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Exposure to sewage water and the development of allergic manifestations in Finnish children

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Abstract

Background: The hygiene hypothesis suggests that a decreased microbial load contributes to an increased risk of allergies. In the Finnish municipality of Nokia, sewage water was accidentally mixed with drinking water for 2 days. We studied the association between exposure and the emergence of allergies in children.

Methods: Children aged 2-5 years living in the accident area and an age-matched cohort from the control municipality were recruited. Based on the questionnaires, we identified 139 children exposed to the contaminated water and selected age- and sex-matched controls for them (mean age 16.59 months at the time of the accident). Allergic symptoms and diseases were recorded by ISAAC questionnaires and skin prick tests (SPTs) performed 2 and 5 years after the accident.

Results: SPT positivity at 5 years of follow-up was decreased in the children exposed to the sewage water below 1 year of age (OR 0.311, 95% CI 0.118-0.820; $P = 0.019$), particularly in children who did not develop gastroenteritis at exposure. In contrast, the children over 1 year of age at the exposure tended more likely to be SPT-positive at 5 years of follow-up (OR 1.997, 95% CI 0.963-4.143; $P = 0.070$).

Conclusions: Sewage water exposure during the first year of life, but not later, decreased the risk of IgE sensitization emphasizing the importance of age as a modulator. The modulation of IgE sensitization by the presence of clinical gastroenteritis at the exposure suggests that the nature of microbial load may have importance or alternatively shared host defense mechanisms protect from infection and atopic sensitization.

KEYWORDS

allergy, atopy, disease outbreaks, epidemics, gastroenteritis, hygiene hypothesis, hypersensitivity, sewage, skin tests, water

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1 | INTRODUCTION

According to the hygiene hypothesis, a decreased microbial load during early life contributes to the risk of allergies.[1,2] In humans, evidence supporting the hygiene hypothesis is mainly epidemiologic and the mechanisms are not completely understood. Recent studies suggest that the composition of the gut microbiome at early age is an important determinant of the later risk of allergic diseases.[3-5]

In several studies, the serologic evidence of microbial infections, mainly foodborne and orofecal, is associated with lower prevalence of allergic diseases or allergen-specific IgE.[6,7] Remarkable differences in allergic diseases between two geographically adjacent areas in Eastern Finland and in the western part of Russia[8-10] have been explained by differences in the microbial exposure; higher prevalence of seropositivity to orofecal microbes and higher exposure to bacterial load in drinking water have been associated with lower prevalence of IgE sensitization and allergies in Russia.[8-10] Also, a negative correlation has been shown between allergies and parasitic infections.[11-13] The reasons could be related to inhibition of specific IgE production by high total IgE levels or an increased regulatory T-cell activity.[11-13] Furthermore, differences in gut microbiota have been reported between children with allergies and healthy children.[14-16]

Based on these observations, probiotics have been tested for the prevention and treatment of allergic diseases.[17] Different probiotics, mainly lactobacilli and bifidobacteria, together with pre-biotics have been used to increase microbial stimuli in order to decrease the development of allergic diseases, and several meta-analyses have shown that combined pre- and post-natal probiotic supplementation reduces eczema development during infancy.[18]

In 2007, between the November 28 and 30, 450 tons of effluent water from a wastewater plant was accidentally mixed with drinking water, resulting in an epidemic of gastroenteritis in the town of Nokia in Southern Finland.[19] Thousands of the over 30 000 inhabitants got gastroenteritis before the end of 2007, most of them during the first week after the water accident.[19] According to a questionnaire study, 6500 cases were a direct result of the water accident when the nearby municipality of Kangasala was used as a control population.[19] The water was contaminated in about one third of the area of Nokia. 53% of the residents in the contaminated area were registered to have had a gastrointestinal disease by the end of the year, compared to 16% in the non-contaminated area in Nokia and only 6.5% in Kangasala.[19]

Altogether, 1222 patients sought professional help in Nokia, most of whom got only ambulatory help in the Nokia Health Center.[19] 145 of them were children, who often tested positive for several different pathogenic bacteria and viruses in their stools.[19,20] Most patients with gastroenteritis stayed at home without seeking any professional help.[19] *Campylobacter jejuni*, norovirus (genotypes GI and GII), *Salmonella enteritidis*, Rotavirus, *Giardia lamblia*, and *Clostridium difficile* were found both in the water and in the stool samples.[19,21] The most common microbiologic finding in the stool samples was *Campylobacter jejuni*. Clinically, norovirus was one of the major causes of gastroenteritis.[19] Mostly, the disease lasted for some days.[22] The main symptoms were diarrhea, vomiting, gastrointestinal pain, and fever.[19]

Key Message

The hygiene hypothesis was tested in a real-life situation of a sewage water accident. The development of allergic immune response was followed by questionnaires and skin prick tests in children. A short exposure to sewage water decreased the risk of IgE sensitization only in the children below 1 year of age at exposure, emphasizing the role of age as a modulator.

The water accident gave us the opportunity to study whether this kind of a short, multimicrobial exposure modulates the IgE sensitization and development of clinical allergies during early life, when IgE-mediated allergies to environmental allergens develop.

2 | METHODS

In 2008-2009, we recruited three age cohorts of children from Nokia, born in 2005, 2006, and 2007, and the same age cohorts from Kangasala, a nearby municipality of the same size belonging to the same University Hospital District area and with similar medical practices, but without a shared border with Nokia (Figure 1). About 1301 and 1289 letters were sent to the families in Nokia and Kangasala, respectively, asking for informed consent and about exposure of the child to the contaminated water and possible symptoms of gastroenteritis. Based on the questionnaires returned by the families (377 from Nokia and 274 from Kangasala), we identified 139 children with exposure to sewage water from Nokia (at the time of the water accident, mean age 16.59 months, SD 9.93 months, range 1.05-34.68) and control children from Kangasala, who were matched for year of birth and sex, and invited them to attend skin prick tests and to answer the International Study of Asthma and Allergies in Childhood (ISAAC) questions[23] 2 and 5 years after the accident. The ISAAC baseline questionnaire on the allergic symptoms and family history of allergies was returned by 121 families from Nokia and 127 from Kangasala. The cohorts did not differ regarding the family history of smoking or allergic diseases (Table 1). The history of atopic diseases in the children did not differ before the water accident (37 of 121 in Nokia vs 31 of 127 in Kangasala).

Two years after the water accident, between August 2009 and May 2010 SPTs (SPT 2 years) were performed in 139 children from Nokia (73 male), of whom 93 developed gastroenteritis at the time of the accident, and 129 from Kangasala (77 male), two of them with a history of a gastroenteritis between the accident and the end of 2007. The mean age at the time of the SPT 2 years was 40.07 months (SD 10.91) and 40.10 months (SD 10.54) in children

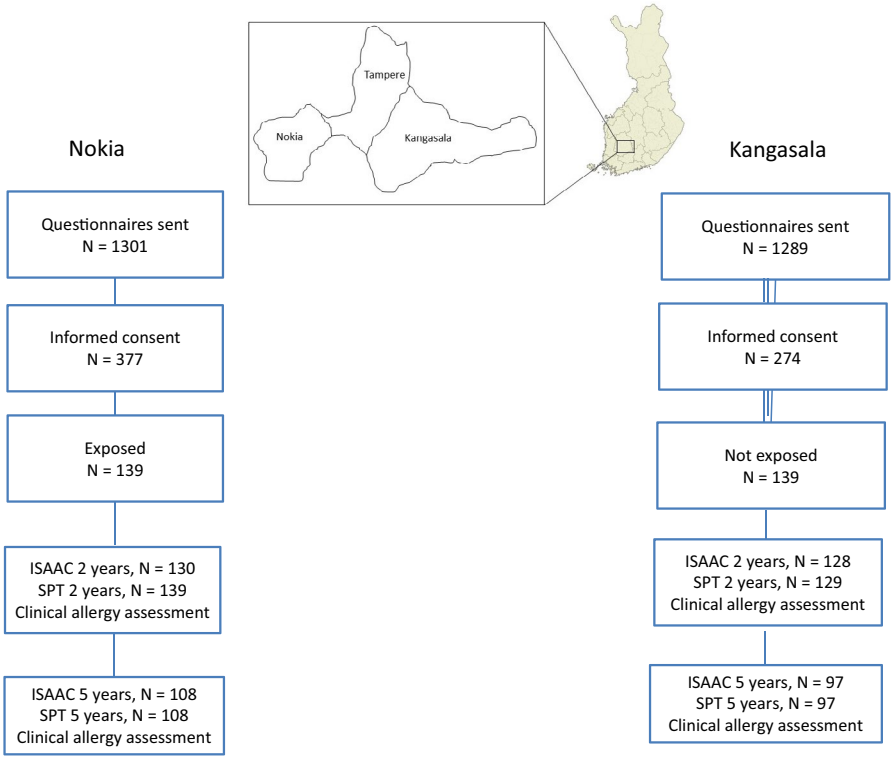

FIGURE 1 The flowchart of the study. Children living in the area of water accident in Nokia and age- and sex-matched children living in the neighboring municipality Kangasala (see the map) were recruited to the study. ISAAC, standardized questionnaire of childhood allergies; SPT, skin prick test [Colour figure can be viewed at wileyonlinelibrary.com]

from Nokia and Kangasala, respectively. The ISAAC questionnaire was answered at 2 years (ISAAC 2 years) by 130 of the 139 families of Nokia children and 128 of the 129 Kangasala children. Based on the clinical consequences of the exposure, the children from Nokia were divided into two subgroups, those who developed (N = 93) and those who did not develop (N = 46) gastroenteritis when exposed to sewage water.

Follow-up SPTs were performed between January and May 2013 (SPT 5 years), on average 63 months after the water accident, and the families also filled in the ISAAC questionnaire (ISAAC 5 years) on the allergic symptoms. 108 children from Nokia (57 male, mean age 78.81 months, SD 10.09) were tested, 71 of them with the history of gastroenteritis. Ninety-seven children from Kangasala (56 male, mean age 79.59 months, SD 10.09) were tested, two of them with the history of gastroenteritis. The drop-out rate was 23%, but it did not cause any bias between the study groups at 5 years of follow-up; the mean age at the time of the water accident was 16.35 months in Nokia and 15.40 months in Kangasala. Eight Nokia and 10 Kangasala children with positive SPTs at 2 years dropped out.

TABLE 1 The history of smoking and allergic diseases in mothers (m) and fathers (f) of the children in the study cohort based on the ISAAC 2 y

	Nokia (N = 130)	Kangasala (N = 128)
Asthma (m)	11 (8.5%)	10 (7.8%)
Asthma (f)	14 (10.8%)	10 (7.8%).
Atopic dermatitis (m)	32 (24.6%)	27 (21.1%)
Atopic dermatitis (f)	19 (14.6%)	16 (12.5%)
Pollen allergy (m)	39 (30%)	38 (29.7%)
Pollen allergy (f)	43 (33.1%)	32 (25%)
Smoking (m)	16 (12.3%)	16 (12.5%)
Smoking (f)	31 (23.8%)	25 (19.5%)

Note: No statistically significant differences were found between the study groups.

The SPTs were performed using the following allergens: birch, timothy, and egg white (Allergopharma, Germany); wheat (Allergy Centre of the Tampere University Hospital); cow milk, dog, cat, and control solution (ALK-Abello, Spain); and gliadin and histamine as the positive control (Pharmacy of the Pirkanmaa Hospital District). The allergens were blinded both from the families and from the professionals. SPT was considered positive when the diameter of the reaction wheal to the allergen was 3 mm or more and at least half of that for histamine.

The pediatric allergologist in our team (MP) blindly read the ISAAC answers of the SPT-positive children and evaluated whether the child had clinical allergy. Clinical IgE-mediated allergy was diagnosed when the child had allergic symptoms and SPT was positive. Children were considered to be allergic when they had a doctor diagnosed atopic disease (asthma, atopic dermatitis, food allergy, allergic rhinitis or atopic eczema), or clinical symptoms of atopic disease treated with medication (hydrocortisone and/or antihistamine and/or antiallergic nasal sprays or eye drops). (Children with doctor-diagnosed atopic disease (asthma, atopic dermatitis, food allergy, allergic rhinitis, or atopic

TABLE 2 Skin prick test positivity for at least one allergen and the occurrence of clinical allergy in the children of Nokia and Kangasala 2 and 5 y after the exposure to sewage water

	All Nokia children with exposure	Kangasala control children	Comparison between Nokia and Kangasala OR (95% CI)
2 y At least one positive SPT	25% (35/139)	28% (36/129)	0.869 (0.487-1.550)
2 y Clinically allergic (SPT+, ISAAC+)	16% (22/139)	16% (21/129)	0.976 (0.484-1.968)
5 y At least one positive SPT	37% (40/108)	37% (36/97)	1.029 (0.562-1.886)
5 y Clinically allergic (SPT+, ISAAC+)	30% (32/108)	27% (26/97)	1.150 (0.598-2.215)

Abbreviations: ISAAC, standardized questionnaire of childhood allergies; SPT, skin prick test.

TABLE 3 Skin prick test (SPT) positivity for at least one allergen and the occurrence of clinical allergy in the children of Nokia who were exposed to the sewage water below or above the age of 1 y and in the control children from Kangasala 2 and 5 y after the exposure to sewage water

	SPT positivity 2 y OR (95% CI) *P*-value	SPT positivity 5 y OR (95% CI) *P*-value	Clinical allergy 2 y OR (95% CI) *P*-value	Clinical allergy 5 y OR (95% CI) *P*-value
Nokia < age 1 GE−	1/26 **0.117 (0.014-0.956)** ***P* = 0.025**	3/21 **0.176 (0.044-0.709)** ***P* = 0.011**	1/26 0.195 (0.023-1.665) *P* = 0.145	3/21 0.481 (0.114-2.029) *P* = 0.503
Nokia < age 1 GE+	6/30 0.729 (0.241-2.211 *P* = 0.783	7/23 0.463 (0.153-1.403) *P* = 0.188	3/30 0.542 (0.132-2.229) *P* = 0.513	5/23 0.802 (0.230-2.794) *P* = 1.000
Kangasala <age 1	12/47	17/35	8/47	9/35
Nokia > age 1 GE−	7/20 1.208 (0.434-3.366) *P* = 0.791	5/16 1.029 (0.314-3.371) *P* = 1.000	4/20 1.327 (0.382-4.611) *P* = 0.739	5/16 1.203 (0.364-3.976) *P* = 0.763
Nokia > age 1 GE+	21/63 1.208 (0.596-1.208) *P* = 0.718	25/48 **2.460 (1.125-5.379)** ***P* = 0.031**	15/63 1.659 (0.724-3.800) *P* = 0.289	19/48 1.734 (0.776-3.874) *P* = 0.220
Kangasala >age 1	24/82	19/62	13/82	17/62

Note: Children with and without gastroenteritis (GE+ and GE−). In all comparisons, children from Kangasala served as a control group.

Statistically significant ORs are bolded.

eczema with corticosteroid treatment) and children with clinical symptoms of atopic disease who used relief medication (atopic eczema with hydrocortisone and not only base creme, allergic rhinitis/conjunctivitis treated with antihistamine and/or anti-allergic nasal sprays or eye drops) were considered having allergic disease.) The pediatric allergologist discussed the positive test results with the families, and they got the written answers of the SPTs. The parents also had the possibility to contact the researchers at any time during the study.

The study was approved by the Ethics Committee of the Tampere University Hospital.

The statistical comparisons were made using the two-tailed Fisher exact test.

3 | RESULTS

3.1 | Skin prick tests (SPTs) 2 and 5 years after the water accident

Two years after the accident, 25% (35/139) of the Nokia children and 28% (36/129) of the Kangasala children were positive for at least one allergen in the SPTs (odds ratios in Table 2). SPT positivity to only aeroallergens was found in 21 and 26 children, to only food allergens in seven and three children, and to both aero- and food allergens in seven and seven children, respectively, from Nokia and Kangasala. Five years after the accident, 37% (40/108) of the children from Nokia and 37% (36/97) of the children from Kangasala were SPT-positive (Table 2).

SPT positivity to only aeroallergens was found in 38 and 33 children and to both aero- and food allergens in two and three children, respectively, from Nokia and Kangasala.

Because earlier studies suggest that the gut microbiota composition before the age of 1 year can predict later IgE sensitization and allergic diseases,[3-5] we analyzed the children below and above 1 year of age at the time of exposure separately. In the children below the age of one at the time of the water accident, SPT positivity at 5 years of follow-up was decreased in Nokia; SPT at 2 years was positive in 7 of 56 Nokia children and in 12 of 47 Kangasala children (OR 0.417, 95% CI 0.149-1.165; $P = 0.126$), and at 5 years in 10 of 44 Nokia children and in 17 of 35 Kangasala children (OR 0.311, 95% CI 0.118-0.820; $P = 0.019$). In the children above one year of age at the time of the water accident, SPT positivity at 5 years tended to be more frequent in Nokia than in Kangasala: 28/83 vs 24/82 SPT-positive children at 2 years (OR 1.230, 95% CI 0.637-2.376; $P = 0.616$) and 30/64 vs 19/62 SPT-positive children at 5 years (OR 1.997, 95% CI 0.963-4.143; $P = 0.070$).

Next, we studied the possible effect of gastroenteritis as a modulator and found that SPT positivity was decreased particularly in the children who did not have gastroenteritis despite the exposure below the age of one: SPT positivity in 1/26 at 2 years and in 3/21 at 5 years ($P = 0.025$ and $P = 0.011$, Table 3). In the children who were exposed to the sewage water older than 1 year of age, those who got gastroenteritis as a result developed SPT positivity more frequently ($P = 0.126$ and $P = 0.031$ at 2 and 5 years, Table 3).

3.2 | Clinical allergy 2 and 5 years after the accident

Two years after the accident, no difference in the development of clinical allergy was seen; clinical allergy (positive SPT and corresponding symptoms in ISAAC) was diagnosed in 16% (22/139) of all the children from Nokia and in 16% (21/129) of those from Kangasala (Table 2).

Two years after exposure, 63% (22/35) of the SPT-positive children from Nokia had clinical allergy, compared with 58% (21/36) of the SPT-positive children from Kangasala.

Five years after the water accident, clinical allergy was diagnosed in 30% (32/108) of all the children from Nokia and in 27% (26/97) of the children from Kangasala (Table 2). 80% (32/40) of the SPT-positive children from Nokia and 72% (26/36) from Kangasala had clinical allergy.

No difference in the development of clinical allergy was found when the children exposed to the sewage water below or above 1 year of age were compared. Furthermore, the occurrence of gastroenteritis at the time of exposure did not show any modulatory effect on the risk of allergic diseases (Table 3).

4 | DISCUSSION

Our results indicate that the overall effect of a short exposure to sewage water during the first three years of life did not change the occurrence of allergies. However, when the age at the exposure was considered, differences in the development of SPT positivity were found. The children exposed to the sewage water below 1 year of age showed a decreased risk of IgE sensitization, while an increased risk was found in the children exposed to the sewage water older than 1 year of age. Our results support the view that the first year of life is a critical window for the gut microbiome as a regulator of IgE sensitization later in life.[3-5,17,18] Early infancy is the time when the priming of the immune response to foreign antigens and allergens takes place, which may provide the opportunity for the modulation.

Although the age at the microbial exposure was a key modulator of the atopic sensitization, clinical gastroenteritis appeared to be of importance too. In the children younger than 1 year at the exposure, protection from IgE sensitization was seen particularly in the children who did not develop gastroenteritis. In the children exposed to the sewage water older than 1 year, a significantly increased risk of IgE sensitization was found in those with gastroenteritis. Thus, clinical gastroenteritis may counteract the protective effect of microbial exposure. In another cohort study, we have shown that a high degree intestinal inflammation during infancy, that is, a high level of fecal calprotectin, increased the risk of allergic diseases.[24] In gastroenteritis, inflammation and epithelial injury can increase gut permeability and exposure to allergens.[25] Earlier studies have used seropositivity for orofecal microbes as a marker of exposure,[4,5,8] but there are no data on the history of subclinical vs clinical infection causing seropositivity. In low-hygiene environment, the continuous exposure to low levels of orofecal microbes in the drinking water[9] may not lead to gastroenteritis.

Because of the real-world nature of our study, we could not verify the cause of the gastroenteritis and can only speculate the possible role of norovirus, which was often associated with gastrointestinal infection in Nokia.[19] In the animal model, murine norovirus infection breaks tolerance to food antigens[26,27] and triggers an allergic IgE response.[28]

Finally, children with an atopic susceptibility may be more susceptible to gastroenteritis due to altered mucosal immunity, or the gut microbiome composition protecting from atopic sensitization may provide protection from pathogens. Indeed, allergies have been related to impaired mechanisms of innate immunity.[29,30]

The small number of children limits the power of our study; therefore, the results should be interpreted with caution. Despite the limitations, which were mainly due to the real-world situation, such as missing data on breastfeeding, the real-world situation was also the strength of our study.

In conclusion, our study highlights the importance of the age as a key factor in the microbiome-mediated protection from allergic immune response. Accordingly, microbial exposure during the first year of life, in a complex interaction with other environmental factors and the host defense mechanisms, could protect from atopic sensitization. The results further suggest that microbial exposure above 1 year of age may actually increase allergic deviation. The association of gastroenteritis with atopic susceptibility may be explained by impaired defense mechanisms in the children with atopic tendency.

Our results emphasize the need for a deeper understanding of the nature of microbial load in the modulation of allergic response. Due to the limitations of the study, these findings can be considered hypothesis generating for the future research.

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CONFLICT OF INTEREST

No conflicts of interests. Not published elsewhere.

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REFERENCES

1. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299:1259-1260.
2. von Hertzen LC, Laatikainen T, Mäkelä MJ, et al. Infectious burden as a determinant of atopy- a comparison between adults in Finnish and Russian Karelia. *Int Arch Allergy Immunol*. 2006;140:89-95.
3. Arrieta M-C, Arévalo A, Stiemsma L, et al. Associations between infant fungal and bacterial dysbiosis and childhood atopic wheeze in a nonindustrialized setting. *J Allergy Clin Immunol*. 2018;142:424-434.
4. Fujimura KE, Sitarik AR, Havstad S, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. 2016;22:1187-1191.
5. Stokholm J, Blaser MJ, Thorsen J, et al. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun*. 2018;9(1):141.
6. Matricardi PM, Rosmini F, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ*. 2000;320:412-417.
7. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol*. 2002;110:381-387.
8. Vonhertzen L, Makela M, Petays T, et al. Growing disparities in atopy between the Finns and the Russians: a comparison of 2 generations. *J Allergy Clin Immunol*. 2006;117:151-157.
9. Seiskari T, Kondrashova A, Viskari H, et al. Allergic sensitization and microbial load–a comparison between Finland and Russian Karelia. *Clin Exp Immunol*. 2007;148:47-52.
10. Von Hertzen L, Laatikainen T, Pitkänen T, et al. Microbial content of drinking water in Finnish and Russian Karelia - implications for atopy prevalence. *Allergy*. 2007;62:288-292.
11. Fishbein AB, Fuleihan RL. The hygiene hypothesis revisited: does exposure to infectious agents protect us from allergy? *Curr Opin Pediatr*. 2012;24:98-102.
12. Lynch NR, Lopez RI, Prisco-fuenmayor MC, et al. Allergic reactivity and socio-economic level in a tropical environment. *Clin Exp Allergy*. 1987;17:199-207.
13. Wilson MS, Taylor MD, Balic A, Finney CA, Lamb JR, Maizels RM. Suppression of allergic airway inflammation by helminth-induced regulatory T cells. *J Exp Med*. 2005;202:1199-1212.
14. Björksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol*. 2001;108:516-520.
15. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol*. 2001;107:129-134.
16. Watanabe S, Narisawa Y, Arase S, et al. Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. *J Allergy Clin Immunol*. 2003;111:587-591.
17. Savilahti E, Kuitunen M, Vaarala O. Pre and probiotics in the prevention and treatment of food allergy. *Curr Opin Allergy Clin Immunol*. 2008;8:243-248.
18. West CE, Dzidic M, Prescott SL, Jenmalm MC. Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. *Allergol Int*. 2017;66:529-538.
19. Laine J, Huovinen E, Virtanen MJ, et al. An extensive gastroenteritis outbreak after drinking-water contamination by sewage effluent, Finland. *Epidemiol Infect*. 2011;139:1105-1113.
20. Räsänen S, Lappalainen S, Kaikkonen S, Hämälainen M, Salminen M, Vesikari T. Mixed viral infections causing acute gastroenteritis in children in a waterborne outbreak in Finland. *Epidemiol Infect*. 2010;138:1227-1234.
21. Rimhanen-Finne R, Hänninen M-L, Vuento R, et al. Contaminated water caused the first outbreak of giardiasis in Finland, 2007: a descriptive study. *Scand J Infect Dis*. 2010;42:613-619.
22. Laine J, Lumio J, Toikkanen S, et al. The duration of gastrointestinal and joint symptoms after a large waterborne outbreak of gastroenteritis in Finland in 2007– a questionnaire-based 15-month follow-up study. *PLoS ONE*. 2014;9:1-6.
23. Asher MI, Keil U, Anderson HR, et al. International Study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483-491.
24. Orivuori L, Mustonen K, de Goffau MC, et al. High level of fecal calprotectin at age 2 months as a marker of intestinal inflammation predicts atopic dermatitis and asthma by age 6. *Clin Exp Allergy*. 2015;45:928-939.
25. Hodges K, Gill R. Infectious diarrhea. Cellular and molecular mechanisms. *Gut Microbes*. 2010;1:4-21.
26. Bouziat R, Hinterleitner R, Brown JJ, et al. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science*. 2017;356:44-50.
27. Bouziat R, Biering SB, Kouame E, et al. Murine Norovirus infection induces TH1 inflammatory responses to dietary antigens. *Cell Host Microbe*. 2018;24:677-688.
28. Chen X, Leach D, Hunter DA, et al. Characterization of intestinal dendritic cells in murine norovirus infection. *Open Immunol J*. 2011;4:22-30.
29. Mustonen K, Orivuori L, Keski-Nisula L, et al. Inflammatory response and IgE sensitization at early age. *Pediatr Allergy Immunol*. 2013;24:395-401.
30. Mattila P, Renkonen J, Toppila-Salmi S, et al. Time-series nasal epithelial transcriptomics during natural pollen exposure in healthy subjects and allergic patients. *Allergy*. 2010;65:175-183.

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