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LETTERS TO THE EDITOR

Preventing Atopic Dermatitis and ALLergies in Children—the PreventADALL study

To the Editor

Reversing or aborting the increase in allergic and other immune-related noncommunicable diseases (NCDs) in the Western world, first observed for allergic rhinitis from the 1890s,[1] requires primary prevention strategies, probably on a general population level. The diseases are likely to be related to changes in lifestyle, environment, or both,[2] including reduced microbial diversity, increased use of xenobiotics in industrial and consumer products, exposure to tobacco or nicotinic products, and variations in diets and nutritional elements. While some primary allergy preventive strategies may be effective in high-risk children,[3] the relevance for preventive strategies on a population level is unclear.[4] We propose using allergic diseases as model diseases for understanding effects of modern lifestyle upon immune-related noncommunicable diseases (NCDs), with allergy manifestations already from the start of life. The Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) study will provide new insight into early life prevention of NCDs. This letter briefly outlines why and how we will determine effects of a dual approach to preventing allergic disease development in early infancy, as well as provide a basis for identification of novel strategies for future prevention of NCDs.

Allergic diseases often start with atopic dermatitis (AD) or food allergy in early infancy, followed by wheeze or asthma and allergic rhinitis in childhood, and frequently occur as comorbidities. The reduced skin barrier in AD may predispose for food and other allergy development, suggesting that primary allergy prevention should start early and target barrier enhancement and the alimentary tract.[5] While no commonly accepted effective primary prevention is currently available, skin emollients have reduced AD in high-risk children[6] and peanut intake from infancy in children with severe AD and/or egg allergy reduced peanut allergy.[3] However, in a general population-based study of breast-fed infants,[7] food allergy was prevented only in children fully adherent to the protocol of regular intake of 6 food items from 3 months of age.

The PreventADALL study has 2 main objectives: primarily to determine whether primary prevention of allergic diseases is possible by simple and low-cost strategies and secondarily to assess early life factors and exposures, including intrauterine environment, microbiota, and xenobiotics, involved in the development of asthma and allergic diseases or other NCDs including cardiovascular diseases, obesity, and diabetes.

A general population-based mother-child birth cohort recruited at 18-week pregnancy will be assessed at follow-up investigations (Figure 1) into adulthood of the children in this international, multicenter study, including a 2 × 2 factorially designed, randomized clinical trial of 2 primary prevention interventions (skin care and early food introduction) in infancy. Based upon an estimated 22% relative risk reduction in AD, deemed clinically relevant, we recruited 2697 women (2701 pregnancies) from December 2014 through October 2016, with their last baby enrolled April 11, 2017 (Online Supplement). Based upon femur length[8] at the 18-week ultrasound investigation, mean (range) gestational age (GA) was 18.7 (15.7-22.7) weeks, among the 2149 women enrolled in Norway (Oslo University Hospital and Østfold Hospital Trust) and the 552 in Sweden (Karolinska Institutet, Stockholm) (Table 1). Most women (mean [range] age 32 [18-42]) were well educated, lived with their husbands (41.2%) or cohabiting partner (55.9%), as is common in Scandinavia (Table 1). With 88.2% (n = 2397) of all fetuses included at birth (52.7% boys), we largely met the targeted 2400 mother-child pairs, which is larger than the 1306 children in the Enquiring About Tolerance (EAT) study.[7] Mean (range) infant estimated GA was 39.2 (35.6-42.9) weeks (Figure S1), and 16.4% were delivered by Caesarian section rate, in line with national practice.[9] The mothers reported at least one (42%) or two (20.1%) doctor diagnosed allergic disease (Table 1).

To ensure a general, nonselected population, all *pregnant women* (GA 16-22 weeks) attending routine ultrasound screening at, or in collaboration with (in Sweden), the 3 participating hospitals were eligible, provided sufficient language skills. Women carrying more than 2 fetuses, fetuses with severe malformations or disease and infants born prior to 35.0 weeks of GA, were excluded.

All infants were randomized at birth to 1 of 4 similar sized groups: (1) no intervention; (2) skin care (oil-bath at least 5 days per week from 0.5 to 9 months of age); (3) consecutive introduction, between 3 and 4 months of age, of peanut, milk, wheat, and egg at least 4 days per week complementary to breastfeeding; or (4) both interventions. Weekly electronic diaries (2-26 weeks of age) recorded skin care, infant feeding, and symptoms of allergic diseases. Adverse events (0-12 months of age) elicited relevant investigations and treatment by direct access for the participants to the local pediatric department.

Data collection (Figure 1, Table S1) includes electronic questionnaires with information of health and disease in the mother, child, and family; lifestyle; environment; stress; quality of life; diet in the mother and offspring; clinical investigations; fetal and child anthropometrics; lung function; skin barrier; allergy; and blood pressure

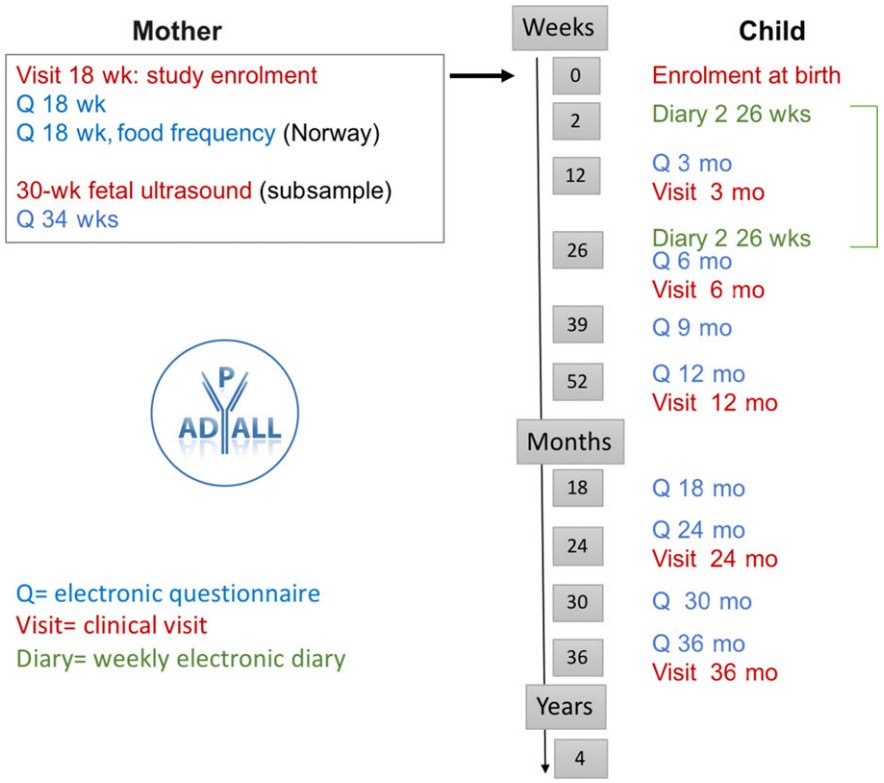

Figure 1. The PreventADALL study overview is shown for the enrolment and follow-up investigations for the first 4 years of the children. The study is planned for future follow-up studies from year 4 onward

measurements. *Biological sampling* includes blood (serum, DNA, RNA), urine, skin swabs and feces for microbiota, placental biopsies and swabs, amniotic fluid (if caesarean section), vernix caseosa, saliva, and breast milk.

The main intervention outcomes are AD and food allergy to intervention foods, assessed first at 12 and 36 months, respectively. Assessment of AD with validated international criteria is performed by a blinded assessor, and food allergy will be confirmed by food challenges, when appropriate. Secondary outcomes assessed annually include recurrent wheeze or asthma, allergic sensitization, allergy to other foods, anaphylaxis, and allergic rhinitis. Other NCDs will be defined in future phases of the study.

The study was approved by the Regional board for Medical Ethics in Oslo (2014/518) and Stockholm (2014/2242-31/4) and registered at clinicaltrial.gov *NCT02449850*.

We are unaware of studies other than the PreventADALL study testing whether primary prevention of allergy in early infancy is effective, based upon the dual allergen exposure hypothesis.[5] The high participant educational attainment reflects that of Scandinavian women and may influence identification of lifestyle factors that affect NCD development. The comprehensive data collected and careful phenotyping of participants will enable identification of personalized novel preventive strategies to related microbial diversity, diet, lifestyle, and gene-environment influence on allergic and other NCD development from fetal life.

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TABLE 1 The Table Shows the background characteristics of the 2701 PreventADALL participants, reported by the 2397 mother-child pairs and the 315 enrolled women who did not have their babies included in the final mother-child cohort. The GA was estimated from ultrasonic measures of femur length at enrollment (GA 16-22)

	Pregnancies registered at 18-w ultrasound (n = 2701)								
		Mother-child cohort							
		Mother (n = 2386)				Father (n = 2260)			
	Not in the mother-child cohort (n = 315)	Total	Oslo (n = 1530)	Østfold (n = 339)	Stockholm (n = 517)	Total	Oslo (n = 1473)	Østfold (n = 301)	Stockholm (n = 486)
Mean age (range) -year	31.8 (18-45)	32.4 (20-48)	32.8 (21-48)	30.6 (20-42)	32.5 (21-47)	34.6 (21-72)	34.9 (23-65)	33.2 (21-52)	34.8 (21-72)
Maternal body measurements									
Height, cm, median (min, max)	168 (147-186)	168 (147-187)	168 (147-186)	167 (152-187)	167 (151-185)				
Weight, kg, median (min, max)	69 (46-121)	68 (45-133)	68 (45-123)	70 (46-134)	69 (49-124)				
Body mass index (median, min, max)	24 (18-45)	24 (17-48)	24 (17-41)	25 (18-48)	25 (19-43)				
Gestational age at 18-w ultrasound	18.9 (16.6-21.8)	18.9 (15.1-22.5)	19.0 (15.4-22.5)	18.6 (15.2-22.2)	19.0 (16.0-21.4)				
Multiple pregnancies (total 4)	1	3							
Twin pregnancies (total 17)	6	11							
Education - no. (%)									
Preliminary school only (9/10 y)	2 (1.1)	16 (0.7)	3 (0.2)	5 (1.7)	8 (1.6)	26 (1.3)	8 (0.6)	10 (3.5)	8 (1.7)
High school only	18 (9.6)	221 (10.3)	66 (4.8)	65 (22.7)	90 (17.9)	388 (18.7)	142 (10.7)	119 (42.2)	127 (26.6)
Higher education <4 y	71 (37.8)	687 (31.9)	394 (28.9)	132 (46.2)	161 (32.0)	629 (30.3)	419 (31.7)	83 (29.4)	127 (26.6)
Higher education 4y or more	90 (47.9)	1167 (54.3)	862 (63.3)	76 (26.6)	229 (45.5)	946 (45.6)	685 (51.9)	62 (22.0)	199 (41.7)
PhD	7 (3.7)	60 (2.8)	38 (2.8)	7 (2.4)	15 (3.0)	70 (3.4)	53 (4.0)	4 (1.4)	13 (2.7)
Country of origin—no. (%)									
Norway	128 (68.1)	1434 (66.3)				1381 (65.4)			
Sweden	32 (17.0)	491 (22.7)				486 (23.0)			
Other Nordic	3 (1.6)	28 (1.3)				29 (1.4)			

(Continues)

TABLE 1 (Continued)

	Pregnancies registered at 18-w ultrasound (n = 2701)								
		Mother-child cohort							
		Mother (n = 2386)				Father (n = 2260)			
	Not in the mother-child cohort (n = 315)	Total	Oslo (n = 1530)	Østfold (n = 339)	Stockholm (n = 517)	Total	Oslo (n = 1473)	Østfold (n = 301)	Stockholm (n = 486)
Rest of the world	25 (13.3)	209 (9.7)				216 (10.2)			
Marital status—no. (%)									
Married	77 (41.0)	891 (41.2)	548 (40)	121 (41.9)	222 (44.1)				
Cohabitants	99 (52.7)	1214 (56.2)	786 (57.4)	159 (55.0)	269 (53.5)				
Single	5 (2.7)	39 (1.8)	27 (2.0)	3 (1.0)	9 (1.8)				
Divorced/ separated		1 (0.0)		1 (0.3)					
Other	7 (3.7)	17 (0.8)	9 (0.6)	5 (1.7)	3 (0.6)				
Previous pregnancies—no. (%)	103 (54.8)	1189 (55.0)	714 (52.1)	177 (38.8)	298 (59.2)				
Previous deliveries—no. (%)									
1	63 (61.2)	678 (57.0)	400 (56.0)	109 (61.6)	169 (56.7)				
2	10 (9.7)	160 (13.5)	81 (11.3)	30 (16.9)	49 (16.4)				
3		17 (1.4)	6 (0.8)	3 (1.7)	8 (2.7)				
4		5 (0.4)	2 (0.3)	2 (1.1)	1 (0.3)				
5 or more		2 (0.2)	1 (0.1)	1 (0.6)					
Living environment—no. (%)									
City, densely populated	77 (41.0)	839 (38.8)	689 (50.3)	25 (8.7)	125 (24.9)				
City, less densely populated	60 (31.9)	822 (38.0)	530 (38.7)	147 (50.9)	145 (28.8)				
Suburb	29 (15.4)	344 (15.9)	106 (7.7)	19 (6.6)	219 (43.5)				
Village	6 (3.2)	46 (2.1)	9 (0.7)	30 (10.4)	7 (1.4)				
Countryside, outside village	16 (8.5)	111 (5.1)	36 (2.6)	68 (23.5)	7 (1.4)				

(Continues)

TABLE 1 (Continued)

	Pregnancies registered at 18-w ultrasound (n = 2701)								
		Mother-child cohort							
		Mother (n = 2386)				Father (n = 2260)			
	Not in the mother-child cohort (n = 315)	Total	Oslo (n = 1530)	Østfold (n = 339)	Stockholm (n = 517)	Total	Oslo (n = 1473)	Østfold (n = 301)	Stockholm (n = 486)
Doctor diagnosed parental diseases—no. (%)									
Total no. of responders	188	2162	1370	289	503	2151	1401	280	470
Asthma	34 (18.1)	371 (17.2)	227 (16.6)	59 (20.4)	85 (16.9)	277 (12.9)	180 (12.8)	34 (12.1)	63 (13.4)
Atopic eczema	32 (17.0)	429 (19.8)	272 (19.9)	66 (22.8)	91 (18.1)	220 (10.2)	141 (10.1)	15 (5.4)	64 (13.6)
Allergic rhinitis	32 (17.0)	445 (20.6)	294 (21.5)	65 (22.5)	86 (17.1)	507 (23.6)	353 (25.2)	60 (21.4)	94 20.0)
Food allergy	29 (15.4)	280 (13.0)	179 (13.1)	37 (12.8)	64 (12.7)	196 (9.1)	140 (10.0)	14 (5.0)	42 (8.9)
Anaphylactic reaction	8 (4.3)	73 (3.4)	34 (2.5)	13 (4.5)	26 (5.2)	92 (4.3)	13 (1.0)	5 (1.8)	24 (5.1)
Urticaria	23 (12.2)	287 (13.2)	199 (14.6)	41 (14.2)	47 (9.3)				
Newborn babies N (% of total)	321	2397	1537	342	518				
Boys (%)		(52.7)	(52.9)	(50.1)	(54.0)				
Caesarian section (%)		391 (16.4)	237 (15.5)	62 (18.3)	92 (17.8)				
Gestational age at delivery, weeks	38.5 (33.2-42.6)	39.6 (35.1-43.0)	39.4 (35.1-42.9)	39.4 (35.1-42.6)	37.9 (35.0-42.0)				

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CONFLICT OF INTEREST

None of the authors have declared real or perceived conflict of interest for the present study, as outlined in the COI forms; however, Eva Maria Rehbinder has received honorary for presentations from Sanofi Genzyme and Omega Pharma.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

APPENDIX 1

ON BEHALF OF THE PREVENTADALL STUDY GROUP (ALPHABETICAL ORDER):

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Human milk oligosaccharide profiles and food sensitization among infants in the CHILD Study

To the Editor,

Allergies originate early in life, and food sensitization is often the first manifestation of allergic disease.[1] Breastfeeding has been inconsistently associated with allergic conditions.[2] These inconsistencies could reflect differences in human milk composition, which varies across different settings and populations. However, it remains poorly understood which of the bioactive components in human milk contribute to the developmental programming of allergic disease.

Human milk oligosaccharides (HMOs) are the third most abundant component of human milk, yet they are absent from most infant formulas.[3] HMO composition is influenced by genetic fucosyltransferase-2 secretor status and also by lactation stage, gestational age, maternal health, ethnicity, geographic location, and breastfeeding exclusivity.[3] Among their many functions,[3] HMOs act as selective substrates to guide development of the infant gut microbiota.[4] We have previously reported that gut microbiota richness in early infancy is associated with subsequent food sensitization, suggesting that HMOs and other determinants of early gut colonization could influence the development of allergic disease.[5] This hypothesis is also supported by experimental research in rodents[6] and a small clinical study where low concentrations of the HMO lacto-N-fucopentaose III (LNFPIII) were associated with higher incidence of cow's milk allergy.[7] However, the potential impact of other individual HMOs on food sensitization is not known, and the impact of overall HMO composition has not been studied, yet this may be important because breastfed infants are naturally exposed to complex combinations of HMOs in human milk.

In this study, among 421 mother–infant dyads from the Canadian Healthy Infant Longitudinal Development (CHILD) cohort,[8] we examined the associations of 19 individual HMOs and overall HMO profiles with food sensitization at 1 year of age using Projection on Latent Structures-Discriminant Analysis (PLS-DA).[9] Detailed methods are provided in Supplementary Materials.

Overall, 59/421 infants (14.0%) were sensitized to 1 or more food allergens at 1 year of age (Table S1). We did not observe any significant associations for the 19 individual HMOs or total HMOs and food sensitization (Figure 1A); however, overall HMO profiles differed significantly in milk consumed by sensitized vs nonsensitized infants ($P < .001$; robust to leave-one-out cross-validation) (Figure 1B). The discrimination performance was "fair," with an area under the curve (AUC) of 0.73, 95% Confidence Interval (CI) 0.66-0.79 (robust to permutation testing with 100 replicates; $P = .02$) (Figure 1C). Similar results were observed in a sensitivity analysis excluding 22 infants with food allergy symptoms prior to milk sample collection (AUC 0.75, 95% CI: 0.69-0.81) (Figure S1).

Restricting our analysis to the top 10 most important HMOs contributing to the PLS-DA score resulted in similar discrimination (AUC 0.71; 95% CI: 0.64-0.78), indicating that these 10 HMOs are sufficient to explain the association of HMO profile and food sensitization. The rankings, PLS-DA scaled importance scores, and direction of association for these 10 HMOs are shown in Figure 1D. HMO profiles associated with lower risk of food sensitization were characterized by relatively higher concentrations of fucodisialyllacto-N-hexaose (FDSLNH), lacto-N-fucopentaose II (LNFPII), lacto-N-neotetraose (LNnT), lacto-N-fucopentaose I (LNFPI), sialyl-lacto-N-tetraose c (LSTc) and fucosyllacto-N-hexaose (FLNH), and relatively lower concentrations of lacto-N-hexaose (LNH), lacto-N-tetrose (LNT), 2′-fucosyllactose (2′FL), and disialyllacto-N-hexaose (DSLNH).

Finally, to account for potential confounders and adjust for known allergy risk factors, we evaluated the PLS-DA score in multivariable logistic regression models (Table 1). Compared to infants consuming milk with a discriminant score in the highest quintile, those in the lowest quintile had a 90% lower risk of food sensitization (Odds Ratio [OR] 0.10 [95% CI: 0.03, 0.34]).

To our knowledge, only 1 previous study has explored the association of HMOs with food sensitization in children, where infants receiving milk with low LNFPIII concentrations were more likely to develop cow's milk allergy.[7] In contrast, we did not observe associations of any individual HMOs with food sensitization, and LNFPIII was not among the most discriminatory HMOs in our analysis. This may reflect differences in study populations (high-risk infants[7] vs our general population cohort), timing of milk collection (1 month vs 3-4 months), or outcomes assessed (confirmed milk allergy[7] vs sensitization to various food allergens).

Recently, a randomized trial reported that infants receiving formula supplemented with 2′FL had more similar immune responses to breastfed controls, compared to infants receiving formula without