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Original Article

Diverse age-incidence patterns of atopic sensitisation in an unselected Finnish population up to 12 years

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Abbreviations:

sIgE; specific immunoglobulin E

OFC; open food challenge

PIC; personal identification code

SPT; skin prick test

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ABSTRACT (Words 257)

Background: The temporal sequence in which allergic sensitisation to different allergens emerges is not well-characterized at the level of general population.

Objective: We describe the incidence patterns of atopic sensitisation to different allergens from birth up to 12 years of age in an unselected Finnish population.

Methods: The study population comprised all children born 2001-2006 identified from the nationwide population register as residents of the province of South Karelia, Finland (N=5564). The results of allergy tests (22380 results from skin prick tests, IgE antibodies, and open food challenges, OFCs, performed in 1827 children) were collected from patient records of all the healthcare units in the area.

Results: The incidence rates of positive results for food and animal allergens as well as positive OFCs for cow's milk showed prominent peaks at 5 months of age. Positive results for pollen allergens started to emerge after 1.5 years of age. The 12-year cumulative incidence of sensitisation to food, animal, pollen, and any allergens was 12%, 8%, 10%, and 18%, respectively. The cumulative incidence of sensitisation to house dust mites was 1% and to moulds or latex less than 1%. Firstborn boys had the highest, and not firstborn girls and children born in rural municipalities the lowest early incidence of sensitisation to inhalation allergens.

Conclusion: In the unselected population, the atopic sensitisation against food and animal allergens began before 6 months of age and was followed by sensitisation to pollen allergens before 2 years of age. Primary prevention of sensitisation to food and inhalation allergens should therefore occur in early infancy.

Introduction

The clinically observed progression of atopic diseases is often described in terms of an 'atopic march'; from atopic eczema to respiratory allergies (allergic rhinitis and/or asthma)[1-5]. The incidence of atopic manifestations has previously been defined by using the first date of hospital admission for these conditions or dispensed prescription of specific medication[6] or by the age at diagnoses of atopic manifestations[7].

The information on the occurrence of allergic sensitisation and different allergies by age has been derived from population-based birth cohorts, mainly from the age of one year, in single or repeated cross-sectional settings[8-18], a laboratory database of positive specific IgE test results among tested subjects[19] or clinical experience[20]. Allergen specific IgEs were detected from birth in the DARC[16] and the PASTURE[10] cohorts, the latter of which being partly carried out in Finland, with the aim of finding out preventive environmental and genetic factors of atopy[21]. However, the patterns of incidence of sensitisation to different allergens from birth until early teenage years has been inadequately described at the level of general population.

The South Karelian Allergy Research Project[22-25] is a large observational population-based cohort study, which contains the information on exact dates and results of allergy testing during a long follow-up period. This paper reports the age-incidence patterns of sensitisation to different allergens from birth up to 12 years of age using survival methods. From a public health perspective, our data add to previous descriptions of allergic sensitisation and food allergies and will be useful for health care authorities, physicians and primary prevention.

Methods

Definition of the population

The target population comprised all children born between April 2001 and March 2006 who resided in the province of South Karelia in south-east Finland at the time they were invited to the questionnaire survey which was conducted during the years 2005 and 2006[22]. The target population (N=5973) of our study was identified and their personal identity codes (PIC; including information on the date of birth) obtained from the Population Register Centre of Finland (Figure 1). The present paper focuses on the entire population, covering both the participants and the non-participants of the survey.

The parents of 53 children had refused the use of the PIC in the questionnaire and their data were excluded. For the remaining 5920 children, information on vital status and migrations by September 2013 was available for 5902 children from the Population Register Centre. Children who had immigrated to the study area after one month of age (N=356) were excluded and those with missing information of migration history (N=18) were included in the data analyses. Thus, the final study population comprised 5564 children (Figure 1).

Data collection

The information on all allergy tests was collected from all the healthcare units in the area with the intention to cover the entire target population. These tests had been performed for diagnostic purposes between April 2001 and September 2013. The PIC was used to merge the individual test data with population register data.

Ethics and permissions

The study protocol was reviewed and approved 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).

Outcomes and explanatory variables

Skin prick tests (SPT) were performed by trained local laboratory personnel or nurses, using standard commercial extracts and using negative controls and histamine as a positive control. SPTs were often ordered and performed as panels including the most common allergens (either for food allergens (cow's milk, hen's egg, wheat, barley, rye, gliadin, oat, fish and often soya and/or nut), or inhalation allergens (dog, cat, horse, birch, alder, timothy, mugwort, meadow fescue or cocksfoot grass, Dermatophagoides pteronyssinus or D.farinae, Cladosporium herbarum), or both, and/or a contact allergen, latex, and sometimes for single allergens. Specific Immunoglobulin E antibodies (sIgE) were used as an alternative method for SPTs depending on their availability in the health care centre. sIgE had been performed for 34 and SPT for 28 individual allergens or group (e.g. root vegetables, fruits, spices, legumes, moulds, grasses, vaccines, or medicines) of allergens.

As the outcome variables, we considered the occurrence of 1) the first test, i.e. SPT, sIgE or open food challenge (OFC), and 2) the first positive result from any of these tests for any allergen, and separately for pollen, animal and food allergens, and also separately for different food and other allergens. Cow's milk, milk supplementary formula (extensively hydrolysed/ amino acid formulae/soya), hen's egg, or cereals (wheat/barley/rye) were considered as *essential food items* and other food items as *non-essential food items*.

The cutoff point for a positive sIgE result was 0.35kU/l with RAST-CAP FEIA or Phadiatop Combi and 1.43 standardised units per ml with Magic Lite and for SPTs as the mean of 2 orthogonal diameters of the urticarial weal of 3 mm, applied to both positive and negative

controls. A wheal diameter of 3 mm or more was regarded as a positive SPT result. Most OFCs were supervised by a paediatrician in the hospitals of the study area, exceptionally three OFCs in two children were performed in health centres. The OFC was considered 'positive' when labelled as such in the patient records (the food allergy diagnosis made by the paediatrician, who supervised the OFC).

The information on gender, birth order and the first place of residence were based on the data obtained from the Population Register Centre and used as explanatory variables.

Statistical methods

For each allergen or a combination of them, the outcome event was either the first allergy test performed, or the first positive test, as appropriate. The risk time was primarily defined as the period between the child's date of birth and the date of the event. Where a pertinent event was not observed during the follow-up, the risk time ended either on the date of death (four children died), date of emigration from the study area (to other regions in Finland or abroad) for a period longer than one year, or on the closing date of data collection (September 30, 2013), whichever occurred first. In analyses of the cumulative incidence of the first event among competing, i.e. mutually exclusive alternative events, the risk time would also end on the date of the first of the competing events.

The R environment release 3.5.1 was used for computations and graphics[26]. The incidence rates for the outcomes by age were analysed and presented as follows[27, 28]. For each outcome the follow-up was organised and split into bimonthly intervals, or age bands, using functions Lexis and `splitLexis` of the Epi package in R[29]. In each age band, the incidence rate was calculated as the number of cases of the outcome in question occurring in the interval divided by the total person-time (summed risk times) accumulated in the same age band and expressed as cases per 100 child-years. Smoothed estimates of incidence rates were obtained

as predictions from a Poisson regression model using function `glm`, in which the effect of age was smoothed by natural cubic splines[28] with prespecified knots at the ages of 0, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 years. The smoothed age-incidence curves were graphically presented, also showing the empirical bimonthly incidence rates at the midpoint of each interval.

The cumulative incidence proportions of each outcome event by age were first computed by the Kaplan-Meier method[30, 31] assuming independent censoring due to possible competing events. In the analyses addressing the cumulative incidence of the major combinations of allergen groups, the Aalen-Johansen method[32] was applied to allow for competing events. Computations of cumulative incidence were performed by the `survfit` function of the survival package[33]. The Cox regression model, fitted by function `coxph` in R, was used to estimate the incidence rate ratios (RR) of the positive test for animal and pollen allergens associated with a history of previous sensitization (a positive sIgE/SPT) to food allergens and of a positive OFC.

Results

Number of tests and tested children

Among the entire population (N=5564), 22 380 individual allergy tests for specific IgE-mediated sensitisation or allergy had been performed on altogether 1827 children (39 973 child-years of follow-up; median 8.42 years), and 4120 tests had yielded a positive result in 874 children (47 242 child-years of follow-up; median 9.23 years) (Table 1). At least one positive result in sIgE or SPT i.e. *sensitisation* was observed in 803 children (3713 positive tests) out of 1822 children tested, the cumulative incidence being 17% by 12 years of age.

Altogether 706 OFCs had been performed on 295 children, of which 407 OFCs had been positive in 207 children. Most OFCs had been performed for cow milk (N=245 children).

Other OFCs had been performed for cereals (N=95), hen's egg (N=14), soya or milk supplementary formulas (N=81), fish (N=11), pork meat (N=2), potato (N=1), and nut (N=1).

Incidence rates of positive test results

The incidence rates of sensitisation to food and animal allergens reached a prominent peak at approximately 5 months of age, while the incidence rates of sensitisation to pollen allergens increased monotonically up to 12 years of age (Figure 2 and eFigure 1). The incidence rates of the first positive test results for cow's milk allergens showed a peak at 5 months of age (Figure 3 and eFigure 2). Other early incidence peaks of the positive tests were those for hen's egg and cereal allergens (wheat, barley or rye).

The incidence rates of *any food allergy (a positive OFC),* cow's milk allergy and cow's milk allergy with sensitisation to cow's milk allergens peaked around the age of 6 months (Figure 4). Altogether 168 children had OFC-confirmed cow's milk allergy. Among them 35% (59) had sensitisation to cow's milk allergens, 32% (53) to some other allergens, 33% (56) to none of the tested specific allergens, and for one child no results of SPT or sIgE tests were found. The incidence rates of cereal allergy, and cereal allergy with sensitisation, peaked at the age of 10 months. Altogether 59 children had OFC-confirmed cereal allergy, and among them 32 children had cereal allergy with sensitisation to cereal allergens.

Cumulative incidence of positive test results

The cumulative incidences for the first positive test were 12% for food, 8% for animal, 10% for pollen, and 18% for any allergens by 12 years of age (Table 1, Figure 5). Positive tests for food, most commonly for cow's milk (Table 1, Figure 5, and Figure 6), started to emerge soon after the birth and those for animal and pollen allergens at 3 months and 1.5 years of age

(Figure 5), respectively. The cumulative incidence of food allergy *(a positive OFC)* was 4%, cow's milk allergy 3%, and cow's milk allergy with sensitisation 1%.

The cumulative incidence curves of sensitisation to pollen and animal allergens crossed at 7 years of age (Figure 4) and those of birch and pet (dog and cat) allergens at approximately 5 years of age (eFigure 3). Sensitisation to tree pollen started to arise earlier than sensitisation to grass pollen allergens.

The most common combination of the first positive test(s) was that for food allergens alone, while food allergens together with animal or pollen allergens, or for any of the latter allergens alone were much more rarely found combinations of the first positive tests (Figure 5). The most common combination of the first positive food tests was that for cow's milk allergens alone (Figure 6).

Previous sensitisation to food allergens (a positive sIgE/SPT) and food allergy (a positive OFC) was a strong predictor of subsequent sensitisation to animal allergens (RR 37.5; 95%CI 28.9-48.5 and 29.1; 21.2-40.6, respectively) and of subsequent sensitisation to pollen allergens (37.6; 29.3-48.2 and 30.1; 22.3-40.6, respectively).

Other allergic sensitisations

Altogether 903 children were tested for house dust mite allergy (SPTs performed on 539 children and sIgE tests on 466), but positive results were found in only 43 cases (Table 1). A positive result for mould allergens was found in only 31 children out of 602 tested subjects. Only two children had a positive test result for latex allergens, although 307 children were tested by SPT and 5 by sIgE for latex. Overall 650 children were tested for fish or other sea food allergens, but only 23 children had positive results.

Incidence rates by gender, birth order and first residence

Incidence rates of positive test results for cow's milk and hen's egg allergens formed early incidence peaks in all subgroups according to the birth order and gender (Figure 7). Early incidence peaks could also be seen for sensitisation to animal allergens among firstborn boys and girls while such early peaks were not seen for not firstborn infants. The incidence curves of sensitisation to pollen allergens started to arise after the first year of life in all subgroups, most steeply among the firstborn boys. Children with the first residence in rural municipalities had a slightly lower incidence rates of sensitisation to inhalation allergens than others, but within the first two years their incidence curves for cow's milk and hen's egg allergens formed at least as high early peaks as other children.

Discussion

The present paper describes the age-incidence patterns of sensitisation for different allergens from birth up to 12 years of age in an unselected general pediatric population. The incidence rates of positive test results started to increase soon after birth, the peak incidence for food and animal allergens being reached at the age of 5 months. In contrast, no unequivocal early peak was seen for sensitisation to pollen allergens during the follow-up time. The cumulative incidence of sensitisation to tree and grass pollen allergens started to rise after 1.5 year and 2.5 years of age, respectively.

Our quantitative estimates for the incidence of positive test results are in line with clinical experience[5] on the 'allergic march' and also with a recent questionnaire survey from Sweden[9], according to which food allergies (and atopic eczema) typically appear first and are followed by rhinoconjunctivitis and asthma. Previous information on the age-specific occurrence of sensitisation is mainly based on point prevalence figures for sensitisation after the first year of

life obtained from cross-sectional studies and can be compared with our incidence figures only with caution.

According to previous studies, the occurrence of sensitisation to food allergens varies depending on the food items studied, the test methods used, the duration of follow-up period (age), and participation rates[34]. In the Isle of Wight cohort[11], the prevalence of food allergy at four years of age, based on SPTs only, was 3.5%. In primary care cohorts from the USA[7], the incidence of food allergy for any food item during the first 5 years of life was 8.2%, the peak incidence locating at 12 to 17 months of age, while we observed a similar figure for the cumulative incidence of sensitisation to food allergens (8.6%), however with the peak incidence occurring already around 6 months of age.

In our real-life setting, the first OFCs had been most commonly performed for essential rather than non-essential food items, usually before two years of age. By the age of two years, the incidence of challenge-proven cow's milk allergy was less than 1% in EuroPreval cohorts[35], which is in line with the incidence of IgE-mediated OFC-confirmed cow's milk allergy in our study (1%). In the SchoolNuts study (in Australia)[12], the prevalence of OFC-confirmed food allergy was 4.5% and most common for peanuts among students aged 10 to 14 years, while the incidence of OFC-confirmed food allergies was similar in our population (4%), although in early childhood only, and most commonly for cow's milk. In these two studies above from the USA and Australia[7, 12], the prevalence of peanut allergy (2.6% and 2.7%, respectively) agree well with our cumulative incidence of sensitisation (not necessarily allergy) to peanuts, tree nuts, or almond combined (2.4%, 92/5564).

In our study, the cumulative incidences of sensitisation to inhalant allergens was lower than the prevalence of sensitisation to inhalant allergens at the respective ages in the MAS[8] (1.5% and 26% at 1 and 6 years, respectively, although the cutoff for sIgE was higher; $\geq 0.7 kU_A/L$), the PARIS[17] (2.5% at 1.5 years), and the Isle of Wight cohorts[11] (19.2% at 4 years). In the

retrospective cohort study from the USA[7], the prevalence of rhinitis was also higher than sensitisation to inhalant allergens in our study (5.6%, 13.7%, 21.7%, 23.3% and 24.8% at ages of 0-3, 3-5, 6-10, 11-13 and 14-17 years, respectively). These differences might be explained by different study settings, variable definition of the outcomes, statistical methods used (point prevalence vs. cumulative incidences with censoring), and genetic variations between populations in different countries.

Our population-based findings provide further support to the conclusion of the PASTURE cohort[10], according to which any potential preventive measures to curtail atopic sensitisation should be timed at prenatal or early postnatal periods. In the DARC[16] and the PASTURE cohorts[10], positive sIgEs for cat and dog allergens were detected at birth while in our cohort the tests were performed for diagnostic purposes months or years after the birth. In addition, we were able to show early incidence peaks for sensitisation to animal and food allergens and their temporal order calculated as competitive risk estimates in a general population. Preventing early sensitisation is also justified because it can be considered as primary prevention of allergic rhinitis and asthma[36].

According to our results, the sensitisation to house dust mite allergens, moulds and latex were rarities, the occurrence of the former has been reported to be very low due to a cold and dry climate in other Nordic countries[37], too. The prevalence of sensitisation to house dust mite (based on sIgEs) was 1.2% at 18 months of age in the PARIS cohort[17], and 12% (a positive SPT) at 4 years of age in the Isle of Wight cohort[11]. In a study population aged 7 years from the USA[38], the prevalence of sensitisation to mould allergens was 12% and 5% among children with and without asthma, respectively. Sensitisation to natural rubber has recently decreased on account of the increased use of powder-free, low-latex gloves[39] and baby's dummies made of silicon replacing latex dummies. The development of allergic sensitisation to house dust mites, mould or latex may also require longer exposure periods than

sensitisation to food or animal allergens. Since the available allergy tests mostly indicate IgE-mediated allergy, possible underlying non-IgE-mediated mechanisms may remain undiagnosed.

In our study population, the proportion of sensitisation was 44% (803/1822) among children tested by either sIgE or SPT, and 40% (572/1444) if tested by sIgE only, while the proportion of children with at least one positive sIgE out of all repeatedly tested children at 4, 8 and 16 years of age was 51% (1328/2607) in the BAMSE cohort[13]. Also a Dutch study from a hospital laboratory reports 40% of sIgE tested children having a positive test result[19].

In accordance with previous reports[6, 24, 25, 40, 41], the incidences of positive test results for different allergens were higher in boys and firstborn than others. Data from the questionnaire survey are available and can be linked with these test results in future. While our focus was to show results among the general population, presenting occurrences of sensitisation according to the questionnaire-based background variables would have restricted the study population to the questionnaire survey participants only. Additionally, the trajectories of sensitisation in the same population may be possible to analyse in the future.

The main strength of this work is the population-based cohort identified from a nationwide population register, which could be individually linked with the results of all allergy tests conducted for the diagnostic purposes on cohort members from birth up to 12 years of age. The record linkage to the national population register also allowed us to take into account the migration histories of almost all cohort members, enabling us to properly allow for censoring during the follow-up time. The follow up time of 12 years seems to be adequate to describe the early phases of sensitisation to food, animal, tree pollen and grass pollen allergens. However, the cumulative incidences of the first positive test result for animal, pollen and non-essential food (e.g. nut) allergens were still increasing in the end of the present follow up period.

In our study, positive results in SPT or sIgE indicate allergic sensitisation[42]. Tests of molecular allergology (the third step of diagnostic workup) had been performed for very few children at the end of the follow up only, therefore, results of these tests were not included here. Oral food challenges are considered a gold standard (an ideal method a double blind, placebo-controlled food challenge was not available in our study area) and a cornerstone of food allergy diagnosis[43,44]. In our population, positive OFCs can be considered to indicate the physician-diagnosed food allergies confirmed in a hospital, which probably underestimate the total number of food allergies in the general population, since no data were available for OFCs carried out at home due to mild or delayed symptoms.

The main limitation of this study is a lack of information on specific indications of physician-ordered allergy tests e.g. specific symptoms of atopy (atopic eczema, rhinoconjunctivitis or asthma) or parental concern only. In Finland, all children are followed up about 25 to 30 times in the child health clinics: scheduled to take place monthly during the first year of life, at 18 months of age, and thereafter annually until 16 years of age. During these visits, the public health nurses have possibility to consult a physician or paediatrician, who will order allergy tests if needed. Our data also cover allergy tests ordered by private doctors and doctors in the municipal health centres. However, the tests had probably not been performed for asymptomatic children among whom sensitisation to allergens could also have occurred. Therefore, observational studies like ours obviously underestimate the occurrences of sensitisation compared to studies in which almost all recruited participants have been tested. However, due to possible false-positives our sensitisation rates probably overestimate the rates of clinical allergies.

Another limitation of our study is that the study population covered only one province of Finland, South Karelia. The collection of allergy test data would have been too expensive and even impossible to carry out in a larger area. South Karelia includes both rural (population

density 2.69 inhabitants/km^2) and urban areas (182/km^2), district of the Lake Saimaa, with several paper and pulp mills, and their surroundings. These characteristics of the area ~~may~~ restrict the generalisability of our results to some extent.

Based on our real-world data, allergic sensitisation was observed first for food and animal allergens, both reaching their incidence peak at the age of approximately 5 months, followed by gradually increasing allergic sensitisation to pollen allergens after 18 months of age. General population-based information on the temporal order, in which sensitisation to different allergens and physician-diagnosed allergies are observed by age, is useful for physicians when choosing appropriate allergy tests and explaining the natural course of allergic conditions to the parents. This information is also useful in primary prevention. Obviously, preventive measures should be targeted at the age before the incidence of the allergic sensitisation starts to arise in a general population.

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Table 1. Cumulative incidences (%, from Kaplan-Meier analyses) and number (n) of children tested for different allergies and those with a positive test result up to 12 years of age among the entire SKARP population (N = 5564).

	Tested children	**Children with a positive test**
Allergen	*% (n)*	*% (n)*
Food	**27 *(1371)***	**12 *(594)***
Essential food items (any) [b]	27 *(1344)*	11 *(541)*
Cow's milk	26 *(1311)*	8 *(401)*
Cow's milk supplementary formula [c]	16 *(750)*	2 *(97)*
Soya	15 *(735)*	2 *(85)*
Hens egg	19 *(908)*	5 *(249)*
Cereal (wheat/rye/oat/barley/etc)	21 *(1056)*	4 *(209)*
Non-essential foods (any) [d]	15 *(692)*	3 *(131)*
Peanuts, tree nuts or almond	13 *(570)*	2 *(92)*
Animal	**25 *(1231)***	**8 *(378)***
Dog	24 *(1170)*	7 *(300)*
Cat	24 *(1150)*	6 *(266)*
Horse	15 *(822)*	2 *(97)*
Pollen	**23 *(1081)***	**10 *(409)***
Birch	22 *(1073)*	7 *(342)*
Alder	14 *(694)*	4 *(184)*
Mugwort	21 *(989)*	3 *(107)*
Timothy	22 *(1029)*	6 *(208)*
Other		
House dust mite	19 *(903)*	1 *(43)*
Mould [e]	14 *(602)*	1 *(31)*
Latex	6 *(310)*	0 *(2)*
Other specific allergen e.g. medicine, vaccine, poison of wasp or bee etc.	1 *(70)*	0 *(3)*
Any test above	**36 *(1827)***	**18 *(874)***

a specific Immunoglobulin E antibodies or skin prick tests for the allergen(s) in question, or additionally an open food challenge regarding food items

b Essential food items (any) include either cow's milk, milk supplementary formula, egg, or cereals (wheat/barley/rye).

c Including extensively hydrolysed and amino acid formulae, and soya.

d Non-essential food items (any) include any other food items than above.

e Include tests for the following mould allergens: Cladosporium herbarum Aspergillus fumigatus, Alternaria alternata (A.tenuis), Penicillium Chrysogenum (P.notatum), Candida albicans, and Helminthopsorium halodes.

Figure legends

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

Figure 2. Smoothed age-incidence curves of *testing* for food (any food test, Food, or open food challenge, OFC), animal, pollen and any allergens (A) and the curves of *positive tests* (B) among the SKARP population (N=5564).

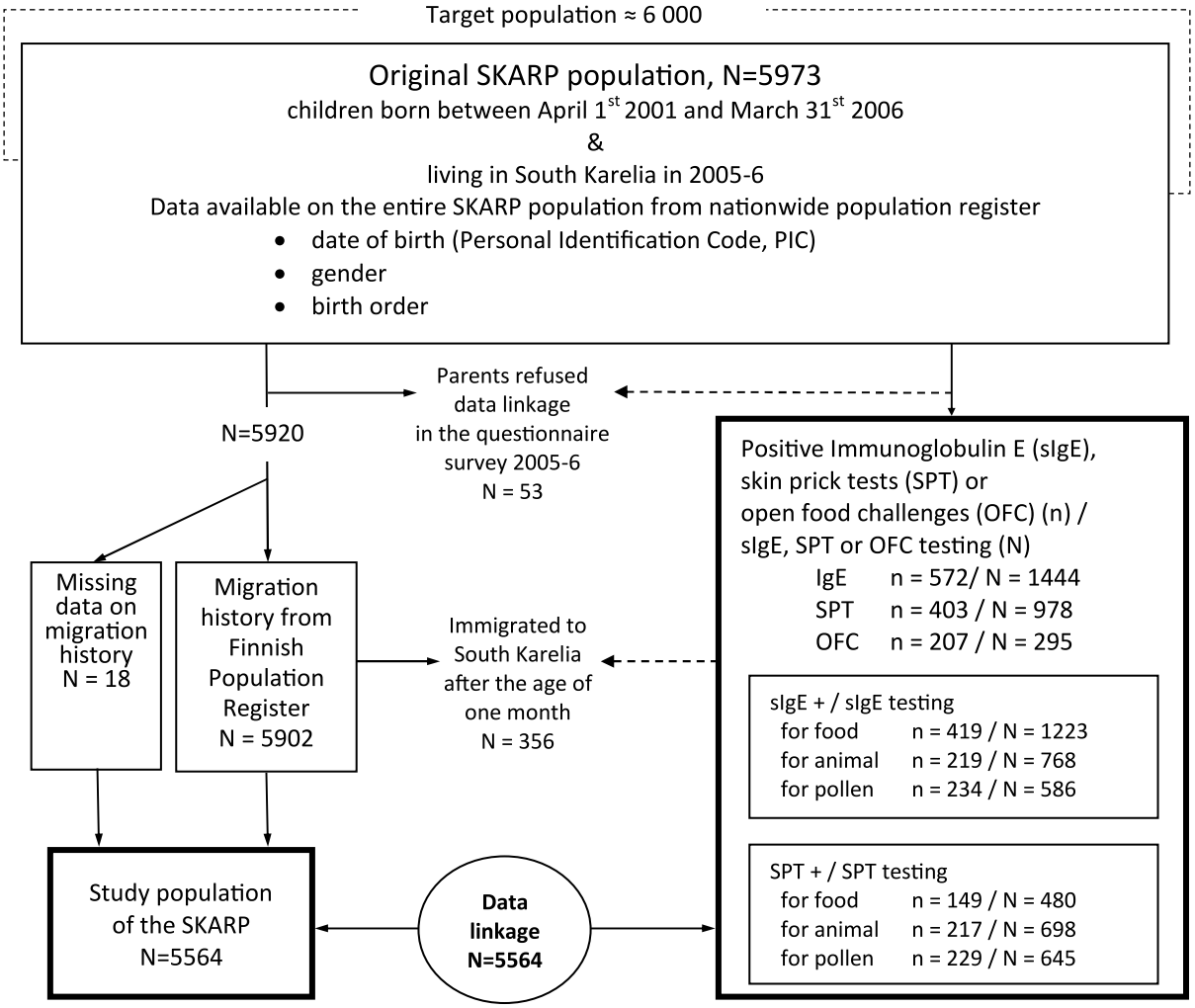
Figure 3. Smoothed age-incidence curves of *testing* for cow's milk, hen's egg, cereals and any essential allergens (A) and the curves of *positive tests* (B) among the SKARP population (N = 5564).

Figure 4. Smoothed age-incidence curves of testing for sensitization (sIgE or skin prick test, SPT, performed) to essential foods (A), the curves of sensitisation (B), and the curves of open food challenge (OFC) confirmed food allergy to cow's milk and cereals, also with respective sensitisation (C) among the SKARP population (N = 5564).

Figure 5. Cumulative incidences by age of *first testing* (A&C) and *positive tests* (B&D) for food, animal, pollen and any allergen shown by Kaplan-Meier curves (A-B) and their first combinations by stacked curves (Aalen-Johansen method; competing risks) (C-D) among the SKARP population (N=5564).

Figure 6. Cumulative incidences by age of *first testing* (A&C) and *positive tests* (B&D) to cow's milk, cereals, hen's egg and essential foods shown by Kaplan-Meier (A-B) and their first combinations by stacked curves (Aalen-Johansen method; competing risks) (C-D) among the SKARP population (N=5564).

Figure 7. Smoothed incidence curves (cases per 100 child-years) by age of *first testing* (greater plots) for cow's milk, hen's egg, animal and pollen allergens and the respective curves for *first positive tests* (nested plots; note the different scaling) according to gender&birth order and first residence among the SKARP population (N=5564).



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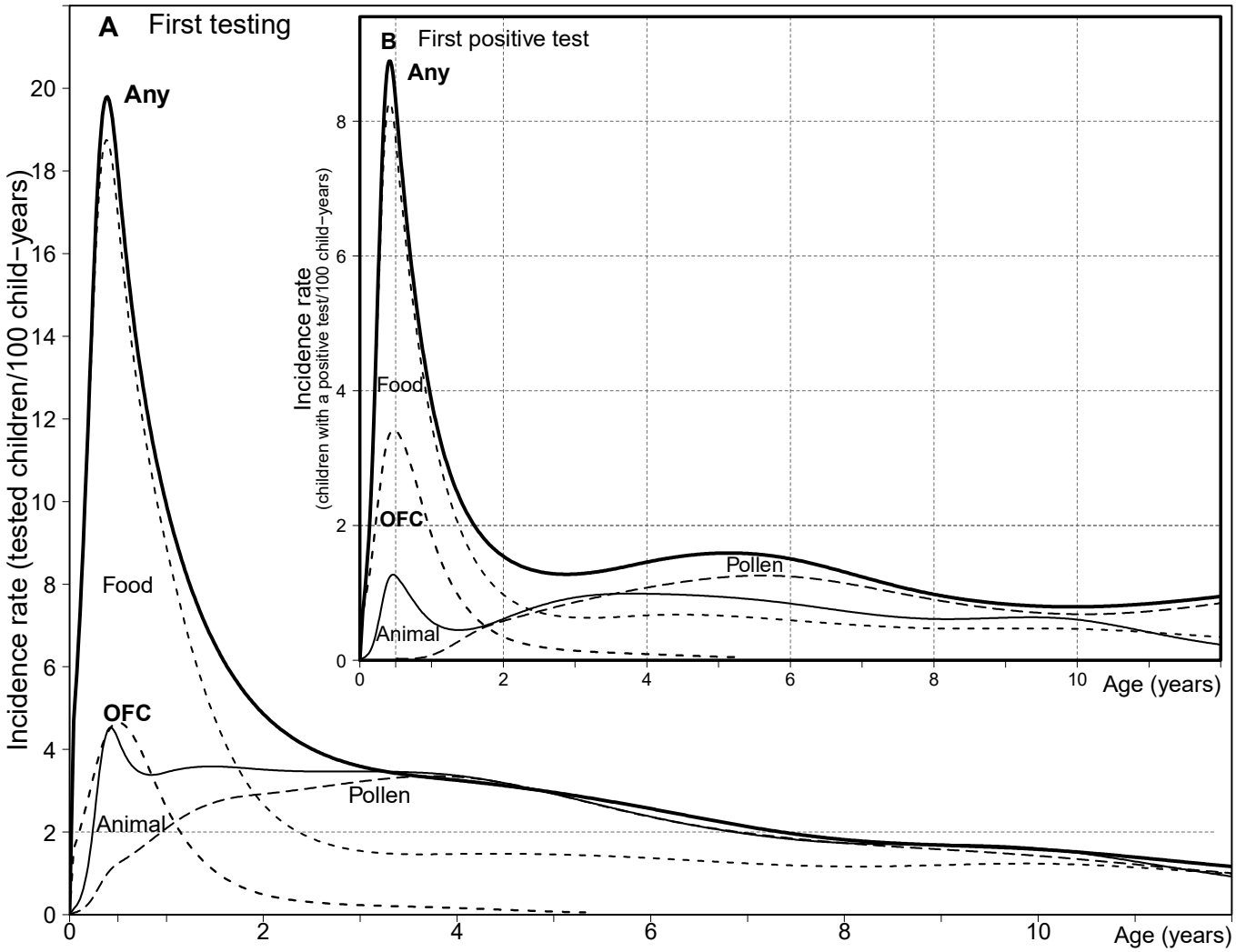

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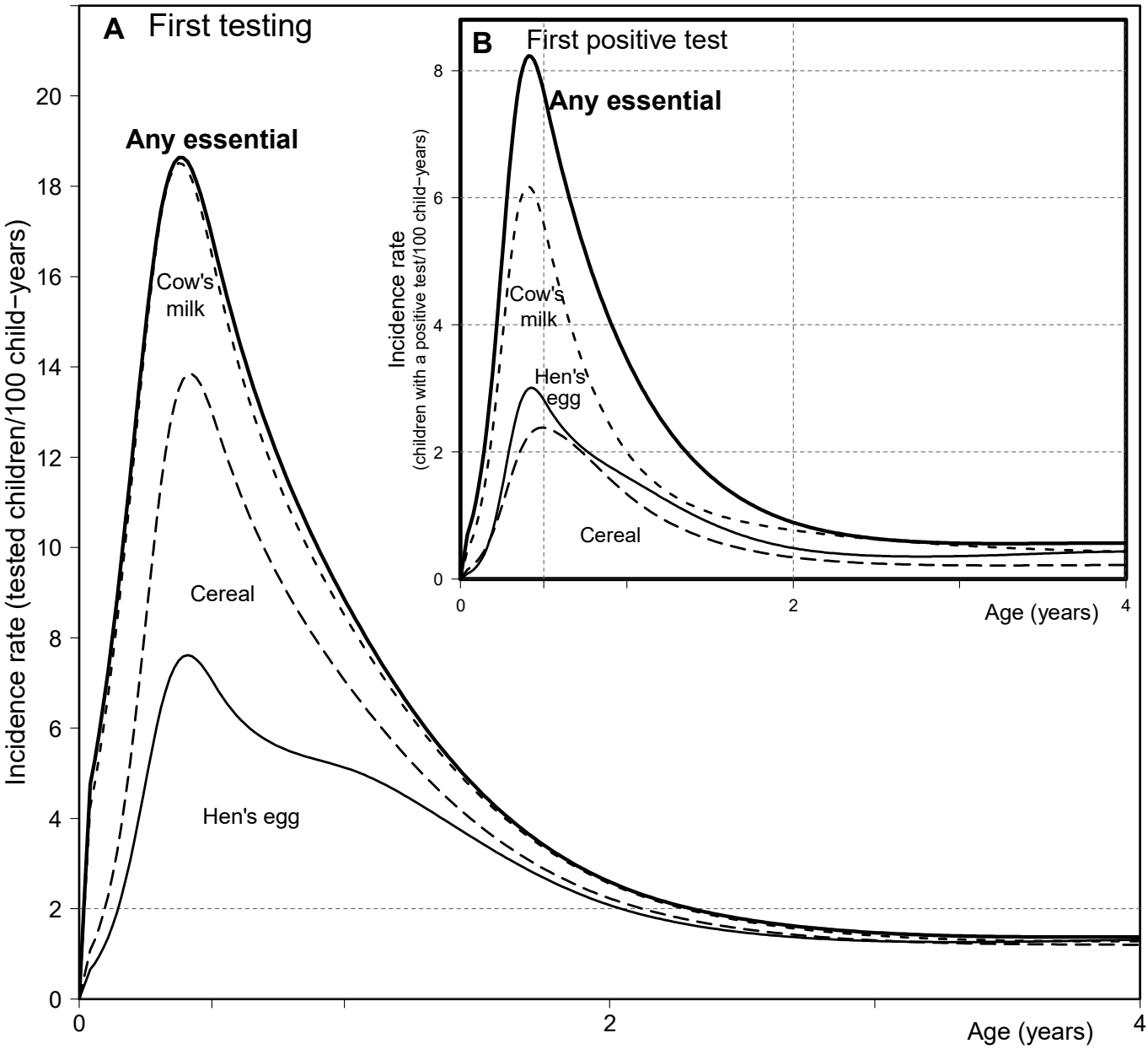

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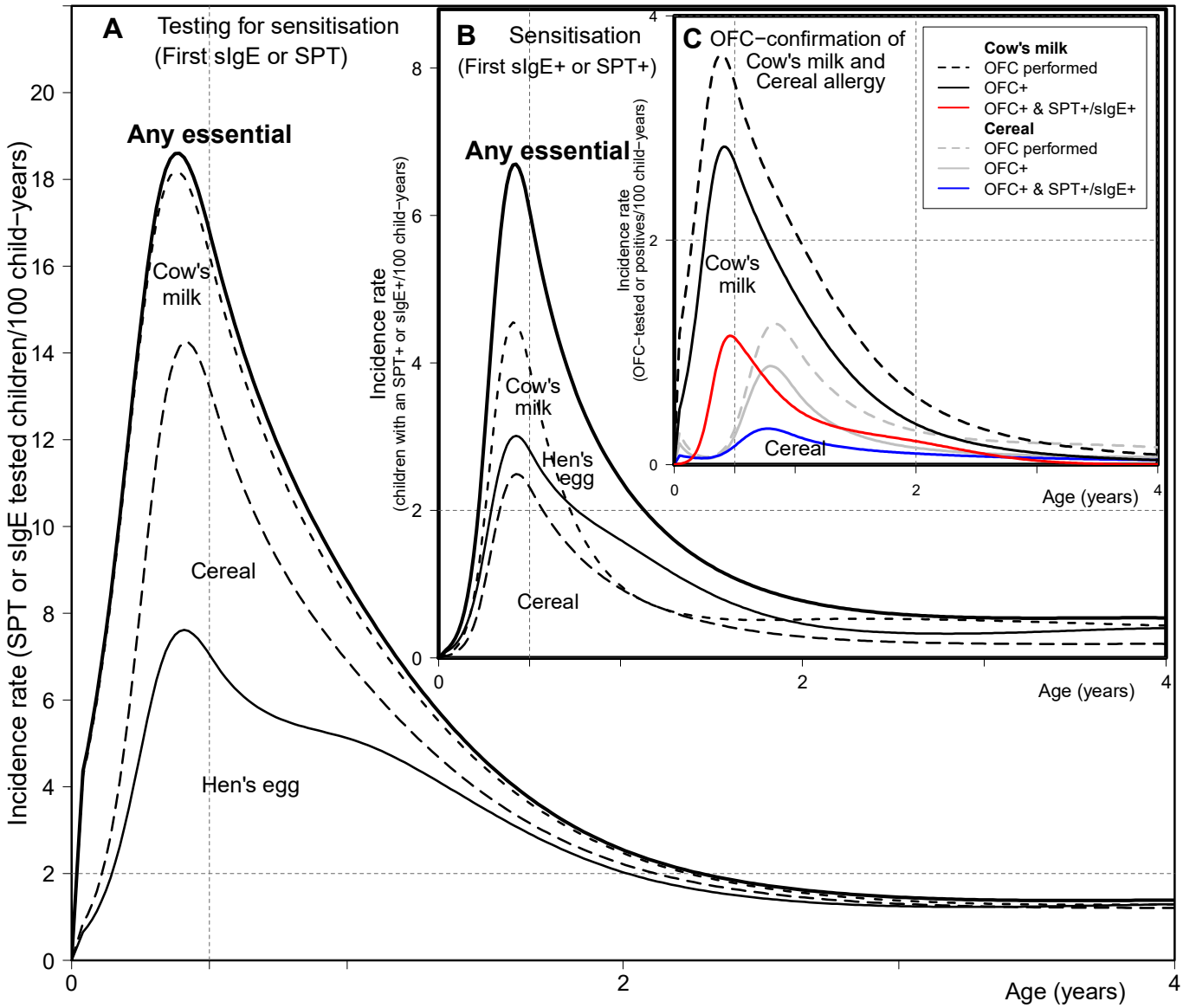

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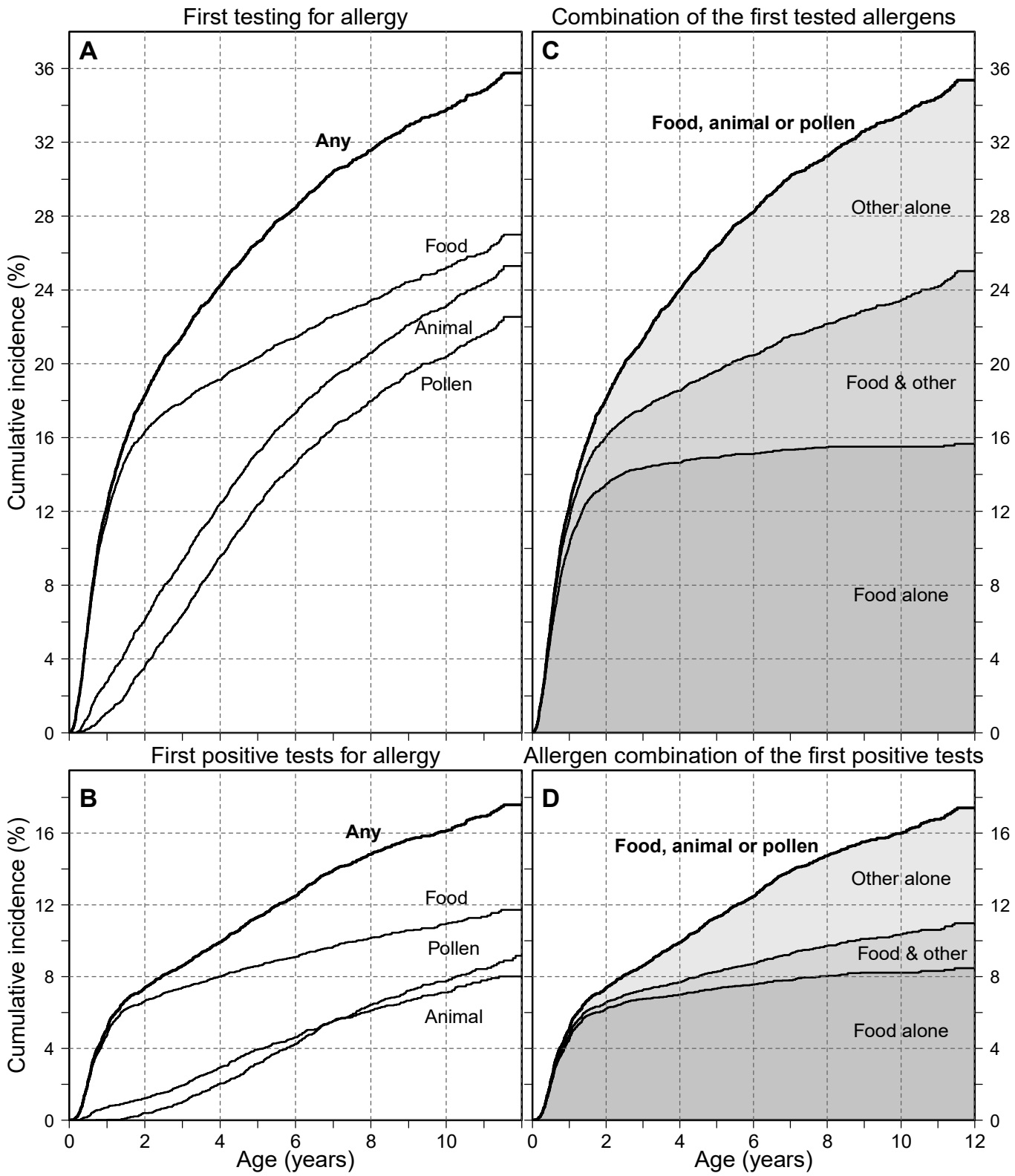

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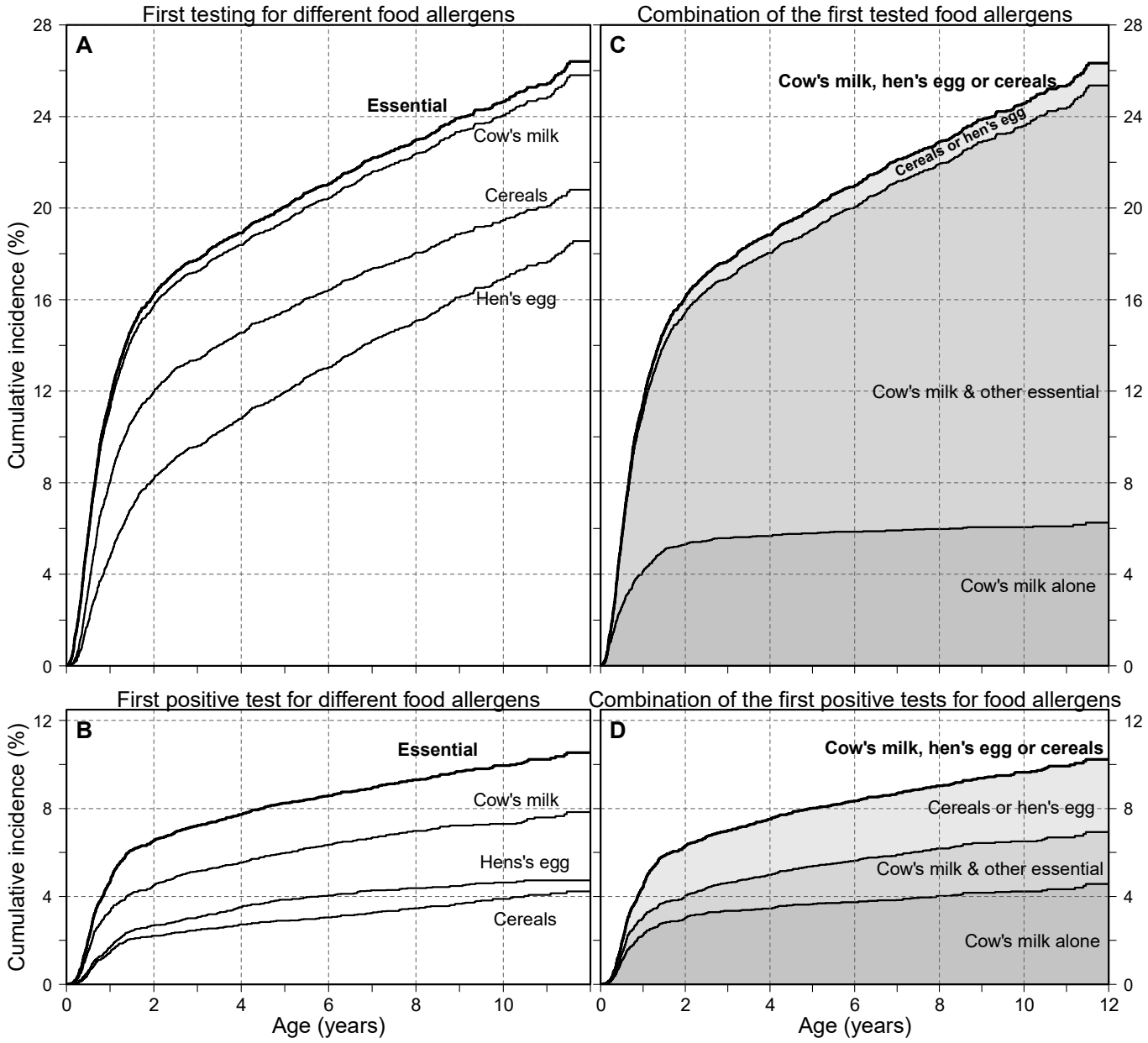
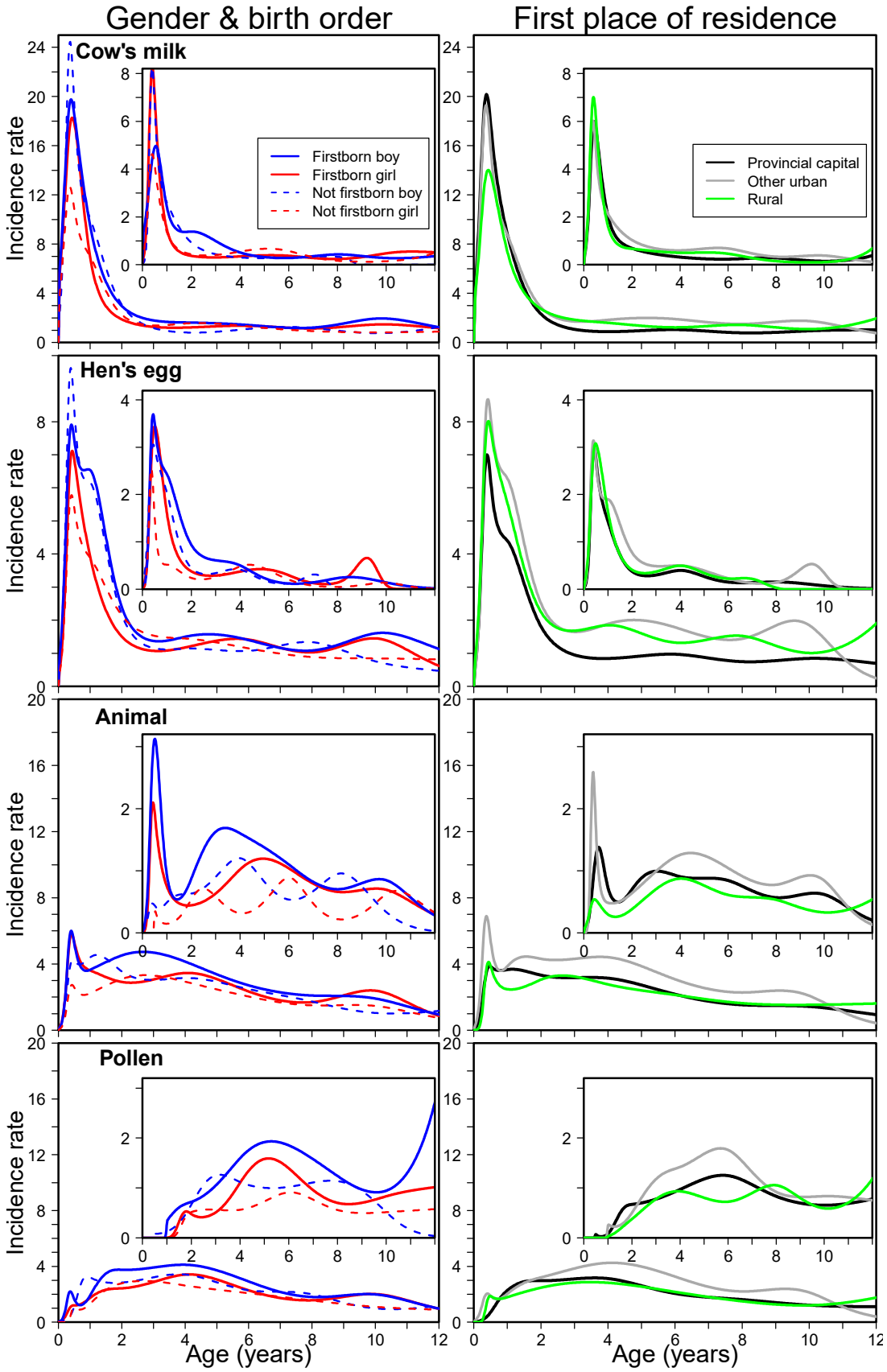


Figure 6. Cumulative incidences by age of *first testing* (A&C) and *positive tests* (B&D) to cow's milk, cereals, hen's egg and essential foods shown by Kaplan-Meier (A&B) and their first combinations by stacked curves (Aalen-Johansen method; competing risks) (C&D) among the SKARP population ($N = 5564$).



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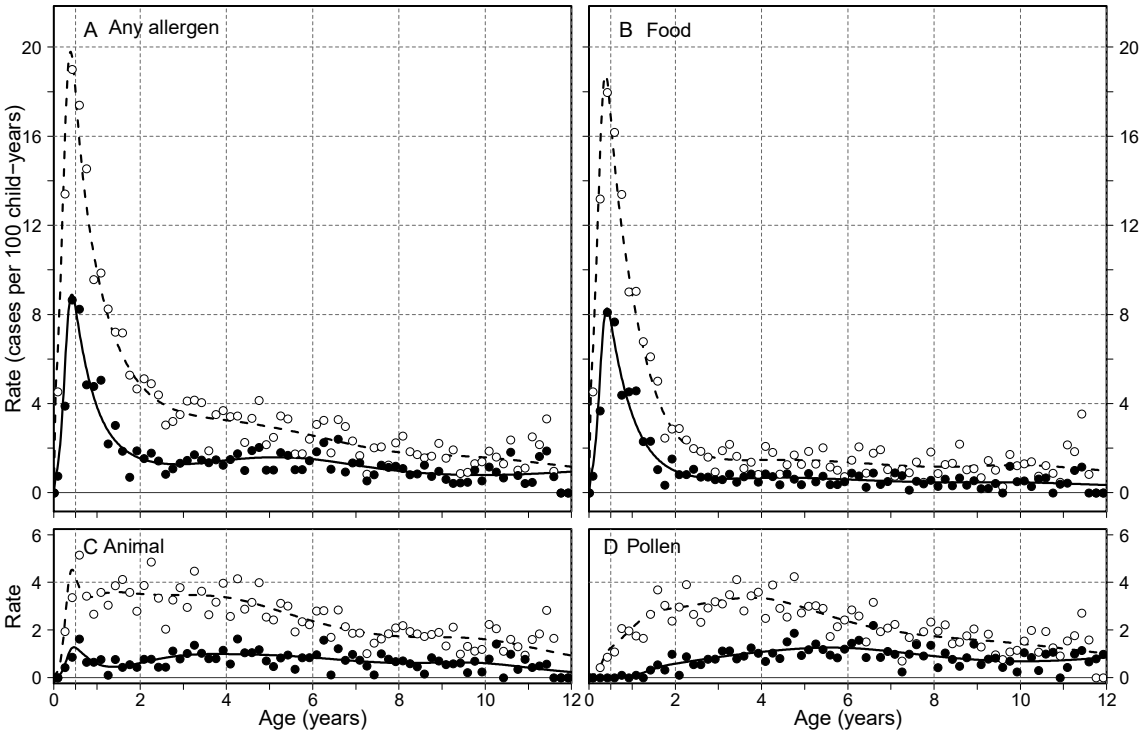
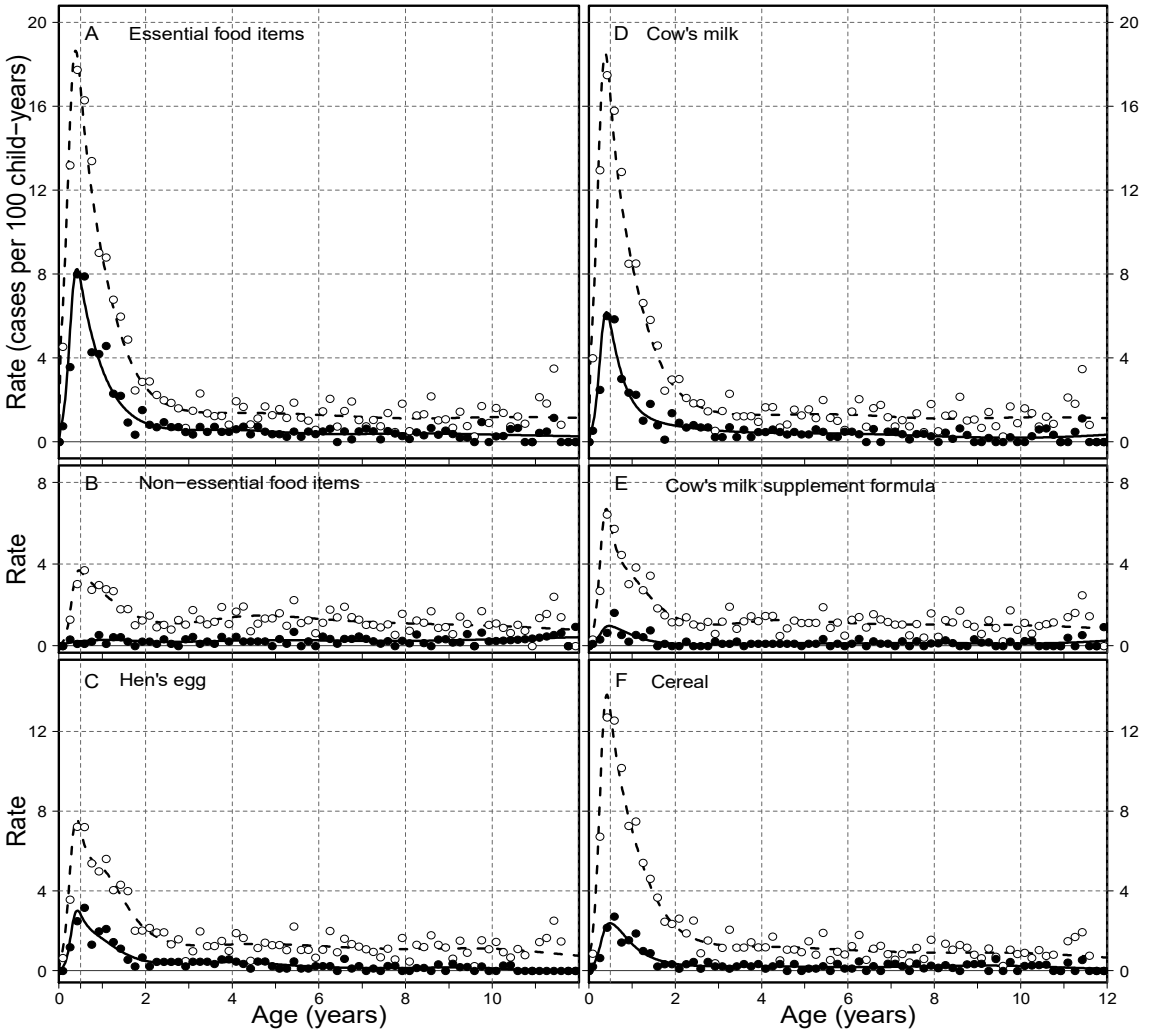
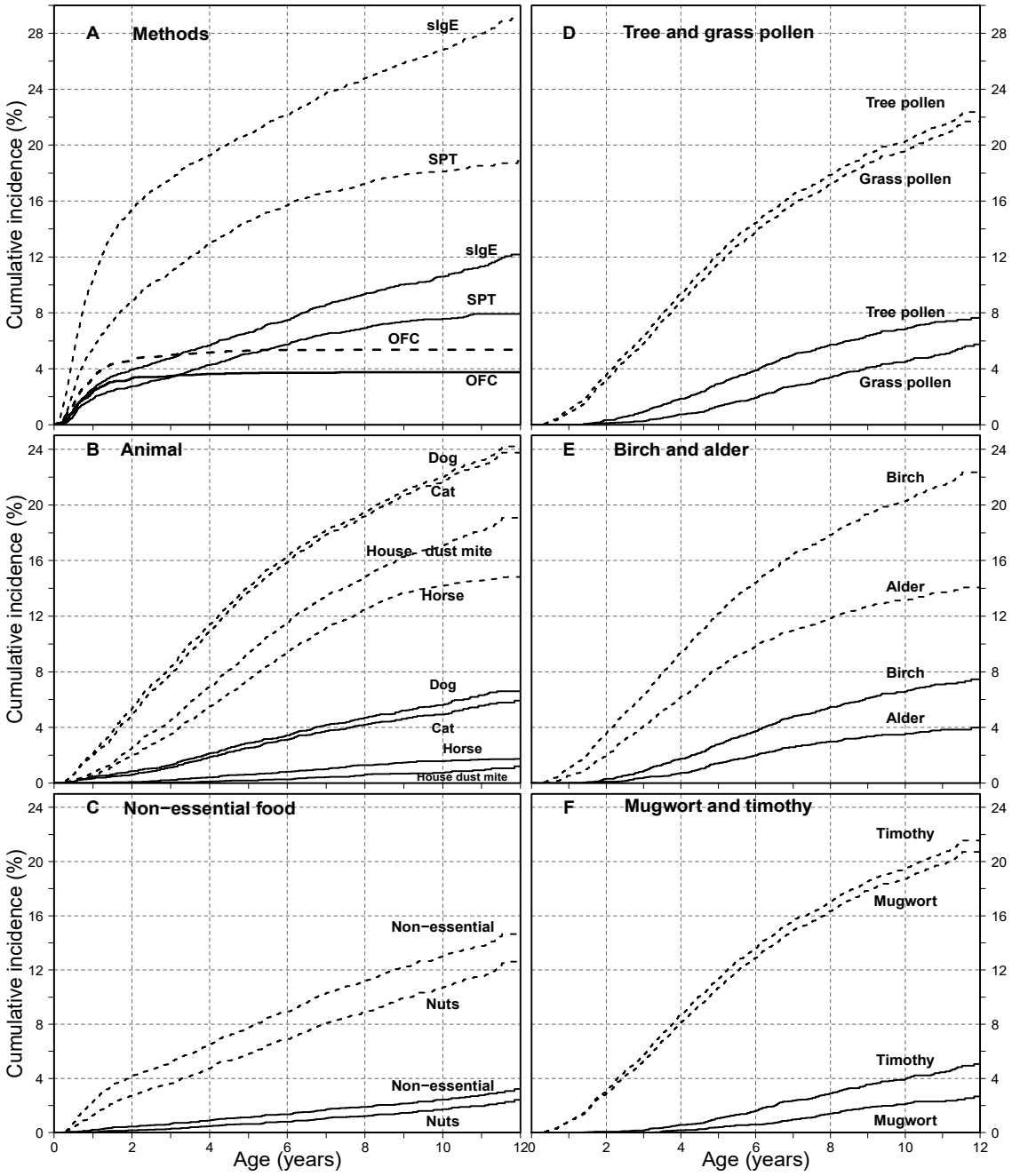


eFigure 1. Incidence rates (number of cases per 100 child-years) by age of allergy testing and positive test results for different allergens estimated by piecewise constant rate approach and smoothed by cubic splines shown by lines (dashed line: testing; solid line: positive tests). Bimonthly point estimates of incidence rates are shown by circles (open circles: testing; filled circles: positive tests) in the SKARP population ($N = 5564$).



eFigure 2. Incidence rates (number of cases per 100 child-years) by age of allergy testing and positive test results for different food allergens estimated by piecewise constant rate approach and smoothed by cubic splines shown by lines (dashed line: testing; solid line: positive tests). Bimonthly point estimates of incidence rates are shown by circles (open circles: testing; filled circles: positive tests) in the SKARP population ($N = 5564$).



eFigure 3. Cumulative incidences by age of allergy testing (dashed lines) and positive test results (solid lines) for different allergens in the SKARP population ($N = 5564$).