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Trends in prevalence of sensitization to milk and egg in Dutch children



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Abstract

Trends in the prevalence of food allergy in Dutch children

A study carried out by the National Institute for Public Health and the Environment (RIVM) for the period 1992–2003 did not detect any indications of an increase in the prevalence of food allergy against cow's milk and chicken egg in 1-year-old Dutch infants. Cow milk and egg allergy in this age group is determined by measuring the presence of IgE antibodies specific for these two foodstuffs. The level of these antibodies is a measure of allergic sensitization, but not all individuals with IgE antibodies will develop clinical symptoms. Of the children assessed in the study, 4-6% were sensitized to milk and 2–5% to egg.

The research was carried out by order of the Food and Consumer Safety Authority (VWA), with the aim of determining whether the number of individuals with food allergy is increasing. Data on this subject are limited and heterogenic. The RIVM used the IgE data available from three epidemiological cohorts. Data were available on 1,874 children born between 1992 and 1994, 1996 and 1997 and 2002 and 2003, respectively.

Children with food allergy can develop different clinical manifestations following exposure to the allergen – from hives to eczema and from abdominal pain to asthma. Many children develop a tolerance to milk and egg as they grow older. Among the 1,874 children of this study, only a small portion had cow's milk IgE at the age of 8 years, and egg IgE was absent in nearly all of the children at this age.

Key words:

food allergy, sensitization, prevalence, cow's milk, chicken egg

Rapport in het kort

Trends in voorkomen van voedselallergie in Nederlandse kinderen

Het RIVM heeft geen aanwijzingen gevonden dat voedselallergie voor koemelk en ei bij Nederlandse kinderen van 1 jaar tussen 1992 en 2003 is toegenomen. In het onderzoek is de mate waarin voedselallergie bij kinderen van deze leeftijd voorkomt gebaseerd op de aanwezigheid van IgE-antistoffen tegen melk of ei in hun bloed. Dit is een maat voor allergische sensibilisatie, hoewel niet alle personen met deze antistoffen daadwerkelijk klachten hebben. Van de onderzochte kinderen van 1 jaar was 4-6 % gesensibiliseerd voor melk en 2-5 % voor ei.

Het onderzoek is uitgevoerd in opdracht van de Voedsel en Warenautoriteit (VWA), die wilde weten of het aantal mensen met voedselallergie in Nederland de afgelopen jaren is toegenomen. Gegevens hierover zijn vooralsnog schaars en variëren nogal. Het RIVM heeft beschikbare data over IgE-antistoffen uit drie epidemiologische studies gebruikt. In totaal waren gegevens voorhanden van 1874 kinderen die zijn geboren tussen 1992-1994, tussen 1996-1997 en tussen 2002-2003.

Voedselallergie kan zich in veel vormen uiten: van galbulten en eczeem tot buikpijn en astma. Veel kinderen groeien over melk- en ei-allergie heen naarmate ze ouder worden. In dit onderzoek had een klein deel van de kinderen op de leeftijd van 8 jaar nog IgE voor melk in zijn bloed en had vrijwel geen van de kinderen op die leeftijd nog IgE voor ei.

Trefwoorden:

voedselallergie, sensibilisatie, prevalentie, koemelk, kippenei

Contents

Summar	y	6
1	Introduction	8
2	Methods	10
2.1	BOKAAL	10
2.1.1	Design and study population	10
2.1.2	Data collection	10
2.1.3	IgE measurements	10
2.2	PIAMA	11
2.2.1	Design and study population	11
2.2.2	Data collection	11
2.2.3	IgE measurements	11
2.3	KOALA	12
2.3.1	Design and study population	12
2.3.2	Data collection	12
2.3.3	IgE measurements	12
2.4	Data analysis	12
2.4.1	Study population, environmental exposure and confounding fac	tors 12
2.4.2	RAST classes	13
2.4.3	Statistics	13
2.5	Reported food allergy	13
3	Results	14
3.1	Characteristics of the cohorts and environmental exposures	14
3.2	Prevalence of sensitization in children aged 1 year	15
3.3	Prevalence of sensitization in children aged 4 or 5 years	17
3.4	Prevalence of sensitization in different age groups	18
3.5	Relationship between specific IgE and reported food allergy	18
4	Discussion	20
Acknowl	edgements	22
Referenc	os	23

Summary

Food allergy is an immunological reaction to food proteins that can involve IgE or non-IgE-mediated mechanisms. The focus of this report will be on IgE-mediated food allergy which accounts for the majority of food allergic reactions. The prevalence of food allergy is estimated to be 1-2% in adults and 2-3% in children. However these estimates are hampered by the fact that there are limited data available on prevalence and that the prevalence estimates are highly heterogenic. There are indications that there is a time trend for prevalence of food allergy, although there are only a few studies that have demonstrated this.

The aim of this project was to obtain information on trends in food allergy and therefore an immunosurveillance was performed. In this immunosurveillance the frequency of sensitization to cow's milk and chicken egg was determined in three Dutch birth cohorts, BOKAAL, PIAMA and KOALA. The children that participated in these cohorts were born between 1992 and 1994 (BOKAAL), 1996 and 1997 (PIAMA) and 2002 and 2003 (KOALA). Cow's milk and chicken egg specific IgE was measured in BOKAAL at the ages of 1 and 5, in PIAMA at the ages of 1, 4 and 8 and in KOALA, at the age of 1. Children were considered to be sensitized when specific IgE was higher than 1.2 IU/ml. Questionnaires taken at the age of 12 months were used to obtain information on characteristics of the study population on general aspects, environmental exposures and possible confounding factors. Also, questionnaires taken at 12 months in all cohorts and the age of 4 and 5 for PIAMA and BOKAAL, respectively, were used for information on doctor's confirmed food allergy. In PIAMA, IgE measurements at the age of 1 were only done in children of allergic mothers. Furthermore, at the age of 4, more children of allergic mothers were selected for blood sampling and IgE measurement. Therefore, frequencies of sensitization are presented for children of allergic and non-allergic mothers separately.

In the 1 year old children the percentage that was sensitized to cow's milk was 6.2% in BOKAAL, 6.4% in PIAMA and 3.8% in KOALA in children of allergic mothers. In children of non-allergic mothers, the prevalence was 4.2% in BOKAAL and 3.9% in KOALA. In the sub group of allergic mothers, these percentages were calculated after exclusion of Rotterdam, because at this age the rate of sensitization in this sub group was considerably higher compared to the other regions of the cohorts (19% vs 6%). Almost all children from Rotterdam were participants in PIAMA. There were no differences in potential confounding factors between Rotterdam and the other areas that could explain this difference. After exclusion of Rotterdam the prevalence data for chicken egg were 4.7%, 3.0% and 5.3%, for BOKAAL, PIAMA and KOALA, respectively in the children of allergic mothers. At the age of 1, there were no IgE measurements done in the PIAMA children of non-allergic mothers. In BOKAAL and KOALA sensitization to egg was observed in 4.7% and 1.9% of the children of non-allergic mothers. At the age of 1, there was no increase in food sensitization, the lowest prevalences were observed in the youngest cohort, but these differences were not significant.

In BOKAAL and PIAMA IgE data of older children were available as well. In PIAMA the average age at which IgE was measured was 4.1 years and in BOKAAL 5.9 years. In the sub cohort of allergic mothers sensitization to cow's milk was observed in 7.7% of the BOKAAL children and 7.0% of the PIAMA children. In children of non-allergic mothers prevalence data of 3.1 and 5.3% were observed in BOKAAL and PIAMA, respectively. For chicken egg, the prevalence of sensitization was 0.51% BOKAAL and 0.96% in PIAMA, for allergic mothers and 0.28% and 1.8%, for non-allergic mothers. In the sub group of children of non-allergic mothers, the prevalence of sensitization for milk and egg is higher in PIAMA children than in BOKAAL children, suggesting a trend in time. However, it is important to consider that the children in PIAMA are on average 1.8 years younger and that

sensitization to milk and egg is known to decrease with age. The higher prevalence in PIAMA is likely partly explained by an age difference rather than a time trend. In a sub cohort of PIAMA a decrease in frequency of sensitization to milk and egg was observed when cow's milk and chicken egg specific IgE was compared at the ages of 1, 4 and 8. Egg sensitization was almost completely absent at the age of 8, whereas milk sensitization was still present in 5% of the children.

In conclusion, in this immunosurveillance no increase of sensitization to cow's milk and chicken egg in 1 year old Dutch infants born between 1992 and 2003 was observed.

1 Introduction

Food allergy is an adverse immunological reaction to food proteins that may be mediated by either IgE or non-IgE mechanisms (Bruijnzeel-Koomen et al., 1995). The focus of this report will be on IgE mediated food allergy, which accounts for the majority of food allergic reactions. Non-IgE mediated food allergy is mediated by immune reactions against food proteins in the absence of IgE, for instance celiac disease caused by gluten.

The prevalence of food allergy is estimated to be 1-2% in adults and 2-3% in children. In infants under age 1 cow's milk allergy is frequently observed and the prevalence is estimated to be 2-3% in these infants (Gezondheidsraad, 2007). Other important allergens in children are egg, peanut, soy and wheat, whereas peanut, tree nuts, fish, crustaceans, and fruits are the most important causes of food allergy in adults and adolescents (Sampson, 1999a). Clinical manifestations of food allergy can vary from mild to fatal anaphylactic reactions. The most frequent form of food allergy in adults is the so-called oral allergy syndrome, in which symptoms such as swelling and itching of lips, mouth, throat, ears and nose are induced. Symptoms in the gastrointestinal tract include nausea, vomiting, abdominal pain, and diarrhea, whereas manifestations in the skin can involve atopic dermatitis, urticaria, angioedema, and contact dermatitis. In addition, symptoms can manifest themselves in the respiratory tract (wheeze, cough, asthma, rhinoconjunctivitis) and cardiovascular system, i.e. hypotension which can eventually lead to fatal anaphylaxis (Sampson, 1999a).

It is estimated that 15-30% of the population is affected with one or more allergies (Aberg et al., 1999). For asthma and rhinitis an increase in prevalence has been reported between 1980 and the mid 1990s (Aberg et al., 1999, Ross Anderson et al., 2007; Woolcock and Peat, 1997). In the US, the Centre of Disease Control (CDC) reported an increase of childhood asthma from 3.7% in 1980 to 7.5% at the peak of the trend in 1995 (CDC, 2006). After this steep increase, the prevalence of asthma has remained relatively stable, and several studies indicate that a plateau seems to be reached (Braun-Fahrlander et al., 2004; Mommers et al., 2005; Nowak et al., 2004; Zollner et al., 2005). In the Netherlands, the prevalence of asthma, based on morbidity registration, shows a similar trend. From 1984 to 1999 the prevalence increased an thereafter the situation has been stabilizing (Smit and Van Schayck, 2006). Data from the UK and US suggest that there is a trend for food allergy as well. A study in the UK has demonstrated that the number of hospital admissions for food-related anaphylaxis has increased since 1990 (Gupta et al., 2007). In addition, the number of children with a positive skin prick test for peanut increased between 1986 to 1996 from 1.1% to 3.3% (Grundy et al., 2002). Finally, information derived from a telephone survey in the USA suggests that peanut allergy has doubled between 1997 and 2000 (Sicherer et al., 2003). The National Health Interview Survey (NHIS) conducted by the CDC demonstrated an increase in reported food allergy between 1997 and 2007 in children under age 18 years. In this period the prevalence of reported food allergy increased from 3.2% to 3.9% (Branum and Lukacs, 2008).

The prevalence of food allergy can be determined by different diagnostic methods. In epidemiological studies, the prevalence of food allergy is often derived from questionnaires. However, in most cases this will lead to an overestimation of prevalence (Osterballe et al., 2005; Venter et al., 2006; Woods et al., 2002). Self-reported food allergy for any food varied from 3 to 35% according to a recent meta-analysis (Rona et al., 2007). The gold standard of diagnosing food allergy is the double blind placebo controlled food challenge (DBPCFC), in which patient and doctor are unaware if the allergen is present during the food challenge (Bindslev-Jensen et al., 2004). Other methods, that are less expensive, time-

consuming, invasive and hazardous for patients and that are more easy to incorporate in large epidemiological studies are skin prick testing and measurement of specific IgE in serum (Asero et al., 2007; Sampson, 1999b). These latter methods can only assess if a person is sensitized to a certain food allergen, but they do not predict clinical reactivity. The diagnostic value of IgE levels depends on the cut-off level that is used. When the detection limit of 0.35 IU/ml is used approximately 50% of children sensitized to cow's milk and 70% of the children sensitized to chicken egg reacted with clinical reactions in a DBPCFC (Niggemann et al., 2001). For several allergens, including milk, peanut and egg cut-off values have been established that are predictive for food allergy. For these allergens it has been shown that higher levels of specific IgE are better predictors of food allergy with clinical symptoms (Benhamou et al., 2008; Celik-Bilgili et al., 2005; Sampson, 2001; Sampson and Ho, 1997; Van der Gugten et al., 2008).

Recently, a large meta-analysis has demonstrated that the prevalence estimates for food allergy are highly heterogenic. When food challenges were used, the prevalence of food allergy for any food was between 0.2% and 5% in children and between 1 and 10.8% in adults (Rona et al., 2007). In 2004, the European Food Safety Authority (EFSA) concluded that there is a lack of reliable data that can be used to estimate the prevalence of food allergy (EFSA, 2004). Furthermore only limited information is available on time trends (Branum and Lukacs, 2008; Grundy et al., 2002; Gupta et al., 2007; Sicherer et al., 2003). The aim of this project, which is initiated by the Dutch Food and Consumer Products Safety Authority (VWA) is to investigate if there is evidence for an increase in food allergy in the Netherlands. To investigate this an immunosurveillance was conducted for which three eligible Dutch birth cohorts were selected that have assessed chicken's egg and cow's milk specific IgE: BOKAAL, PIAMA and KOALA. In these birth cohorts children were born between 1992 and 2003, which makes it possible to study trends in sensitization over a period of 11 years. The design and aims of these epidemiological studies will be described in more detail in the Methods section.

2 Methods

2.1 BOKAAL

2.1.1 Design and study population

BOKAAL (acronym in Dutch for Borstvoeding en Koemelk Afwisselend: ALlergy?) has been conducted as a feeding intervention trial and designed as a prospective birth cohort study, not selected for allergy risk. The objective of the study was to investigate the effect of brief and early exposure to cows' milk protein on the development of atopic disease in children (De Jong et al., 1998).

Mothers of potential participants were recruited by midwives who practiced in the western and centre part of the Netherlands, including rural and urban areas, between February 1992 and January 1994. Seventy midwifes from 28 practice centers of these regions, approached women at approximately 35 weeks of gestation to inquire about their interest in participating in the study. The general eligibility criteria for the study were healthy, full term newborns whose mothers intended to breast feed for at least six weeks (Eysink et al., 1999).

A total of 1533 children entered the study. Mothers who agreed with the terms and signed an informed consent were randomly selected for intervention and placebo groups and received a double blind intervention package. The intervention group received a preparation containing cow milk protein and the placebo group received a preparation containing only glucose and a mix that was cow's milk protein free. The preparation was given during the first three days of life, in substitution to or next to at least one time breast feeding. All mothers were encouraged to breastfeed during at least 6 weeks, the minimum required for the study protocol.

2.1.2 Data collection

The follow-up was high, being 97% of the children responded at the age of one year and 80% at the age of two years. The instruments used to collect information included questionnaires filled in by the mother or father at 37 weeks of pregnancy, at two weeks of life, at six weeks of life, at 6 months of life, at one year, 18 months and two years. All children were submitted to physical examination by a pediatrician at age one. From 1434 children, venous blood samples were obtained at 1 year of age (De Jong et al., 1998). A follow-up study was done at age 5 years, including questionnaire, blood samples (n=934) and physical examination (De Jong et al., 2002).

2.1.3 IgE measurements

Total IgE and specific IgE for house dust mite, cat, dog, cow's milk and egg were measured in serum samples. Specific IgE was determined by radioallergosorbent test (RAST), as described previously in detail (Aalberse et al., 1981) and was expressed in five RAST categories (Table 1). Specific IgE against cow's milk and chicken egg was assessed in 735 children at age 1 and in 564 children at age 5.

Table 1 RAST classes

RAST class	Specific IgE (IU/ml)
0	< 0.45
1	$\geq 0.45 - 1.2$
2	$\geq 1.2 - 2.8$
3	$\geq 2.8 - 7.8$
4	≥ 7.8 - 66
5	≥ 66

2.2 PIAMA

2.2.1 Design and study population

The aim of the PIAMA (acronym for Prevention and Incidence of Asthma and Mite Allergy) study is to investigate the natural history of asthma and allergy in children and to identify risk factors for the development of asthma and allergic disease. In addition, the feasibility and effectiveness of measures to reduce exposure to allergens have been studied.

The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent. Recruitment started in March 1996 and continued until May 1997 (Brunekreef et al., 2002). Of the baseline population of 4,146 pregnant women, 183 (5%) were lost to follow-up before any data on the child had been collected. The study therefore started with 3,963 newborns.

2.2.2 Data collection

Postal questionnaires including questions on the child's lifestyle and health were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At the ages of 1, 4 and 8 years, sub groups of the population were invited for a medical examination, which included collection of a blood sample for the measurement of IgE. At the age of 1 year, only children of allergic mothers were invited for the medical examination. For the medical examinations at the ages of 4 and 8 years, children of allergic and of non-allergic mothers were invited, but children of allergic mothers were over-sampled. The numbers of children invited at the ages of 1,4 and 8 were 765, 1806 and 3518 respectively and the numbers of blood samples obtained 577, 750 and 1897, respectively.

2.2.3 IgE measurements

Specific IgE against cow's milk and hen's egg was measured at Sanquin Research (Amsterdam, the Netherlands), as described earlier (Aalberse et al., 1981). The detection limit for specific IgE was <0.36 IU/ml. Specific IgE against cow's milk and chicken egg was measured in 543 children at age 1. In 4 year old children, specific IgE against cow's milk and chicken egg was measured in sera of 703 and 696, respectively. Furthermore, specific IgE was measured in sera of 8 year old children. This was done in a sub cohort consisting of children that were analyzed at age 1 and 4 too. Specific IgE was measured at these three ages in sera of 196 children of allergic mothers. In 370 children of non-allergic mothers specific IgE was measured at the ages of 4 and 8.

2.3 KOALA

2.3.1 Design and study population

The aim of the KOALA Birth Cohort Study (acronym in Dutch for: Kind, Ouder en gezondheid: Aandacht voor Leefwijzen en Aanleg; Child, Parent and Health, Focus on Lifestyle and Predisposition) in the Netherlands is to identify factors that influence the clinical expression of atopic disease with a main focus on lifestyle (e.g., anthroposophy, vaccinations, antibiotics, dietary habits, breast feeding and breast milk composition, intestinal microflora composition, infections during the first year of life, and gene—environment interaction). The recruitment of pregnant women (34 weeks of gestation) started in October 2000 and finished in 2002 (Kummeling et al., 2005). Participants (n = 2343) with 'conventional lifestyles' (n = 2343) were retrieved from an ongoing prospective cohort study (n = 7020) on pregnancy-related pelvic girdle pain, recruited among healthy pregnant women by midwives in the general population in the South of the Netherlands. A second group, recruited separately among pregnant women with 'alternative lifestyles', was not included in the present immunosurveillance.

2.3.2 Data collection

Questionnaires were taken from mothers at 14, 30 and 37 weeks pregnancy and from parents at the child's age of 3, 7, 12 and 24 months, including questions (amongst others) on highest maternal education, history of atopy and asthma in parents and sibs maternal smoking during pregnancy, the child's environmental tobacco smoke exposure, indoor pet exposure (cats, dogs, other furry animals), number of older sibs and daycare attendance. Parents of a sub group of children born from 2002 onward (n=1355) from the conventional and alternative cohort were also asked to collect feces and were asked to consent to collecting capillary blood at age 1 year and venous blood at 2 years (Kummeling et al., 2005; Penders et al., 2006). Only results at age 1 year are used for the present immunosurveillance, because no data at age 2 years were available in BOKAAL and PIAMA (Kummeling et al., 2005; Penders et al., 2006).

2.3.3 IgE measurements

At age 1 and 2, total IgE and specific IgE against food (chicken's egg, cow's milk, and peanuts) and inhalant allergens were measured at Sanquin Research (Amsterdam, the Netherlands) as described earlier (Aalberse et al., 1981) with modifications to accommodate the use of capillary blood samples (Stapel et al., 2004). The detection limit for specific IgE was <0.10 IU/ml. At age 1, 596 sera were analyzed for cow's milk-specific IgE and 583 samples for chicken egg-specific IgE.

2.4 Data analysis

2.4.1 Study population, environmental exposure and confounding factors

Characteristics of the study population, environmental exposure and confounding factors that could influence sensitization to egg and milk were derived from the questionnaires taken at 12 months for each birth cohort. From these questionnaires information on general aspects such as region, sex, date of birth, and date of blood sampling was derived. To determine the exact age at which IgE levels were measured the date of birth and date of blood sampling were used. Also environmental exposures and potential confounding factors were collected, including, intervention, education of the mother, number

of siblings duration of breast feeding, parental history of allergy, maternal smoking during pregnancy, environmental tobacco smoke (ETS) at home in the first year and pets in the household.

In BOKAAL and PIAMA an intervention group was included. In BOKAAL children in the intervention group received cow's milk formula in the first three days of their life (De Jong et al., 1998). In PIAMA the intervention was application of mite-impermeable mattress covers and pillows (Brunekreef et al., 2002). Interventions done in BOKAAL and PIAMA did not influence prevalence of sensitization to food allergens. In the KOALA study no interventions were done, and as indicated above, the present immunosurveillance was restricted to the pregnant women recruited in the general population.

2.4.2 RAST classes

Specific IgE data from the BOKAAL study were only available in RAST classes and not in IU/ml. IgE data from PIAMA and KOALA were available in kU/L but were divided in the same RAST classes as BOKAAL (Table 1). Children were considered to be sensitized to milk or egg if their IgE levels were ≥ 1.2 IU/ml, i.e. RAST class ≥ 2 .

2.4.3 Statistics

Statistical analyses were performed by using SAS statistical software (SAS Institute, Cary, NC). Differences between the birth cohorts concerning prevalence of sensitization were assessed with a chi-square test.

2.5 Reported food allergy

Information on doctor's confirmed food allergy from questionnaires was used to compare the percentage of sensitized children with complaints reported at that age. The relationship between sensitization and reported food allergy was done for each birth cohort independently. This relationship was not compared between the three cohorts, because different formulations were used in the questionnaires.

From the BOKAAL questionnaire at the age of 1, no reliable information on food allergy could be derived. The questions asked to the parents in the PIAMA questionnaire of 1 year were: 'Did a doctor ever diagnose cow's milk allergy?' and 'Did a doctor ever diagnose food allergy?'. The questions in the questionnaire of KOALA were: 'Did a doctor diagnose your child in the last five months with food intolerance or allergy and if so, to which food?' Information on cow's milk and chicken egg was derived from this list.

The questions, derived from the BOKAAL questionnaire at age 5 were 'Did a doctor ever diagnose cow's milk allergy?' and 'Did a doctor ever diagnose another food allergy and to which food?'. Data concerning egg allergy were obtained from these questionnaires. The following questions from the PIAMA questionnaire at age 4 were used: 'Did a doctor ever diagnose another food allergy?' When this was answered positive, the questions relating to which food were used to select children with an allergy for cow's milk or egg. In addition, the question 'Is your child still allergic?' was also used.

3 Results

3.1 Characteristics of the cohorts and environmental exposures

Table 2 shows the characteristics and environmental exposures of the participants of the three birth cohorts, in which specific IgE was assessed. Information is derived from questionnaires taken at the age of 12 months.

The three birth cohorts recruited participants from different regions in the Netherlands. In all cohorts children born in Utrecht and Gelderland participated. Only PIAMA has recruited participants in the northern part of the Netherlands, whereas KOALA is the only cohort with participants from the southern part. BOKAAL has recruited predominantly in Noord-Holland, Almere and Lelystad. Maternal education differed between the cohorts. In PIAMA there were more mothers with a low education, and fewer with a high education compared to the other cohorts. For BOKAAL and KOALA the percentages were similar.

There were no differences in gender and number of older siblings between the three cohorts. In BOKAAL the percentage of households reporting to have a cat at home was the highest, followed by PIAMA and KOALA. The percentage that reported to have a dog at home was similar between BOKAAL and PIAMA but higher in KOALA. Furthermore, in KOALA maternal smoking during pregnancy and ETS in the first year was lower than in the other cohorts.

In BOKAAL the percentage of mothers who breast fed was almost 100%, since one of the inclusion criteria was breast feeding for at least 6 weeks. In PIAMA and KOALA an average of 17% of the children were not breast fed. The percentage that was breast fed in the first 3 months was the highest in BOKAAL, followed by PIAMA and KOALA. Prolonged breast feeding (>12 weeks) was done by almost 60% of the KOALA mothers, whereas this was lower for PIAMA and BOKAAL.

There was no difference in the percentages of children that had an allergic father. In addition, maternal allergy was not different between BOKAAL and KOALA. However, for PIAMA the percentage is 100%, since at the age of one only children of allergic mothers were selected for blood sampling and IgE measurements. In PIAMA the total study population was representative for the general population regarding parental allergy. However, in the sub groups in which IgE was measured at age 4 and 8 a higher percentage of children of allergic mothers were selected. Therefore, all IgE data are presented for children of allergic and non-allergic mothers separately.

Table 2 Characteristics of the study population of each birth cohort*

	BOKAAL (N=735)		
	%	%	%
Region ¹			
1	0	28.9	0
2	70.6	0	0.2
3	27.6	25.8	20.8
4	1.8	45.3	0
5	0	0	30.5
6	0	0	48.5
Gender			
boys	52.4	49.5	49.8
Older siblings			
No	44.6	49.4	44.3
1	38.2	36.3	42.7
>1	17.1	14.2	13.0
-	17.1	· ··-	15.0
Maternal allergy	37.7	100	35.3
Paternal allergy	57.7	100	50.5
Yes	38.7	33.7	36.7
Maternal education	30.7	33.7	30.7
Low	11.0	22.8	8.7
Intermediate	37.0	41.1	42.6
High	52.0	36.2	48.7
Breast feeding	32.0	30.2	40.7
No	0.5	15.5	17.8
1-12 weeks	60.2	38.3	24.1
> 12 weeks	39.3	46.3	58.1
Smoking during pregnancy	37.3	40.5	36.1
Yes	15.5	13.5	5.4
ETS ² first year	13.3	13.3	5.4
Yes	31.0	23.8	12.6
	31.0	23.8	12.0
Cat at home	22.0	20.5	22.0
Yes	33.9	28.5	22.0
Dog at home	12.2	12.4	22.1
Yes	13.3	13.4	23.1

^{*} Based on data from questionnaires at the age of 12 months;

3.2 Prevalence of sensitization in children aged 1 year

The effects of regional differences were studied by pooling the IgE data from all three cohorts. One remarkable observation was the high prevalence of milk sensitization at the age of 1 in children from Rotterdam. When combining the data from all cohorts 19% of the children from Rotterdam were sensitized to milk compared with an average of 6% for children from the other areas (data not shown).

¹ 1 = Friesland, Groningen, Drenthe, 2 = Noord-Holland, Almere, Lelystad, 3 = Utrecht, Gelderland, 4 = Rotterdam, Zuid-Holland, 5 = Limburg, 6 = Brabant; ² ETS: environmental tobacco smoke

Almost all children from Rotterdam were participants of PIAMA. Potential confounding factors for allergy were not different between Rotterdam and the other regions and there is no explanation for this large difference. The prevalence is therefore calculated with and without Rotterdam.

In Table 3, the prevalence of sensitization to cow's milk at age 1 is presented. In children of allergic mothers, the percentage of children sensitized to milk is almost double in PIAMA compared to BOKAAL. However, when Rotterdam is excluded the prevalence of milk-specific IgE in BOKAAL and PIAMA are similar. The prevalence of milk sensitization is the lowest in KOALA children of allergic mothers, which suggests a decrease in time, but this difference was not statistically significant. At the age of 1, there were no IgE data from PIAMA children of non-allergic mothers. The prevalence in the other two cohorts was not different.

Table 3 Prevalence of specific IgE against cow's milk in 1 year old children

	_	KAAL 2-1994	PIAMA 1996-1997		KOALA 2002-2003	
Allergic mothers	%	n§	%	n	%	n
total cohort	6.3	21/331	12.9	70/543	3.8	8/211
Rotterdam excluded	6.2	20/322	6.4	19/297	3.8	8/211
Non-allergic mothers	4.2	17/404	ND*	ND	3.9	15/385

A cut-off value of 1.2 IU/ml IgE is used to select IgE-positive children; § n is the number of sensitized children compared to the total number of children analyzed for specific IgE against cow's milk. May not add up to total numbers because of missing values * ND: not determined

Table 4 shows the percentages of children who were sensitized to egg at the age of 1. As was demonstrated for milk, but to a lesser extent, in Rotterdam a higher percentage of sensitization to egg was observed in children of allergic mothers. After exclusion of Rotterdam the prevalence of egg sensitization was lower in PIAMA children of allergic mothers, but this was not statistically significant. In children of non-allergic mothers, the prevalence in the KOALA cohort is lower than in BOKAAL, but this decrease was also not statistically significant.

Table 4 Prevalence of specific IgE against chicken egg in 1 year old children

		KAAL 2-1994	PIAMA 1996-1997		KOALA 2002-2003	
Allergic mothers	%	n [§]	%	n	%	n
total cohort	5.1	17/331	4.2	23/543	5.3	11/211
Rotterdam excluded	4.7	15/322	3.0	11/297	5.3	11/211
Non-allergic mothers	4.7	19/404	ND*	ND	1.9	7/372

A cut-off value of 1.2 IU/ml IgE is used to select IgE-positive children; § n is the number of sensitized children compared to the total number of children analyzed for specific IgE against chicken egg. May not add up to total numbers because of missing values; * ND: not determined

3.3 Prevalence of sensitization in children aged 4 or 5 years

Specific IgE against cow's milk and chicken egg was measured in older PIAMA and BOKAAL children. The average age at which the blood samples were taken was 4.1 years in PIAMA and 5.9 years in BOKAAL.

The percentage of children of allergic mothers that is sensitized to milk is not different in the three cohorts. In children of allergic mothers, both with and without Rotterdam, no time trend was observed in the prevalence of milk sensitization. In non-allergic mothers the prevalence of milk sensitization is higher in PIAMA children than in BOKAAL, but this was not significant (Table 5). The PIAMA children are on average 1.8 years younger than BOKAAL children, which is important to consider. The prevalence of sensitization to milk and egg is known to decrease with age, and therefore the observed lower prevalence in BOKAAL is probably explained by the age difference rather than by a trend in time.

Table 5 Prevalence of specific IgE against cow's milk in 4 and 5 year old children

	BOKAAL 1992-1994			AMA 6-1997
	%	n§	%	n
Allergic mothers				
total cohort	8.0	16/201	8.8	42/477
Rotterdam excluded	7.7	15/195	7.0	22/316
Non-allergic mothers				
total cohort	3.0	11/363	5.8	13/226
Rotterdam excluded	3.1	11/359	5.3	9/169

A cut-off value of 1.2 IU/ml IgE is used to select IgE-positive children; § n is the number of sensitized children compared to the total number of children analyzed for specific IgE against cow's milk. May not add up to total numbers because of missing values.

Table 6 Prevalence of specific IgE against chicken egg in 4 and 5 year old children

	BOKAAL 1992-1994			AMA i-1997
	%	n§	%	n
Allergic mothers				
total cohort	0.50	1/201	1.7	8/472
Rotterdam excluded	0.51	1/195	0.96	3/312
Non-allergic mothers				
total cohort	0.28	1/363	$2.2^{\#}$	5/224
Rotterdam excluded	0.28	1/359	1.8	3/168

A cut-off value of 1.2 IU/ml IgE is used to select IgE-positive children; § n is the number of sensitized children compared to the total number of children analyzed for specific IgE against chicken egg. May not add up to total numbers because of missing values; $^{\#}$ significantly different (p<0.05) from BOKAAL

In Table 6 the prevalence of egg sensitization is shown. In both sub groups of BOKAAL (allergic and non-allergic mothers) only 1 child is sensitized to egg at the age of 5. These numbers are slightly higher in PIAMA children at the age of 4, resulting in a higher prevalence in this cohort, both in children of allergic as well as non-allergic mothers. In the sub group of children of non-allergic mothers, this difference was statistically significant. Due to the low number of sensitized BOKAAL children it is difficult to interpret these percentages. Furthermore, the difference between BOKAAL and PIAMA became smaller and was no longer statistically significant when children from Rotterdam were excluded. In addition, the difference in age may play a role in the higher prevalence observed in PIAMA.

3.4 Prevalence of sensitization in different age groups

In Table 7 the prevalence data of a sub cohort of PIAMA children, in which specific IgE was measured at all ages is shown. IgE data were available from 196 children of allergic mothers that were analyzed at the age of 1, 4 and 8 and from 370 children of non-allergic mothers at the age of 4 and 8. In this sub group milk sensitization decreased gradually with increasing age, both in children from allergic and non-allergic mothers. The same holds true for egg sensitization. At the age of 8, egg sensitization has almost disappeared, whereas milk sensitization was still present in 5% of the children.

Table 7 Prevalence of specific IgE against cow's milk and chicken egg in a sub cohort of PIAMA

	Allergic mothers		Non-aller	gic mothers
Milk	%	n§	%	n
1 year	11.2	51/196	ND*	
4 years	8.7	17/196	8.7	32/370
8 years	5.6	11/196	5.1	19/370
Egg				
1 year	3.1	6/196	ND	
4 years	2.0	4/196	1.4	5/370
8 years	1.0	2/196	0.54	2/370

A cut-off value of 1.2 IU/ml IgE is used to select IgE-positive children; § n is the number of sensitized children compared to the total number of children analyzed at all ages; * ND: not determined

3.5 Relationship between specific IgE and reported food allergy

From children that were sensitized to either milk or egg information on doctor's diagnosed food allergy was obtained from questionnaires. In Table 8 these data are summarized for the 1 year old sensitized children from PIAMA and KOALA. Only a minority of the children sensitized to milk reported to have been diagnosed with cow's milk allergy, both in PIAMA and KOALA. There was no specific information on reported egg allergy available from the PIAMA cohort. In the KOALA cohort, only 11% of the children sensitized to egg, reported to have been diagnosed with egg allergy.



Table 8 Percentage of sensitized 1 year old children with reported food allergy

	Specific IgE	against milk	Specific IgE against eg	
	%	n§	%	n
PIAMA				
Ever diagnosed with cow's milk allergy	7.5	5/67		
Ever diagnosed with another food allergy			9.1	2/22
KOALA				
Diagnosed with food allergy	17.4	4/23	27.8	5/18
Cow's milk	13.0	3/23		
Chicken egg			11.1	2/18

 $^{^{\}S}$ n= the number of children sensitized to either milk or egg (specific IgE ≥ 1.2 IU/ml) that confirm in the questionnaire to have doctor's diagnosed milk or egg allergy compared to the total number of children sensitized to either milk or egg

Table 9 gives an overview of the percentage of sensitized children that report to have been diagnosed with a food allergy at the age of 4 (PIAMA) or 5 (BOKAAL). Of the BOKAAL children sensitized to milk, 30% reported to have been diagnosed with milk allergy. All children sensitized to egg, reported to have been diagnosed with egg allergy. In PIAMA children sensitized to milk, 18% reported to be diagnosed with milk allergy and 12% reported to be still were allergic. For egg, these percentages were considerably higher, almost 50% of the sensitized children reported that they were diagnosed with egg allergy.

Table 9 Percentage of sensitized 4 or 5 year old children with reported food allergy

	Specific IgE against milk		•	gE against
	%	n [§]	%	n
BOKAAL				
Ever diagnosed with cow's milk allergy	30.8	12/39		
Ever diagnosed with egg allergy			100	4/4
PIAMA				
Ever diagnosed with cow's milk allergy	18.2	10/55		
Ever diagnosed with cow's milk allergy and still	11.8	6/51		
allergic				
Ever diagnosed with egg allergy			41.7	5/12
Ever diagnosed with egg allergy and still allergic			36.4	4/11

 $^{^{\}S}$ n= the number of children sensitized to either milk or egg (specific IgE ≥ 1.2 IU/ml) that confirm in the questionnaire to have doctor's diagnosed milk or egg allergy compared to the total number of children sensitized to either milk or egg

4 Discussion

In this immunosurveillance we did not find evidence for an increase in prevalence of sensitization to milk and egg between 1992 and 2003. At the age of 1 year, the prevalence of sensitization was lowest in the most recently performed cohort, KOALA, but differences were not statistically significant. For the 4-5 years old children, the results showed some evidence for a higher prevalence of sensitization in PIAMA as compared to BOKAAL, especially in the sub group of children of non-allergic mothers. The difference in sensitization to egg was statistically significant in this sub group, but the difference became smaller and was no longer statistically significant when children from Rotterdam were excluded. This might suggest an increase in prevalence between 1992 and 1998; however, the difference in age should also be taken into account. The PIAMA children were on average 1.8 years younger than the BOKAAL children. Sensitization to milk and egg is known to decrease with increasing age (Hattevig et al., 1993; Venter et al., 2008). Also, in the sub cohort of PIAMA frequencies of sensitization to milk and egg were lower in older children. At the age of 8, egg sensitization had disappeared almost completely, whereas milk sensitization decreased too, but persisted in a small percentage of children. This is in line with results found in a German birth cohort in which it was demonstrated that sensitization to cow's milk in 5 years old was comparable with 2 years old children, whereas egg sensitization decreased from 4-2% (Matricardi et al., 2008). Therefore, the higher prevalence of milk and egg sensitization that was found in PIAMA children of non-allergic mothers is probably partly due to a difference in age, rather than a trend in time.

Due to methodological differences between the studies, analyses had to be conducted separately for children of allergic mothers and children of non-allergic mothers. In addition, specific sub groups had to be excluded (those with an 'alternative lifestyle' in KOALA and children from Rotterdam, for example) to obtain comparable study populations from the 3 cohorts. As a result, the numbers of children available for the analyses were smaller than initially anticipated. With these numbers, a doubling of prevalences would be needed for differences to become statistically significant (power calculation based on the prevalences at the age of 1 year).

Sensitization to food allergens does not predict clinical manifestations in all sensitized persons. In this immunosurveillance, additional information on reported food allergy was used to establish associations with food sensitization. In the 1 year old, only a minority of the sensitized children reported to have cow's milk or chicken egg allergy. This could imply that the elevated IgE levels were not associated with clinical reactivity or that the food allergy was resolved at this age. In approximately 50% of the children with cow's milk allergy developed tolerance for cow's milk at the age of 1 (Host, 2002; Host et al., 2002). The correlation between reported food allergy and sensitization was better in the 4/5 year old, especially for egg. Importantly, although allergic sensitization to foods is often asymptomatic, it is known that sensitized children are more prone to developed atopic diseases later in life (Hattevig et al., 1993; Sigurs et al., 1994). Especially, sensitization to egg has been shown to be an important marker for atopy later in life (Kulig, 1998; Kulig et al., 1999; Nickel et al., 1997), whereas sensitization to milk is not so predictive (Sigurs et al., 1994).

From other epidemiological studies it is known that several risk factors can influence the development of atopic diseases. Risk factors for sensitization to food allergens are not that extensively studied as for asthma, but there is evidence that exposure to pets can influence food sensitization (Gern et al., 2004). In addition, tobacco smoke exposure has been shown to influence the sensitization to foods, resulting in increased prevalence (Kulig et al., 1999b; Kulig et al., 1999c). We considered the possibility that the

associations studied, were influenced by confounding factors, such as paternal allergy, the presence of siblings, cats or dogs, prenatal and/or postnatal tobacco smoke exposure, breast feeding or maternal education. For instance the breastfeeding rates were not comparable between the studies. BOKAAL was restricted to women with the intention to breastfeed, while PIAMA and KOALA did not select on this, and the duration of breastfeeding in the KOALA study was somewhat longer than in PIAMA, consistent with an increasing trend from the late 90-ies into the first years of 2000 (Kools et al., 2006). The influence of breastfeeding duration on the incidence of food allergy is still controversial, and may depend on specific fatty acid concentrations in breast milk (Thijs et al., 2006; Wijga et al., 2006) and timing of introduction of complementary feeding (Snijders et al., 2008). Therefore, it is presently not possible to explain or predict time trends of food allergy from its alleged risk factors. In addition, it was not possible, due to the low numbers of sensitized children, to adjust for risk factors by conducting multivariate analyses. We therefore assessed, for each of the potential confounders separately, its association with the exposure (being in either BOKAAL, PIAMA or KOALA) and with the outcome variables. These analyses showed that confounding by these factors is unlikely to have influenced our results.

There is currently only limited information on prevalence of food allergy and especially on time trends. The results of our study are based on two food allergens, but especially in young children these are very relevant. Published studies that show an increase in prevalence have looked at peanut allergy (Grundy et al., 2002; Sicherer et al., 2003) or at hospital admissions for food-related anaphylaxis (which are often caused by peanuts and nuts) (Gupta et al., 2007). In addition, a recent report from the US shows evidence for a trend in food allergy, basing their data on all types of food allergy in children from 0 to 18 years (Branum and Lukacs, 2008). In our study, we assessed the prevalence in a restricted time period; monitoring prevalence over a longer period, in children of different ages and in adults and for different food allergens will provide a more complete overview of time trends, as is evident for asthma.

In conclusion, in this immunosurveillance there was no increasing or decreasing trend in sensitization to cow's milk and chicken egg in Dutch children aged 1 year, that were born between 1992 and 2003.

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