VILNIUS UNIVERSITY

INDRE BUTIENE

FOOD ALLERGY IN LITHUANIAN BIRTH COHORT

Summary of the Doctoral Dissertation

Biomedical Sciences, Medicine (06B)

Vilnius, 2013

This Doctoral Dissertation was prepared at the Vilnius University, Faculty of Medicine, department of Pathology, Forensic medicine and Pharmacology in 2009−2013.

Scientific Supervisor:
Prof. Dr. Habil. Rūta Dubakienė (Vilnius University, Biomedical Sciences, Medicine – 06 B)

Scientific Consultant:
Prof. Dr. Virginija Grabauskienė (Vilnius University, Biomedical Sciences, Medicine – 06 B)

The Doctoral Dissertation will be defended at the Vilnius University, Faculty of Medicine

Chairman:
Prof. Habil. Dr. Vytautas Usonis (Vilnius University; Biomedical Sciences; Medicine – 06B)

Members:
Prof. Dr. Regina Ėmužytė (Vilnius University; Biomedical Sciences; Medicine – 06B)
Prof. Habil. Dr. Arvydas Ambrozaitis (Vilnius University; Biomedical Sciences; Medicine – 06B)
Prof. Dr. Artūras Razbadauskas (Klaipeda University; Biomedical Sciences; Medicine - 06B)
Prof. Habil. Dr. Vytas Antanas Tamošiūnas (State Research Institute Centre for Innovative Medicine; Biomedical Sciences; Biology - 01B)

Opponents:
Dr. Audronė Eidukaitė (State Research Institute Centre for Innovative Medicine; Biomedical Sciences; Medicine - 06B)
Prof. Dr. Dainius Characiejus (Vilnius University; Biomedical Sciences; Medicine - 06B).

The Doctoral Dissertation will be defended at the public session on 4th of December, 2013, 2.00 p.m., in the Grand Hall of Faculty of Medicine of Vilnius University.
Address: 21 M.K.Čiurlionio str., LT-03101 Vilnius, Lithuania.

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The Doctoral Dissertation is publicly available at the Library of Vilnius University.

VILNIAUS UNIVERSITETAS

INDRĖ BŪTIENĖ

MAISTO ALERGIJA LIETUVOS NAUJAGIMIŲ KOHORTOJE

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Mokslinis vadovas:
Prof. habil. dr. Rūta Dubakienė
(Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Mokslinis konsultantas:
Prof. dr. Virginija Grabauskienė
(Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Disertacija ginama Vilniaus universiteto Medicinos mokslo krypties taryboje:
Pirmininkas:

Prof. habil. dr. Vytautas Usonis (Vilniaus universitetas, biomedicinos mokslai, medicina - 06B)

Nariai:

Prof. dr. Regina Ėmužytė (Vilniaus universitetas, biomedicinos mokslai, medicina - 06B)

Prof. habil. dr. Arvydas Ambrozaitis (Vilniaus universitetas, biomedicinos mokslai, medicina - 06B)

Prof. dr. Artūras Razbadauskas (Klaipėdos universitetas, biomedicinos mokslai, medicina - 06B)

Prof. habil. dr. Vytas Antanas Tamošiūnas (Valstybinis mokslinių tyrimų institutas Inovatyvios medicinos centras, biomedicinos mokslai, biologija - 01B)

Oponentai:

Dr. Audronė Eidukaitė (Valstybinis mokslinių tyrimų institutas Inovatyvios medicinos centras, biomedicinos mokslai, medicina - 06B)

Prof. dr. Dainius Characiejus (Vilniaus universitetas, biomedicinos mokslai, medicina - 06B).

Disertacija bus ginama viešame Medicinos mokslo krypties tarybos posėdyje 2013 m. gruodžio 4 d., 14.00 val., Vilniaus universiteto Medicinos fakulteto Didžiojoje auditorijoje.
Adresas: M.K. Čiurlionio g. 21, LT - 03101, Vilnius, Lietuva.

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PADĖKA

Šios disertacijos rašymas nebūtų pavykęs be daugybės žmonių paramos.

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1. INTRODUCTION

Environmental factors more often is thought to have influence in determining children's health and development. Although some diseases are predominantly environmental or genetic, both environmental and genetic factors play an important role in most common diseases. Evidence is mounting that the biological, physical and social environment, to which a child is exposed early in life, particularly during critical periods of development, may lead to disease or disability in childhood and adulthood.

Longitudinal cohort studies are recognised as the best available scientific approach for identifying and evaluating a broad range of environmental factors affecting on children's health through development from conception through early childhood, adolescence and to adulthood.

Prevalence of atopic diseases over the last decades is increasing, especially in Western Europe, and it cannot be explained only by genetic susceptibility. Lifestyle, nutrition, environmental exposures and interactions between genes and environmental factors most likely play a causal role. Food allergy usually manifest as one of the first forms of allergy and it is considered as the first step of „atopic march". Food allergies, defined as an adverse immune response to food proteins, affect as many as 6% of young children and 3%-4% of adults in westernized countries and their prevalence appears to be rising, but exact data are still not known. There is increasing public concern about the true prevalence and a possible increase of food allergies over time, particularly among parents, child care and school staff, health care providers, regulators and food producers.

Allergic reactions to food products, such as cow's milk, hen's egg, peanut, tree nuts, wheat, soy and fish, often develop within the first few years of life. Whereas cow's milk and hen's egg allergy can resolve by school age, peanut and fish allergy tend to persist throughout childhood and adulthood. Recent meta-analyses of population-based studies show considerable heterogeneity in the prevalence of perceived and confirmed allergic reactions, as well as sensitization to food. However, it remains unclear whether the variation observed was related to differences in study design, methodology or genuine differences between populations. Adverse reactions to food have different prevalence patterns in different age groups. In children between birth and 4 years of age, the prevalence of perceived reactions to any food in population-based studies varied markedly and ranged from 3% to 35%. In Lithuania exact prevalence of food allergy is not known as most of data were collected using interviews and questionnaires and most reveal prevalence of self-reported food allergy.

The aim of the study

To determine the prevalence and risk factors for food allergy in EuroPrevall Lithuanian birth cohort.

Objectives of the study

1. To describe Lithuanian birth cohort based on collected data from questionnaires.
2. To determine most common food allergens and changes in prevalence of sensitization to them during first 2.5 years of life.
3. To assess parental and children risk factors for food allergy.
4. To evaluate different food allergy diagnostic methods and provide recommendations for food allergy diagnosis.

Practical significance and novelty of the study

In this study, we present Lithuanian data from implementing EuroPrevall – an EU-funded multidisciplinary integrated research project "The Prevalence, Costs, and Basis of Food Allergy across Europe" first theme WP 1.1 "Eurorevall birth cohort". The EuroPrevall birth cohort study, in which participated Vilnius University, was the most comprehensive investigation of food allergies in the first years of life with over 12,000 participants from 9 different countries. Collected Lithuanian data had significant value in determining prevalence of food allergy in all Europe and gathered valuable information about the differences and similarities of Eastern Europe region.

During the project comprehensive data about Lithuanian birth cohort have been collected – maternal diseases, nutrition, use of food additives and medicines, contact with tabacco smoke during pregnancy, birth and breastfeeding, also sociodemographic data and information about pets at home. Data about maternal, paternal and siblings' allergic diseases, infections, cohort children nutrition, vaccination, passive smoking, signs and symptoms of allergic diseases were collected too. During this project real prevalence and risk factors for food hypersensitivity and allergy in infants and small children in Lithuania have been determined, the most common food allergens were assessed and changes in prevalence of sensitization to them during first 2.5 years of life were analysed. It was one of the biggest research project in this area and collected data will provide useful information about the food allergy and common food allergens to scientists, public health specialists, politics, doctors and patients.

2. MATERIALS AND METHODS

Vilnius University in collaboration with other European research centres was a partner in EuroPrevall integrated project – "The prevalence cost and basis of food allergy in Europe", that was an EU-funded multi-disciplinary research study within the 6th framework programme (Contract Number: FOOD-CT-2005-514000). The project was launched at June 2005 and officially completed at December 2009. All project has been coordinated by Clare Mills at the Institute of Food Research in Norwich, UK. It is EuroPrevall's aim that by integrating information and developing tools for the use of European food allergy scientists, health professionals, food and biotech industries and consumers, that causes of food allergy can become better understood, diagnosis of food allergy can become swifter and the quality of life of food allergy sufferers improved.

Vilnius University took part in the first theme of the project called „Epidemiology of Food Allergy Across Europe" working group. The first objective of this theme was to obtain an authoritative estimates of the food allergy prevalence across the different areas of Europe and to provide a qualitative assessment of the variance of this prevalence. The EuroPrevall birth cohort study, subtheme of first theme WP 1.1 in which participated Vilnius University, was the most comprehensive investigation of food allergies in the first years of life with over 12,000 participants from 9 different countries (Germany, Poland, Greece, Great Britain, Spain, The Netherlands, Island, Lithuania and Italy). Primary aim of this research was to establish and compare the prevalence of confirmed allergic reactions to food in young children across major climatic and cultural regions in Europe. Secondary aims were to examine the role of possible determinants for the

development of food allergies, such as genetic background, maternal diet during pregnancy and breast feeding, infections, psycho-social and environmental factors.

In this disertation data from EuroPrevall Lithuanian birth cohort are provided.

Recruitment procedure

Approval of Lithuanian Bioethics Committee was given to conduct this biomedical research (2005-12-21, No. 60).

EuroPrevall Lithuanian birth cohort was formed in the Vilnius city clinical hospital, clinic of obstetrics and gynaecology. 1558 newborns from 1st of January, 2006 till 25th of April, 2007 were included into cohort. Both parents have been informed about the Project and have signed the informed consent form for participation in the Project.

Baseline and follow-up questionnaires

At day of inclusion, we collected information regarding the mother's pre-existing diseases, nutrition, intake of food supplements, medications and exposure to cigarette smoke before and during pregnancy, as well as extensive socio-demo-graphic data. Data about allergic diseases of the mother, father and any blood-related siblings were assessed in detail. At the three routine follow-up time points, we collected comprehensive data on the mother's nutrition, intake of food supplements, medications and exposure to cigarette smoke during breastfeeding, weaning and food intake of the child, food supplements, infections, medications, vaccinations, exposure to cigarette smoke, mould and pets, as well as any signs and symptoms of allergic diseases. Any changes in the allergy status and socio-demographics of the parents and siblings were also identified.

Identification and evaluation of children with food allergy

Parents were advised to report to the study center if any signs or symptoms that could be caused by food (e.g. eczema, gastrointestinal symptoms, wheezing) appear. Using a standardized screening form, parents were invited to the Vilnius University Antakalnio clinic Republic allergology center if defined criteria fulfilled.

At this visit a physical examination was conducted including standart scoring for signs of eczema using the Scoring Atopic Dermatitis (SCORAD) assessment in children with atopic dermatitis, a symptomatic questionnaire was completed, 4–5ml blood obtained for measurement of food-specific IgE and skin tests were performed. Skin prick tests (SPT) were carried out in children with symptoms of a possible allergic reaction to food using ALK allergen solutions, histamine dihydrochloride as positive and saline solution as negative controls (ALK- Abello´ , Hørsholm, Denmark). The SPT result for each allergen was defined as positive if the mean wheal diameter was 3 mm or larger and the Skin Index was greater than 0.6. The serums of children with symptoms of a possible allergic reaction to food were tested for the six most common food allergens using the Phadia fx5 screening test (Phadia Diagnostics, Uppsala, Sweden). If the screening test was positive, the serum was analyzed for specific IgE antibodies to cow's milk, hen's egg, soy, wheat, fish and peanut. All measurements were performed centrally (allergy laboratory of the Department of Paediatric Pneumology and Immunology, Charite´ University Medical Center Berlin, Germany) using the Phadia ImmunoCAP 250 system (Phadia Diagnostics, Uppsala, Sweden). Using this information the decision was made whether the child was eligible for a DBPCFC. If criteria for eligibility for a DBPCFC

were met, two age-matched control children were to be recruited from the pool of noneligible children and followed with the same evaluation. To obtain a confirmed diagnosis for food allergy, DBPCFC tests were conducted in the Vilnius University Hospital Santariskiu Klinikos Children‘s Hospital under the supervision of a trained pediatrician using a standardized protocol and recipes. Food allergies were classified as perceived (parents call with allergic symptoms related to food), probable (meets eligibility criteria for a DBPCFC, e.g., elevated allergen-specific serum IgE, but parents refused the food challenge) and confirmed (positive DBPCFC).

Data analysis

Statistical data analysis was performed using statistical package IBM SPSS Statistics 20.0. Categorical data were analyzed using chi-square and Fisher's exact tests. The results were considered as statistically significant if p-value was ≤ 0.05. Prevalence ratio (PR) and its 95% CI (confidence interval) were counted to test possible associations. Logistic regression was used to evaluate risk factors. Odds ratio (OR) and its 95% CI were counted to estimate association between risk factors and food allergy. We used stepwise multiple logistic regressions with backward elimination for model building in children group. Due to the small sample size of symptomatic group, exact logistic regression method was used.

3. RESULTS

3.1 DESCRIPTION OF LITHUANIAN BIRTH COHORT BASED ON DATA FROM QUESTIONNAIRES

1558 newborns, among them 6 pairs of twins, were included into Lithuanian birth cohort. 88 (5.3%) of newborns or their parents did not fulfilled inclusion criteria, 4 (0.25%) families officially refused to continue participation in the project, whereas contact with 127 (8.1%) families have been lost during the project (due to emigration, change of phone numbers, living place, etc.).

51.2% (797/1558) of cohort were boys, 48.2% (761/1558) – girls, thus distribution by age was equal in the cohort. Mean age of mothers at the time of inclusion to cohort was 28.3 ± 5.3 years (mean ± SD), mean age of fathers – 30.9 ± 6,2 years (mean ± SD).

Pregnancy and birth data

Evaluation of data from questionnaires, filled-in during inclusion to the cohort, showed that majority of mothers delivered for the first (610 (39%)) or second (421 (27%)) time, 95 mothers delivered for the 4th time, and for one mother there was 10th delivery. Medium duration of pregnancy was 39.22 ± 1.16 weeks. Medium weight of newborn was 3523 ± 437g. Detailed pregnancy and birth data are shown in Table 1.

Table 1 *Lithuanian birth cohort data about birth, gender and family composition*

Factor	Cohort, N=1558	
	n, number.	**%**
Number of deliveries for mother	n = 1289	
- 1st time	610	47.3
- 2nd time	421	32.7
- 3rd time	163	12.6
- 4th and more times	95	7.4
- *Data not known*	*269*	*20.9*
Meconium staining during the birth	n = 1533	
- Present	154	10
- *Data not known*	*25*	*1.6*
Form of delivery	n = 1556	
- normal, unassisted	1298	83.4
- forceps assisted	8	0.5
- vacuum assisted	8	0.5
- Caesarian section	242	15.5
Planned	110	7.1
Emergency	132	8.4
- *Data not known*	*2*	*0.1*
Gender	n = 1558	
- Boy	797	51.2
- Girl	761	48.8
Number of siblings in family	n = 1534	
- None	838	54.6
- One	494	32.2
- Two or more	202	13.1
- *Data not known*	24	1.6

83.4% of newborns were born during usual unassisted delivery, whereas for 258 (16.5%) mothers delivery was complicated: 16 newborns were born with assistance of forceps or vacuum, 15.7% of cohort newborns were born during Caesarian section, 8.4% of these cases was urgent. Meconium staining during birth was documented for 154 (10%) births. Almost half of families included into cohort (696 (45%)) had already one or more children, for 54.6% of families newborn included into cohort was the first child.

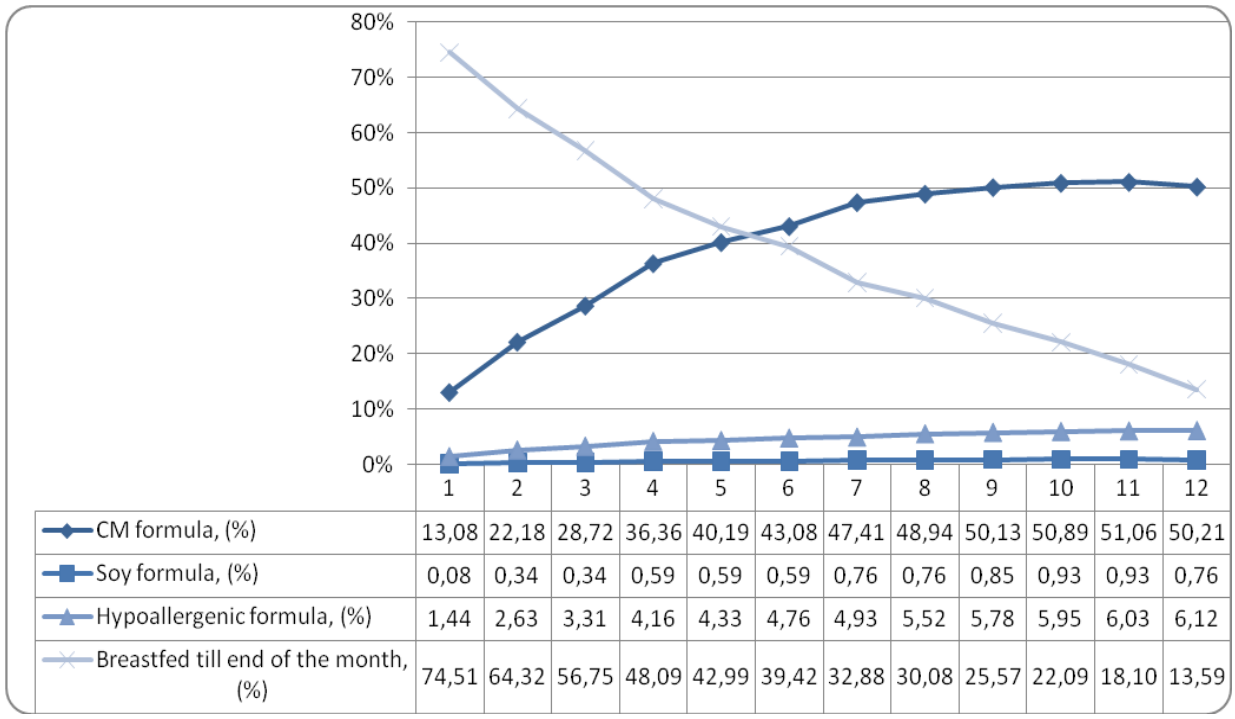
Table 2 *Medicines used by mothers during pregnancy, birth and just after the birth*

Medications	Cohort, N=1558			
	n	**%**	**unknown, n**	**%**
Used during pregnancy				
- Antibiotics	220	14.1	236	15.1
- Acetilsalicilic acid or paracetamol	276	17.7	236	15.1
- Other anti-inflamatory medications	87	5.6	260	16.7
- Folic acid preparations	807	51.8	104	6.8
- Polyvitamins	1240	79.6	78	5.0
- Vitamine D	65	4.2	291	18.7
- Fish oil products	93	6.0	283	182
Antibiotics used during delivery	146	9.4	166	10.7
Antibiotics used just after delivery	196	12.3	34	2.2

As shown in Table 2, antibiotics use during pregnancy, delivery and just after the birth was not very common – 14.1% (220/1558), 9.4% (146/1558) and 12.3% (196/1558) of mothers, respectively. Majority, about 80%, of mothers used polyvitamins during pregnancy; use of food supplements with folic acid was less common – in about 52% of mothers. An antiinflamatory medications have been used often too – 276 (17.7%) mothers used acetilsalicilic acid or paracetamol, whereas other medications of this group – 87 (5.6%) mothers.

Nutrition of infants during first years of life

Data about breastfeeding and nutrition revealed that 69.2% (815/1177) of infants were breastfed till 12 months of age, and 13.6% (160/1173) still were breastfed till 24 months of age. 5% (59/1177) mothers did not breastfed their children at all. Even 65% (772/1177) newborns at least once during first year of life tried formula, whereas 27.4% of infants did not received formula at any time. More detailed data about breastfeeding and feeding with formula are provided in Figure 1.

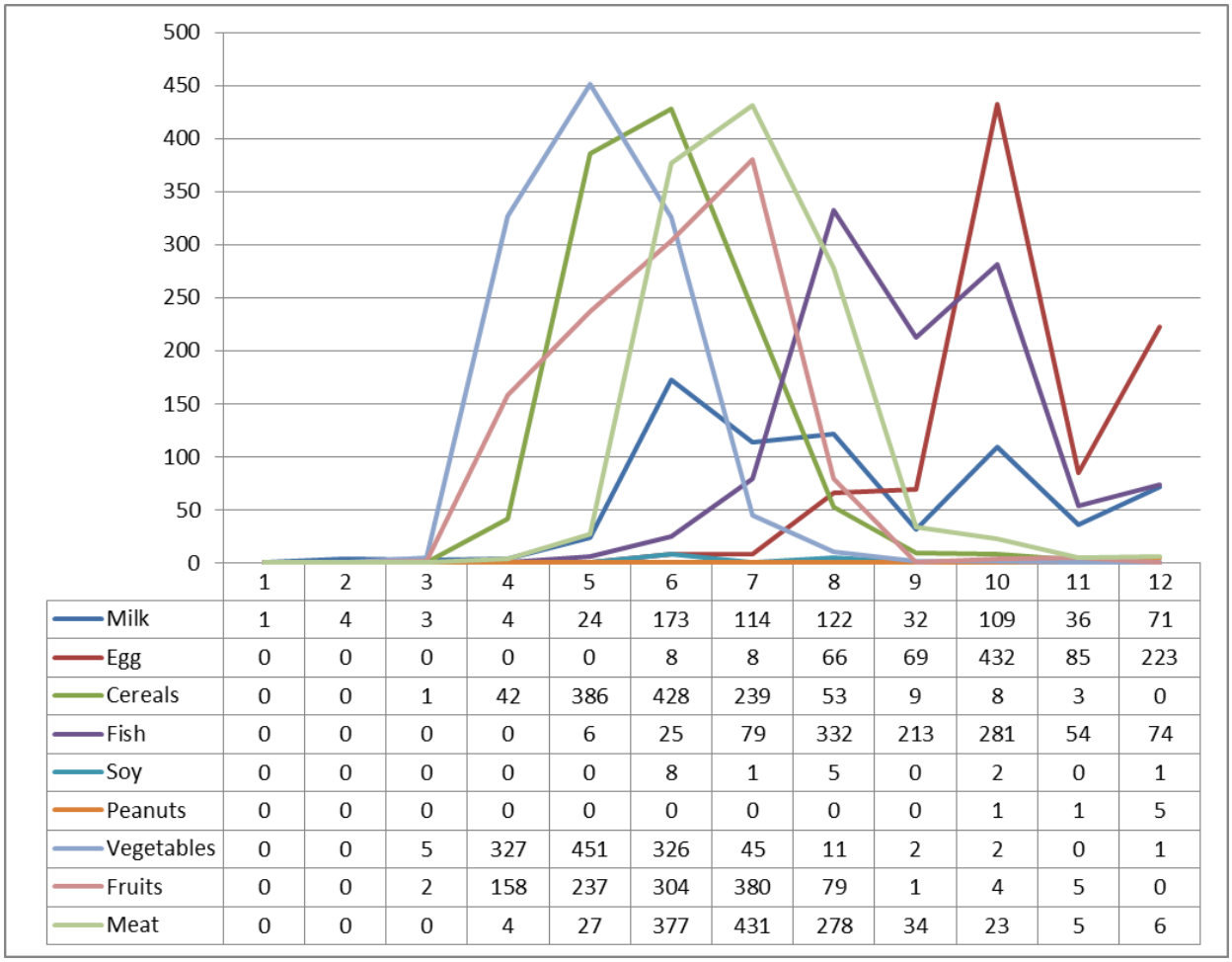


	1	2	3	4	5	6	7	8	9	10	11	12
CM formula, (%)	13,08	22,18	28,72	36,36	40,19	43,08	47,41	48,94	50,13	50,89	51,06	50,21
Soy formula, (%)	0,08	0,34	0,34	0,59	0,59	0,59	0,76	0,76	0,85	0,93	0,93	0,76
Hypoallergenic formula, (%)	1,44	2,63	3,31	4,16	4,33	4,76	4,93	5,52	5,78	5,95	6,03	6,12
Breastfed till end of the month, (%)	74,51	64,32	56,75	48,09	42,99	39,42	32,88	30,08	25,57	22,09	18,10	13,59

Figure 1 *Infants breastfeeding and feeding with formulas during first year of life*

Majority of infants - about 75% - were breastfed during the first month of life, and during first 12 months of life this number was gradually decreasing till 14% at the end of first year. Prevalence of feeding with CM formula was conversely proportional – the least number of children (13%) were feeded during the first month and it was gradually increasing and reached 50% at the end of first year. Figure 1 reveales that minimal number of infants drunk soy formula - maximum about 0.93% of kids when they were 10-11 months of age, and hypoallergenic CM formula – at the age of 12 months – about 6% of infants.

Data about introduction of solid foods are shown in Figure 2.



	1	2	3	4	5	6	7	8	9	10	11	12
Milk	1	4	3	4	24	173	114	122	32	109	36	71
Egg	0	0	0	0	0	8	8	66	69	432	85	223
Cereals	0	0	1	42	386	428	239	53	9	8	3	0
Fish	0	0	0	0	6	25	79	332	213	281	54	74
Soy	0	0	0	0	0	8	1	5	0	2	0	1
Peanuts	0	0	0	0	0	0	0	0	0	1	1	5
Vegetables	0	0	5	327	451	326	45	11	2	2	0	1
Fruits	0	0	2	158	237	304	380	79	1	4	5	0
Meat	0	0	0	4	27	377	431	278	34	23	5	6

Figure 2 *Data about solid foods introduction during first year of life*

In the above provided Figure 2 can be seen, that majority of infants started to eat solid food at the age of 4 – 6 months, and only several children (16 (1%)) tried solid food earlier than they became 4 months of age. First food products introduced into diet were vegetables, fruits and food made from different cereals. Fish was mostly introduced when children were 8 months of age (332 (28%)), similar number of children tried fish at 9–10 months of age, whereas egg was introduced into infants diet most commonly when children were 10 months of age (432 (37%)). Even 90% (1086/1177) of children first tried meat a bit earlier than fish – at 6–8 months of age. Products derived from soy and peanuts in the first year of life were given very rarely – just 1.4% (17/1177) and 0.6% (7/1177) of children, respectively, tried soy products and peanuts at this age.

Allergic diseases in family members

14.3% (222/1556) of mothers and 6.8% (106/1556) of fathers indicated that they were allergic to one or few allergens or they have ever been diagnosed with any allergic disease. Sibling's data analysis showed that 12.3% (153/1556) of siblings were indicated as allergic (Table 3).

Table 3 *Lithuanian birth cohort family members' allergic diseases*

	Mother		**Father**		**Siblings**	
	N=1556[1]	%	N=1556[1]	%	N=897	%
Indicated allergy	222	14.3	106	6.8	153	12.3
Allergic rhinitis, polinosis	68	4.3	49	3.1	24	2.7
Bronchial asthma	25	1.6	14	0.9	20	2.2
Atopic dermatitis	40	2.6	5	0.3	92	10.2
Allergy to house dust mites	37	2.4	25	1.6	22	2.5
Allergy to animals	28	1.8	15	1.0	11	1.2
Allergy to latex	0	0.0	2	0.1	0	0.0
Drug allergy	87	5.6	16	1.0	12	1.3
Venom allergy	5	0.3	7	0.4	3	0.3
Hypersensitivity to food	79	5.1	15	1.0	87	9.7
- *Do not know are they allergic to food*	2	0.1	6	0.4	4	0.3

[1] *Data about allergic disease of 2 families are not known*

Collected data revealed that prevalence of allergic diseases such as bronchial asthma, allergis rhinitis and eczema in cohort mothers was 8.5%: 1.6%, 4.3% and 2.6%, respectively; in fathers – 4.3%: 0.9%, 3.1% and 0.3%; in siblings – 15.2%: 2.2%, 2.7% and 10.2%. Prevalence of self-reported hypersensitivity reactions to food varied from 1.0% between fathers to 9.7% between siblings.

Environment and addictions

Table 4 *Lithuanian birth cohort environmental factors*

Factor	**Cohort, N=1558**	
	N	**%**
Living place		
- Urban	1335	86.2
- Rural, (<5000 population):	211	13.6
- rural, no farm	141	9.1
- rural, farm	70	4.5
- Lives nearby highway	329	21.3
- *not specified*	*10*	*0.6*
Animals or pets in family	676	44.6
- Cats	343	22.6
- Dogs	336	22.2
- Other pets (birds, fishes, reptiles, rodents, etc.)	213	14.0
- Farm animals and birds	71	4.7
- *Not specified*	44	2.8
Mother's smoking		
Smokes	126	7.8
Was smoking (or tried to smoke at once), but have stopped before to get pregnant	506	32.5
During pregnancy:		
- have stopped smoking when she has become aware that she is pregnant	336	21.6
- reduced number of cigarettes	107	6.8

Factor	Cohort, N=1558	
	N	%
- smoked as much as before pregnacy	7	0.4
- have stopped smoking when she started to plan to become pregnant	154	9.9
- *non specified*	*28*	*1.8*
Smoking family members	668	42.9
Passive smoking during pregnancy	133	8.5
Never smoked	924	59.4

As shown in Table 4, majority of Lithuanian cohort at the time of inclusion lived in urban area (86.3%), and one quarter of them lived nearby highway with huge traffic, and 9.1% of them - in villages, but no in farm, and 4.5% lived in farms. 676 families indicated that they hold pets or farm animals. More than 40% of cohort familes had cats or dogs inside house, and other animals were in 213 (14%) families. Farming animals (chickens, gouts, cows, horses or pigs) were indicated by almost 5% of families.

Responses to questions about smoking posed in questionnaires showed that about 7.8% of mothers smoked during pregnancy and childbirth. 8.5% of mothers stated that they were exposed to passive smoking (at home, at work or in public places) during pregnancy, although collected data shows that smoking in households was 43%. About 60% of mothers were never-smokers.

3.2 MOST COMMON FOOD ALLERGENS AND CHANGES IN PREVALENCE OF SENSITISATION TO THEM DURING FIRST 2.5 YEARS OF LIFE

Due to symptoms similar to the food allergy 221 (14.2%) parent called to the research center, of which 111 children were invited for more detailed examination. Food allergy was suspected in 45 children from telephone interviews. So, the prevalence of parental-reported was 17.1% in Lithuania birth cohort of children. In total, 156 children were invited to the research center for detailed examination.

In order to analyze changes of sensitization to the food allergens during the first 2.5 years of life, children diagnosed with food sensitization were divided into four age groups: group 1 included children from birth to 6months of age (till 5 months and 30 days), group 2 - 6-12 months (till 11 months 30 days), group 3 - 12-18 months (till 17 months and 30 days), and group 4 - 18 months and older children.

Food sensitisation during first 6 years of life

Early, under six months of age, sensitization to food was established in 1.3 % of children (20/1558) (Figure 3).

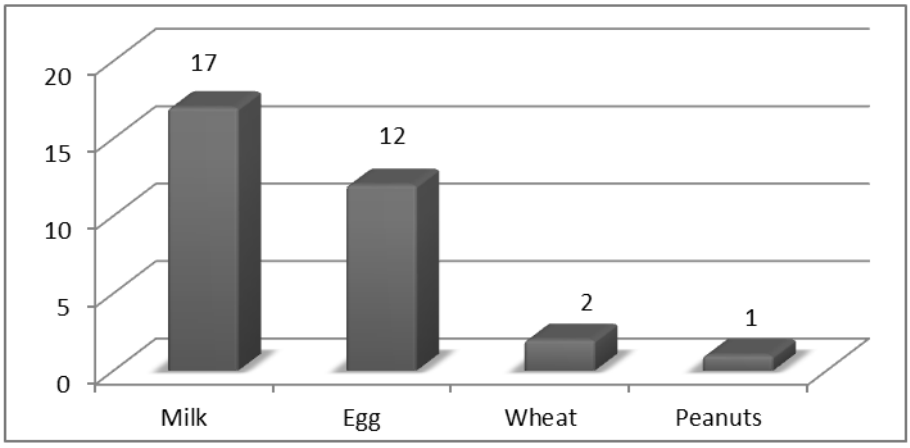


Figure 3 *Sensitisation to food allergens during first 6 months of life*

Sensitization to cow's milk was diagnosed in 85% (17/20) and egg - in 60% of children (12/20). Sensitisation to wheat was detected in 2 children, to peanuts – in one child. Even 50% (10/20) of symptomatic children under 6 months of age were sensitized to more than one food allergen (Figure 4).

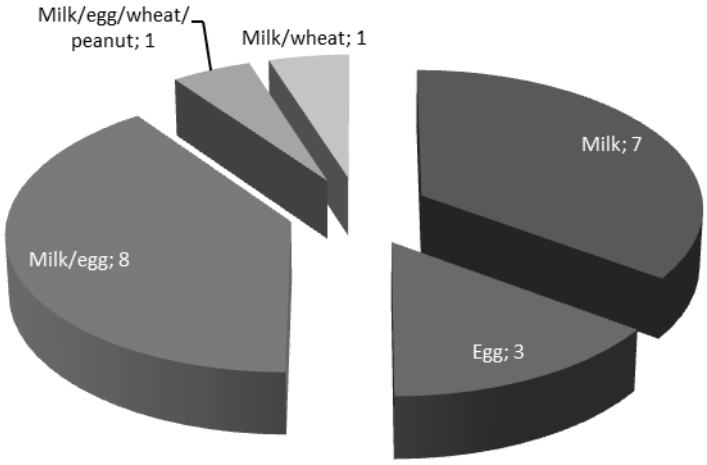


Figure 4 *Distribution of children under 6 months of age according to sensitization to the food allergens*

As showed in Figure 4, 7 children were sensitized only to milk, only to egg – 3, other children were sensitized to more than one food allergen: 8 children had hypersensitivity both to milk and egg, other 2 children – to milk and wheat, and milk, egg, wheat and peanut.

Food sensitisation during first 12 months of life

Sensitization to the food allergens was identified in 1.5% (23/1558) of 6-12 months of age children. When comparing this age group with group 1, sensitization to

egg was found more often than to milk. In group 2 sensitization to egg was found in 15 children, milk - 12, wheat - 5, carrot - 2, to potatoes, soy, peanuts and fish were sensitized one child to each. Data about sentization of children under 12 months of age are shown in Figure 5.

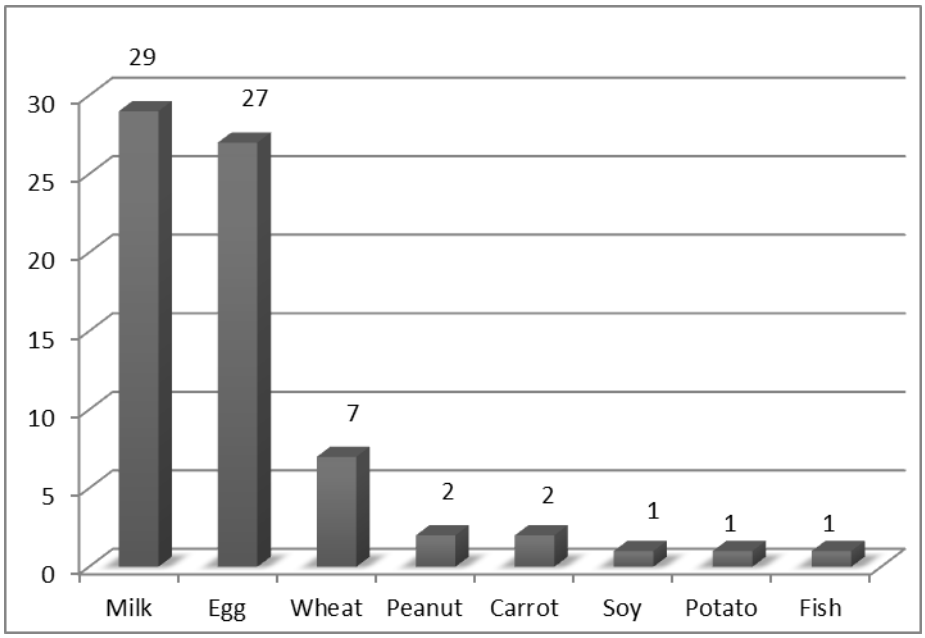


Figure 5 *Sensitisation to food allergens during the first year of life*

Sensitization at this group of age was identified in 2.8% (43/1558) of symptomatic children: sensitization to milk was identified in 67% (29/43) of children, to egg - 63% (27/43). Sensitization to wheat was identified in 7 patients, to peanuts and carrots –in 2 children each, to fish, soy and potatoes sensitization was detected once. Sensitization to more than one food allergen was diagnosed in 23 of 43 (54 %) children under one year of age (Figure 6).

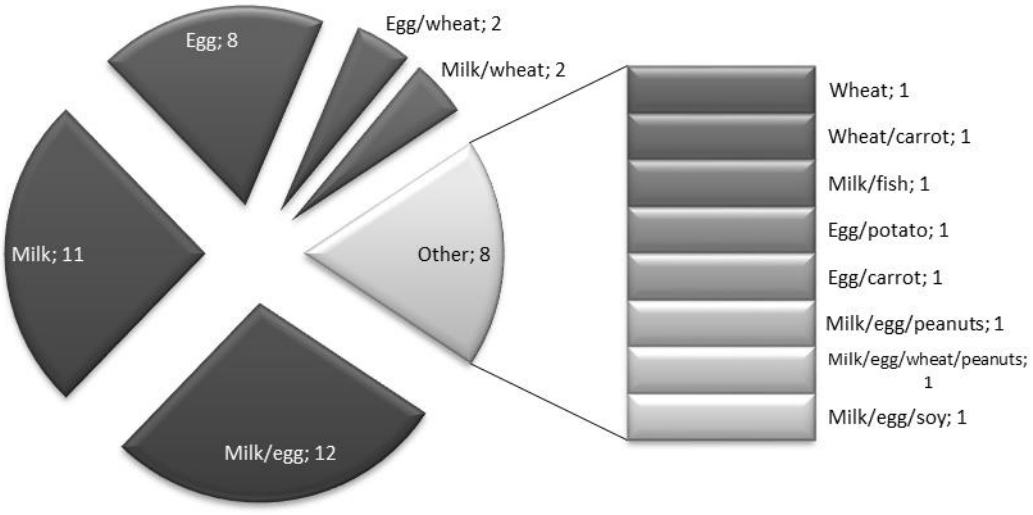


Figure 6 *Distribution of children under 1 year of age according to sensitization to the food allergens*

From 43 symptomatic children, sensitization only to milk was detected in 11 (26%) children, only to egg – in 8 (19%), only to wheat – in 1 (2%) child. Figure 6 shows, that 12 (28%) children were sensitized to milk and egg, whereas other 11 (26%) were sensitized to few or more food allergens.

Food sensitization in children under 18 months of age

Food sensitization was diagnosed in 1.5% (23/1558) of 12–18 months of age children. 12 of 23 (52%) children were sensitized to milk, 15 (62%) – to egg. Hypersensitivity to wheat was confirmed in 3 children, to fish and peanuts – in 2 children each, to soy was allergic one child. Thus, sensitization to food allergens in general has been diagnozed in 4.2% of symptomatic children under 18 years of age of analyzed cohort (66/1558). Sensitization to different food allergens in children under 18 months of age is shown in Figure 7.

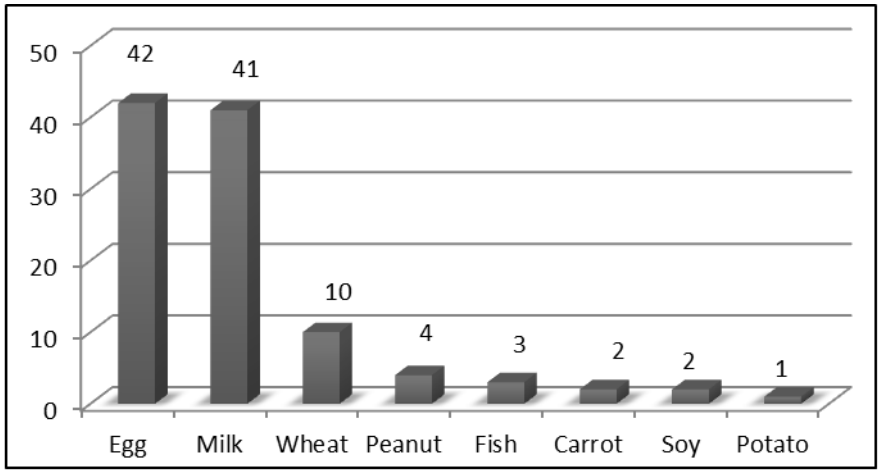


Figure 7 *Sensitization to food allergens in children under 18 months of age*

Majority of children under 1.5 years of age were sensitized to egg – 64%, slightly less – to milk (62%), more less – to wheat (15%), peanut (6%) and fish (4,5%). To carrot and soy were sensitized 2 children to each, to potato – one child under 18 months of age.

General distribution according to sensitization to the different food allergens is presented in Table 5.

Table 5 *Distribution of sensitization to the food allergens in children under 18 moths of age*

Food allergen	**n=66**	**%**
Milk	18	27,3
Egg	17	25.8
Milk/egg	13	19.7
Egg/wheat	3	4.6
Milk/egg/wheat/peanuts	3	4.6
Milk/egg/fish	2	3
Milk/wheat	2	3

Egg/potato	1	1.5
Wheat	1	1.5
Milk/egg/peanut	1	1.5
Milk/fish	1	1.5
Soy	1	1.5
Egg/carrot	1	1.5
Wheat/carrot	1	1.5
Milk/egg/soy	1	1.5

Sensitization only to milk was diagnosed to 27% (18/66), only to egg – 26% (17/66) of children from this age group. Sensitization to wheat was identified only to one child; to soy was sensitized also one child only. Sensitization to more than one allergen was found in 29 children: 13 (39%) children were sensitized both to milk and egg, 3 (5%) children – both to egg and wheat, and to milk and wheat – 2 (3%) children. Other 11 (17%) children were sensitized to few or more food products, and 3 of them were sensitized to milk, egg, wheat and peanuts.

Food sensitization in children under 2.5 years of age

Sensitization to the food allergens was detected in 22 (1.4%) children in 18 - 30 months of age group, but only 4 of them were older than 2 years of age. Sensitization to milk was diagnosed in 55% (12/22) of children, to egg – in 41% (9/22) of children. Sensitization to peanuts was confirmed in 4 (18%), to soy – in 3 (14 %) children. 2 children were sensitized to wheat or fish each, and sensitization to carrot, tomato, orange, hazelnut, yeast, beef was found once. General sensitization to the food allergens in children under 2.5 years of age is presented in Figure 8.

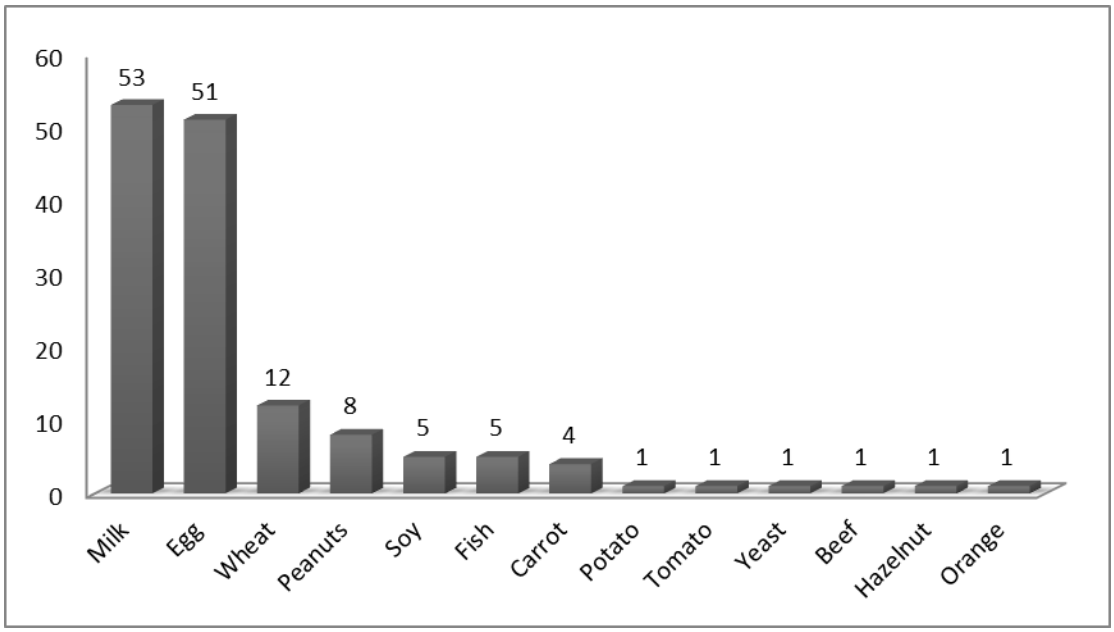


Figure 8 *Sensitization to the food allergens in children under 2.5 years of age*

Most commonly sensitization of symptomatic children under 2.5 years of age was diagnosed to milk (60.2%) and egg (58.0%). Less frequent sensitization was diagnosed to wheat (13.6%) and peanuts (9.1%). 5 (5.7%) children were sensitized to soy, the same

number of children – to fish. To carrot were sensitized 4 (4.5%) symptomatic children. Sensitization to potato, tomato, yeast, beef, hazelnut and orange was diagnosed once.

Only to milk were sensitized 26, only to egg - 22, only to soy – 2 children, only to wheat, carrot, orange, tomato was sensitized only one child to each product. 38.6% (34/88) of children were sensitized to more than one allergen (Table 6).

Table 6 *Distribution of sensitization to the food allergens in children under 2.5 years of age*

Food allergen	**N=88**	**%**
Milk	26	29,5
Egg	22	25
Milk/egg	14	15,9
Egg/wheat	3	3,4
Milk/egg/wheat/peanuts	3	3,4
Milk/egg/fish	2	2,3
Milk/egg/peanuts	2	2,3
Polysensitization[1]	2	2,3
Soy	2	2,3
Milk/wheat	2	2,3
Milk/soy	1	1,14
Egg/potato	1	1,14
Wheat/carrot	1	1,14
Egg/carrot	1	1,14
Milk/fish	1	1,14
Egg/peanuts	1	1,14
Wheat	1	1,14
Carrot	1	1,14
Orange	1	1,14
Tomato	1	1,14

[1] *2 children were sensitized to lots of food allergens – one child was sensitized to milk, egg, soy, wheat, peanuts, fish, yeast, carrot, beef; other child was sensitized to milk, egg, soy, hazelnut and peanut, wheat and fish.*

Relationship between atopic dermatitis and food sensitization

Collected data revealed that atopic dermatitis was diagnosed in 86% (76/88) sensitized to food children: 21.6% (19/88) were under 6 months of age, 23.7% (21/88) – 6-12 months of age, 21.6% (19/88) – 12-18 months of age, and 19.3% (17/88) - 18-30 months of age. Distribution of the mean SCORAD index between the age groups is presented in Figure 9.

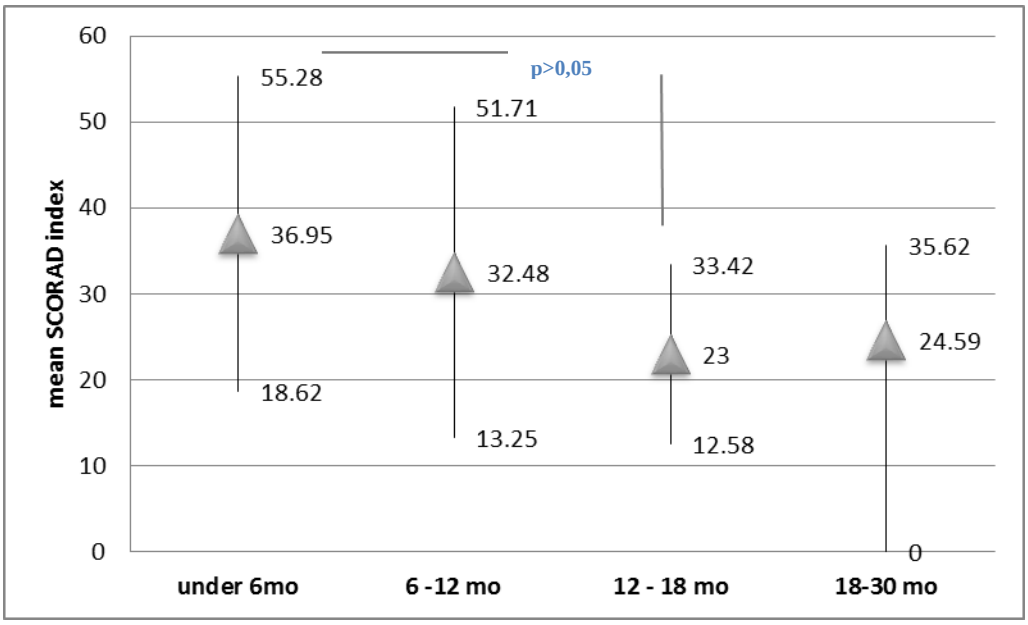


Figure 9 *Distribution of mean SCORAD index between the age groups*

Significant difference of mean SCORAD indices was identified between first and second age groups – in children under 6 months of age atopic dermatitis was more severe (mean SCORAD index: 36.95±18.33), than in 12-18 months of age children (23±10.42) (p=0.043). Difference between mean indices in 6-12 months of age children group (32.48±19.23) and in older than 18 months of age group (24.59±11.03) was not statistically significant.

Data of analysis on severity of atopic dermatitis and number of food products to which each child was sensitized are presented in Figure 10.

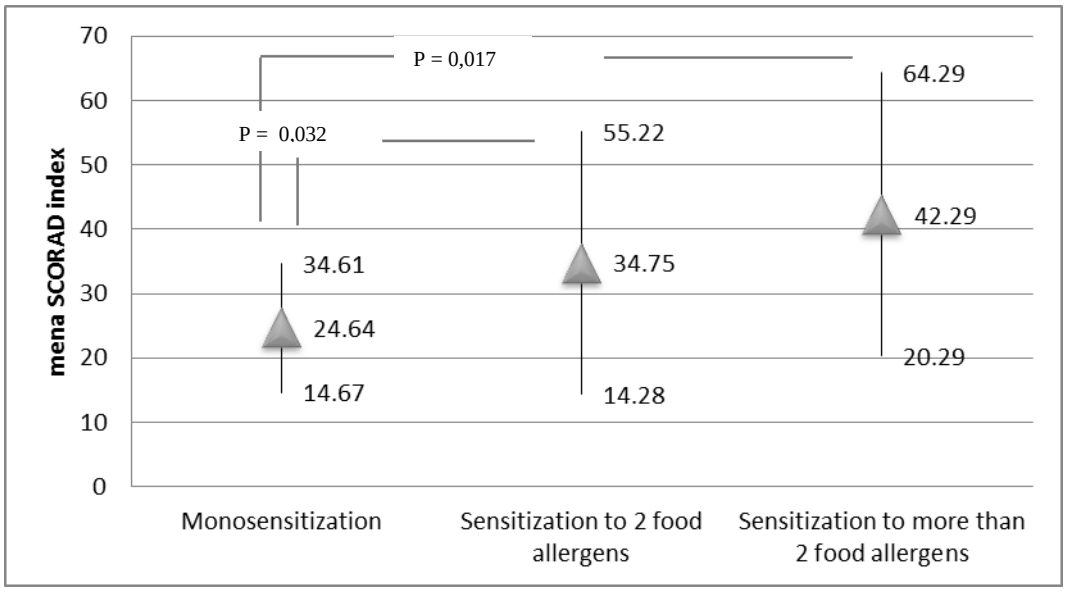


Figure 10 *Distribution of mean SCORAD index according the number of food sensitizations in children*

Atopic dermatitis was more severe in children sensitized to more than one food allergen comparing with children who were sensitized to one allergen only ($p > 0.05$). It

was also found that younger children (mean age 9.65±6.12) were sensitized to more than one food allergen significantly more often than older (mean age 12.8±6.66) (p=0.039).

In summary, in EuroPrevall Lithuanian birth cohort sensitization to food was detected in 88 (5.6%) children and they were eligible for 144DBPCFC with different food products. At the end of project, when children reached 2,5 years of age or during reevaluation after one year, just 4 from 53 (7.5%) children had symptoms after ingestion of cow's milk products, although sensitization was still found in 10 children. Sensitization to egg was still detected in 12 children, but 22% of children had symptoms to egg (11/51), to wheat – 4 were still sensitized, 2 from 12 (17%) – had symptoms, soy – 2 and 1 from 5 (20%) children respectively. At the end of the project 2 from 8 children had symptoms to peanuts (25%), and 3 from 5 – to fish (40%). Thus, at the end of the project 1.4% of cohort children still had allergic reactions after ingestion specific food.

3.3 PARENTAL AND CHILREN RISK FACTORS FOR DEVELOPMENT OF FOOD ALLERGY

In order to identify the risk factors for food allergy, an analysis of the inclusion, 12, and 24-month questionnaires was performed. Data of symptomatic, control and remaining cohort children were compared, so, it was compared data of 88 symptomatic, 176 control and 1470 non-sensitised children and their families.

Pregnancy and birth factors

Data analysis of birth factors that may play a role in food sensitization and comparison with the control and cohort children are presented in Tables 7 and 8.

Table 7 *Influence of birth factors on development of food sensitization*

Factors	**Children**			**p[1]**	**p[2]**
	Cohort N=1470 (%)	**Control N=176 (%)**	**Symptomatic N=88 (%)**		
Delivery	n=1224	n=138	n=65		
- first	577 (47.1)	78 (56.5)	33 (50.8)	0.568	0.443
- second	399 (32.6)	44 (31.9)	22 (33.8)	0.834	0.781
- third	157 (12.8)	15 (10.9)	6 (9.2)	0.396	0.721
- fourth and more	91 (7.4)	1 (0.7)	4 (6.2)	0.700	0.021*
- *data not shown*	*246 (17.3)*	*48 (27.0)*	*23 (26.0)*	-	-
Meconium staining during the birth	n=1446	n=171			
	144 (9.8)	18 (10.5)	10 (11.4)	0.626	0.813
- *data not shown*	*24 (1.7)*	*6 (3.4)*	*1(1.1)*	-	-
Form of delivery:	n=1468	n=174	n=88		
- normal, unassisted	1233 (84.0)	147 (84.5)	65 (73.9)	0.013*	0.040*
- forceps assisted	7 (0.5)	0 (0.0)	1 (1.1)	0.400	-
- *vacuum* extraction	7 (0.5)	1 (0.6)	1 (1.1)	0.400	0.622
- Caesarean section	221 (15.1)	26 (14.9)	21 (21)	0.027*	0.077
- planned	104 (7.1)	10 (5.7)	6 (6.8)	0.925	0.733
- emergency	117 (8.0)	16 (9.2)	15 (17)	0.003*	0.064
- *Data not shown*	*2 (0.1)*	*2 (1.2)*	-	-	-

P[1] – p value comparing symtomatic and cohort children
P[2] – p value comparing symptomatic and control children

Analysis of the collected data revealed that development of food sensitization were not related to the mother's number of births, comparing with the cohort of healthy children (p>0.05), but comparing cohort children group with the symptomatic children there was a significant difference between the mothers who gave birth to four or more times: 6.2% mothers of symptomatic children and only 0.7% mothers of control children gave birth four or more times (p=0.21). Data evaluation on risk revealed that for those mothers who gave birth more than once, the risk of food allergy in children was 1.2 times higher, compared with control children (OR 1.178 (95% CI: 0.64, 2.16)).

Healthy cohort and control group children was born significantly more often without complications (84.0% and 84.5%) compared with sensitised (73.9%) (p=0.013 and p=0.040, respectively). Birth during Caesaren section was identified as risk factor for a food sensitization (OR 1.926 (95% CI: 1.028, 3.610)). The difference between children groups evaluating vacuum or forceps assisted birth was not statistically significant (p> 0.05), but the birth rate during Caesarean section of sensitized newborns was significantly higher (p=0.027), particularly in an emergency Caesarean section operation (p=0.003), as compared with remaining cohort children. For those children who were born during planned Caesarean section the risk for food allergy was 1.2 times higher (OR 1.200 (95% CI: 0.421, 3.416), and those who were born during emergency Caesarean section - even 2.2 times higher, as compared with control group. Meconium staining in amniotic fluid was not identified as a risk factor for food sensitization (p=0.626).

Table 8 *Influence of newborn gender and number of family members on food allergy*

Factors	**Children**			**p^1**	**p^2**
	Cohort N=1470 (%)	**Control N=176 (%)**	**Symptomatic N=88 (%)**		
Gender	n=1470	n=176	n=88		
- Boy	750 (51.2)	82 (46.6)	47 (53.4)	0.663	0.338
- Girl	720 (48.8)	94 (53.4)	41 (46.6)	0.663	0.257
Number of siblings in the family	n=1470	n=176	n=88		
- None	785 (53.8)	97 (55.1)	53 (60.2)	0.238	0.490
- One	466 (31.7)	58 (33.0)	28 (31.8)	0.983	0.805
- Two or more	195 (13)	21 (11.9)	7 (8)	0.170	0.310
- *Data not shown*	24 (1.5)	-	-	-	-

P^1 – p value comparing symtomatic and cohort children
P^2 – p value comparing symptomatic and control children

Food sensitization was identified both for boys (53.4%) and girls (46.6%) in the same prevalence, and distribution by gender did not differ from all cohort children (p>0.05), but comparing symptomatic and control groups it was found that the risk for development of food sensitization was 1.4 times higher for boys (OR 1.381 (95% CI: 0.823, 2.318)). The presence of older brothers and sisters did not differ statistically significant between analysed groups of children (p>0.05), e.g., the number of children as family members had no impact on development of food sensitization. Mean body weight of healthy children was 3523.8±436g, symptomatic children – 3522.2±437g, and did not differ significantly (p=0.89).

Allergic diseases of family members as risk factors for food allergy

Comparison of data on maternal, parental and siblings' allergic diseases within symptomatic, control and non-sensitized cohort children is presented in Tables 9-11.

Table 9 *Influence of maternal allergic diseases on their childrens' food allergy*

Type of allergy	Cohort n=1470 (%)	Control n=176 (%)	Symptomatic n=88 (%)	p^1	p^2
	children mothers				
Mothers, who indicated any allergy	207 (14.1)	32 (18.,2)	15 (170)	0.440	0.820
Pollen-related rhinitis („hay fever")	62 (4.2)	11 (6.25)	6 (6.8)	0.246	0.859
Asthma	22 (1.5)	4 (2.3)	3 (3.4)	0.166	0.588
Atopic dermatitis	37 (2.5)	4 (2.3)	3 (3.4)	0.607	0.588
Allergy to house dust mites	31 (2.1)	5 (2.8)	6 (6.8)	0.005*	0.129
Alergija to animals	24 (1.6)	5 (2.8)	4 (4.5)	0.046*	0.472
Latex allergy	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Drug allergy	82 (5.6)	11 (6.25)	5 (5.7)	0.967	0.855
Allergy to bee or wasp stings	4 (0.3)	0 (0.0)	1 (1.1)	0.164	-
Adverse reaction to food	72 (4.9)	10 (5.7)	7 (8.0)	0.205	0.479
- do not know had they adverse reaction to food	1 (0.1)	-	1 (1.1)	-	-

P^1 – p value comparing symtomatic and cohort children
P^2 – p value comparing symptomatic and control children

Table 10 *Influence of paternal allergic diseases on their childrens' food allergy*

Type of allergy	Cohort n=1470 (%)	Control n=176 (%)	Symptomatic n=88 (%)	p^1	p^2
	Children fathers				
Fathers, who indicated any allergy	102 (6.9)	16 (9.1)	5 (5.7)	0.651	0.335
Pollen-related rhinitis („hay fever")	47 (3.2)	7 (4.0)	2 (2.3)	0.629	0.473
Asthma	12 (0.8)	2 (1.1)	2 (2.3)	0.160	0.477
Atopic dermatitis	4 (0.3)	1 (0.6)	1 (1.1)	0.164	0.616
Allergy to house dust mites	24 (1.6)	6 (3.4)	1 (1.1)	0.719	0.280
Alergy to animals	14 (1.0)	0 (0.0)	1 (1.1)	0.864	-
Latex allergy	2 (0.1)	0 (0.0)	0 (0.0)	-	-
Drug allergy	15 (1.0)	3 (1.7)	1 (1.1)	0.917	0.722
Allergy to bee or wasp stings	7 (0.5)	0 (0.0)	0 (0.0)	-	-
Adverse reaction to food	14 (1.0)	4 (2.3)	1 (1.1)	0.864	0.524
- do not know had they adverse reaction to food	6 (0.4)	-	(0.0)	-	-

P^1 – p value comparing symtomatic and cohort children
P^2 – p value comparing symptomatic and control children

Table 11 *Influence of siblings' allergic diseases on childrens' food allergy*

Type of allergy	Cohort n=897 (%)	Control n=91 (%)	Symptomatic n=44 (%)	p^1	p^2
	Children siblings				
Siblings, who indicated any allergy	142 (15.8)	17 (18.7)	11 (25.0)	0.108	0.257
Pollen-related rhinitis („hay fever")	24 (2.7)	2 (2.2)	2 (4.5)	0.460	0.452
Asthma	20 (2.2)	2 (2.2)	0 (0.0)	-	-
Atopic dermatitis	92 (10.3)	13 (14.3)	5 (11.4)	0.814	0.641
Allergy to house dust mites	22 (2.5)	1 (1.1)	0 (0.0)	-	-
Alergy to animals	11 (1.2)	1 (1.1)	0 (0.0)	-	-
Latex allergy	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Drug allergy	12 (1.3)	2 (2.2)	2 (4.5)	0.087	0.452
Allergy to bee or wasp stings	3 (0.3)	0 (0.0)	0 (0.0)	-	-
Adverse reaction to food	87 (9.7)	12 (13.2)	7 (8.0)	0.180	0.671
- *do not know had they adverse reaction to food*	4 (0.4)	-	0 (0.0)	-	-

P^1 – p value comparing symtomatic and cohort children
P^2 – p value comparing symptomatic and control children

As shown in the tables, parental and siblings' allergic diseases (asthma, allergic rhinitis, atopic dermatitis, etc.) had no impact on food sensitization in cohort children, whereas in children whose mothers were allergic to house dust mites and animals more often were sensitized to food (6.8% and 4.5%, respectively) comparing with cohort children (2.1% and 1.6%) (p=0.005 and p=0.046). It was also detected that children whose mothers were allergic to house dust mites or animals had 2,1 and 1,2 times higher risk, respectively, to become sensitized to food ((OR 2.125 (95% CI: 0.598, 7.550) and OR 1.229 (95% CI: 0.287, 5.266)). Risk assessment data showed that the risk to become sensitized having allergic mothers for symptomatic and control children were: OR 0.988 (95% CI: 0.501, 1.948), having allergic fathers - OR 0.617 (95% CI: 0.218, 1.74), and siblings - OR 1.451 (95% CI: 0.613, 3.434).

Relationship between medicinal products used by mothers and newborns and food allergy

Differences in mothers' antibiotics use during pregnancy, delivery and breasfeeding, as well as use of antibiotics in newborns are shown in Figure 11.

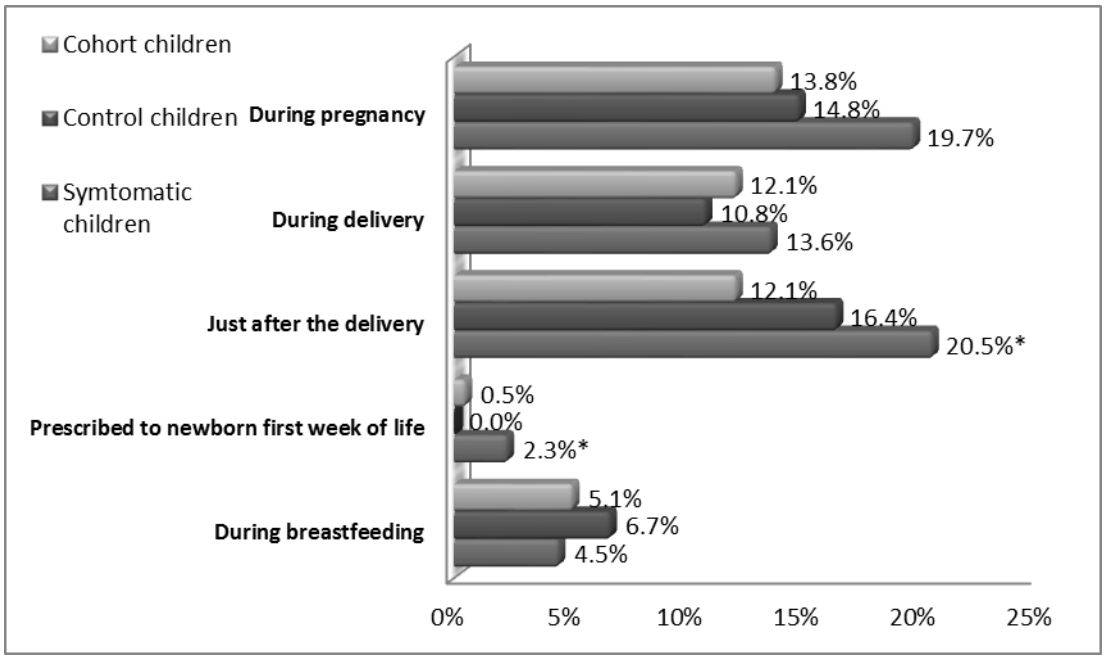


Figure 11 *Impact of antibiotics use to food sensitization*

During pregnancy 17 (19.7%) mothers of symptomatic children used antibiotics, in non-sensitized cohort children group - 203 (13.8%) mothers, in control children group - 26 (14.8%), thus, there was no statistically significant difference. Antibiotics used during delivery had also no significant impact on food sensitization – the rate of antibiotics use in mothers of all cohort, control and symptomatic children was similar (134 (12.1%), 19 (10.8%) and 12 (13.6%), respectively). However, use of antibiotics of mothers just after delivery was significantly more often in symptomatics - 18 (20.5%) comparing to controls - 134 (12.1%) (p=0.022). Antibiotics prescribed to newborns during first week of life could also had had impact on food sensitization – the difference in data of cohort (7 (0.5%)) and symptomatic children (2 (2.3%)) is statistically significant (p=0.032). Use of antibiotics during breastfeeding was not a risk factor for food sensitization.

Table 12 *Influence of medicines taken during pregnancy and children food allergy*

Medicines used during pregnancy	**Cohort N=1470 (%)**	**Control N=176 (%)**	**Symptomatic N=88 (%)**	**p^1**	**p^2**
- aspirin or paracetamol	259 (17.6)	33 (18.6)	17 (19.3)	0.685	0.912
- other anti-inflamatory	84 (5.7)	12 (6.8)	3 (3.4)	0.360	0.260
- for reflux disease	98 (5.7)	14 (8.0)	7 (8.0)	0.640	1.000
- for diabetes mellitus	2 (0.1)	0 (0.0)	0 (0.0)	-	-
- for asthma	13 (0.9)	1 (0.6)	2 (2.3)	0.195	0.219
- for high blood pressure	73 (5.0)	5 (2.8)	7 (8.0)	0.217	0.061
- folic acid	755 (51.4)	100 (56.8)	52 (59.1)	0.159	0.725
- multivitamins	1168 (79.5)	145 (82.4)	72 (81.8)	0.593	0.910
- vitamin D	61 (4.1)	9 (5.1)	4 (4.5)	0.857	0.841
- fish oil capsules	87 (5.9)	13 (7.4)	6 (6.8)	0.729	0.866

P^1 – p value comparing symtomatic and cohort children
P^2 – p value comparing symptomatic and control children

Performed data analysis about the medications taken by pregnant mother revealed that use of aspirin or paracetamol (19.3% and 17.6%), other anti-inflamatory medicines (3.4% and 5.7%), folic acid (51.4% and 59.1%), vitamin D (4.1% and 4.5%) and other medicines did not significantly differ between mothers of cohort and symptomatic children. The difference between symptomatic and control childrens' mothers use of different medicines during pregnancy was not significant too. Use of vitamin D slightly decreased risk for development of food allergy (OR 0,884 (95% CI: 0,264; 2,953) comparing with symptomatic and control children groups. Use of fish oil during pregnancy also did not have statistically significant impact on food sensitization (OR 0.903 (95% CI: 0.329, 2.479)).

Impact of environmental factors to food sensitization

In order to ascertain whether the environment influences the development of food allergy in young children, the data about cohort families living area, in-house or farm animals and smoking was assessed (Table 13).

Table 13 *Impact of environmental factors on food allergy*

Factor	Children			p^1	p^2
	Cohort n=1470 (%)	**Control n=176 (%)**	**Symptomatic n=88 (%)**		
Living area					
- urban	1259 (85.6)	162 (92.0)	76 (86.4)	0.852	0.145
- rural (population <5000):	200 (13.6)	12 (6.8)	11 (12.5)	0.629	0.124
- rural, not farm	135 (9.2)	8 (4.5)	6 (6.8)	0.453	0.438
- rural, farm	65 (4.4)	4 (2.3)	5 (5.7)	0.580	0.151
- *not indicated*	*11 (0.7)*	*2 (1.2)*	*1 (1.1)*	-	-
- live on the main road	311 (21.2)	35 (19.9)	18 (20.5)	0.876	0.914
Animals or pets in families:	648 (44.1)	74 (42.0)	28 (31.8)	0.024*	0.110
- cat	330 (22.4)	40 (22.7)	13 (14.8)	0.092	0.130
- dogs	321 (21.8)	26 (14.8)	15 (17.0)	0.289	0.631
- other animals (birds, fish rodents, insects)	208 (14.1)	19 (10.8)	6 (6.8)	0.053	0.299
- farm animals and birds	69 (4.7)	3 (1.7)	2 (2.3)	0.290	0.750
- *Not indicated*	*14 (0.1)*	-	*2 (2.3)*	*0.233*	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Type of living area (town, village) had not been identified as a risk factor for food allergy: 85.6% (1259/1470) of nonsensitized, 92% of controls and 86.4% of symptomatic children lived in urban areas. In rural areas lived 13.6%, 12% and 12.5% children, respectively. But it was detected that a risk to become allergic was 2 times higher to those children, who lived in urban areas comparing to those, who lived in villages (OR 2.007 (95% CI: 0.847, 4.757)). Data analysis about pets and animals revealed that pets at home had protective role for food sensitization: 44.1% of cohort children and 31.8% of symptomatic children kept at home pets of any kind and the

difference was statistically significant (p=0.002) - OR 0.700 (CI: 0.408, 1.201). It was found also that especially cats kept at home decreases risk for sensitization - OR 0.605 (95% CI: 0.304, 1.204), whereas dogs kept at home the risk increased 1.2 times (OR 1.220 (CI: 0.608, 2.447)).

Table 14 *Impact of smoking on food sensitisation*

Factor	Children			p^1	p^2
	Cohort n=1470 (%)	**Control n=176 (%)**	**Symptomatic n=88 (%)**		
Mother smokes	118 (8.0)	8 (5.1)	8 (9.1)	0.722	0.146
Mother smoked, but stopped before pregnancy	480 (32.7)	63 (35.8)	26 (29.6)	0.545	0.312
During pregnancy:					
- Quit smoking when realized that is pregnant	318 (21.6)	39 (22.2)	18 (20.5)	0.794	0.751
- Reduced number of cigarettes	100 (6.8)	12 (6.8)	7 (8.0)	0.678	0.736
- Smokes at the same level	7 (0.5)	0 (0.0)	0 (0.0)	-	-
- Stopped smoking when was planning pregnancy	148 (10.1)	18 (10.2)	6 (6.8)	0.321	0.365
Anyone smokes at home	631 (42.9)	69 (39.2)	37 (42.0)	0.871	0.657
Exposed to passive smoking during pregnancy	124 (8.4)	9 (5.1)	9 (10.2)	0.559	0.121
Have never smoked	870 (59.2)	104 (59.1)	54 (61.4)	0.686	0.723

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Maternal smoking during pregnancy and exposure to passive tabacco smike had no significant impact on food sensitization (p>0.05), but according to the odds ratio it was found that children of smoking mothers had 2 times higher risk to become allergic to food (OR 2.156 (95% CI: 0.780, 5.958)). Passive smoking during pregnancy revealed the same risk: OR 2.171 (95% CI: 0.829, 5.688) (see Table 21).

Maternal and newborn nutrition as food allergy risk factor

Data about additional to breast milk nourishment during the first week of life and its impact on food sensitization are provided in Tables 15 and 16.

Table 15 *Data of symptomatic and cohort children about additional nourishment during first week of life*

Additional nourishment during first week of life	Cohort children n=1470			Symptomatic children n=88			p
	Given, n (%)	Not given, n (%)	Mother does not know, n (%)	Given, n (%)	Not given, n (%)	Mother does not know, n (%)	
Total:	449 (30.5)	880 (60.0)	141 (9.6)	37 (42.0)	37 (42.0)	14 (16.0)	0.024*
Sugar water	224 (15.2)	32 (2.2)	1214 (82.6)	19 (21.6)	5 (5.7)	64 (72.7)	0.111
Cows milk formula	233 (15.6)	19 (1.3)	1218 (82.9)	17 (19.3)	1 (1.1)	70 (80.0)	0.389
Hypoallergenic cows milk formula	2 (0.1)	46 (3.2)	1422 (96.7)	1 (1.1)	4 (4.5)	84 (95.5)	0.038*
Soy formula	0 (0.0)	43 (3.1)	1427 (96.9)	0 (0.0)	5 (5.7)	83 (94.3)	-

Table 16 *Data of symptomatic and control children about additional nourishment during first week of life*

Additional nourishment during first week of life	Control children n=176			Symptomatic children n=88			p
	Given, n (%)	Not given, n (%)	Mother does not know, n (%)	Gived, n (%)	Not given, n (%)	Mother does not know,n (%)	
Total:	54 (30.7)	93 (52.8)	29 (16.5)	37 (42.0)	37 (42.0)	14 (16.0)	0.100
Sugar water	29 (16.5)	4 (2.3)	143 (81.2)	19 (21.6)	5 (5.7)	64 (72.7)	0.311
Cows milk formula	23 (13.1)	3 (1.7)	150 (85.2)	17 (19.3)	1 (1.1)	70 (80.0)	0.183
Hypoallergenic cows milk formula	1 (0.6)	7 (4.0)	168 (95.4)	1 (1.1)	4 (4.5)	84 (95.5)	0.616
Soy formula	0 (0.0)	9 (5.1)	167 (94.9)	0 (0.0)	5 (5.7)	83 (94.3)	-

Data analysis revealed that children, who ate additional than breastmilk food during first week of their life was at higher risk to develop food allergy: 30.5% healthy cohort children and 42% symptomatic children were additionally feeded with sugar water or CM formula (normal or hypoallergenic) (p=0.024). Statistically significant difference between control and symptomatic children was not found, but evaluation of OR revealed that these children who were additionally feeded during first week of their life had 1,2 times higher risk to develop food allergy (OR 1.242 (95% CI: 0.630, 2,447)).

In order to identify impact of mothers' diets on development of food allergies, an analysis of questions related to the mother’s eating habits during pregnancy and breasfeeding was performed. The results are provided in Table 17.

Table 17 *Impact of mother's cow's milk products eating on development of food allergy*

Cow's milk	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=53		
During pregnancy:					
- did not eat	10 (0.7)	1 (0.6)	0 (0.0)	-	-
- ate an increased amount	566 (38.5)	92 (52.3)	20 (37.7)	0.910	0.065
- ate the same amount	708 (48.2)	66 (37.5)	28 (52.8)	0.504	0.048*
- limited intake /avoided	64 (4.4)	4 (2.3)	2 (3.8)	0.839	0.550
- *no data about eating habits*	*122 (8.2)*	*13 (7.4)*	*3 (5.7)*	-	-
During breastfeeding:					
- did not eat	79 (5.4)	16 (9.1)	4 (7.5)	0.494	0.727
- ate an increased amount	32 (2.2)	1 (0.6)	0 (0.0)	-	-
- ate the same amount	292 (19.9)	21 (11.9)	8 (15.1)	0.391	0.545
- limited intake /avoided	645 (43.8)	107 (60.8)	29 (54.8)	0.119	0.430
- *no data about eating habits*	*422 (28.7)*	*31 (17.6)*	*12 (22.6)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Sensitized, non-sensitized cohort and control children mothers diet during pregnancy data analysis revealed that both maternal avoidance of drinking milk and eating dairy products during pregnancy and eating of these products in big quantities, according to the mother opinion, had no significant impact on sensitizing to milk ($p>0.05$). The analysis of maternal diet during breastfeeding found that both maternal avoidance of milk products during lactation, as well as the normal use of these products had also no significant impact on the occurrence of sensitization ($p>0.05$). No mothers of the child with sensitization to cow's milk, were eaten very much cow's milk products during breastfeeding.

Table 18 *Impact of mother's eggs eating on development of food allergy*

Egg	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=51		
During pregnancy:					
- did not eat	44 (3,0)	6 (3,4)	4 (7,8)	0,052	0,176
- ate an increased amount	93 (6,3)	12 (6,8)	1 (2,0)	0,203	0,190
- ate the same amount	1071 (73,0)	133 (75,6)	40 (78,4)	0,378	0,673
- limited intake /avoided	123 (8,4)	13 (7,4)	5 (9,8)	0,716	0,574
- *no data about eating habits*	*139 (9,3)*	*12 (6,8)*	*1 (2,0)*	-	-
During breastfeeding:					
- did not eat	104 (7,1)	14 (8,0)	1 (2,0)	0,157	0,131
- ate an increased amount	8 (0,5)	0 (0,0)	0 (0,0)	-	-
- ate the same amount	222 (15,1)	17 (9,7)	5 (9,8)	0,297	0,976
- limited intake /avoided	701 (47,7)	113 (64,2)	28 (54,9)	0,311	0,229
- *no data about eating habits*	*437 (29,6)*	*32 (18,2)*	*17 (33,3)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Evaluation of the data presented in Table 18 revealed that mother's egg products eating during pregnancy and breastfeeding (both in big amounts and avoiding and completely absent) had no significant impact on development of sensitization to the egg in their child.

Table 19 *Impact of mother's wheat eating on development of food allergy*

Wheat	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=12		
During pregnancy:					
- did not eat	61 (4.2)	6 (3.4)	1 (8.3)	0.471	0.385
- ate an increased amount	311 (21.2)	41 (23.3)	3 (25.0)	0.746	0.893
- ate the same amount	944 (64.3)	116 (65.9)	8 (66.7)	0.860	0.957
- limited intake /avoided	40 (2.7)	3 (1.7)	0 (0.0)	-	-
- *no data about eating habits*	*114 (7.6)*	*10 (5.7)*	*0 (0.0)*	-	-
During breastfeeding:					
- did not eat	3 (0.2)	1 (0.6)	0 (0.0)	-	-
- ate an increased amount	2 (0.1)	51 (29.0)	0 (0.0)	-	-
- ate the same amount	1025 (69.8)	90 (51.1)	8 (66.7)	0.818	0.299
- limited intake /avoided	8 (0.5)	2 (1.2)	0 (0.0)	-	-
- *no data about eating habits*	*432 (29.4)*	*32 (18.2)*	*4 (33.3)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Table 20 *Impact of mother's soy products eating on development of food allergy*

Soy	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=5		
During pregnancy:					
- did not eat	963 (65.5)	131 (74.4)	2 (40.0)	0.231	0.087
- ate an increased amount	18 (1.2)	2 (1.2)	1 (20.0)	0.000*	0.001*
- ate the same amount	372 (25.3)	35 (19.9)	1 (20.0)	0.785	0.995
- limited intake /avoided	103 (7.0)	8 (4.5)	1 (20.0)	0.257	0.119
- *no data about eating habits*	*14 (1.0)*	*0 (0.0)*	*0 (0.0)*	-	-
During breastfeeding:					
- did not eat	740 (50.3)	101 (57.4)	3 (60.0)	0.666	0.907
- ate an increased amount	0 (0.0)	0 (0.0)	0 (0.0)	-	-
- ate the same amount	158 (10.8)	12 (6.8)	2 (40.0)	0.036*	0.007*
- limited intake /avoided	159 (10.8)	34 (19.3)	0 (0.0)	-	-
- *no data about eating habits*	*413 (28.1)*	*29 (16.5)*	*0 (0.0)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Table 21 *Impact of mother's peanuts eating on development of food allergy*

Peanuts	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=8		
During pregnancy:					
- did not eat	398 (27.1)	54 (30.7)	4 (50.0)	0.146	0.252
- ate an increased amount	104 (7.1)	10 (5.7)	2 (25.0)	0.050*	0.032*
- ate the same amount	725 (49.4)	85 (48.3)	2 (25.0)	0.170	0.198
- limited intake /avoided	154 (10.4)	19 (10.8)	0 (0.0)	-	-
- *no data about eating habits*	*89 (6.0)*	*8 (4.5)*	*0 (0.0)*	-	-
During breastfeeding:					
- did not eat	486 (33.1)	58 (33.0)	0 (0.0)	-	-
- ate an increased amount	10 (0.7)	1 (0.6)	0 (0.0)	-	-
- ate the same amount	138 (9.4)	15 (8.5)	1 (12.5)	0.764	0.697
- limited intake /avoided	405 (27.6)	71 (40.3)	4 (50.0)	0.157	0.587
- *no data about eating habits*	*431 (29.2)*	*31 (17.6)*	*3 (37.5)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Table 22 *Impact of mother's fish products eating on development of food sensitisation*

Fish	Cohort, n (%)	Control, n (%)	Symptomatic, n (%)	p^1	p^2
	n=1470	n=176	n=5		
During pregnancy:					
- did not eat	73 (5.0)	9 (5.1)	0 (0.0)	-	-
- ate an increased amount	208 (14.1)	26 (14.8)	0 (0.0)	-	-
- ate the same amount	999 (68.0)	117 (66.5)	5 (100.0)	0.125	0.117
- limited intake /avoided	81 (5.5)	12 (6.8)	0 (0.0)	-	-
- *no data about eating habits*	*109 (7.4)*	*12 (6.8)*	*0 (0.0)*	-	-
During breastfeeding:					
- did not eat	6 (0.4)	2 (1.2)	0 (0.0)	-	-
- ate an increased amount	342 (23.3)	62 (35.2)	1 (20.0)	0.863	0.482
- ate the same amount	587 (40.0)	64 (36.4)	2 (40.0)	0.998	0.868
- limited intake /avoided	100 (6.8)	15 (8.5)	1 (20.0)	0.244	0.374
- *no data about eating habits*	*435 (29.5)*	*33 (18.8)*	*1 (20.0)*	-	-

P^1 – p value when comparing symptomatic and cohort children groups
P^2 – p value when comparing symptomatic and control children groups

Evaluation of mothers diet during pregnancy and breastfeeding revealed that use of wheat and fish products in different quantities had no significant impact on children's sensitizing to the relevant food allergens - data about eating of these products during pregnancy and breastfeeding was not significantly different ($p>0.05$).

Evaluation of soy products eating habits revealed that the children of mothers who ate during pregnancy a lot of soy products were significantly more often diagnosed sensitization to soy ($p=0.001$), compared to both the healthy cohort children and control children. Analysis of the data about peanut consumption has also shown that mothers eating peanuts in big quantities during pregnancy had a significant impact on development of sensitization to the nuts in their children, comparing with both healthy cohort children ($p=0.05$) and control children ($p=0.032$).

3.4 EVALUATION OF DIFFERENT FOOD ALLERGY DIAGNOSTIC METHODS. RECOMMENDATIONS FOR FOOD ALLERGY DIAGNOSING

During the project 374 skin prick tests in symptomatic, control and other cohort children who came to the study center for evaluation possible food allergy were performed. 234 symptomatic and control children's blood serum samples were collected and tested for specific IgE during the project. Results of these diagnostic tests in symptomatic children are provided in Table 23.

Table 23 *Tests results in symptomatic childrens*

Allergen	Symptomatic children, n = 88					Confirmed sensitization, n
	Only positive SPT, n (%)	Only positive sIgE		Positive both SPT and sIgE n (%)	Only symptoms	
		n (%)	Parents refused n (%)			
Cow's milk	16 (30.1)	25 (67.5)	16 (30.8)	6 (11.3)	6 (11.3)	53
Egg	22 (43.1)	6 (17.1)	16 (31.2)	15 (29.4)	8 (15.6)	51
Wheat	4 (33.3)	4 (50)	4 (33.3)	-	4 (33.3)	12
Peanuts	-	6 (75)	-	2 (25)	-	8
Soya	4 (80)	1 (20)	2 (40)	-	-	5
Fish	1 (20)	1 (20)	1 (20)	2 (40)	1 (20)	5
Carrots	4 (100)	-	-	-	-	4
Other food products[1]	6 (100)	-	-	-	-	6
TOTAL	57 (39.6)	43 (29.9)	39 (27)	25 (17.4)	19 (13.2)	144

[1] - potato, tomato, yeast, beef, hazelnuts, orange.

Sensitization to cow's milk was identified in 53 children, for 16 (30%) of them just positive SPTs to milk were detected. Sixteen children's parents refused for sIgE determination in the children's serum, thus sIgE was determined in 25 of the 37 (68%) children. According to the both positive SPT and positive blood serum sIgE sensitization to cow's milk was identified only in 6 children. Sensitization to cow's milk in six (11.3%) children was identified only due to immediate or repretitive symptoms after ingestion of milk products.

Sensitization to egg was identified in 51 children, for 22 (43%) of them just positive SPTs to egg were detected. 16 children's parents refused for sIgE determination in the children's serum, thus sIgE was determined in 6 (17.1%) children. According to the both positive SPT and positive blood serum sIgE sensitization to egg was identified only in 15 children. Sensitization to cow's milk in eight children was identified only due to immediate or repretitive symptoms after ingestion of egg products, even if the SPT and sIgE tests were negative.

Sensitisation to wheat was confirmed only by positive SPT in 4 children, and by increased sIgE level in blood serum – in 4 children too (blood sample for testing was not collected in 4 childrens). Evaluation of immediate or repretitive symptoms when eating wheat products revealed sensitization in four children. There was no childrens with sensitization to wheat confirmed by both SPT and sIgE. Sensitization to soy was

confirmed by positive sIgE only to one from five children (two refused, two - negative), in four - only by positive SPT (one - negative). Sensitization to peanuts was confirmed by positive sIgE only in 6 children, by both SPT and sIgE testing – 2, and by SPT results only – sensitilization was not identified. Only positive SPT to fish was detected in one child, specific IgE against fish – in one child, sensitization was confirmed by both positive SPT and sIgE testing in two children, and in one child the symptoms occurred when eating fish, but SPT and sIgE testing were negative. Sensitization to the other food allergens was identified by clinical symptoms and positive SPT.

Food allergy confirmed by oral challenges

In order to confirm food allergy a Double Blind Placebo Controlled Food Challenges (DBPCFC) were performed. Detailed information regarding performed oral challenges is provided in Figure 12.

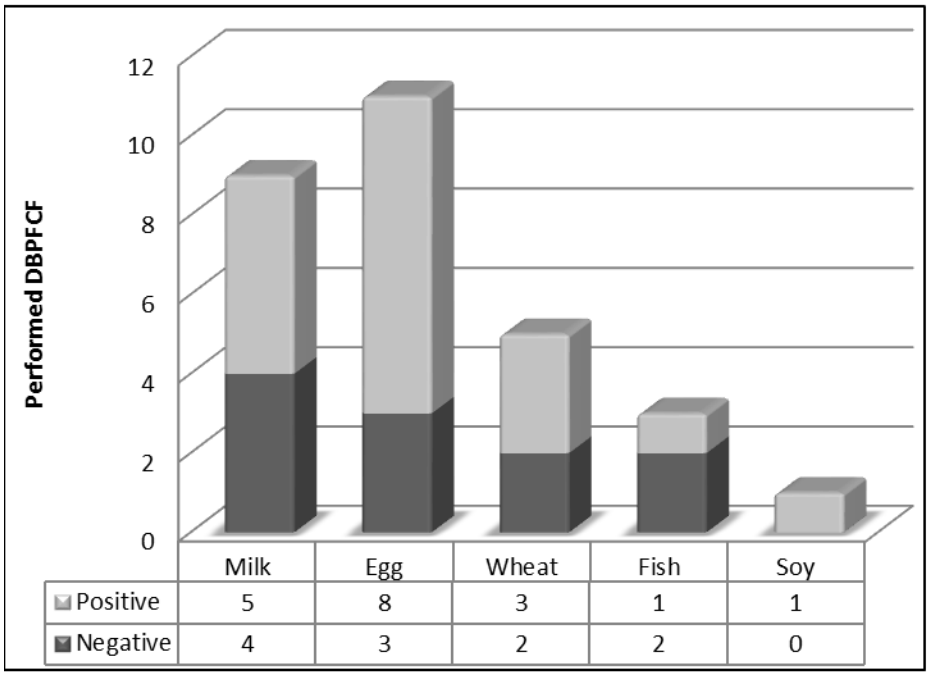


Figure 12 *DBPCFC performed during the project*

During the project 29 oral challenges with a 5 food products were performed in Lithuania, including 18 (62%) positive. 9 challenges were carried out with milk, 11 – with egg, 5 – with wheat, 1 – with soya, and 3 – with fish. For one child sensitized to milk, and for one child sensitized to egg, oral challenges were carried out twice with interval more than one year in order to assess changes in sensitization to related food allergens. Thus, accordind to performed oral food challenges, food allergy was confirmed in 18% (16/88) symptomatic children, which accounted 1.02% of total cohort children. Prevalence of suspected and confirmed food allergy in the Lithuanian birth cohort is presented in Table 24.

Table 24 *Probable and confirmed food allergy in the Lithuanian birth cohort*

Food allergen	Probable allergy to food allergens		Food allergy, confirmed by DBPCFC	
	N=1558	%	N=1558	%
Milk	53	3.40	5	0.32
Egg	51	3.27	8	0.55
Wheat	12	0.77	3	0.19
Peanuts	8	0.55	-	-
Soya	5	0.32	1	0.06
Fish	5	0.32	1	0.06
Carrot	4	0.25	-	-
Potato	1	0.06	-	-
Tomato	1	0.06	-	-
Yeast	1	0.06	-	-
Beef	1	0.06	-	-
Hazelnuts	1	0.06	-	-
Orange	1	0.06	-	-

Results of performed diagnostic tests (SPT and sIgE) and DBPCFC using logistic regression model an attempt was made to determine the threshold values at which the probability that allergic reactions after ingestion of the particular food product will occur is 95% or 99% (Table 25).

Table 25 *Correlations between performed tests results and probability of the allergic reactions*

Specific sIgE, IU/ml	SPT diameter, mm	Probability of the allergic reaction (%)
22.30	0.00	100
22.30	10.00	100
12.00	3.00	100
8.19	2.00	99,6
0.15	9.50	98,6
2.14	7.00	98,5
1.93	6.00	97
1.41	6.00	95,8
1.49	5.50	94,8
0.39	5.00	86,6
0.73	4.50	86
0.00	4.50	78,9
3.33	0.00	73,8
0.00	3.00	61,6
0.00	2.50	54,7
1.54	0.00	45,5
1.11	0.00	38,4
1.08	0.00	38
0.51	0.00	29,3
0.04	0.00	23,2

Assessment of the results provided in Table 25 is revealed that when a sIgE levels are ≥1.49 IU/ml and SPT diameter is ≥ 5.5 mm, then probability of the allergic reactions occurrence is 95%, and when sIgE levels are ≥ 2.14 IU/ml and SPT diameter is ≥ 7 mm, then probability of the allergic reactions occurrence is 99%.

On the basis of the literature review and tests results obtained during the project recommendations for food allergy diagnosis were prepared: „ *Guidelines for evaluation of sensitized to food children who are known have never used a specific food product*“ (Figure 13), „*Guidelines for evaluation of exclusively breastfed infants with atopic dermatitis*“ (Figure 14), and „*Guidelines for evaluation of children who probably experienced food related symptoms*“ (Figure 15).

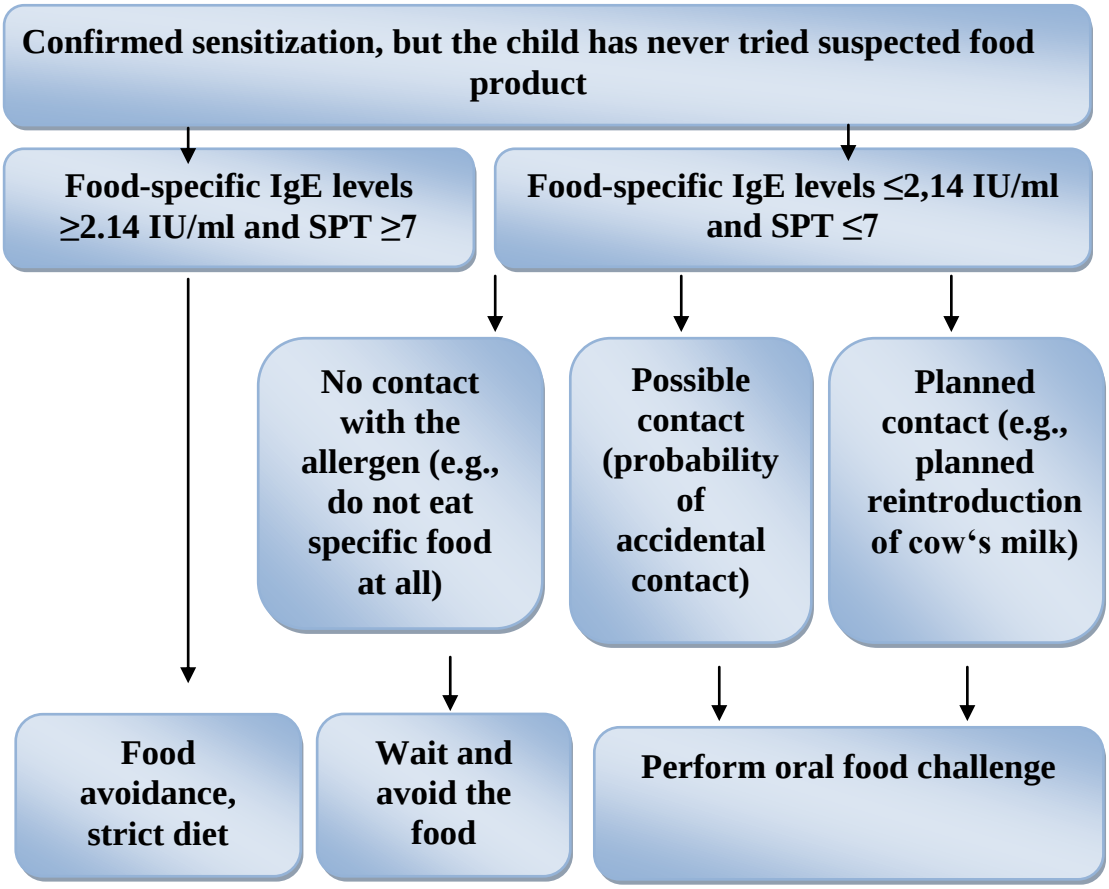


Figure 13 *Guidelines for evaluation of sensitized to food children who are known have never used a specific food product*

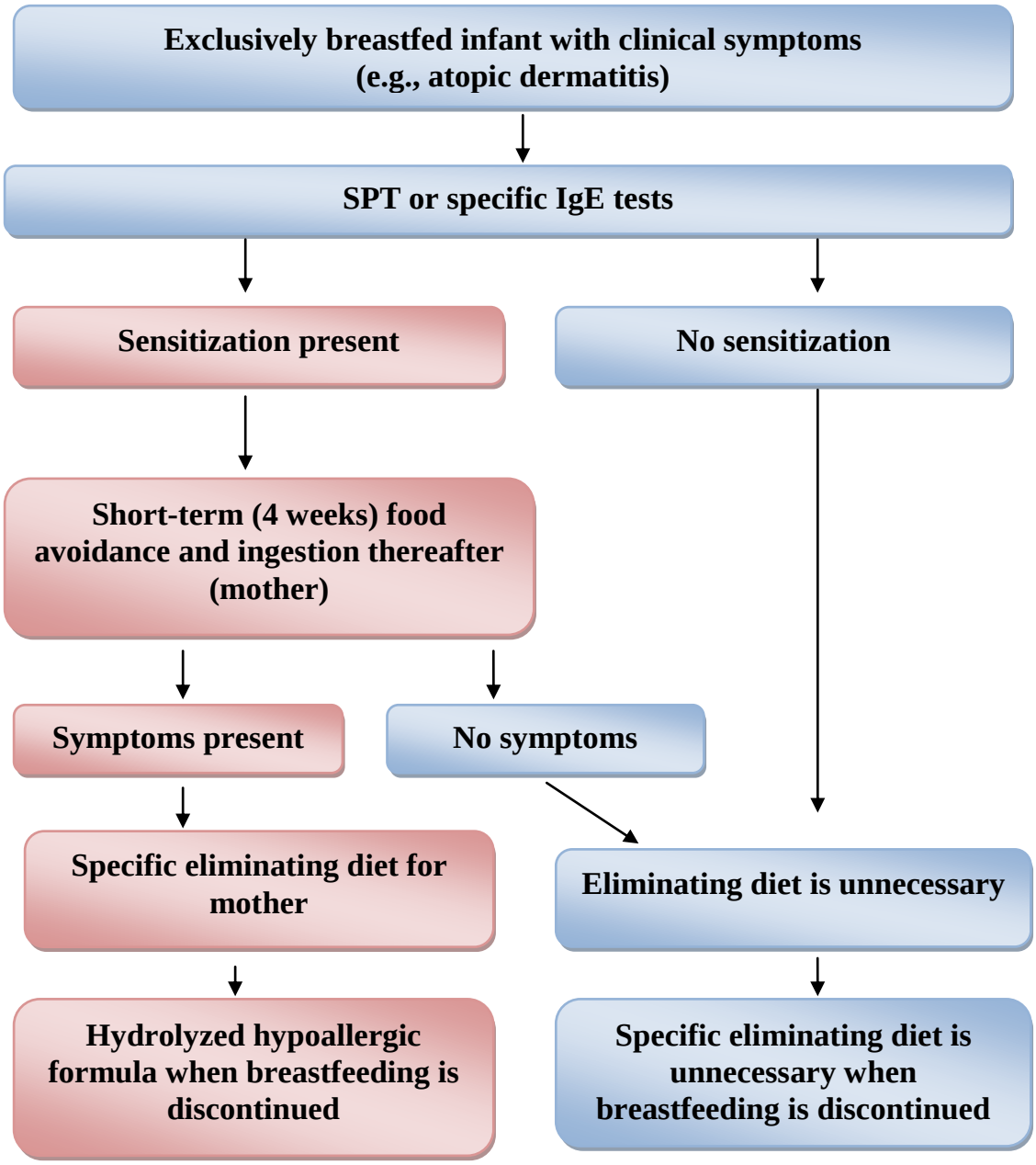


Figure 14 *Guidelines for evaluation of exclusively breastfed children with atopic dermatitis*

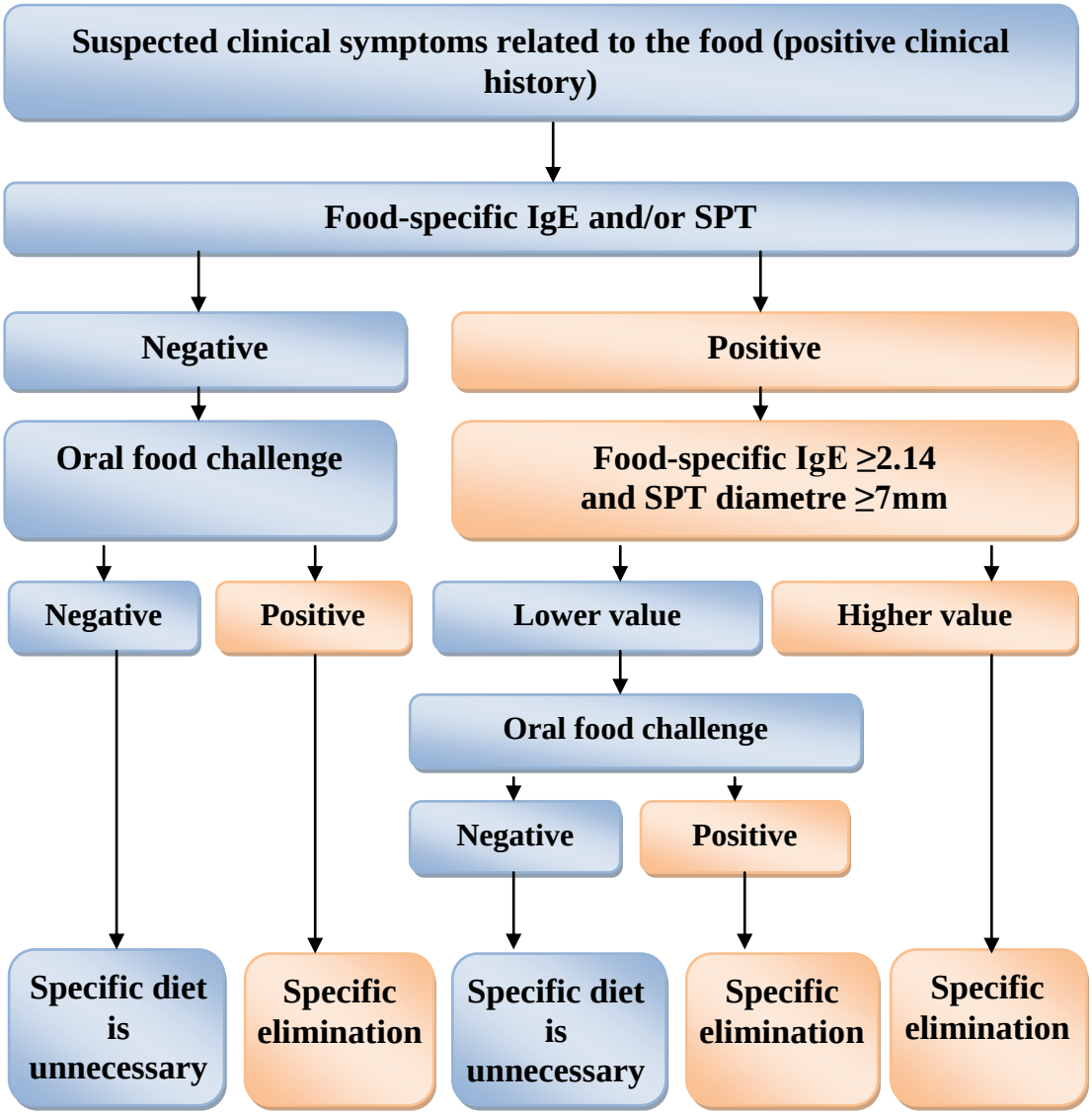


Figure 15 *Guidelines for evaluation of children who probably experienced food related symptoms*

4. CONCLUSIONS

1. Based on collected data from questionnaires Lithuanian birth cohort, consisting of 1558 newborns and formed on the basis EuroPrevall project specifically for IgE-related food allergy has been described.
2. Prevalence of parental-reported food allergy in EuroPrevall Lithuanian birth cohort was 17% and prevalence of probable food allergy was 5.6% among children under 2.5 years of age. Most common food allergens to which children with food related symptoms from Lithuanian birth cohort have been sensitized were milk and egg. Sensitization to wheat, peanuts, soybeans and other food products was diagnosed less frequently.
3. Relationship between food sensitization and atopic dermatitis was determined - 86% of children sensitized to food had atopic dermatitis. It was found that atopic dermatitis in children younger was significantly more severe than in older children. Also in children, sensitized to more than one allergen, atopic dermatitis was more severe than in sensitized to one food allergen.
4. At the end of the project, when children turned 2.5 years of age, food related allergic reactions still occurred just in 25% of children with pre-existing food sensitization.
5. Birth during Caesarean section, maternal use of antibiotics just after the birth, maternal allergic diseases, newborn additional feeding during the first week of life was related with development of food sensitization.
6. Infant's gender, number of siblings in the family, parental and siblings' allergic diseases and living area had no significant impact on food sensitization.
7. Maternal active and passive smoking during pregnancy had 2 times higher risk for development of food allergy in their children.
8. Maternal nutrition during pregnancy and breastfeeding had no significant impact on development of food allergy to their children, only use of peanuts and soy products in elevated amounts during pregnancy possibly influenced development of allergy to related food products.
9. Obtained data allowed to evaluate a variety of used during the project food allergy diagnostic methods (skin prick tests, detection of specific IgE, food challenge tests) in the cohort.
10. It was determined ranges of food allergy diagnostic tests (specific IgE and skin prick test) under which probability of occurrence of allergic reactions is more than 95% and, therefore, it reduces the need to carry out food challenge tests to confirm the diagnosis of food allergy.
11. Based on project results new algorithms and recommendations for food allergy diagnosis have been created and introduced.

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Butienė I., Dubakienė R. Dažniausiai alergiją maistui sukeliantys produktai ir įsijautrinimo jiems kaita per pirmuosius dvejus su puse gyvenimo metų. Vaikų pulmonologija ir alergologija, 2013: XVI(2) 5309–5320.

Oral presentations

Butiene, I., Rudzeviciene, O., & Dubakiene, R. (2011). Early sensitisation to food allergents in Lithuanian birth cohort. *Clinical and Translational Allergy*, *1*(Suppl 1), O4. doi:10.1186/2045-7022-1-S1-O4, at Food Allergy Anaphylaxis Meeting (FAAM), February 17-19, 2011, Venice, Italy.

Butiene, I, Dubakiene, R. „The multinational EuroPrevall project: data from Lithuanian birth cohort“ at Ist Baltic Paediatric Congress, May 19-21, 2011, Vilnius, Lithuania

Butiene, I, Dubakiene, R. „Prevalence of sensitization to cow‘s milk in EuroPrevall Lithuanian birth cohort“ at Food Allergy Anaphylaxis Meeting (FAAM), February 7-9, 2013, Nice, France.

Butiene, I, Dubakiene, R. „Influence of parental risk factors on the development of early sensitization to food“ at IInd Baltic Paediatric Congress, May 31- June 01, 2013, Piarnu, Estonia.

Poster presentations

Butiene, I, Rudzeviciene, O, Dubakiene, R. “Prevalence of food sensitization in young children from EuroPrevall Lithuanian birth cohort” at EAACI annual congress June 11-15, 2011, Istanbul, Turkey.

General information about the author

First name / Surname	Indre BUTIENE
Address	H.Manto 6A-41, Klaipeda LT-92133, Lithuania
Telephone	Mobile: +370 685 553 05
E-mail	indre.butiene@gmail.com
Nationality	Lithuanian
Date of birth	31/10/1979
Gender	Female
Occupational field	Physician in General paediatrics and paediatric pulmonology

Education and training

From 01/10/2010	PhD student Vilnius University, Faculty of Medicine, Department of Pathology, Pharmacology and Forensic medicine
01/08/2004– 31/06/2009	Residency of Paediatric pulmonologist Children‘s Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos
01/09/1997 - 30/06/2004	Undergraduate medical studies, internship Vilnius University, Faculty of Medicine
1994-1997	Kaunas University of Technology gymnasium

Work experience

From 2011	- General Paediatrician Kretinga hospital, Department of paediatrics
From 2009	- General Paediatrician, Paediatric Pulmonologist Medical Center “Lorna”
From 2010	- Lecturer assistant of “Environmental health” Klaipeda University, faculty of Health Sciences
2009 – 2013	- General Paediatrician, Paediatric Pulmonologist Klaipeda’s Children Hospital
2009 – 2011	- General Paediatrician,Paediatric Pulmonologist Medical Center “Vilnius house of health”
2005 – 2008	- Watching physician Abromiskiu Rehabilitation Hospital, children department;

Research experience

From 2013	National Food Expert-researcher REGFOOD project
From 2012	Member of EAACI Task Force groups “Health related quality of life in allergic diseases”,

	Exposure to multi-pollution and threshold", „Recommendations for improving indoor air quality and preventing allergies in schools (RIAQS)"
2007 – 2011	Junior researcher in EU-funded multidisciplinary integrated project (FP6) Europrevall and Alergemol project. Vilnius University, faculty of Medicine

Personal skills and competences

Mother tongue	Lithuanian
Other languages	English (C1), Russian (C1), French (B2)

Additional information	Family status – married. Daughter (9Y) and son (7Y).

Societies

- European Academy of Allergy and Clinical Immunology (EAACI): member of JMA Working Group, Junior Member of, official JMA Representative and board member of EAACI Aerobiology and Pollution IG
- European Respiratory Society (ERS): Chair of Junior Members Committee
- Member of ERS association of Lithuanian Paediatric Respiratory Society
- Member of Lithuanian Pediatric Society
- EJD (European Junior Doctors - Permanent Working Group): Board member, Chair of PGT (Postgraduate Medical Training) committee, Liaison Officer to UEMS, representative to UEMS (European Union of Medical Specialists) Pulmonology, Allergology and Pediatric sections.

Awards

12/06/2008 Award for poster presentation XXVII EAACI Congress, Barcelona, Spain
22/05/2009 Award of Lithuanian Paediatric Society for scientific studies in Pediatric allergy
24/03/2009 Award of Lithuanian Academy of Sciences for scientific study in drug allergy
2009/2010 Winner of the World Federation of Scientists national scholarship for a scientific job “Prevalence, diagnosis and treatment of chronic cough”
01/01/2012 Research Council of Lithuania scholarship for „Studies on early allergic sensitization in the EuroPrevallLithuanian birth cohort“

REZIUMĖ

Svarbus vaidmuo, nulemiantis vaikų sveikatą ir vystymąsi, vis dažniau priskiriamas vaiką supančiai aplinkai. Nors kai kurias ligas daugiau lemia paveldėjimas, tiek genetiniai, tiek aplinkos veiksniai vaidina svarbų vaidmenį dažniausiai paplitusių ir sudėtinių ligų vystymęsi.

Alergija maistui yra viena iš anksčiausiai pasireiškiančių alergijos formų ir, manoma, kad ji gali būti pirmasis „atopinio maršo“ žingsnis. Išsivysčiusiose šalyse apie 6 % mažų vaikų ir 3-4 % suaugusiųjų kenčia nuo potencialiai mirtinų padidėjusio jautrumo reakcijų į maistą, tačiau naujausių ir tikslių alergijos maistui duomenų iki šiol nėra. Dėl to visuomenės, t.y. tėvų, vaikų priežiūros specialistų, mokyklos darbuotojų, visuomenės sveikatos specialistų, nerimas ir noras kuo daugiau žinoti apie alergiją maistui, jos priežastis ir paplitimą, vis didėja.

Alerginės reakcijos į maisto produktus, tokius kaip karvės pienas, kiaušinis, žemės ir medžių riešutai, kviečiai, soja ir žuvis, dažniausiai pasireiškia pirmaisiais gyvenimo metais. Nors alergija karvės pienui ir kiaušiniui gali išnykti iki mokyklinio amžiaus, alergija žemės riešutams ir žuviai paprastai išlieka visą gyvenimą. Norint tiksliai įvertinti galimų rizikos veiksnių įtaką ligos atsiradimui, kuri gali prasidėti jau kūdikystėje ir išnykti iki mokyklinio amžiaus, tinkamiausias tyrimo metodas yra būtent prospektyvinis naujagimių kohortos tyrimas su reguliaria į tyrimą įtrauktų vaikų ir jų šeimų stebėsena.

Problema

Sergamumas alerginėmis ligomis sparčiai didėja, o pastaraisiais dešimtmečiais jis itin išaugo, ypač Vakarų Europoje. Nepaisant daugelio atliktų tyrimų, vis dar lieka neaišku, kodėl alerginių ligų paplitimas nuolat didėja. Manoma, kad lemiamos reikšmės turi gyvenimo būdas, mityba, oro užterštumas, o svarbiausia – genų ir aplinkos sąveika.

Kaip ir kitų alerginių ligų, alergijos maistui paplitimas pastaraisiais dešimtmečiais didėja. Pacientai ir jų šeimų nariai, sveikatos priežiūros ir vaikų ugdymo įstaigų darbuotojai, maisto gamintojai ir politikai yra sunerimę, kadangi iki šiol nėra visiškai aišku, kaip alergija maistui yra paplitusi visuomenėje. Vaikams alergija maistui pasitaiko dažniau, lyginant su suaugusiaisiais, be to, ji dažnėja, todėl tai tampa vis svarbesne visuomenės sveikatos problema. Pastaruoju metu atlikti populiacijos tyrimai nustatė gana didelius skirtumus tarp pastebėtų ir patvirtintų alerginių reakcijų paplitimo visuomenėje, taip pat ir tarp padidėjusio jautrumo maistui paplitimo. Dauguma atliktų tyrimų remiasi tik numanomomis reakcijomis į maistą ir greičiausiai pervertina alergijos maistui paplitimą. Objektyvūs diagnostiniai tyrimai nustatė, kad tėvai pervertina maisto reikšmę simptomų atsiradimui jų vaikams, ir kad tik nuo 1/3 iki 2/3 pasireiškusių reakcijų būna patvirtinamos. Tad būtini išsamūs tyrimai, kurie nustatytų objektyvų alergijos maistui paplitimą įvairiose amžiaus grupėse.

Darbo tikslas

Nustatyti padidėjusio jautrumo maisto produktams ir alergijos maistui paplitimą ir rizikos veiksnius Lietuvos naujagimių kohortoje.

Darbo uždaviniai

1. Pagal anketinius tyrimo duomenis apibūdinti Lietuvos naujagimių kohortą.
2. Nustatyti dažniausius maisto alergiją sukeliančius maisto produktus ir įsijautrinimo jiems kaitą kohortoje pirmųjų 2,5 metų laikotarpiu.
3. Išsiaiškinti tėvų ir kūdikių rizikos veiksnius, sąlygojančius maisto alergiją.
4. Įvertinti įvairius maisto alergijos diagnostikos metodus kohortoje ir pateikti alergijos maistui diagnostikos rekomendacijas.

Darbo mokslinis naujumas

Europrevall naujagimių kohorta - tai pirmasis pasaulyje tyrimas, kuriame dalyvavo ir Vilniaus Universitetas, specialiai suformuotas tik alergijos maistui ištyrimui. Šios naujagimių gimimo kohortos pradinis tikslas buvo nustatyti ir palyginti patvirtintų alerginių reakcijų į maistą paplitimą tarp mažų vaikų devyniose Europos šalyse. Antriniai tikslai – ištirti galimų lemiamų veiksnių reikšmę alergijos maistui išsivystymui, tokių kaip genetinis pagrindas (tiriant ir vaikų ir tėvų pavyzdžius), mamos mityba nėštumo metu ir maitinant krūtimi, maisto vartojimas po gimimo, infekcijos, psicho-socialiniai ir aplinkos faktoriai. Šiuo tyrimu pirmąkart Lietuvoje ištirtas padidėjusio jautrumo maistui ir alergijos maistui paplitimas tarp mažų vaikų ir nustatyti dažniausiai alergiją sukeliantys maisto produktai ir sensibilizacijos maisto alergenams kaita pirmaisiais 30 gyvenimo mėnesių. Lietuvoje tai vienas didžiausių tokio mąsto tyrimų, kurio metu surinkti duomenys pateiks naudingos informacijos mokslininkams, visuomenės sveikatos specialistams, politikams, įstatymų kūrėjams, gydytojams, pacientams ir vartotojams apie alergijos maistui paplitimą ir dažniausiai sukeliančius alergiją maisto produktus.

Tyrimo medžiaga

Vilniaus universitetas dalyvavo projekto pirmosios temos „Alergijos maistui epidemiologija Europoje“ darbo grupėje. Pirmosios temos pirmoji potemė WP 1.1, kurioje tai pat dalyvavo Vilniaus universitetas, buvo *EuroPrevall* naujagimių kohorta. Tai išsamiausias kada nors atliktas tyrimas, tyręs alergiją maistui pirmaisiais gyvenimo metais, kuriame iš viso dalyvavo 12000 naujagimių ir jų šeimų 9 Europos šalyse (Vokietijoje, Lenkijoje, Graikijoje, Didžiojoje Britanijoje, Ispanijoje, Olandijoje, Islandijoje, Lietuvoje ir Italijoje). Šioje disertacijoje pateikiami I temos I potemės (WP 1.1) *EuroPrevall* naujagimių kohortos tyrimų rezultatai, gauti tiriant Lietuvos naujagimių kohortą.

Metodika

Šio darbo tikslui ir uždaviniams pasiekti atlikti dviejų tipų tyrimai – prosperktyvinis kohortinis ir atvejo – kontrolės tyrimai. Pirmiausia buvo atliktas kohortinis tyrimas, norint nustatyti įsijautrinimo ir alergijos maistui paplitimą ir kaitą kohortoje pirmaisiais gyvenimo metais. Norint patvirtinti ar atmesti alergijos maistui diagnozę, įtariami turėję nepageidaujamas reakcijas į maistą tiriamieji buvo kviečiami klinikiniam ištyrimui į šio tyrimo centrą. Projekto metu buvo sudarytos dvi (atvejo – patvirtinta sensibilizacija/alergija maistui - ir kontrolės) grupės, leidžiančios atlikti įvairius palyginimus apie galimas alergijos maistui priežastis ir rizikos veiksnius.

EuroPrevall Lietuvos naujagimių kohorta buvo formuojama Vilniaus miesto Universitetinėje ligoninėje, Akušerijos ir ginekologijos klinikoje. Į kohortą nuo 2006 m. sausio 1d. iki 2007 m. balandžio 25d. įtraukti 1558 naujagimiai.

Klausimynai apie veiksnius, galinčius turėti įtakos alerginių ligų atsiradimui, buvo pildomi įtraukimo momentu, 12-ąjį, 24-ąjį ir 30-ąjį amžiaus mėnesį. Šie klausimynai buvo pildomi visiems tiriamiesiems. Kohortoje dalyvaujančių kūdikių tėvai buvo paprašyti pranešti tyrimo centrui, jei pasireikštų kokie nors simptomai ar požymiai, kurie leistų įtarti alergiją maistui. Atvykus vaikui į tyrimo centrą, jis buvo apžiūrimas, užpildomas klausimynas, fizinio ištyrimo forma (priedas Nr.4), nustatomas atopinio dermatito eigos sunkumo laipsnis – SCORAD (angl. *Severity Scoring of Atopic Dermatitis*) indeksas[121], atliekami odos dūrio mėginiai dažniausiems maisto alergenams (karvės pienui, kiaušiniui, kviečiams, sojai, žemės riešutams, žuviai), paimamas venino kraujo mėginys (4–5 ml) maistui specifiniams IgE kraujo serume nustatyti. Įvertinus visą surinktą informaciją buvo sprendžiama, ar vaikas tinkamas atlikti ASPKPOM. Jeigu jis atitikdavo ASPKPOM atlikimo kriterijus, iš kohortos būdavo atrenkami du tokio paties amžiaus kontroliniai vaikai, netinkami atlikti ASPKPOM, ir tiriami pagal tokį patį ištyrimo protokolą. Alergija maistui buvo klasifikuojama kaip *pastebėta* (tėvai paskambino dėl pasireiškusių susijusių su maistu simptomų), *galima* (atitinka tinkamumo atlikti ASPKPOM kriterijus, t.y. padidėjęs alergenui specifinis IgE, bet tėvai atsisakė atlikti provokaciją maistu) ir *patvirtinta* (teigiamas ASPKPOM).

Rezultatai

1. Į Lietuvos naujagimių kohortą buvo įtraukti 1558 naujagimiai, tarp jų – 6 dvynių poros. 51,2 % visos kohortos sudarė berniukai, 48,2 % – mergaitės. Dauguma motinų gimdė pirmą (610 (39 %)) arba antrą kartą (421 (27 %)), ketvirtą kartą ir daugiau gimdė 95 motinos. Vidutinė nėštumo trukmė buvo 39,22 ± 1,16 savaičių (vidurkis ± SN). Vidutinė naujagimio kūno masė buvo 3523 ± 437 g. 83,4 % naujagimių gimė natūraliu būdu, o 258 (16,5 %) motinų gimdymai buvo komplikuoti: replių ir vakuumo ekstrakcijos pagalba gimė po 8 vaikus, 15,7 % kohortos naujagimių gimė Cezario pjūvio operacijos metu, iš jų 8,4 % atvejų operacija buvo skubi. Antibiotikai motinoms nėštumo, gimdymo metu ir iš karto po gimdymo nebuvo labai dažnai skiriami – atitinkamai, 14,1 %, 9,4 % ir 12,3 %, be to, 0,6 % naujagimių pirmąją gyvenimo savaitę taip pat buvo gydomi antibakteriniais preparatais. Vertinant ką tik gimusių kūdikių mitybą nustatyta, kad pirmąją gyvenimo savaitę net 31,2 % naujagimių kartu su motinos pienu buvo duodamas papildomas maitinimas. 14,3 % motinų ir 6,8 % tėvų nurodė esą alergiški vienam ar keliems alergenams arba sergantys alergine liga. Artimiausių giminaičių (brolių ir seserų) klausimynų analizė parodė, kad alergiški yra 12,3 % (kohortos naujagimių broliai ar seserys. Didžioji Lietuvos kohortos dalis įtraukimo į kohortą metu gyveno mieste (86,3 %), 9,1 % gyveno kaime, bet ne ūkiuose, ir tik 4,5 % – ūkiuose. 676 šeimos nurodė, kad augina naminius arba žemės ūkio gyvūnus. Apie 7,8 % į kohortą įtrauktų naujagimių motinų nėštumo ir gimdymo metu rūkė. 8,5 % motinų nurodė, kad nėštumo metu jas veikė pasyvus rūkymas.

2. Tad tėvų pastebėtos alergijos maistui paplitimas Lietuvos naujagimių kohortoje nustatytas 17,1 % vaikų. Vertinant pagal skirtingus maisto produktus, dažniausiai sensibilizacija iki 2,5 metų amžiaus vaikams buvo nustatyta pienui (60,2 % simptominių vaikų) ir kiaušiniui (58,0 %). Rečiau sensibilizacija simptomus turintiems vaikams buvo nustatyta kviečiams (13,6 %) ir žemės riešutams (9,1 %). Penki (5,7 %) vaikai buvo

įsijautrinę sojai, tiek pat vaikų – žuviai. Morkai įsijautrinę buvo 4 (4,5 %) simptominiai vaikai. Bulvei, pomidorui, mielėms, jautienai, lazdyno riešutams, apelsinui sensibilizacija buvo nustatyta po vieną kartą. Vertinant visus simptominius vaikus, tik karvės pienui įsijautrinę buvo 26 vaikai, tik kiaušiniui - 22, tik sojai – 2 vaikai, tik kviečiams, morkai, apelsinui, pomidorui buvo įsijautrinę po vieną vaiką. 38,6 % (34 iš 88) vaikų buvo įsijautrinę daugiau nei vienam alergenui. Nustatyta, kad vaikams, kuriems pasireiškė sensibilizacija daugiau nei vienam maisto alergenui, atopinis dermatitas buvo sunkesnės formos, nei tiems, kurie buvo įsijautrinę tik vienam alergenui ($p > 0,05$). Vertinant vaikų amžiaus vidurkius nustatyta, kad jaunesni vaikai (amžiaus vidurkis 9,65 ± 6,12) reikšmingai dažniau buvo įsijautrinę daugiau nei vienam alergenui, nei vyresni (amžiaus vidurkis 12,8 ± 6,66) vaikai ($p = 0,039$). Apibendrinus visus duomenis, EuroPrevall Lietuvos naujagimių kohortinio tyrimo metu 88 (5,6 %) vaikams buvo nustatyta sensibilizacija maistui ir jie buvo tinkami atlikti ASPKPOM su 144 maisto produktais. Projekto pabaigoje, kai vaikams sukako 2,5 metų arba praėjus vieneriems metams po atlikto alergologinio ištyrimo nustatyta, kad tik 1,4 % kohortos vaikų vis dar pasireikšdavo reakcijos valgant atitinkamus maisto produktus.

3. Nustatyta, kad gimimas Cezario pjūvio operacijos metu yra rizikos veiksnys sensibilizacijai maistui (OR 1,926 (95 % PI: 1,028; 3,610)). Lyginant simptominių ir kontrolinių vaikų grupes nustatyta, kad berniukams yra 1,4 karto didesnė rizika sensibilizacijai maistui išsivystyti (OR 1,381 (95 % PI: 0,823; 2,318)). Vyresnių brolių ar seserų buvimas šeimoje statistiškai reikšmingai tarp analizuojamų vaikų grupių nesiskyrė ($p > 0,05$). Tėvų ir artimiausių giminaičių alerginės ligos (astma, alerginė sloga, atopinis dermatitas, kt.) sensibilizacijai maistui įtakos neturėjo, tačiau vaikams, kurių mamos buvo alergiškos namų dulkių erkėms ir gyvūnams, reikšmingai dažniau buvo nustatyta sensibilizacija (6,8 % ir 4,5 %) lyginant su kohortiniais vaikais, kuriems sensibilizacija nebuvo nustatyta (2,1 % ir 1,6 %) ($p = 0,005$ ir $p = 0,046$). Taip pat nustatyta, kad vaikams, kurių mamos buvo alergiškos namų dulkių erkėms ar gyvūnams buvo atitinkamai 2,1 ir 1,2 kartų didesnė rizika tapti alergiškais ((OR 2,125 (95 % PI: 0,598; 7,550) ir OR 1,229 (95 % PI: 0,287; 5,266)). Nustatyta, kad gyvenamoji vieta (miestas, kaimas) reikšmingos įtakos sensibilizacijai neturėjo: 85,6 % (1259 iš 1470) nesensibilizuotų, 92 % kontrolinių ir 86,4 % simptominių vaikų šeimų gyveno mieste. Vertinant galimybių santykį, nustatyta, kad galimybė tapti simptominiu OR 2 kartus didesnė yra gyvenantiems kaime (OR 2,007 (95 % PI: 0,847; 4,757)). Nustatyta, kad gyvūnų laikymas namuose turi apsauginę funkciją. 44,1 % kohortos vaikai, kurie nebuvo sensibilizuoti ir tik 31,8 % simptominių vaikų laikė naminius gyvūnus ($p = 0,024$) - OR 0,700 (95 % PI: 0,408; 1,201). Nustatyta, kad kačių laikymas namuose sumažina galimybę vaikui tapti alergišku maistui - OR 0,605 (95 % PI: 0,304; 1,204), tuo tarpu šuns laikymas šią galimybę 1,2 karto padidino - OR 1,220 (95 % PI: 0,608; 2,447). Motinų rūkymas nėštumo metu ir pasyvus rūkymas reikšmingos įtakos sensibilizacijai maistui neturėjo, bet vertinant galimybių santykį nustatyta, kad rūkančių motinų vaikai turi 2 kartus didesnę riziką tapti alergiškais maistui (OR 2,156 (95 % PI: 0,780; 5,958)). Motinų pasyvus rūkymas taip pat padidino riziką jų vaikams tapti alergiškais maistui - OR 2,171 (95 % CI: 0,829; 5,688). Nustatyta, kad vaikams, kuriems pirmąją gyvenimo savaitę buvo duodamas papildomas nei krūties pienas maitinimas, yra didesnė rizika sensibilizacijai maistui išsivystyti: 30,5 % sveikų kohortos vaikų ir 42 % simptominių vaikų buvo primaitinti arba cukringu vandeniu arba KP mišiniu (įprastu ar hipoalerginiu) ($p = 0.024$).

4. Iš viso buvo buvo atlikti 374 kartus odos dūrio mėginiai simptominiams, kontroliniams ir kitiems kohortos vaikams, kurie atvyko į tyrimo centrą ištyrimui dėl galimos alergijos maistui. Taip pat projekto metu Lietuvoje buvo paimti ir ištiriti 234 simptominių ir kontrolinių vaikų kraujo serumai specifiniams IgE nustatyti. Sensibilizacija karvės pienui buvo nustatyta 53 vaikams, iš jų teigiami ODM pienui buvo nustatyti 16 (30 %) tiriamųjų, sIgE padidėjimas nustatytas 25 iš 37 (68 %) vaikų. Tik 6 vaikams sensibilizacija KP buvo nustatyta ir teigiamais ODM, ir radus sIgE kraujo serume. Šešiems (11,3 %) tiriamiesiems sensibilizacija KP nustatyta tik pagal pasikartojančius, greitai atsirandančius simptomus valgant pieną.

Sensibilizacija kiaušiniui buvo nustatyta 51 vaikui, iš jų teigiami ODM kiaušiniui buvo nustatyti 22 (43 %) tiriamajam. 16 vaikų tėvai atsisakė, kad jų vaikams būtų imamas kraujas iš venos, tad sIgE padidėjimas nustatytas 6 (17,1 %) vaikams. 15 vaikų sensibilizacija nustatyta remiantis ir teigiamais ODM, ir padidėjusiu sIgE prieš kiaušinio baltymus kiekiu kraujo serume. Aštuoniems vaikams sensibilizacija kiaušiniui nustatyta tik pagal pasireiškiančius klinikinius simptomus, net jei ODM ir sIgE tyrimas buvo neigiami. Sensibilizacija kviečiams tik teigiamais ODM buvo patvirtinta 4 vaikams, padidėjusiu sIgE kiekiu kraujo serume – taip pat 4 vaikams (4 vaikams kraujo serumas ištyrimui nebuvo paimtas). Įvertinus pasikartojančius ir greitai atsirandančius simptomus valgant kviečių produktus sensibilizacija buvo nustatyta taip pat 4 vaikams. Vaikų, kuriems sensibilizacija kviečiams būtų patirtinta ir ODM, ir sIgE, nebuvo. Sensibilizacija sojai iš penkių vaikų vienam buvo patvirtinta tik teigiamu sIgE tyrimu (du atsisakė, dviem - neigiami), keturiems – tik teigiamu ODM (vienam – neigiamas). Sensibilizacija žemės riešutams tik pagal sIgE buvo patvirtinta 6 vaikams, ir ODM, ir IgE tyrimu – 2, o tik pagal ODM rezultatus sensibilizacija nebuvo nustatyta. Vienam vaikui buvo teigiami tik ODM, vienam – žuviai specifiniai IgE, dviem vaikams sensibilizacija nustatyta tiek teigiamais ODM, tiek ir sIgE tyrimu, vienam vaikui simptomai pasireikšdavo valgant žuvį, bet ODM ir sIgE tyrimas buvo neigiami. Kitiems maisto alergenams sensibilizacija nustatyta įvertinus klinikinius simptomus ir teigiamus ODM.

Iš viso projekto metu Lietuvoje buvo atliktos 29 provokacijos su 5 maisto produktais, iš jų teigiamos buvo 18 (62 %). Pienui buvo atlikti 9, kiaušiniui – 11, kviečiams - 5, sojai - 1, žuviai – 3 mėginiai. Vienam vaikui, įsijautrinusiam pienui ir vienam, įsijautrinusiam kiaušiniui provokaciniai mėginiai buvo atlikti 2 kartus su daugiau nei vienerių metų pertrauka, kad įvertinti alergijos minėtiems produktams pokyčius. Taigi, įvertinus atliktas provokacijas, alergija maistui buvo patvirtinta 18 % (16 iš 88) simptominių vaikų, kas sudarė 1,02 % visos naujagimių kohortos.

Įvertinus gautus rezultatus, nustatyta, kad sIgE vertėms esant ≥1,49 TV/ml ir ODM ≥ 5,5mm, alerginių reakcijų pasireiškimo tikimybė bus 95 %, o sIgE vertėms esant ≥ 2,14 TV/ml ir ODM ≥ 7 mm alerginių reakcijų pasireiškimo tikimybė bus 99 %.

Įvertinus atliktą literatūros analizę ir gautus projekto metu tyrimų rezultatus, sudarytos alergijos maistui ištyrimo rekomendacijos: „Sensibilizuotų maistui vaikų, kurie žinomai niekada nevartojo atitinkamo maisto, ištyrimo rekomendacijos“, „Tik krūtimi maitinamų kūdikių, sergančių atopiniu dermatitu, ištyrimo rekomendacijos“ ir „Vaikų, kuriems pasireiškia galimai su suvalgytu maistu susiję simptomai, ištyrimo rekomendacijos“.

Išvados

1. Naudojantis anketiniais tyrimo duomenimis apibūdinta Lietuvos 1558 naujagimių kohorta, kuri buvo suformuota Europrevall projekto pagrindu specialiai tik su IgE susijusios alergijos maistui ištyrimui.

2. *EuroPrevall* Lietuvos naujagimių kohortinio tyrimo metu tėvų pastebėtos alergijos maistui paplitimas nustatytas 17 %, galima alergija maistui nustatyta 5,6 % iki 2,5 metų amžiaus vaikų. Lietuvos naujagimių kohortoje dažniausiai vaikai buvo įsijautrinę pienui ir kiaušiniui. Rečiau sensibilizacija simptomus turintiems vaikams buvo nustatyta kviečiams, žemės riešutams, sojai ir kitiems maisto produktams.

3. Nustatytas ryšys tarp sensibilizacijos maistui ir atopinio dermatito. 86 % įsijautrinusių maistui vaikų sirgo atopiniu dermatitu. Jauniausių vaikų, įsijautrinusių maisto alergenams atopinis dermatitas buvo sunkesnės formos, nei vyresniems vaikams. Taip pat vaikams, kuriems pasireiškė sensibilizacija daugiau nei vienam maisto alergenui, atopinis dermatitas buvo sunkesnės formos, nei tiems, kurie buvo įsijautrinę tik vienam alergenui.

4. Projekto pabaigoje, vaikams esant 2,5 metų amžiaus, tik 25 % vaikų, kuriems anksčiau buvo nustatyta sensibilizacija maisto produktams, vis dar pasireikšdavo reakcijos valgant atitinkamus maisto produktus.

5. Nustatyta, kad gimimas Cezario pjūvio operacijos metu, motinų antibiotikų vartojimas iš karto po gimdymo, motinos alerginės ligos, naujagimio primaitinimas pirmąją gyvenimo savaitę įtakojo alergijos maistui atsiradimą.

6. Vaiko lytis, brolių ir seserų skaičius šeimoje, tėvų ir artimiausių giminaičių alerginės ligos, gyvenamoji vieta reikšmingos įtakos sensibilizacijai maistui neturėjo.

7. Rūkančių nėštumo metu ir pasyvaus rūkymo veikiamų motinų vaikai turi 2 kartus didesnę riziką tapti alergiškais maistui.

8. Motinos mityba nėštumo ir žindymo metu reikšmingos įtakos alergijos maistui jų vaikams atsiradimui neturėjo, tik žemės riešutų ir sojos produktų vartojimas dideliais kiekiais nėštumo metu galėjo sąlygoti alergijos šiems produktams atsiradimą.

9. Gauti duomenys leido įvertinti darbe naudotus įvairius maisto alergijos diagnostikos metodus (odos dūrio mėginius, specifinių IgE tyrimus, provokacinius maisto mėginius) kohortoje.

10. Nustatytos alergijos maistui diagnostinių tyrimų (specifinių IgE ir odos dūrio mėginių) vertės, kurioms esant alerginių reakcijų pasireiškimo tikimybė yra daugiau nei 95 % ir todėl sumažėja būtinybė provokaciniams oraliniams mėginiams atlikti norint patvirtinti alergijos maistui diagnozę.

11. Gautų tyrimų pagrindu sukurti nauji maisto alergijos diagnostikos algoritmai, sudarytos ir pateiktos maisto alergijos diagnostikos rekomendacijas.