*pteronyssinus*), cats, and grass pollen. In addition, serum 25-hydroxyvitamin D concentration was measured, and primary care visits were reviewed to assess the incidence of acute respiratory illnesses among the treatment groups.

RESULTS. Skin prick tests for the selected aeroallergens were available for 184 out of 186 children from whom serum was also collected at 18 months of age. Less than 5% of children had measurable specific IgE to aeroallergens other than dust mites. As a result, group comparisons were made for the mite antigen groups only. For the skin prick testing, children who received higher-dose vitamin D supplementation had a reduced risk of mite antigen sensitization ($P = .03$). The proportion of children with serum-specific IgE positivity to dust mites was significantly decreased for both low-dose and high-dose vitamin D supplementation. In regard to primary care visits, the number of children presenting with asthma and in whom asthma was listed as a diagnosis was significantly smaller in the groups receiving vitamin D supplementation.

CONCLUSIONS. Vitamin D supplementation during the third trimester and first 6 months of life decreases sensitization to house dust mites and the number of primary care visits for asthma at the age of 18 months.

REVIEWER COMMENTS. Vitamin D has immune-modulating effects, and it is known that atopic sensitization can start before birth. The authors of this study suggest that early vitamin D supplementation in utero and in early infancy can decrease the sensitization to dust mites later in life. These results are especially important for populations at risk for vitamin D deficiency, such as in breastfed infants. Current guidelines recommend supplementation with 400 IU per day, yet the authors of this study suggest that a higher dose of 800 IU per day may decrease infants' sensitization to house dust mites. Further studies are needed to determine optimum doses and durations of vitamin D supplementation as a possible allergy prevention measure.

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## Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans

Vatanen T, Kostic AD, d'Hennezel E, et al. *Cell*. 2016; 165(4):842–853

PURPOSE OF THE STUDY. Characterize the gut microbiota during the first 3 years of life and elucidate a mechanism by which it can shape the immune system and impact the incidence of autoimmune diseases such as type 1 diabetes (T1D).

STUDY POPULATION. A subcohort from the DIABIMMUNE (http://www.diabimmune.org) study of 1000 infants from Finland, Estonia, and Russia matched by sex, age, and human leukocyte antigen–associated risk factors. In Finland and Estonia, autoimmunity is more common than in Russia.

METHODS. Stool and serum samples were collected periodically from birth up to 3 years of age. Stool samples were sequenced and their functional potential was compared by HUMAn2 software (http://huttenhower.sph.harvard.edu/humann2). NF-$\kappa$B–dependent cytokines were determined in peripheral blood mononuclear cells after *Escherichia coli* or *Bacteroides dorei* lipopolysaccharide (LPS) stimulation. A nonobese-diabetic mouse model was used to evaluate effects of these 2 types of LPSs in the development of autoimmunity.

RESULTS. Sequencing of stool samples revealed a substantially different composition between Russian and Finnish or Estonian microbiota. Finns and Estonians had a greater abundance of *B dorei*, and the amount of *B dorei* correlated directly with insulin autoantibody levels. In terms of functional potential, glycolytic functions associated to milk oligosaccharide metabolism were increased in Russian samples, whereas LPS and lipid A biosynthetic processes were increased in the Finnish infants. Lipid A was mainly derived from *E coli*, but in Finland and Estonia it was also derived from *B dorei*. The authors show that *E coli* and *B dorei* LPSs are structurally and functionally different and that *B dorei* LPS inhibits NF-$\kappa$B–dependent cytokine production induced by *E coli* LPS in a dose-dependent manner. Thus, in peripheral blood mononuclear cells, *B dorei* dampens the immunomodulatory effect of *E coli*. This was translated into an in vivo model because mice injected with *E coli* LPS had a lower incidence and later onset of T1D than mice injected with *B dorei* LPS. In these latter mice, their splenocytes were hyporesponsive 24 hours after *E coli* LPS injection.

CONCLUSIONS. Despite their geographical proximity, there is a significant difference in the composition and function of gut microbiota in infants from 3 different countries with distinct prevalence of autoimmune and allergic diseases. The presence of *B dorei* during early infancy could inhibit endotoxin tolerance induced by *E coli* LPS and predispose for autoimmunity.

REVIEWER COMMENTS. The incidence of T1D is increasing worldwide, with an exponential increase in prevalence over the last 40 years. Despite extensive research, the specific causes of this rise are unknown, and primary prevention strategies are lacking. Recent evidence highlights the relevance of gut microbes and its impact on immunity and immunopathology. However, the definition of a protective microbiota is poorly defined. The authors of this study identify *E coli* as a protective element in microbiota and *B dorei* as a deleterious

microbe and potential driver of autoimmune disease. Moreover, it provides direct evidence of a mechanistic link between these 2 components of the microbiota and the selective disruption of a specific immunomodulatory mechanism by which the risk of developing an autoimmune disease, specifically T1D, could increase. Future research should be focused on establishing specific causes of detrimental changes in the composition of gut microbiota, understanding its full range of implications, and developing strategies to favor the presence of protective microbes in an attempt to modify the increasing incidence of autoimmune and allergic diseases.

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### Elevated Blood Eosinophils in Early Infancy Are Predictive of Atopic Dermatitis in Children With Risk for Atopy

Rossberg S, Gerhold K, Geske T, et al. *Pediatr Allergy Immunol*. 2016;27(7):702–708

PURPOSE OF STUDY. To investigate the association between serum eosinophil levels and the development of atopic dermatitis (AD) in a birth cohort of patients at risk for atopic disease.

STUDY POPULATION. This study included pediatric patients from a German randomized placebo-controlled trial for primary prevention of AD by using Pro-Symbioflor, an oral bacterial lysate treatment (ISRCTN60475069), conducted between 2002 and 2007.

METHODS. Study participants were randomly assigned to receive either Pro-Symbioflor or placebo, from 5 weeks until 7 months of age. Blood samples were collected at 4 weeks (preintervention) and 7 months of age (postintervention) and were used to measure blood eosinophil counts. The infants were evaluated by trained pediatricians for the development of AD until 3 years of life. Disease severity was assessed by using Scoring Atopic Dermatitis criteria. The study authors defined elevation of blood eosinophils as >5% of total leukocytes and used 2×2 tables and odds ratio analyses to assess for the association between elevated blood eosinophils (EEs) and the occurrence of AD.

RESULTS. Blood samples were collected from 559 infants at 4 weeks and 467 infants at 7 months of age who met study inclusion criteria. The eosinophil counts for the total study population ranged from 0.9% to 15.1% of total leukocytes at 4 weeks of life; the 50th percentile was 4%. This value was similar among all subgroups (1 or both parents with atopy, single or double heredity). In the overall study population, EEs observed at 4 weeks of life were associated with the development of AD at ages 7 months ($P = .007$), 1 year ($P = .004$), 2 years ($P = .007$), and 3 years ($P = .006$). EEs had a positive predictive value of 23.9%, sensitivity of 52.3%, and a specificity of 63.3% for the development of AD in the overall study population. Subjects with EEs at 4 weeks of life were predicted to develop AD 12 weeks earlier than infants with normal eosinophil levels. EEs at 7 months of life were not found to be associated with an increased development of AD. However, when the study authors performed receiver operating characteristic curve analysis for sensitivity and specificity at a lower elevated eosinophil cutoff (>4.5%), there was an association between EEs at 7 months of age and the development of AD: $P = .005$, 1 year ($P = .039$), 2 years ($P = .033$), and 3 years ($P = .034$).

CONCLUSIONS. EEs at 4 weeks of life is associated with the early onset of AD in infants and young children with a family history of atopy. Early eosinophil counts may prove useful in identifying at-risk infants, and providing those families with early interventions could reduce morbidity associated with AD.

REVIEWER COMMENTS. The authors of this study prospectively evaluated a birth cohort of infants at high risk for atopy by using blood eosinophil levels to predict the development of AD. The use of biomarkers in predicting atopic risk is emerging in several studies and could be a potential tool for helping clinicians identify high-risk patients. More studies are necessary to validate and justify the use of eosinophil counts as screening tools. Earlier identification of children at risk for AD could help clinicians implement earlier interventions (ie, skin care regimens) and potentially reduce disease severity.

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## ENVIRONMENTAL EXPOSURES AND TOBACCO SMOKE

### Domestic Dog Exposure at Birth Reduces the Incidence of Atopic Dermatitis

Thorsteinsdottir S, Thyssen JP, Stokholm J, Vissing NH, Waage J, Bisgaard H. *Allergy*. 2016;71(12):1736–1744

PURPOSE OF THE STUDY. To investigate the longitudinal effect of dog exposure on the risk of atopic dermatitis (AD) in children during the first 3 years of life. The study also evaluated the relationship between parental atopic disease, number of dogs, and cluster of differentiation 14 or filaggrin mutation genotypes on the development of AD.

STUDY POPULATION. The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) are ongoing prospective clinical birth cohort studies. Data from 411 children born

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