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Atopic diseases of the parents predict the offspring's atopic sensitization and food allergy

Kaisa Pyrhönen[1,2] | Petri Kulmala[2,3]

[1]Center for Life Course Health Research, University of Oulu, Oulu, Finland

[2]PEDEGO Research Unit and MRC Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland

[3]Biomedicine Research Unit, Medical Microbiology and Immunology, University of Oulu, Oulu, Finland

Correspondence
Kaisa Pyrhönen, Center for Life Course Health Research, University of Oulu, Oulu, Finland.
Email: kaisa.pyrhonen@oulu.fi

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Abstract

Background: In genetic studies and selected study populations, parental atopy has been associated with atopic diseases in offspring. Our aim was to identify the association between parental atopic diseases and the offspring's atopic sensitization and food allergies, and their effect modifications due to the offspring's sex.

Methods: The study population (*N* = 5564) (born between 2001 and 2006) was identified from the population register and live in the province of South Karelia, Finland. Questionnaire-based information on parental atopic diseases was available for 3592 children. The results of skin prick tests, specific IgE tests, and open food challenges (OFC) were collected from patient records.

Results: By 12 years of age, the cumulative incidence of sensitization to food (14% vs 7%, hazard ratio 2.13; 95% CI 1.68–2.69), animal (10% vs 6%, 1.86; 1.42–2.44), and pollen allergens (12% vs 6%, 2.43; 1.85–3.19), as well as food allergies (positive OFC, 5% vs 2%, 2.28; 1.57–3.33), was higher in the offspring of parents with atopic diseases. The cumulative incidence for pollen sensitization was twofold higher for the female offspring of parents with atopic diseases than those of parents without, while it was almost threefold higher among males. The association between parental pollen allergy and the offspring's pollen sensitization was modified by sex according to additive scale estimates (RERI 1.03; 95% CI 0.13–1.91).

Conclusion: Until adolescence, parental atopic diseases have a relatively strong association with the offspring's, particularly male offspring's, atopic sensitization, and food allergies. A pronounced association was found between parental pollen allergy and the male offspring's pollen sensitization.

KEYWORDS
allergic sensitization, atopic sensitization, cohort study, food allergy, open food challenge, parental animal allergy, parental asthma, parental atopic diseases, parental atopic eczema, parental food allergy, parental pollen allergy, population-based evidence, sensitization to animals, sensitization to food, sensitization to pollen, sIgE, skin prick test

1 | INTRODUCTION

Genetic studies have identified a total of 41 risk loci for allergic rhinitis,[1] 31 for atopic dermatitis,[2] and 26 for asthma.[3] Some of these loci are related to several atopic diseases[3,4]; therefore, several manifestations of these diseases often coexist in the same individuals.[4] Genetics has been estimated to have a greater impact than environmental factors on the pathogenesis of atopic diseases, from atopic eczema to allergic rhinitis or asthma.[5] However, the genetic mechanisms behind the first manifestation of atopic diseases (ie, food allergies) have been considered heterogeneous and complex.[6]

The occurrence of allergic diseases varies according to sex.[7–9] It has been explained by differences in male and female genotypes, and possible X chromosome-linked recessive genes are more likely to be revealed in the phenotypes of males than in those of females. This pattern of genetic inheritance has been suggested to explain a higher prevalence of wheezing among males than among females.[10]

The occurrences of atopic diseases and their associations with parental atopic diseases have varied between studies. At 10 and 13 years of age, the prevalence of allergic rhinitis was found to be twofold higher in the offspring of parents with allergic diseases than in those of parents without.[11] An association between parental history of allergic diseases and the offspring's food allergies has been found to be stronger if the mother had an allergic disease,[12] while we did not find such a predominant association between the maternal atopic diseases and food allergies in their offspring up to 4 years of age.[13] Here, we report the age-incidence patterns of sensitization to different groups of allergens and those of food allergies from birth up to 12 years of age in relation to the atopic phenotype of the biologic parents and the effect of modifications via the offspring's sex.

Key Message

In our cohort study (*N* = 3592), based on a questionnaire survey and real-world test data, we found that parental atopic diseases have a relatively strong association with the offspring's atopic sensitization and food allergies. The predominance of these atopic outcomes in males might be explained by X chromosome-linked recessive genes.

2 | MATERIALS AND METHODS

2.1 | Population

The target population (*N* = 5,973) of the South Karelia Allergy Research Project (SKARP) study[13-19] was identified, and their personal identification codes (PICs) were obtained from the Finnish Population Register Centre[14,16,20] (Figure 1). The target population was defined according to their date of birth and their place of residence. Therefore, all children born between April 2001 and March 2006 (five age classes) who live in the province of South Karelia in South-East Finland at the time of the questionnaire survey were included in the study.

2.2 | Data collection

The questionnaire survey was conducted in close cooperation with local child health clinics between March 2005 and September 2006, when the children had their regular checkups at 6 weeks (newborn infants), and one, two, three, or 4 years of age.[15,16] The parents of 3681 children returned the questionnaire, in which they had been asked the atopic phenotypes of the biologic parents of the child. After the survey, the questionnaires were translated into English (available at www.oulu.fi/ltk/node/29090).

The information (the date of testing and the measurement of the results) on all allergy tests was collected from all the healthcare units in the area independently from the questionnaire survey with the intention to cover the entire child population in the area. These tests had been ordered by a physician for diagnostic purposes and were performed between April 2001 and September 2013.

The children's PICs were used to merge the individual test and questionnaire data.[16,18] The data linkage was denied by the parents of 53 children (ethics and permissions section), who were therefore excluded from the analyses. By September 2013, information on vital status and migrations was obtained for 5902 children from the Population Register Centre. One-month-old children who had immigrated to the study area (*N* = 356) were excluded, and those with missing information regarding migration history (*N* = 18) were included in the data analyses. Thus, the final study population comprised 5,564 children (Figure 1).

2.3 | Outcomes and explanatory variables

The outcome events comprised the first test and the first positive test for food, animal, pollen, and any of these allergens. The cutoff point for a positive result from a specific immunoglobulin E (sIgE) was 0.35 kU/L with RAST-CAP FEIA or Phadiatop Combi, and 1.43 standardized units per ml with Magic Lite. The cutoff point for the skin prick tests (SPTs) was defined as the mean of two orthogonal diameters of a urticarial weal of 3 mm, which was applied to both positive and negative controls. A positive test result for either sIgE or SPT was considered as a *sensitization* to the respective group of specific allergens. Based on patient records, a positive result for an open food challenge (OFC) was considered as a *food allergy*.

A history of parental atopic diseases included physician-diagnosed food allergy, atopic eczema (atopic rash in the questionnaire), allergic asthma, and pollen and animal allergies, of which the overall number in both biologic parents was included in the variable of the number of atopic diseases in the parents. The information on

sex, birth order, first place of residence in the area and the mother's age at the time of delivery were obtained from the population register.

2.4 | Statistical methods

The cumulative incidence of each outcome event by age was described by the Kaplan-Meier method, using the survfit function of the survival package[21] in the R environment release 4.0.3.[22] The cumulative incidences were regressed according to the explanatory variables by using the Cox proportional hazard model (the coxph function of the survival package), of which the estimates are shown here as hazard ratios (HR) with 95% confidence intervals (95% CI). More detailed descriptions of these methods, estimations of incidence rates,[23–25] and the effect modification by the relative excess risk due to interaction (RERI) in additive and the HR ratio in multiplicative scales[26–28] are shown in the Appendix S1. The RERI above zero and HR ratio above the unity can be interpreted as the positive effect modification, of which statistical significance is indicated by the CI exceeding zero and the unity, respectively.

The cumulative incidence curves of competing events, the first combinations of allergen groups, were produced by the stackedCIF function of the Epi package in R,[25] which is based on the Aalen-Johansen method.

3 | RESULTS

3.1 | Description of the study population

Information on atopic diseases of the biologic parents was available for 3592 children, covering 98% of all those responding to the questionnaire and 65% of the study population (*N* = 5,564) (Figure 1). By 12 years of age, the cumulative incidence of testing for any allergens was 37%, and that of the positive tests among participants was 18% for any allergens, 12% for food, 8% for animal, and 9% for pollen allergens. Compared with our previous paper,[13] our continued data collection (between October 1, 2006, and September 30, 2013) yielded a substantial number of additional children tested for allergy, and children with first or repeated positive tests and respective tests for different allergens (Table S1).

Altogether, 55% (1,966/3,592) of the children were reported to have an atopic disease in either or both biologic parents. First-year pet exposure was more common, and mothers' education levels were lower among the offspring of parents without atopic diseases (Table 1).

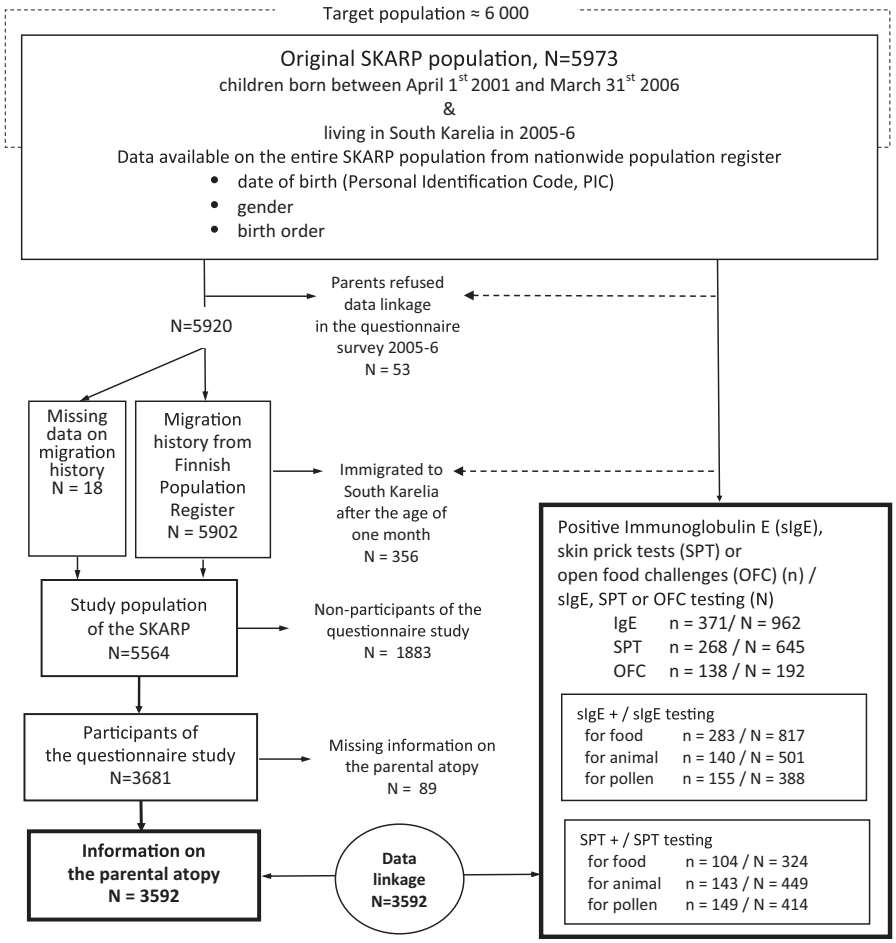

FIGURE 1 Flow diagram showing the data sources and data linkages of the South Karelia Allergy Research Project (the SKARP)

TABLE 1 Offspring of parents with and without atopic diseases according to background variables. The comparison between these groups according to each variable is shown by overall *p* values[a]

Background variable	Parents without atopic diseases *N* = 1,626		Parents with atopic diseases *N* = 1,966		Background variable	Parents without atopic diseases *N* = 1,626		Parents without atopic diseases *N* = 1,966	
	%	(*N*)	%	(*N*)		%	(*N*)	%	(*N*)
POPULATION REGISTER BASED VARIABLES					QUESTIONNAIRE BASED VARIABLES				
Sex	*p*.overall = 0.880				**Gestational age (weeks)**	*p*.overall = 0.888			
Female	49.4	(803)	49.7.3	(977)	<38	9.29	(151)	9.72	(191)
Male	50.6	(823)	50.3	(989)	38–39	35.1	(571)	36.5	(717)
Birth order	*p*.overall = 0.526				40–41	26.2	(426)	25.5	(502)
Not firstborn	53.3	(866)	54.4	(1069)	41-	22.8	(370)	22.9	(450)
Firstborn	46.7	(760)	45.6	(897)	Missing	6.64	(108)	5.39	(106)
					Birth weight (kg)	*p*.overall = 0.611			
Municipality of residence	*p*.overall = 0.098				<2500	3.57	(58)	3.81	(75)
Other urban	23.6	(383)	25.1	(494)	2500–3500	41.6	(676)	43.3	(851)
Provincial capital	52.0	(845)	53.4	(1049)	3500–4200	45.9	(746)	44.7	(879)
Rural	24.5	(398)	21.5	(423)	>4200	8.36	(136)	7.53	(148)
Native language	*p*.overall <0.001				Missing	0.62	(10)	0.66	(13)
Finnish	95.2	(1548)	98.3	(1933)	**Birth length (cm)**	*p*.overall = 0.558			
Other	4.80	(78)	1.68	(33)	<48	9.90	(161)	10.1	(198)
					48–49	23.4	(381)	24.8	(488)
Mother's age at delivery (years)	*p*.overall = 0.027				50–51	37.1	(603)	38.1	(749)
<20	2.03	(33)	1.17	(23)	52–53	23.4	(381)	21.7	(427)
20–25	13.8	(225)	15.0	(294)	>53	5.41	(88)	4.58	(90)
25–30	34.9	(568)	33.5	(659)	Missing	0.74	(12)	0.71	(14)
30–35	29.2	(475)	32.7	(642)	**Head circum.(cm)**	*p*.overall = 0.797			
35–40	16.9	(274)	14.3	(282)	<34	19.7	(320)	20.8	(409)
>40	3.14	(51)	3.36	(66)	34	32.0	(521)	33.3	(655)
					35	15.5	(252)	14.5	(286)
					36	20.2	(329)	20.8	(408)
					36	6.15	(104)	4.83	(95)
					Missing	6.40	(104)	4.83	(95)

(Continues)

TABLE 1 (Continued)

Background variable	Parents without atopic diseases N = 1,626 %	(N)	Parents with atopic diseases N = 1,966 %	(N)	Background variable	Parents without atopic diseases N = 1,626 %	(N)	Parents without atopic diseases N = 1,966 %	(N)
QUESTIONNAIRE BASED VARIABLES									
Type of dwelling	*p*.overall = 0.003				**Exclusive breastfeeding**[b] **(months)**	*p*.overall = 0.761			
Block	20.4	(331)	18.3	(359)	0	3.69	(60)	4.53	(89)
Detached house	54.8	(891)	59.5	(1170)	0–2	15.4	(251)	15.7	(309)
Row house or semi-detached house	16.3	(265)	16.4	(323)	2–4	22.5	(366)	22.8	(449)
Farmhouse	7.75	(126)	5.24	(103)	>4	38.3	(622)	39.3	(772)
Missing	0.80	(13)	0.56	(11)	Missing	20.1	(327)	17.7	(347)
Mother's education level	*p*.overall < 0.001				**Overall breastfeeding**[b] **(months)**	*p*.overall = 0.396			
Low	6.95	(113)	4.32	(85)	0	0.55	(9)	1.02	(20)
Middle	62.3	(1013)	59.3	(1166)	0–4	17.8	(290)	16.9	(333)
High	30.0	(488)	35.4	(696)	4–6	8.92	(145)	9.10	(179)
Missing	0.74	(12)	0.97	(19)	>6	51.1	(831)	52.3	(1029)
					Missing	21.6	(351)	20.6	(405)
Father's education level	*p*.overall = 0.002				**Pet exposure**	*p*.overall < 0.001			
Low	10.9	(177)	8.80	(173)	Unexposed	45.5	(740)	55.5	(1091)
Middle	66.4	(1080)	63.6	(1251)	Exposed	51.0	(829)	39.5	(776)
High	20.7	(377)	25.3	(497)	Missing	3.51	(57)	5.04	(99)
Missing	1.97	(32)	2.29	(45)					
Maternal smoking during pregnancy	*p*.overall = 0.022				**Dog exposure**	*p*.overall <0.001			
Never	79.3	(1290)	82.7	(1625)	Unexposed	61.6	(1002)	66.5	(1307)
Occasionally	7.26	(118)	5.49	(108)	Exposed	34.9	(567)	28.5	(560)
Regularly	6.95	(113)	5.75	(113)	Missing	3.51	(57)	5.04	(99)
Missing	6.46	(105)	6.10	(120)	**Cat exposure**	*p*.overall <0.001			
Mode of delivery	*p*.overall = 0.553				Unexposed	71.7	(1166)	76.5	(1504)
Vaginal	81.5	(1325)	82.3	(1618)	Exposed	24.8	(403)	18.5	(363)
Caesarean Section	18.3	(297)	17.4	(343)	Missing	3.51	(57)	5.04	(99)
Missing	0.25	(4)	0.25	(5)					

Note: N; number of children. %; proportion of children in categories of the variables separately among offspring of parents with and without atopic diseases.

[a]Children with missing information were excluded from these comparisons.

[b]Not available for the youngest age class, whose age was only few weeks at the time of the survey.

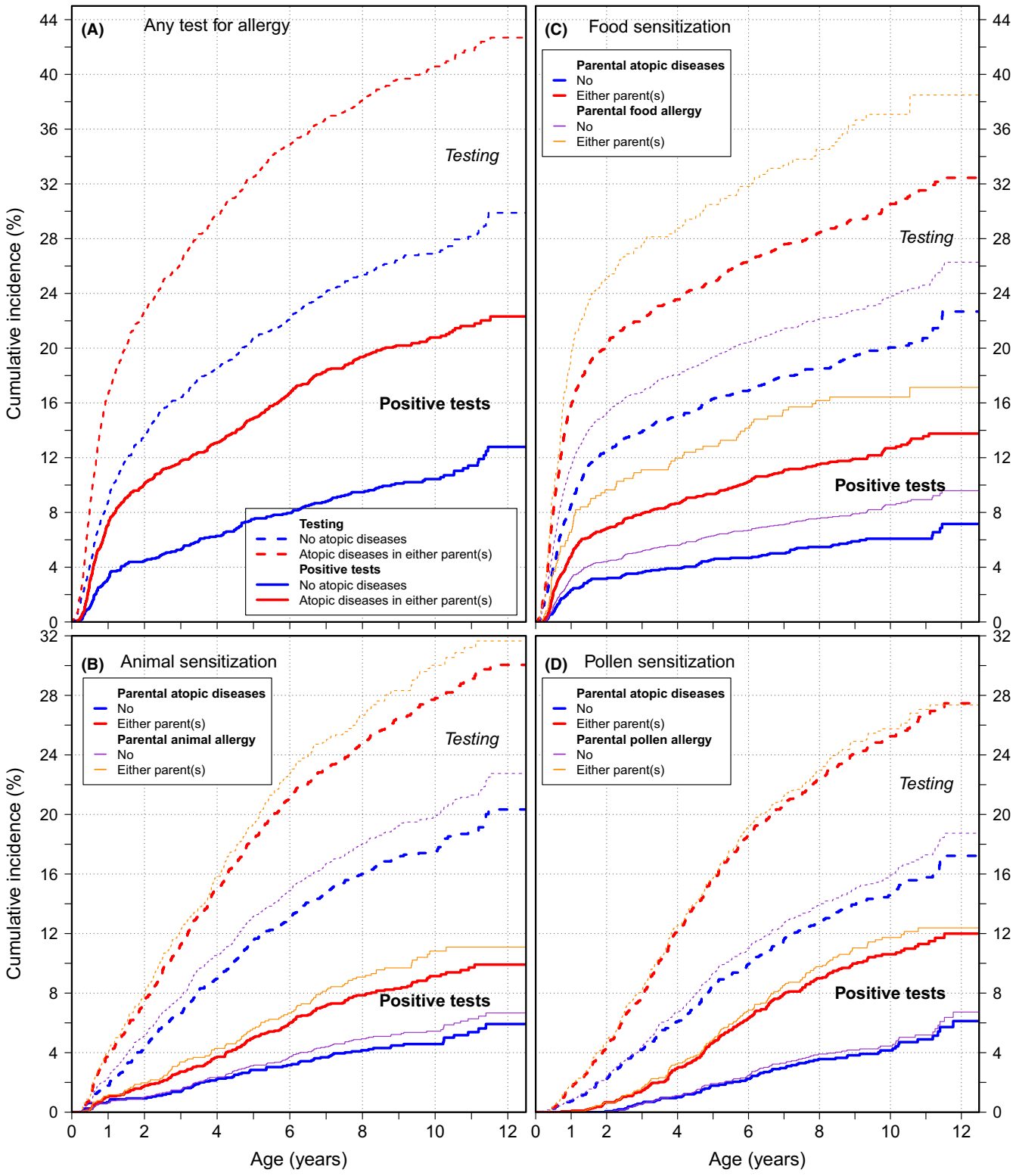

FIGURE 2 Cumulative incidences of testing for different allergens (dashed lines) and their positive test results (solid lines) according to any parental atopic disease and comparable parental atopic diseases

3.2 | Parental atopic diseases and the offspring's allergic sensitization or food allergy

Altogether, 70% (366/520) of the children with *sensitization* to any group of specific allergens, 71% (243/341) to food, 69% (170/247) to animal, and 74% (199/269) to pollen allergens, and 73% (101/138) of children with *food allergies* had been reported to have at least one atopic disease in either parent. The cumulative incidence of sensitization was higher for any (21% vs 12%, HR 2.08; 95% CI 1.72–2.51), food (14% vs 7%, 2.13; 1.68–2.69), animal (10% vs 6%, 1.86; 1. 42–2.44), and

TABLE 2 Cumulative incidence (%) for allergic sensitization, food allergies, any positive food test and any positive allergy test up to the age of 12 years and the Hazard ratios (from Cox models) according to parental atopic diseases, the overall number of atopic manifestations[a] and comparable parental atopic diseases

		Sensitization								
		Food			Animal			Pollen		
Explanatory variable	N[b]	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)
Parental atopic disease										
None	1,626	7	(98)	1.0	6	(77)	1.0	6	(70)	1.0
Mother	938	13	(110)	2.01 (1.53–2.63)	10	(77)	1.76 (1.28–2.41)	12	(89)	2.26 (1.65–3.09)
Father	626	13	(73)	2.02 (1.49–2.74)	9	(47)	1.63 (1.13–2.34)	12	(61)	2.38 (1.69–3.35)
Both	402	17	(60)	2.59 (1.88–3.57)	13	(46)	2.47 (1.71–3.56)	13	(49)	2.93 (2.03–4.22)
No. of atopic diseases in the parents										
0	1,371	7	(81)	1.0	6	(65)	1.0	6	(55)	1.0
1–2	985	11	(94)	1.65 (1.22–2.22)	7	(62)	1.34 (0.94–1.89)	10	(75)	1.93 (1.36–2.74)
3–5	580	17	(89)	2.77 (2.05–3.74)	12	(63)	2.40 (1.69–3.39)	15	(77)	3.56 (2.52–5.03)
6–9	56	25	(13)	4.51 (2.51–8.09)	14	(7)	2.97 (1.36–6.48)	18	(9)	4.66 (2.31–9.44)
Parental comparable atopic disease										
None	2,738	10	(228)	1.0	7	(123)	1.0	7	(91)	1.0
Mother	304	14	(42)	1.74 (1.25–2.41)	12	(56)	1.92 (1.40–2.63)	12	(70)	2.32 (1.70–3.16)
Father	160	21	(31)	2.59 (1.78–3.77)	10	(34)	1.71 (1.17–2.50)	13	(59)	2.61 (1.88–3.62)
Both	25	25	(6)	3.25 (1.45–7.32)	11	(11)	2.09 (1.13–3.87)	12	(19)	2.35 (1.43–3.85)
		Food allergy			Any food test+			Any test+		
Explanatory variable	N	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)
Parental atopic disease										
None	1,626	2	(37)	1.0	8	(114)	1.0	13	(172)	1.0
Mother	938	6	(52)	2.48 (1.62–3.78)	15	(133)	2.10 (1.64–2.70)	21	(181)	1.92 (1.56–2.37)
Father	626	4	(22)	1.56 (0.92–2.64)	14	(82)	1.96 (1.47–2.60)	21	(118)	1.90 (1.50–2.40)
Both	402	7	(27)	2.97 (1.81–4.87)	19	(71)	2.65 (1.97–3.56)	27	(101)	2.57 (2.01–3.29)
No. of atopic diseases in the parents										
0	1,371	2	(34)	1.0	8	(96)	1.0	12	(143)	1.0
1–2	985	3	(31)	1.27 (0.78–2.06)	12	(108)	1.60 (1.21–2.10)	18	(158)	1.58 (1.26–1.98)
3–5	580	8	(45)	3.22 (2.06–5.03)	21	(110)	2.93 (2.23–3.85)	28	(149)	2.75 (2.18–3.46)
6–9	56	14	(8)	5.93 (2.75–12.8)	28	(15)	4.35 (2.53–7.50)	32	(17)	3.46 (2.09–5.72)
Parental food allergy										
None	2,738	3	(91)	1.0	11	(269)	1.0	17	(396)	1.0
Mother	304	7	(22)	2.23 (1.40–3.55)	16	(48)	1.68 (1.24–2.29)	21	(62)	1.49 (1.14–1.95)
Father	160	10	(15)	2.86 (1.66–4.94)	26	(39)	2.77 (1.98–3.87)	30	(45)	2.23 (1.64–3.04)
Both	25	8	(2)	2.43 (0.60–9.85)	25	(6)	2.68 (1.19–6.02)	29	(7)	2.20 (1.04–4.65)

Abbrviations: CI, confidence intervals; HR, Hazard ratios; *n*, number of cases.

[a]The overall number of atopic manifestations in both parents include food allergy, atopic eczema, allergic asthma, pollen allergy and animal allergy.

[b]Total number (*N*) of children in the groups according to explanatory variables on parental comparative atopic disease i.e food allergy shown in this column. Total number (*N*) of children in the groups according to parental animal allergy as None, Mother, Father and Both were 2,232, 543, 376, and 103, respectively, and according to parental pollen allergy 1,941, 671, 515 and 176, respectively.

pollen allergens (12% vs 6%, 2.43; 1.85–3.19) (Figure 2), as well as for food allergies (5% vs. 2%, 2.28; 1. 57–3.33), in the offspring of parents with atopic diseases. The respective hazard ratios were consistently 2.5 or more than 2.5 times higher for the offspring of two parents with atopic diseases (Table 2). The cumulative incidences and incidence rates of allergic sensitization were consistently higher for the offspring of the parents with comparable atopic diseases, as mentioned above upon the inspection of these outcomes considering the history of any atopic diseases in the parents (Table 2, Tables S2–S3, Figure 2). The cumulative incidences of allergy testing for any test, or testing for

sensitization to food, animal, and pollen allergens, were higher for the offspring of parents with atopic diseases (43% vs 30% [1.65; 1.46–1.85], 33% vs 23% [1.63; 1.43–1.87], 30% vs 20% [1.63; 1.41– 1.88], and 27% vs 17% [1.81; 1.54–2.11], respectively) (Figure 2). However, the proportions of children with a positive test result out of all tested children for each respective allergen at almost every age band (censoring not taken into account) were higher (although statistically insignificant) among the offspring of parents with atopic diseases (Table S4).

3.3 | Number of atopic diseases in the parents and the offspring's atopic sensitization

Compared with the offspring of two parents without atopic diseases, the cumulative incidences of sensitization to different allergens and the risk of food allergy, positive food test, and any positive allergy test were 1.3 or over 1.3 times higher when the overall number of atopic diseases in the parents was one to two, over 2.4 times higher when it was three to five, and threefold or more than threefold higher when it was six to nine (Table 2).

The cumulative incidences and respective hazard ratios of sensitization to food, animal, and pollen allergens increased consistently by the number of atopic diseases in the parents (Figure 3), and males had an unequivocally higher risk than females, according to the number of parental atopic diseases.

3.4 | Subgroup analysis

According to both the children's sex and parental atopic diseases, the highest cumulative incidences for any positive test (30%), for any positive food test (22%), and for sensitization to food (20%), animal (15%), and pollen allergens (16%) were seen in males with two parents with atopic diseases, and the lowest cumulative incidences were seen for either male or female offspring of parents without atopic diseases (Table 3). Similar incidence patterns could be seen according to parental comparable atopic diseases as well, although no strong conclusions can be drawn due to a low number of cases in the category of two parents with atopic diseases (Table 3).

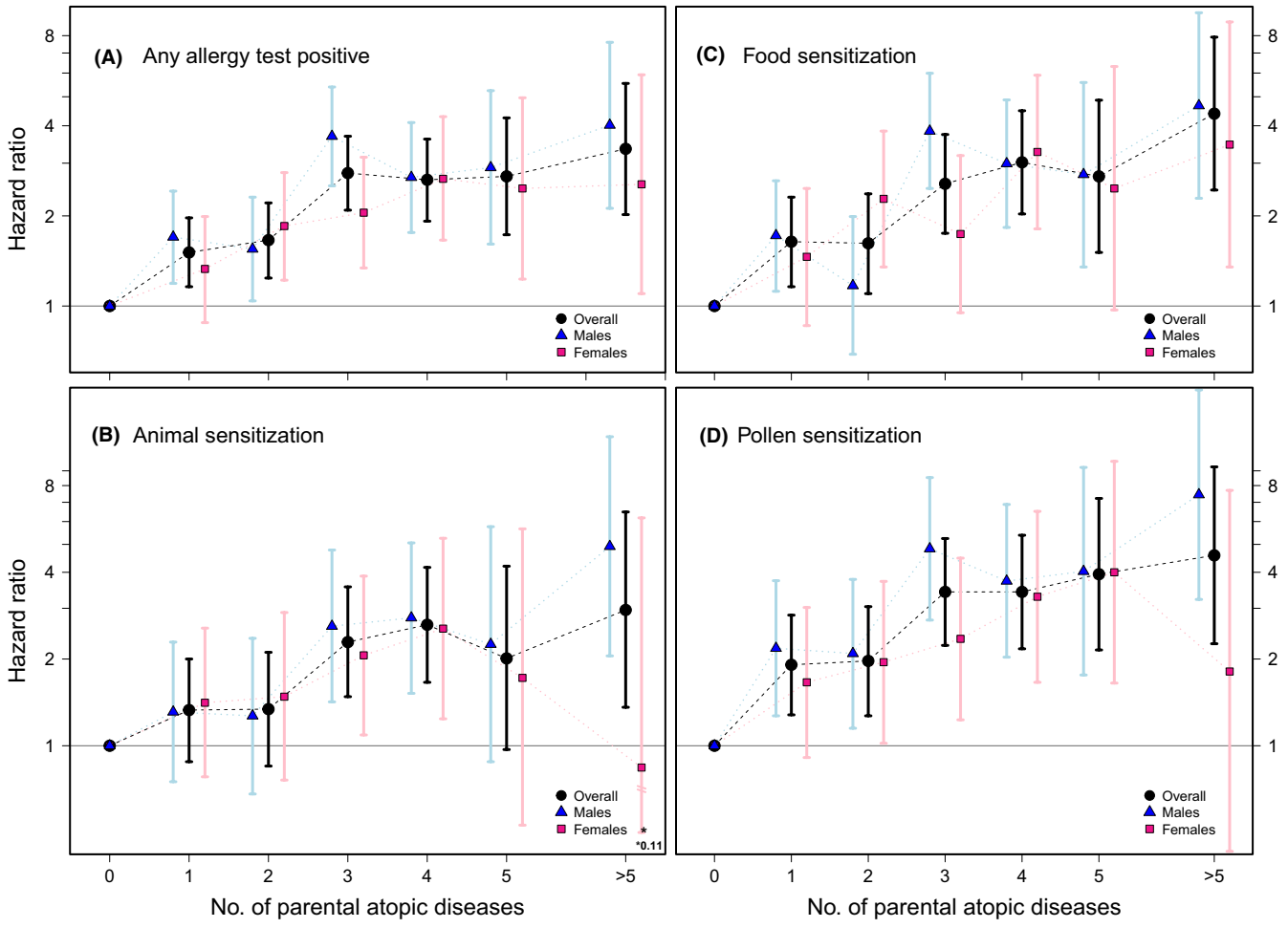

FIGURE 3 Hazard ratios (indicated by points from the Cox models with 95% CI, indicated by vertical lines) of positive test results for any allergy tests (A), animal sensitization (B), food sensitization (C), and pollen sensitization (D) in the offspring, according to the number of atopic diseases (food allergy, atopic eczema, allergic asthma, pollen allergy, or animal allergy) in both biologic parents. Note the logarithmic scale of the *y*-axes

TABLE 3 Cumulative incidence (%) of sensitization to food, animal and pollen allergens, food allergies, any positive food test and any positive allergy test above up to 12 years of age and the Hazard ratios (from Cox models) according to parental atopic diseases, number of atopic diseases[a] and comparable atopic diseases together with the child's sex

		Sensitization								
		Food			Animal			Pollen		
Explanatory variable	N[b]	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)
Sex & parental atopic disease										
Female & neither	803	7	(45)	1.0	6	(37)	1.0	6	(35)	1.0
Female & mother	482	10	(44)	1.66 (1.09–2.51)	9	(35)	1.59 (1.00–2.53)	11	(40)	1.93 (1.23–3.04)
Female & father	300	13	(35)	2.21 (1.42–3.44)	7	(20)	1.52 (0.88–2.62)	9	(23)	1.88 (1.11–3.18)
Female & both	195	13	(21)	1.96 (1.17–3.29)	11	(18)	2.03 (1.15–3.56)	10	(18)	2.16 (1.22–3.81)
Male & neither	823	7	(53)	1.15 (0.78–1.72)	6	(40)	1.06 (0.68–1.66)	6	(35)	0.98 (0.61–1.56)
Male & mother	456	15	(66)	2.72 (1.86–3.97)	10	(42)	2.06 (1.32–3.20)	13	(49)	2.56 (1.66–3.95)
Male & father	326	13	(38)	2.16 (1.40–3.32)	10	(27)	1.83 (1.11–3.00)	14	(38)	2.78 (1.75–4.40)
Male & both	207	20	(39)	3.61 (2.35–5.54)	15	(28)	3.05 (1.87–4.99)	16	(31)	3.61 (2.23–5.86)
Sex & no. of atopic diseases in the parents										
Female & 0	685	7	(37)	1.0	6	(30)	1.0	6	(27)	1.0
Female & 1–2	479	11	(45)	1.77 (1.15–2.74)	7	(29)	1.40 (0.84–2.34)	8	(32)	1.73 (1.03–2.88)
Female & 3–5	301	14	(36)	2.34 (1.48–3.70)	10	(27)	2.15 (1.28–3.61)	12	(32)	2.87 (1.72–4.79)
Female & 6–9	27	20	(5)	3.79 (1.49–9.65)	4	(1)	0.90 (0.12–6.60)	9	(2)	2.04 (0.49–8.60)
Male & 0	686	7	(44)	1.19 (0.77–1.84)	6	(35)	1.17 (0.72–1.91)	6	(28)	1.03 (0.61–1.75)
Male & 1–2	506	10	(49)	1.83 (1.20–2.81)	7	(33)	1.50 (0.91–2.45)	11	(43)	2.18 (1.35–3.53)
Male & 3–5	279	21	(53)	3.80 (2.49–5.78)	15	(36)	3.10 (1.91–5.03)	18	(45)	4.42 (2.74–7.13)
Male & 6–9	29	30	(8)	6.07 (2.83–13.0)	23	(6)	5.67 (2.36–13.6)	28	(7)	7.59 (3.30–17.4)
Sex & parental comparable atopic disease										
Female & neither	1,372	9	(106)	1.0	7	(58)	1.0	7	(44)	1.0
Female & mother	137	10	(13)	1.26 (0.71–2.24)	8	(21)	1.42 (0.86–2.34)	10	(29)	1.92 (1.20–3.08)
Female & father	78	17	(11)	1.94 (1.04–3.62)	10	(15)	1.67 (0.95–2.95)	10	(23)	2.06 (1.25–3.42)
Female & both	12	33	(4)	5.07 (1.87–13.8)	6	(3)	1.22 (0.38–3.90)	8	(7)	1.67 (0.75–3.71)
Male & neither	1,366	10	(122)	1.16 (0.89–1.50)	6	(65)	1.10 (0.77–1.57)	7	(47)	1.03 (0.68–1.55)
Male & mother	167	18	(29)	2.40 (1.59–3.62)	16	(35)	2.69 (1.77–4.10)	14	(41)	2.78 (1.82–4.26)
Male & father	82	25	(20)	3.68 (2.28–5.93)	11	(19)	1.90 (1.13–3.20)	16	(36)	3.22 (2.07–5.00)
Male & both	13	16	(2)	2.17 (0.54–8.80)	16	(8)	3.12 (1.49–6.53)	15	(12)	3.17 (1.68–6.01)
		Food allergy			Any food test+			Any test+		
Explanatory variable	N	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)	%	(n)	HR (95% CI)
Sex & parental atopic disease										
Female & neither	803	2	(16)	1.0	8	(52)	1.0	12	(82)	1.0
Female & mother	482	4	(21)	2.20 (1.15–4.22)	13	(55)	1.80 (1.23–2.63)	18	(78)	1.64 (1.20–2.23)
Female & father	300	4	(12)	2.05 (0.97–4.33)	14	(39)	2.13 (1.41–3.23)	19	(51)	1.80 (1.27–2.55)
Female & both	195	6	(12)	3.10 (1.47–6.56)	16	(27)	2.21 (1.39–3.52)	23	(41)	2.18 (1.50–3.17)
Male & neither	823	3	(21)	1.28 (0.67–2.45)	9	(62)	1.17 (0.81–1.69)	13	(90)	1.08 (0.80–1.46)
Male & mother	456	7	(31)	3.50 (1.91–6.39)	18	(78)	2.81 (1.98–3.99)	25	(103)	2.40 (1.80–3.21)
Male & father	326	3	(10)	1.53 (0.70–3.38)	15	(43)	2.11 (1.41–3.17)	23	(67)	2.15 (1.55–2.96)
Male & both	207	7	(15)	3.65 (1.80–7.38)	22	(44)	3.52 (2.35–5.26)	30	(60)	3.17 (2.27–4.42)

(Continued)

TABLE 3 (Continued)

		Food allergy			Any food test+			Any test+		
Explanatory variable	*N*	%	(*n*)	HR (95% CI)	%	(*n*)	HR (95% CI)	%	(*n*)	HR (95% CI)
Sex & no. of atopic diseases in the parents										
Female & 0	685	2	(16)	1.0	8	(44)	1.0	12	(68)	1.0
Female & 1–2	479	3	(14)	1.25 (0.61–2.55)	12	(52)	1.72 (1.15–2.57)	17	(70)	1.51 (1.08–2.10)
Female & 3–5	301	7	(21)	3.08 (1.61–5.91)	17	(45)	2.49 (1.64–3.77)	23	(63)	2.31 (1.64–3.26)
Female & 6–9	27	19	(5)	8.27 (3.03–22.6)	23	(6)	3.87 (1.65–9.08)	23	(6)	2.59 (1.13–5.98)
Male & 0	686	3	(18)	1.12 (0.57–2.20)	8	(52)	1.18 (0.79–1.76)	13	(75)	1.11 (0.80–1.54)
Male & 1–2	506	3	(17)	1.44 (0.73–2.84)	12	(56)	1.76 (1.19–2.61)	20	(88)	1.82 (1.33–2.50)
Male & 3–5	279	9	(24)	3.77 (2.00–7.09)	25	(65)	3.97 (2.71–5.82)	33	(86)	3.55 (2.58–4.88)
Male & 6–9	29	10	(3)	4.50 (1.31–15.4)	33	(9)	5.60 (2.73–11.5)	41	(11)	4.68 (2.47–8.85)
Sex & parental food allergy										
Female & neither	1372	3	(40)	1.0	10	(125)	1.0	15	(181)	1.0
Female & mother	137	7	(10)	2.56 (1.28–5.11)	11	(15)	1.23 (0.72–2.10)	16	(21)	1.20 (0.76–1.88)
Female & father	78	8	(6)	2.69 (1.14–6.33)	22	(15)	2.27 (1.33–3.87)	26	(18)	1.92 (1.18–3.11)
Female & both	12	8	(1)	2.83 (0.39–20.6)	33	(4)	4.14 (1.53–11.2)	33	(4)	2.97 (1.10–7.99)
Male & neither	1,366	4	(51)	1.28 (0.85–1.94)	12	(144)	1.16 (0.91–1.47)	18	(215)	1.20 (0.99–1.47)
Male & mother	167	7	(12)	2.53 (1.33–4.82)	21	(33)	2.32 (1.58–3.41)	26	(41)	2.02 (1.44–2.84)
Male & father	82	11	(9)	3.80 (1.84–7.82)	29	(24)	3.73 (2.41–5.78)	33	(27)	3.03 (2.02–4.53)
Male & both	13	8	(1)	2.70 (0.37–19.6)	16	(2)	1.81 (0.45–7.31)	24	(3)	1.95 (0.62–6.10)

Abbreviations: CI, confidence intervals; HR, Hazard ratios; *n*, the number of cases.

[a]The overall number of atopic manifestations include food allergy, atopic eczema, allergic asthma, pollen allergy and animal allergy in both parents.

[b]Total number (*N*) of children in the variable categories on parental comparative atopic diseases i.e food allergy shown in this column. Total number (*N*) of children in the groups according to Sex & parental animal allergy as Female & Neither, Female & Mother, Female & Father, Female & Both, Male & Neither, Male & Mother, Male & Father and Male & Both were 1,106, 282, 181, 49, 1,126, 261, 195, and 54, respectively, and according to Sex & parental pollen allergy 954, 336, 258, 90, 987, 335, 257, and 86, respectively.

In the subgroups of females and males, the cumulative incidences of food allergies were threefold higher (2% vs 6%, 3.10; 1.47–6.56 and 3% vs 7%, 2.86; 1.47–5.54, respectively) among the offspring of two parents with atopic diseases. The cumulative incidence for pollen sensitization was twofold higher (10% vs 6%, 1.97; 1.32–2.93) for the female offspring of parents with atopic diseases than those of parents without, while it was almost threefold higher (14% vs 6%, 2.90; 1.99–4.24) among males. Furthermore, the highest cumulative incidence of pollen sensitization was found among the female offspring of parents with three to five atopic diseases (6% vs 12%, 2.88; 1.72–4.80) and among the male offspring of parents with more than five atopic diseases (6% vs 28%, 7.32; 3.20–16.8), compared with the offspring of two parents without any atopic diseases (Table 3 and Table S5).

Male sex was associated with a higher cumulative incidence of positive tests for any and food allergens and sensitization to food, pollen, and any (food, animal, or pollen) allergens, but only in the offspring of either or both parents with an atopic disease (Table S6). Among the offspring of parents with and without an atopic disease, the most common combination for the first sensitization was that for food allergens alone in early childhood, while food allergens together with animal or pollen allergens, or for any of the latter allergens alone, were a more commonly found combination for the first sensitization after 2 years of life (Figure 4 and Figure S2). Among the offspring of parents with atopic diseases, the combination curves for the first sensitizations rose more steeply for the male offspring than for the female offspring, although the most common combination of the first sensitization for both groups was sensitization to food allergens alone (Figure 4 and Figure S3).

3.5 | Effect modification due to the offspring's sex

Potential modifications of the association between parental atopic diseases and the outcomes by the offspring's sex are shown in Tables S7–S9. The association between parental atopic diseases and the offspring's pollen sensitization and the association between parental pollen allergies and the offspring's pollen sensitization were modified by sex according to the estimates of the additive scale (RERI 0.91; 95% CI 0.11–1.71 and 1.03; 0.13–1.91, respectively) and the multiplicative scale (HR ratio 1.48; 95% CI 0.83–2.70 and 1.50; 95% CI 0.86–2.60, respectively), although the confidence intervals of the multiplicative scale included the unity (Tables S7–S8). Additionally, a statistically significant positive effect modification by sex could be observed according to the additive scale, but this could not be observed according to multiplicative scale estimates for the associations between the number (more than two) of parental atopic diseases and the offspring's

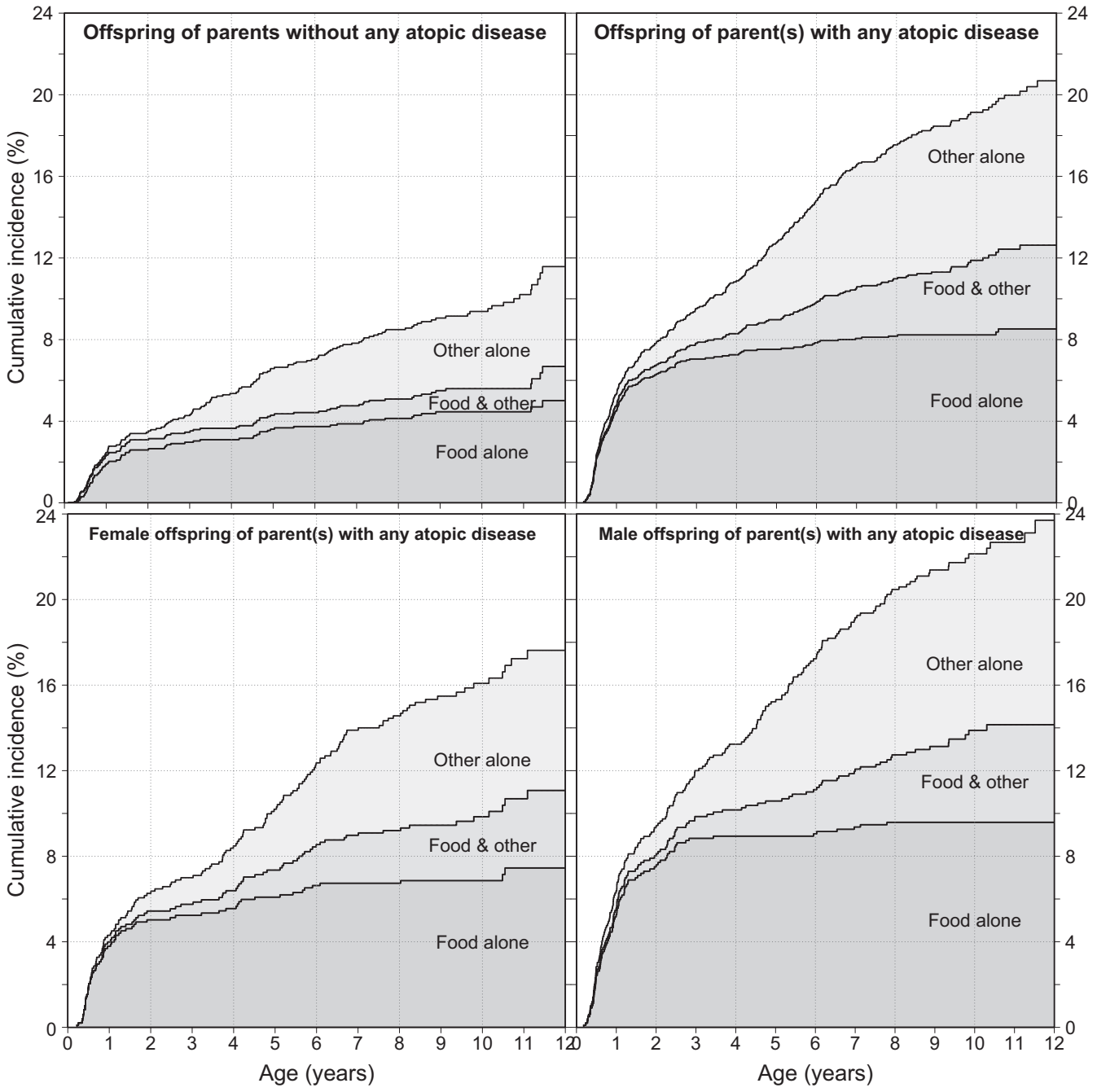

FIGURE 4 The combinations of first positive tests for food alone, food and other (animal and/or pollen) and other allergen(s) alone are shown by stacked cumulative incidence curves (Aalen-Johansen method; competing risks) in the offspring of parents with and without atopic diseases in the upper left and right plots, respectively. In the lower plots, combinations of the first atopic sensitization are shown separately among the female (left plot) and male offspring (right plot) of parents with atopic diseases

positive food tests (1.08; 0.14–2.07 and 1.44; 0.90–2.26, respectively), and sensitization to food allergens (1.06; 0.08–2.03 and 1.46; 0.88–2.50, respectively) (Table S9).

4 | DISCUSSION

We found general population-based evidence for an association between a history of atopic diseases in the biologic parents and the incidence of atopic sensitization and food allergies among their offspring until adolescence. The number of atopic diseases in the parents was also associated with the offspring's allergic sensitization. The associations between parental atopic diseases and the offspring's allergic sensitization were stronger among males than among females.

In a real-world patient register-based study, an inaccuracy regarding the following of current guidelines on diagnosing food allergies[29] must be tolerated. It is notable that our study population

was under 2 years of age before 2003–2008, at a time before the current diagnostic guidelines regarding food allergy. Within the survey, a diagnosis of an allergy to cow's milk and cereals was usually based on an OFC particularly in early childhood, but after 2 years of age and for other food allergens, a food allergy diagnosis might also have been based on the objective evidence of SPT and/or sIgE results and the history of parentally perceived food-related symptoms. Thus, the outcome of any positive food test can be interpreted here as objective evidence of a possible food allergy to any food items. Here, we did not evaluate the association between the parental atopic diseases and offspring's allergies to single food items, which has been previously reported.[13] In addition to sensitization tests (sIgE and/or SPT), animal or pollen allergy cannot be objectively confirmed by any challenge tests, as such tests are not available for clinical use; therefore, the results of the sensitization tests provide the strongest evidence for these allergies in a child population.

We found a slightly weaker association between the parental-specific atopic diseases and their offspring's comparable positive allergy tests compared with any of the parental atopic diseases and the offspring's positive tests, particularly with food allergens. This finding might be explained by the comorbidities of atopic diseases due to common genetic loci,[3,4] but a lower number of cases in the offspring of parents with comparable atopic diseases make the comparison difficult.

Our results are in line with previous findings on the predominant occurrence of allergic diseases in males.[7–9] Our subgroup analysis was in line with the findings of the Multi-Center Allergy Study (MAS),[11] in which the male sex was associated with allergic rhinitis but only among those with allergic parents. We also showed an association between sex and sensitization to food, and separately to pollen, and a weaker association between sex and sensitization to animal allergens among the offspring of parents with atopic diseases. Here, the positive effect modification due to offspring's sex could be shown by estimates of both the additive and multiplicative scales for any positive food test and sensitization to food, animal, and pollen allergens. However, the confidence intervals of the additive scale estimates exceeded zero for the outcome of pollen sensitization, indicating the most unequivocal positive effect modification by the offspring's sex, regarding the association between the outcome and parental atopic diseases, parental pollen allergy, and number of parental atopic diseases. Regarding the public health perspective and the biologic notion of synergism, the positive effect modification is more relevantly indicated by the estimates of additive scale than by those of the multiplicative scale.[30] Our findings on higher incidences among male offspring of parents with atopic diseases and the association between parental pollen allergies and the offspring's pollen sensitization modified by sex support the previous explanation that X chromosome-linked recessive genes are more likely to be revealed in the phenotype of males than in those of females.[10]

The main strength of our study is a longitudinal and population-based setting comprising real-world data on five age classes that could be individually linked with the information on atopic diseases of the biologic parents. Such a large number of allergy tests comprising a long follow-up period for a large cohort would have been very expensive to include in an experimental study, and the information on parental atopic diseases is rarely available in registers comprising a general population. In general, a low participation rate in questionnaire surveys may lead to selection bias, but the participation rate of our questionnaire survey regarding a general population is relatively high, and the occurrences of outcomes among participants shown here and among entire population do not refer to the selective participation.[14]

One potential weakness of our data is related to the information on parental atopic diseases, which was only collected at the time of the survey because atopic diseases often appear before adult age, but they may have been diagnosed after the survey. Another potential weakness of our results is the higher incidences of testing in the offspring of parents with atopic diseases. In line with our previous findings on food allergies up to the age of 4 years,[13] the proportions of positive tests out of all the children tested for different allergens were higher among the offspring of parents with atopic diseases potentially referring to an inherited immune response. In Finland, public health nurses regularly screen for allergic symptoms in children at child health clinics and schools, and when needed, appropriate allergy tests are ordered and atopic diseases diagnosed by physicians.

In conclusion, we found a relatively strong positive association between any atopic disease of the biologic parents and the incidence of atopic sensitization and food allergies among their offspring. This association strengthened according to the increasing number of specific atopic diseases in the parents, particularly among their male offspring. The predominance of sensitization and food allergies in males might be explained by the X chromosome-linked recessive genes associated with allergic diseases.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Kaisa Pyrhönen: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Validation (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Petri Kulmala:** Conceptualization (equal); Funding acquisition (supporting); Supervision (supporting); Validation (equal); Visualization (supporting); Writing-review & editing (equal).

ETHICAL APPROVAL

This study was reviewed by the Ethical Committee of the Northern Ostrobothnia Hospital District (95/2003) and the South Karelia District of Social and Health Services (979/13.01.02/2014). The test data were collected with the permission of the Finnish Ministry of Social Affairs and Health (49/07/2003) and the National Institute for Health and Welfare (THL/1490/5.05.01/2014 and THL/1519/5.05.00/2014). All eleven healthcare centers in the region consented to cooperate. In the questionnaires, the parents were asked for their permission to use their children's PICs for the data linkage.

ORCID

Kaisa Pyrhönen https://orcid.org/0000-0001-5455-5288
Petri Kulmala https://orcid.org/0000-0003-2895-8563

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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