Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis

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Evidence for a possible role of early infant-feeding pattern in the development of asthma and allergic rhinitis is inconsistent and scarce. We set out to study these associations. A prospective birth cohort of infants with increased HLA-DQB1-conferred risk for type 1 diabetes was recruited in 1996–2000. The families completed at home a record on the age at introduction of new foods. Persistent asthma and allergic rhinitis were assessed at the age of 5 years with an International Study of Asthma and Allergies in Childhood-type questionnaire. The Cox proportional hazards regression analyses were adjusted for parental asthma and allergic diseases, and several perinatal and sociodemographical factors. Out of the 1293 children, 77 (6.0%) developed persistent asthma; and out of the 1288 children, 185 (14.4%) developed allergic rhinitis by the age of 5 years. Early age at introduction of oats was associated with a reduced risk of persistent asthma (hazard ratio (HR; 95% CI) for the first and mid-tertiles compared with the latest tertile was 0.36 (0.15, 0.85) and 0.37 (0.22, 0.62), respectively, P < 0.001). Early age at introduction of fish was dose dependently associated with a decreased risk of allergic rhinitis (HR (95% CI) for the first and mid-tertiles compared with the latest tertile was 0.34 (0.22, 0.54) and 0.45 (0.28, 0.70), respectively, P < 0.001). The present finding that age at introduction of oats is inversely and independently associated with development of persistent asthma is novel. We confirmed the earlier observation that the age at introduction of fish is inversely related to the risk of allergic rhinitis. Clinical implications remain to be determined.


Evidence for a possible role of early infant-feeding pattern in the development of asthma and allergic diseases is inconsistent. Early introduction of solid foods in infancy may not increase the risk of developing allergic diseases and asthma1,2. Previous studies suggest that early introduction of fish, fruits, vegetables, egg and milk may reduce the risk of atopy and allergic rhinitis3–5.

In a series of prospective cohort studies, exclusive breastfeeding for at least 3 months has been linked to a reduced frequency of asthma, allergic rhinitis and atopic eczema compared with shorter breastfeeding6–8. There are, however, prospective studies showing contrasting results9,10. Whether breastfeeding protects from allergies only in families with a known allergic propensity remains unclear9,11,12.
Breastfeeding may also increase the risk when maternal asthma is present\(^{(13)}\). Various cytokines and the function of macrophages in breast milk of mothers whose infants later developed allergic disorders have been claimed to be the culprit\(^{(14)}\).

We set out to assess how age at introduction of different main foods or food groups such as fruits and berries, roots, milk products and cereals as well as breastfeeding during the first year of life is related to the emergence of asthma and allergic rhinitis by the age of 5 years in a population-based cohort of young children with increased HLA-DQB1-conferred risk for type 1 diabetes. Our primary endpoints were assessed by an International Study of Asthma and Allergies in Childhood type of questionnaire, where also the age at diagnosis of the diseases was inquired. In accordance with international guidelines\(^{(15,16)}\), Finnish families are advised to start solid foods in their offspring at the age of 4–6 months.

**Experimental methods**

**Subjects**

The Diabetes Prediction and Prevention Study is a multidisciplinary prospective population-based cohort study\(^{(17)}\). Newborn infants from the areas of three university hospitals in Finland are screened for HLA-DQB1-conferred susceptibility to type 1 diabetes using cord blood samples. Infants who have increased genetic susceptibility (HLA-DQB1*02/0302 heterozygous and DQB1*0302/x-positive subjects; x stands for homozygosity or neutral alleles) are monitored for diabetes-associated autoantibodies, growth and viral infections at 3–12 months intervals, HLA-DQB1 alleles were analysed as described previously\(^{(18)}\). Procedures were approved by the local ethics committees.

The Diabetes Prediction and Prevention Nutrition Study falls within the framework of The Diabetes Prediction and Prevention Study\(^{(19)}\). The at-risk children born between 2 September 1996 and 31 March 2000 at Oulu University Hospital and between 20 October 1997 and 31 March 2000 at Tampere University Hospital, and who took part in the dietary follow-up, were invited to take part in the present study on asthma, allergic rhinitis and atopic eczema at the age of 5 years. All those children who attended the 5 year visit were invited to take part in the allergy study: 1302 out of the 1374 attending (94.8 %) participated. Among the children, 1293 had information on asthma status and 1288 on allergic rhinitis.

**Dietary methods**

Information on infant-feeding patterns was collected using a structured dietary questionnaire, which was completed when the child was 3, 6, 12 and 24 month old and in addition to the ‘age at introduction of new foods’ form. Trained study nurses checked the questionnaires during the visits (at 3, 6, 9, 12, 18 and 24 months). In the 3-month dietary questionnaire, the feeding in the delivery hospital was assessed in detail: whether the child was breastfed; had received banked breast milk; was exposed to infant formula and if so to which formula; and which of these was/were the main type of feed during the delivery hospital stay. The duration of breastfeeding and the age at introduction and brand names of all infant formulas, which the child had received, as well as the age at introduction of other cow’s milk and sour milk products and foods and drinks containing cow’s milk were requested in all questionnaires. The brand name of the infant formula was recorded and the formulas were later classified as regular cow’s milk based, special (hydrolysed) or soya based. At the age of 3 months, all the food items the infant had so far received were carefully recorded in the questionnaire. During the first 2 years of life, the family was asked to complete at home continuously the age at introduction of new foods form, which was checked at every visit. The form included the following food groups: fruits and berries; potato; carrot; spinach or beetroot; turnip and swede; cabbages; lettuce; wheat; barley; oats; rye; maize, rice, millet or buckwheat; pork; beef; chicken; other meats; sausage; fish; egg; sour milk products; foods containing cow’s milk; cow’s milk and ice cream; soya products. In the analysis, the following food groupings were used: (1) fruits and berries; (2) roots: potato, carrot, turnip and swede; (3) wheat, barley, rye and oats; (4) other cereals: maize, rice, millet and buckwheat; (5) cabbages (cauliflower, broccoli, kale and Chinese, red and turnip cabbage); (6) milk products; (7) fish; (8) meat (pork, beef, chicken and other meat); (9) egg. In addition, wheat, barley, rye and oats were analysed separately. Exclusive breastfeeding was defined as the period during which the child received, in addition to breast milk, only water and/or vitamin/mineral supplements.

**Asthma, allergic rhinitis and atopic eczema**

The participating families completed a questionnaire on the child’s possible history and symptoms of asthma, allergic rhinitis and atopic eczema when the child was 5 year old. The questionnaire was modified from the validated International Study of Asthma and Allergies in Childhood questionnaire\(^{(20,21)}\). For all outcomes, we added the question about the age of appearance of first symptoms. We used as endpoint of asthma persistent asthma: the child’s asthma was diagnosed by a physician and he/she has either had wheezing or asthma medication during the previous 12 months. Allergic rhinitis was defined as: sneezing, nasal congestion or rhinitis other than with respiratory infection and together with the symptoms of rhinitis eye itching and tearing\(^{(20)}\). Parental asthma, allergic rhinitis and atopic eczema were considered in the analyses of the results. Also the presence of pets at home during the first year of the life was used as a covariate.

**Sociodemographic and perinatal characteristics**

Information on child’s sex, maternal age and educational level and the number of siblings were recorded in a structured questionnaire completed by the parents after the delivery. Information on duration of gestation, mode of delivery, birth weight and height and maternal smoking during pregnancy was received from the Medical Birth Registries of the Oulu and Tampere University Hospitals (Table 1).

**Statistical methods**

In order to use also the information on the age of onset of asthma and allergic rhinitis and to gain in statistical power
in the analysis, survival analysis was used. Cox proportional hazards regression was selected to analyse the association between dietary variables and the disease endpoints. The assumption of proportionality was not strongly violated. All the final analyses were repeated with logistic regression, which identified the same significant associations (results not shown).

There were nine twin pairs and forty-four other sibling pairs. The sibling effect was taken into account in the analysis (clustering by family in STATA). The statistical significance of dietary variables was tested with the Wald test. The STATA 9.0 program (College Station, TX, USA) was used in the analysis. We used tertiles of the dietary variables to avoid ad hoc or outcome-dependent choices of categorisation.

### Table 1. Characteristics of the participating infants and hazard ratio (HR) and 95 % CI of development of persistent asthma and allergic rhinitis* (HR and 95 % CI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n (no. of endpoints)</th>
<th>Model†</th>
<th>Asthma*</th>
<th>Allergic rhinitis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex of the child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>677 (54)</td>
<td>1·64</td>
<td>0·98, 2·74</td>
<td>675 (119)</td>
</tr>
<tr>
<td>Girl</td>
<td>616 (23)</td>
<td>1·00</td>
<td></td>
<td>613 (66)</td>
</tr>
<tr>
<td>Parental asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>182 (21)</td>
<td>1·46</td>
<td>0·81, 2·65</td>
<td>184 (48)</td>
</tr>
<tr>
<td>No</td>
<td>1100 (55)</td>
<td>1·00</td>
<td></td>
<td>1093 (135)</td>
</tr>
<tr>
<td>Missing information</td>
<td>11 (1)</td>
<td></td>
<td></td>
<td>11 (2)</td>
</tr>
<tr>
<td>Parental allergic rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>779 (64)</td>
<td>3·20</td>
<td>1·56, 6·55</td>
<td>778 (141)</td>
</tr>
<tr>
<td>No</td>
<td>503 (12)</td>
<td>1·00</td>
<td></td>
<td>499 (43)</td>
</tr>
<tr>
<td>Missing information</td>
<td>11 (1)</td>
<td></td>
<td></td>
<td>11 (1)</td>
</tr>
<tr>
<td>Parental atopic eczema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>615 (49)</td>
<td>1·12</td>
<td>0·67, 1·88</td>
<td>614 (117)</td>
</tr>
<tr>
<td>No</td>
<td>655 (27)</td>
<td>1·00</td>
<td></td>
<td>651 (65)</td>
</tr>
<tr>
<td>Missing information</td>
<td>23 (1)</td>
<td></td>
<td></td>
<td>23 (3)</td>
</tr>
<tr>
<td>Number of siblings in the family‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>496 (35)</td>
<td>1·00</td>
<td></td>
<td>494 (81)</td>
</tr>
<tr>
<td>One</td>
<td>404 (21)</td>
<td>0·72</td>
<td>0·40, 1·28</td>
<td>403 (56)</td>
</tr>
<tr>
<td>Two</td>
<td>187 (12)</td>
<td>0·96</td>
<td>0·44, 2·09</td>
<td>184 (22)</td>
</tr>
<tr>
<td>Three or more</td>
<td>133 (4)</td>
<td>0·47</td>
<td>0·14, 1·61</td>
<td>133 (13)</td>
</tr>
<tr>
<td>Missing information</td>
<td>73 (5)</td>
<td></td>
<td></td>
<td>74 (13)</td>
</tr>
<tr>
<td>Maternal age (years)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>206 (17)</td>
<td>1·00</td>
<td></td>
<td>199 (28)</td>
</tr>
<tr>
<td>25–29</td>
<td>426 (25)</td>
<td>0·78</td>
<td>0·39, 1·56</td>
<td>428 (61)</td>
</tr>
<tr>
<td>30 or more</td>
<td>661 (35)</td>
<td>0·83</td>
<td>0·39, 1·77</td>
<td>661 (96)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile: &lt;39</td>
<td>319 (25)</td>
<td>1·00</td>
<td></td>
<td>320 (44)</td>
</tr>
<tr>
<td>Second tertile: 39</td>
<td>300 (19)</td>
<td>0·73</td>
<td>0·39, 1·39</td>
<td>299 (47)</td>
</tr>
<tr>
<td>Third tertile: 40–40·7</td>
<td>312 (13)</td>
<td>0·41</td>
<td>0·19, 0·88</td>
<td>309 (40)</td>
</tr>
<tr>
<td>Fourth tertile: 40·8</td>
<td>359 (20)</td>
<td>0·62</td>
<td>0·32, 1·19</td>
<td>357 (54)</td>
</tr>
<tr>
<td>Missing information</td>
<td>3 (0)</td>
<td></td>
<td></td>
<td>3 (0)</td>
</tr>
<tr>
<td>Route of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>154 (11)</td>
<td>1·04</td>
<td>0·49, 2·19</td>
<td>152 (27)</td>
</tr>
<tr>
<td>Other</td>
<td>1137 (66)</td>
<td>1·00</td>
<td></td>
<td>1134 (158)</td>
</tr>
<tr>
<td>Missing information</td>
<td>2 (0)</td>
<td></td>
<td></td>
<td>2 (0)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>113 (10)</td>
<td>1·56</td>
<td>0·71, 3·43</td>
<td>110 (19)</td>
</tr>
<tr>
<td>No</td>
<td>1149 (86)</td>
<td>1·00</td>
<td></td>
<td>1147 (163)</td>
</tr>
<tr>
<td>Missing information</td>
<td>31 (1)</td>
<td></td>
<td></td>
<td>31 (3)</td>
</tr>
<tr>
<td>Atopic eczema at the age of 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>189 (22)</td>
<td>1·82</td>
<td>1·06, 3·13</td>
<td>189 (66)</td>
</tr>
<tr>
<td>No</td>
<td>1069 (53)</td>
<td>1·00</td>
<td></td>
<td>1066 (116)</td>
</tr>
<tr>
<td>Missing information</td>
<td>35 (2)</td>
<td></td>
<td></td>
<td>33 (3)</td>
</tr>
<tr>
<td>Pets in the family during the first year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>260 (10)</td>
<td>0·56</td>
<td>0·28, 1·62</td>
<td>261 (31)</td>
</tr>
<tr>
<td>No</td>
<td>954 (65)</td>
<td>1·00</td>
<td></td>
<td>948 (145)</td>
</tr>
<tr>
<td>Missing information</td>
<td>79 (2)</td>
<td></td>
<td></td>
<td>79 (9)</td>
</tr>
<tr>
<td>Total*</td>
<td>1293 (77)</td>
<td></td>
<td></td>
<td>1288 (185)</td>
</tr>
</tbody>
</table>

*Information on asthma status was available for 1293 children and information on allergic rhinitis for 1286 children. Altogether, there were 77 cases of asthma and 185 cases of allergic rhinitis. The age at onset of the disease information was available for 75 cases with asthma and 121 cases with allergic rhinitis.

† A Cox regression survival model was used in the analysis. Adjusted for all the variables in the table and for area (hospital) of birth: Oulu and Tampere University Hospitals. P values are indicated for terms that are significantly associated with the endpoint.

‡ At the time of the birth of the child.
(Tables 2 and 3). The exclusive and overall durations of breastfeeding were also used as continuous variables. The strategy of analysis when testing the associations of the dietary variables with the endpoints was the following: first, all dietary variables were tested separately in single variate models. Then, the least significant one/ones were removed from the multiple regression model and the possible confounding variables were included in the model, and this was repeated until all dietary variables remaining in the model were statistically significant at the 5% level. Among the models, the least significant one/ones were removed from the multiple regression model and the possible confounding variables were included in the model, and this was repeated until all dietary variables remaining in the model were statistically significant at the 5% level. Among the (HR and 95% CI).

### Table 2. Unadjusted and adjusted hazard ratios (HR) and 95% CI for persistent asthma related to age at introduction of different cereals*

<table>
<thead>
<tr>
<th>Foods separately</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)†</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Wheat, barley, rye or oats</td>
<td>0.042</td>
<td>0.013</td>
</tr>
<tr>
<td>First tertile: &lt; 5-0</td>
<td>13 (215)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mid-tertile: 5-0–5-49</td>
<td>23 (583)</td>
<td>0.50</td>
</tr>
<tr>
<td>Last tertile: ≥ 5-5</td>
<td>37 (479)</td>
<td>1.00</td>
</tr>
<tr>
<td>Rye</td>
<td>0.030</td>
<td>0.026</td>
</tr>
<tr>
<td>First tertile: &lt; 5-5</td>
<td>7 (296)</td>
<td>0.33</td>
</tr>
<tr>
<td>Second tertile: 5-5–6-0</td>
<td>14 (362)</td>
<td>0.82</td>
</tr>
<tr>
<td>Third tertile: ≥ 6-0</td>
<td>32 (394)</td>
<td>1.00</td>
</tr>
<tr>
<td>Oats</td>
<td>&lt; 0.001</td>
<td>0.020</td>
</tr>
<tr>
<td>First tertile: &lt; 5-0</td>
<td>6 (164)</td>
<td>0.36</td>
</tr>
<tr>
<td>Second tertile: 5-0–5-5</td>
<td>24 (639)</td>
<td>0.37</td>
</tr>
<tr>
<td>Third tertile: ≥ 5-5</td>
<td>32 (317)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Cox regression survival model was used in the analysis. Model 1 includes wheat, rye, oats and barley and model 2 includes rye and oats. In addition, both of the models are adjusted for parental asthma, rhinitis and atopic eczema, gestational age, maternal age and smoking during pregnancy, mode of delivery, child's sex, study area, presence of atopic eczema during the first 6 months of life, number of siblings and presence of pets at home during the first year of life.

† The variables were categorised into tertiles. In some cases, the same age was reported for many children, which resulted in categories unequal in size. The nearest cut point was always used.

### Table 3. Unadjusted and adjusted hazard ratios (HR) and 95% CI for persistent asthma related to age at introduction of different foods*

<table>
<thead>
<tr>
<th>Foods separately</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)†</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Fish</td>
<td>0.003</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>0-6</td>
<td>22 (461)</td>
<td>0.54</td>
<td>0.32, 0.92</td>
</tr>
<tr>
<td>6.1–8-5</td>
<td>11 (359)</td>
<td>0.35</td>
<td>0.18, 0.68</td>
</tr>
<tr>
<td>Third tertile: &gt; 8-5</td>
<td>39 (451)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Egg</td>
<td>0.004</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>8.5–11</td>
<td>15 (354)</td>
<td>0.50</td>
<td>0.27, 0.90</td>
</tr>
<tr>
<td>Oats</td>
<td>0.0003</td>
<td>0.001</td>
<td>0.0007</td>
</tr>
<tr>
<td>First tertile: &lt; 5-0</td>
<td>6 (164)</td>
<td>0.36</td>
<td>0.15, 0.85</td>
</tr>
<tr>
<td>Second tertile: 5-0–5-5</td>
<td>24 (639)</td>
<td>0.37</td>
<td>0.22, 0.62</td>
</tr>
<tr>
<td>Third tertile: &gt; 5-5</td>
<td>32 (317)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Cox regression survival model was used in the analysis. Model 1 includes fish, egg and oats, model 2 includes fish and oats and model 3 includes oats. In addition, all the models 1–3 are adjusted for parental asthma, rhinitis and atopic eczema, gestational age, maternal age and smoking during pregnancy, mode of delivery, child's sex, study area, presence of atopic eczema during the first 6 months of life, number of siblings and presence of pets at home during the first year of life.

† The variables were categorised into tertiles. In some cases, the same age was reported for many children, which resulted in categories unequal in size. The nearest cut point was always used.
cereals, wheat, oats, rye and barley were all significantly associated with the asthma endpoint in single variate models. Due to high correlations between these variables, the strategy of analysis described was first applied to these cereals separately (Table 2).

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Ethical Committee of Pirkannaa Hospital District and the Ethical Committee of Pohjois-Pohjanmaa Hospital District. Written informed consent was obtained from all subjects/patients.

Results

Among the children participating, 6.0 % (77 out of 1293) developed persistent asthma and 14.4 % (185 out of 1288) allergic rhinitis by the age of 5 years (Table 1). The age at onset information was not available for two cases with asthma and sixty-four cases with allergic rhinitis. Among the baseline characteristics of the study population, parental rhinitis and the presence of atopic eczema in the child during the first 6 months of life were related to increased risk of persistent asthma (Table 1). Parental asthma and atopic eczema, the presence of atopic eczema in the child during the first 6 months of life and male sex were associated with increased risk of allergic rhinitis and having had a pet in the family during the first year of the life of the child was associated with a reduced risk of allergic rhinitis (Table 1).

Age at introduction of wheat, rye, oats and barley

The age at introduction of wheat, rye, oats and barley was not differentiated during the first year of the study (September 1996-August 1997). Using the combined variable for the age at introduction of any of these exposures allowed us to model the effects on outcomes separately. The models are adjusted for parental asthma, rhinitis and atopic eczema, gestational age, maternal age and smoking during pregnancy, mode of delivery, child’s sex, age at introduction of any of these exposures and the potential confounders (Table 4).

<table>
<thead>
<tr>
<th>Age (months)†</th>
<th>No. of cases (total n)</th>
<th>HR</th>
<th>95 % CI</th>
<th>P</th>
<th>HR</th>
<th>95 % CI</th>
<th>P</th>
<th>HR</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile: ≤ 6-0</td>
<td>25 (443)</td>
<td>0.34</td>
<td>0.22, 0.54</td>
<td>&lt;0.001</td>
<td>0.51</td>
<td>0.29, 0.88</td>
<td>0.049</td>
<td>0.28, 0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second tertile: 6.1–8-5</td>
<td>25 (341)</td>
<td>0.45</td>
<td>0.28, 0.70</td>
<td>0.049</td>
<td>0.94</td>
<td>0.57, 1.54</td>
<td>0.091</td>
<td>0.56, 1.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third tertile: &gt; 8-5</td>
<td>69 (422)</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheat, barley, rye or oats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>First tertile: ≤ 5-0</td>
<td>21 (206)</td>
<td>0.77</td>
<td>0.47, 1.25</td>
<td>0.003</td>
<td>0.91</td>
<td>0.57, 1.54</td>
<td>0.003</td>
<td>0.91</td>
<td>0.56, 1.48</td>
<td></td>
</tr>
<tr>
<td>Mid-tertile: 5.0–5-49</td>
<td>37 (549)</td>
<td>0.48</td>
<td>0.32, 0.73</td>
<td>0.65</td>
<td>0.39, 1.08</td>
<td>1.00</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last tertile: &gt;5-5</td>
<td>62 (457)</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Cox regression survival model was used in the analysis. Model 1 includes fish and combined cereals (wheat, barley, rye or oats) and model 2 includes fish. In addition, both of the models are adjusted for parental asthma, rhinitis and atopic eczema, gestational age, maternal age and smoking during pregnancy, mode of delivery, child’s sex, study area, presence of atopic eczema during the first 6 months of life, number of siblings and presence of pets at home during the first year of life.

<table>
<thead>
<tr>
<th>Month of birth</th>
<th>No. of cases (total n)</th>
<th>HR</th>
<th>95 % CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-tertile: 5.0–5-49</td>
<td>37 (549)</td>
<td>0.48</td>
<td>0.32, 0.73</td>
<td>0.65</td>
</tr>
<tr>
<td>Last tertile: &gt;5-5</td>
<td>62 (457)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age at introduction of fish and egg

Early introduction of fish and egg was related to a decreased risk of persistent asthma (Table 3), but when age at introduction of fish, egg and oats together with potential confounders was introduced to the same model, only oats remained significant (Table 3).

Early introduction of fish was related to a decreased risk of allergic rhinitis (Table 4). Also early age at introduction of wheat, rye, oats or barley was related to the decreased risk of allergic rhinitis, but this association became non-significant after adjustment for fish and potential confounding variables (Table 4). Fish remained significant when adjusted for the before-mentioned cereals and the potential confounders (Table 4).

Duration of breastfeeding and age at introduction of cow’s milk

Duration of total and exclusive breastfeeding was associated with neither asthma (HR (95 % CI) for the lowest and mid-tertiles compared with the highest was 1.35 (0.71, 2.55) and 1.30 (0.69, 2.45) for total breastfeeding, respectively, and 0.93 (0.53, 1.63) and 0.73 (0.38, 1.42) for exclusive breastfeeding, respectively) nor allergic rhinitis (HR (95 % CI) for the lowest and mid-tertiles compared with the highest was 1.10 (0.64, 1.88) and 1.08 (0.61, 1.63) for total breastfeeding, respectively, and 0.96 (0.57, 1.66) and 0.84 (0.48, 1.46) for exclusive breastfeeding, respectively), neither among infants from families with parental asthma, allergic rhinitis or atopic eczema (results not shown). The results regarding exclusive breastfeeding were similar when the information on feeding at the delivery hospital was taken into account (results not shown). Several measures of cow’s milk exposure were used: any type of cow’s milk exposure, exposure to cow’s milk-based infant formulas (hydrolysed and soya-based formulas were excluded) and early exposure in the delivery hospital. The age at introduction of any of these exposures was unrelated to the endpoints.

Effects of parental asthma, allergic rhinitis or atopic eczema on infant feeding

Parental asthma and allergic rhinitis were associated with later introduction of some foods. For example, oats and fish were
introduced to the child at the age of 5.8 v. 5.6 months
(P=0.214) and 8.8 v. 8.0 (P=0.013) months in the families
with and without parental asthma, respectively. The respective
figures in the families with and without parental allergic
rhinitis were 5.7 v. 5.4 months for oats (P=0.020) and 8.4 v. 7.7 months for fish (P<0.001). To take into account the
possibility that parental asthma, allergic rhinitis or atopic
eczema affected the way the parents fed their children, the
final analyses were repeated for those families for whom
one or both parents were affected by at least one of these
three diseases. Among these ‘atopic’ families (n 836), the
association between an early age at introduction of oats and
a decreased risk of persistent asthma in the child remained
significant (HR (95 % CI) for the first and mid-tertiles compared
with the latest tertile was 0·31 (0·11, 0·90) and
0·39 (0·23, 0·69), respectively, P for the term=0·002).
Among families in which either or both of the parents had
asthma (n 154), there was no significant association between
early introduction of oats and development of persistent
asthma (HR (95 % CI) for the first and mid-tertiles compared
with the latest tertile was 0·28 (0·04, 2·30) and 0·48 (0·17,
1·36), respectively, P for the term=0·251), although the
direction of the association remained the same.

Among the ‘atopic’ families (n 890), an early age at intro-
duction of fish remained significantly associated with a
decreased risk of allergic rhinitis in the child (HR (95 % CI)
for the first and mid-tertiles compared with the latest tertile was
0·34 (0·20, 0·56) and 0·38 (0·22, 0·64), respectively,
P for the term <0·0001). Among families in which either or
both of the parents had allergic rhinitis (n 715), there was
also a significant association between early introduction of
fish and decreased development of allergic rhinitis (HR
(95 % CI) for the first and mid-tertiles compared with
the latest tertile 0·35 (0·20, 0·60) and 0·41 (0·23, 0·72),
respectively, P for the term <0·0001).

Discussion

The present findings suggest that early introduction of certain
foods into the infant diet is associated with reduced develop-
ment of asthma and allergic rhinitis. Specifically, early
introduction of oats was associated with decreased risk of
asthma and early introduction of fish with decreased risk of
allergic rhinitis. The main virtues of the present study are
a well-defined study population and basing endpoints on
standardised and validated international questionnaire(20)
adapted for the Finnish situation(21).

In the present study, the collection of dietary data before the
development of the endpoints excluded the possibility of
differential bias in the selection of subjects or in the reporting
of dietary habits. We chose to use predefined categories of the
explanatory variables to avoid post hoc or outcome-dependent
choices of categorisation. In contrast to previous analyses in
similar studies, we have accommodated between-sibling
dependence, i.e. taken into account that there were fifty-
three sibling pairs from the same families in our series. The
strength of the study is that it was not defined as an allergy
study, nor an allergy prevention study, but rather as a study
focusing on nutrition, diet and type 1 diabetes.

The time window for the first exposure is conspicuously
narrow in Finland for some of the supplementary foods
introduced in infancy, e.g. rye and oats. This reflects that
most Finnish parents comply in this respect closely with the
national recommendations on infant feeding conveyed by the
staff at the well-baby clinics. The narrow age range would
make the analyses less sensitive for detecting any risk or
protective effects of early exposure to various foods in relation
to asthma or allergic rhinitis.

The reason for the present findings might be reverse
causation: the presence of allergic diseases and/or asthma in
the family could have influenced infant feeding. Some foods
(e.g. fish) were indeed introduced later in families with
parental asthma or rhinitis. To exclude this, we first adjusted
for parental asthma, allergic rhinitis and eczema in the multi-
variate analysis. Second, we looked at the associations
between feeding and the risk of persistent asthma and allergic
rhinitis separately in atopic families; third, separately in
families with parental asthma or parental allergic rhinitis.
The findings remained consistent in all these comparisons.
Neither did adjusting for the presence of eczema by 6
months of age change the results.

The present population comprised only children with
increased HLA-conferred genetic susceptibility to type 1 dia-
betes (15 % of all newborn infants). The evidence concerning
whether children with type 1 diabetes have less allergic
diseases and asthma than other children is inconsistent(22,23).
In previous Finnish studies, the prevalence of clinically
diagnosed asthma in school-aged children was 4 % and that
of allergic rhinitis 16 %, the figures being quite similar to the
present findings(21,24). Most importantly, it is quite unlikely a
priori that the association between diet and allergic disease
would differ between subjects genetically susceptible to type
1 diabetes and the general population.

The dietary exposures measured can act at least partly as
proxies of other lifestyle characteristics. In industrialised
countries, low educational attainment, young age, single
marital status and smoking of the mother, low gestational
age, Caesarean section, having a first baby, having a baby of
male sex, high number of siblings, and urban environment
are factors that associate inversely with total and exclusive
durations of breastfeeding and with age at introduction of sup-
plementary foods(19,25–28). Conversely, allergic diseases and
asthma have been inconsistently linked to improved hygiene,
decreased or changed exposure to common infections during
infancy, small number of siblings, high educational
level, Caesarean section, low birth order and day care non-
attendance(29–31). The adoption of hygiene practices is
influenced to some degree by social, lifestyle and environ-
mental factors(32). Adjustment for several putative confounding
factors, however, had minor effects on the present results.

Primary prevention of allergic diseases has on occasion
been a subject of heated debate(16) Research has focussed on
high-risk families, i.e. those already including members with
allergic diseases. Eliminating foods from maternal diet
during pregnancy or lactation or infant diet has been the
primary prevention method, combined with the promotion of
breastfeeding. The European recommendation strongly
advocates exclusive breastfeeding and avoidance of solids
for the first 4–6 months of life. We could not demonstrate
any association between long duration of total or exclusive
breastfeeding and a decrease in the frequency of asthma or
allergic rhinitis. This is in agreement with a systematic
review concluding that exclusive breastfeeding for 6 months has not been shown to significantly reduce atopic eczema, asthma or other atopic outcome\textsuperscript{(40)}.

There are two interesting observations in the present study. The first is the apparent association between early introduction of oats and protection against persistent asthma. Oats is a commonly used cereal in Finland, as porridge and bread. It is often grouped together with wheat, rye and barley, but it is not closely related to these; e.g. patients with coeliac disease cannot eat wheat, rye or barley, but can use oats\textsuperscript{(33)}. Animal and cell experiments suggest that oats may have immunomodulatory and anti-inflammatory properties\textsuperscript{(34,35)}. The same is true for fish – the second interesting finding was that early introduction of fish associates with a reduced frequency of allergic rhinitis. Fish oils may modulate inflammatory responses and have inconsistently modified the risk of allergic diseases and asthma\textsuperscript{(36)}.

The present findings imply that delaying introduction of oats in infancy may increase the risk of asthma by the age of 5 years at least in children with genetic susceptibility for type 1 diabetes. As shown before, delaying introduction of fish may increase risk of allergic rhinitis. These observations need to be confirmed in other populations.

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Contribution of each author. S. M. V., M. K. and J. P. designed the present study, M. G. K. and S. M. V. planned the statistical analysis and S. M. V. analysed the data. S. M. V. wrote the manuscript. C. K.-K. and U. U. participated in preparing and interpreting the data. P. P. and T. H. participated in interpreting the data. O. S., J. I., R. V. and M. K. were responsible for the clinical study. All authors participated in drafting and revising of the manuscript, and approved the final version to be published.

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