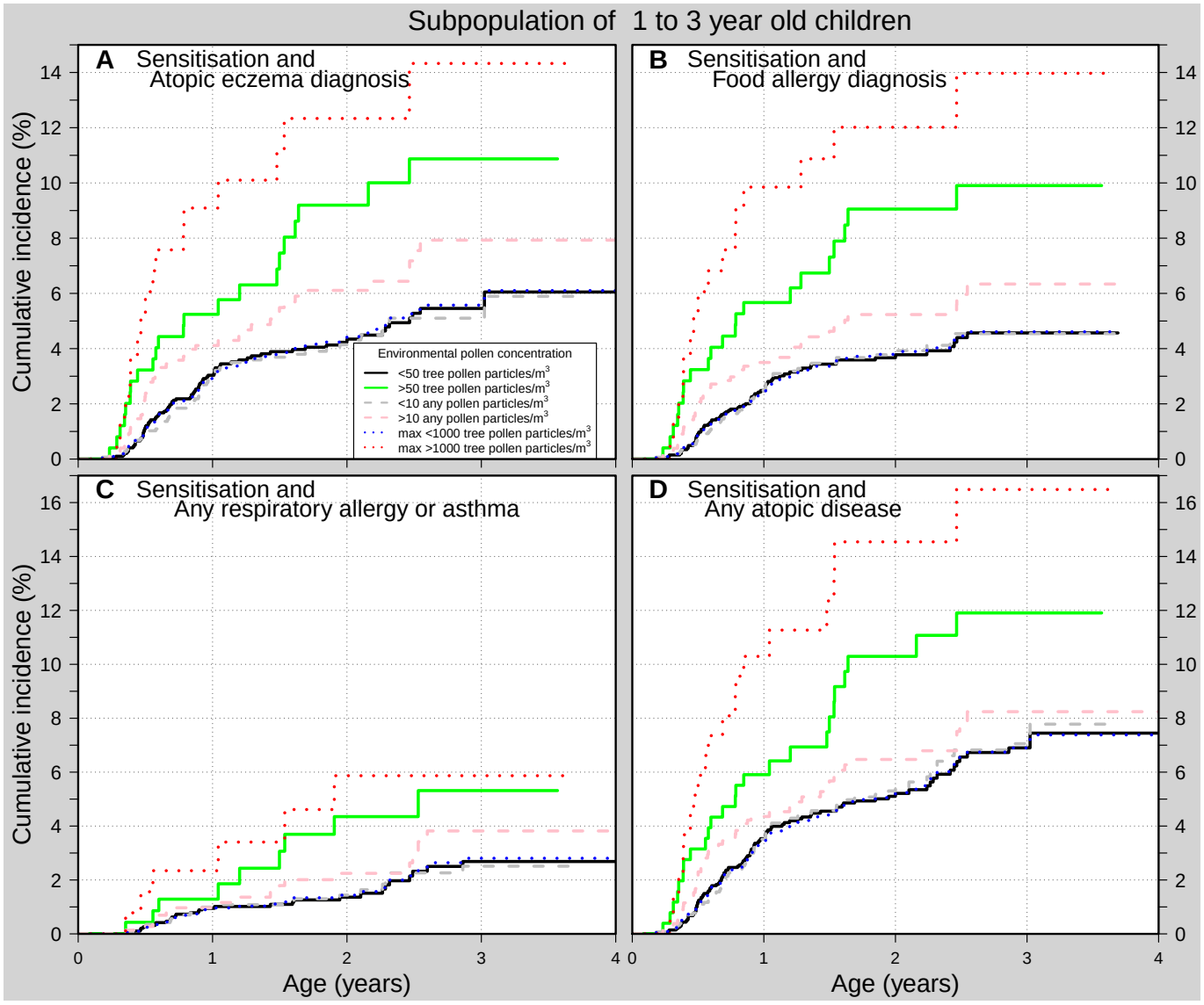


Figure A.4. Cumulative incidences of sensitisation with respective physician-diagnosed atopic disease (A-D) according to the different categories of pollen concentrations (< 10 vs. > 10 particles/m^3, < 50 vs. > 50 particles/m^3 and maximum < 1000 vs. > 1000 particles/m^3) in environment at the 11^{th} fetal week among subpopulation of children in the age classes born between April 2002 to March 2005.