

# Food consumption and risk of childhood asthma

Mirka Lumia<sup>1,2,3</sup>, Hanna-Mari Takkinen<sup>1,2</sup>, Päivi Luukkainen<sup>3</sup>, Minna Kaila<sup>4,5</sup>, Susanna Lehtinen-Jacks<sup>2</sup>, Bright I. Nwaru<sup>6</sup>, Jetta Tuokkola<sup>3</sup>, Onni Niemelä<sup>7</sup>, Anna-Maija Haapala<sup>8</sup>, Jorma Ilonen<sup>9,10</sup>, Olli Simell<sup>11</sup>, Mikael Knip<sup>3,5,12,13</sup>, Riitta Veijola<sup>14</sup> & Suvi M. Virtanen<sup>1,2,15</sup>

<sup>1</sup>Nutrition Unit, Department of Lifestyle and Participation, National Institute for Health and Welfare, Helsinki, Finland; <sup>2</sup>School of Health Sciences, University of Tampere, Tampere, Finland; <sup>3</sup>Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; <sup>4</sup>Faculty of Medicine, Department of Public Health, University of Helsinki, Helsinki, Finland; <sup>5</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland; <sup>6</sup>Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University Of Edinburgh, Edinburgh, UK; <sup>7</sup>Department of Laboratory Medicine and Medical Research Unit, Seinäjoki Central Hospital and University of Tampere, Seinäjoki, Finland; <sup>8</sup>Center for Laboratory Medicine, Pirkanmaa Hospital District, Tampere, Finland; <sup>9</sup>Immunogenetics Laboratory, University of Turku, Turku, Finland; <sup>10</sup>Department of Clinical Microbiology, University of Eastern Finland, Kuopio, Finland; <sup>11</sup>Department of Pediatrics, University of Turku, Turku, Finland; <sup>12</sup>Folkhälsan Research Institute, University of Helsinki, Helsinki, Finland; <sup>13</sup>Diabetes and Obesity Research Program, University of Helsinki, Helsinki, Finland; <sup>14</sup>Department of Pediatrics, University of Oulu, Oulu, Finland; <sup>15</sup>Research Center for Child Health and Science Centre of Pirkanmaa Hospital District, Tampere University Hospital and University of Tampere, Tampere, Finland

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## Keywords

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## Correspondence

Mirka Lumia, Nutrition Unit, Department of Lifestyle and Participation, National Institute for Health and Welfare, PO Box 30, FIN-00271 Helsinki, Finland  
Tel.: +35 85 04 94 49 99  
Fax: +35 82 06 10 85 91  
E-mail: mirka.lumia@hus.fi

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## Abstract

**Background:** The consumption of foods rich in n-3 polyunsaturated fatty acids has been proposed to protect against childhood asthma. This study explores the association of food consumption (including cow's milk (CM)-free diet) in early life and the risk of atopic and non-atopic asthma.

**Methods:** Food intake of 182 children with asthma and 728 matched controls was measured using 3-day food records, within the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study cohort. The diagnoses of food allergies came both from the written questionnaire and from the registers of the Social Insurance Institution. Conditional logistic regression with generalized estimating equations framework was used in the analyses.

**Results:** The diagnosis of cow's milk allergy (CMA) led to multiple dietary restrictions still evident at 4 yr of age. Even after adjusting for CMA, higher consumption of CM products was inversely associated with the risk of atopic asthma and higher consumption of breast milk and oats inversely with the risk of non-atopic asthma. Early consumption of fish was associated with a decreased risk of all asthma.

**Conclusions:** Dietary intake in early life combined with atopy history has a clear impact on the risk of developing asthma. Our results indicate that CM restriction due to CMA significantly increases and mediates the association between food consumption and childhood asthma risk.

## Abbreviations

CM, cow's milk; CMA, cow's milk allergy; DIPP, the Finnish Type 1 Diabetes Prediction and Prevention Study; EER, estimated energy requirement; FADS, fatty acid desaturase; GEE, generalized estimating equation; HLA, human leukocyte antigen; IgE, immunoglobulin E; ISAAC, The International Study of Asthma and Allergies in Childhood; PUFA, polyunsaturated fatty acids; TEE, total energy requirement.

The development of asthma has been suggested to require multiple environmental exposures in genetically predisposed individuals. Exposures, such as dietary and microbial ones, can interact with each other resulting in different asthma phenotypes (1). Nutrition in early life is increasingly considered to be an important factor influencing later health. The nutrition during the perinatal period and infancy has been proposed to modulate the development of the respiratory, digestive, and immune systems (2–5).

There is evidence that foods rich in antioxidants and n-3 polyunsaturated fatty acids (PUFA) have protective effects on oxidative damage and on inflammation of the lung tissue (6). Earlier studies have reported associations between higher consumption of fruits, vegetables, nuts, whole-grain cereals and whole-fat dairy products during childhood and a decreased risk of asthma (4, 7). Also, Mediterranean diet has been protective against childhood wheeze and asthma (8, 9). The evidence on the associations between fish intake and the risk of asthma is inconsistent (7).

Despite some promising findings, evidence of the role of diet in early life in the development of childhood asthma is limited and inconclusive. In particular, studies investigating the role of longitudinal dietary intake and the development of childhood asthma are few. We have previously shown that cow's milk allergy (CMA) confounds associations between serum fatty acids and childhood asthma risk (10). The aim of this study was to prospectively investigate the associations between food consumption in early life with special emphasis on CM-restricted diet due to CMA and the risk of developing atopic and non-atopic asthma.

## Methods

### Subjects and study design

In the DIPP birth cohort study, newborn infants at three University Hospitals in Finland (Turku, Tampere, and Oulu) were screened for human leukocyte antigen (HLA)-conferred (HLA-DQB1) susceptibility to type 1 diabetes from cord blood samples. Infants carrying a high or moderate genetic risk were invited to participate as described earlier (11). This study was approved by the local ethical committees of the respective hospitals, and a written informed consent was obtained from the parents.

The nutritional arm (DIPP Nutrition Study) of the larger DIPP started in 1996. Children still participating in the dietary follow-up at the age of 5 yr were invited to participate in the Allergy Study. The parents completed a modified, the International Study of Asthma and Allergic diseases (ISAAC)-based questionnaire on the family's history of asthma and allergic diseases. The asthma component of the questionnaire has been validated for epidemiological research (12). A blood sample was obtained from each child for serum Immunoglobulin E (IgE) analysis at the age of 5 yr.

The present analysis is nested within the cohort of children born between 1996 and 2004 in Tampere ( $n = 3916$ ) and Oulu ( $n = 3866$ ). All subjects must have completed the ISAAC questionnaire and have at least one-three-day food record available under the age of 5 yr. For each case, four controls free of asthma until the age when the case was diagnosed with asthma, and matched for gender, genetic risk group for type 1 diabetes, hospital (Oulu or Tampere), and time of birth (range  $\pm 3$  months), were randomly selected. The control must have been followed-up for asthma at least until the age of 5 yr and must not come from the same family as the case.

The controls were independently selected, and thus, one control child can be a control for more than one case and can become a case at a later time point. The present analysis comprises 182 asthma cases and 728 matched controls.

### Assessments of end-points

Asthma was defined as doctor-diagnosed asthma *plus* either any wheezing symptom or use of asthma medication during the past 12 months preceding the completion of the written questionnaire (12). All the cases still had asthma at the age of 5 yr indicating persisting asthma.

Specific IgE concentrations were measured from serum samples obtained at the age of 5 yr using ImmunoCAP fluoroenzyme immunoassay (Phadia Diagnostics, Uppsala, Sweden). IgE-positivity cutoff value was set at  $\geq 0.35$  kU/l. Atopy was defined as sensitization to any of the tested allergens (egg, cow's milk [CM], fish, wheat, house dust mite, cat, timothy grass, or birch). Atopic asthma was determined as IgE-positive and non-atopic asthma as IgE-negative asthma.

Food allergies and special diets were asked from the parents at the study center visits with open questions at the ages of 6 months, and 1 and 2 yr, and also with a structured questionnaire at the ages of 3, 4, and 6 yr. The structured questionnaire was validated against hospital records and against information on CMA diagnosis from the registers of the Social Insurance Institution (13). The diagnoses of food allergies came both from the structured questionnaire and from the registers of the Social Insurance Institution. The occurrences of CMA, lactose intolerance, celiac disease, any food allergies, vegetarian diet, and elimination of any allergenic food were asked in a standardized questionnaire. The starting and ending dates of special diets were enquired separately (14).

### Dietary methods

The dietary information was enquired by means of 3-day food records, completed by parents at home, at the ages of three, six, and 12 months and thereafter annually up to 6 yr of age. The collection and procession of the food consumption data have been described in detail earlier (14). Data on timing of introduction of new foods to the diet were collected up to 2 yr of age by means of structured dietary questionnaires (15).

Among breastfed infants, the quantity of breast milk consumed was calculated based on estimated energy requirements and growth by 1 yr of age (16). Energy need was estimated based on energy requirements for weight and age, plus the estimated amount of incremental energy needed to support tissue accretion (energy deposition) (16). Estimated energy requirement (EER) equals to total energy requirement (TEE) plus energy deposition. Estimated energy from breast milk equals to EER minus energy intake from food records (Table 1). Based on this, the amount of breast milk consumed per day was calculated. The growth of children was measured every 3–12 months at the study center visits.

**Table 1** Calculation of estimated energy requirement (EER) for infants and young children: EER equals to total energy requirement (TEE) plus energy deposition (16)

| Age (months) | TEE (kcal)                     | Energy deposition (kcal) |
|--------------|--------------------------------|--------------------------|
| 0–3          | 89 × weight of infant (kg)-100 | 175                      |
| 4–6          | 89 × weight of infant (kg)-100 | 56                       |
| 7–12         | 89 × weight of infant (kg)-100 | 22                       |

### Sociodemographic and perinatal characteristics

Information on the child's sex, maternal age, and parental vocational education was obtained from a structured questionnaire completed by the parents after delivery. Information on birth weight, duration of gestation, mode of delivery, number of previous deliveries, and maternal smoking during pregnancy was received from the Medical Birth Registries of Oulu and Tampere University Hospitals. Information on parental asthma or allergic rhinitis and dogs at home during the first year of life was determined from the ISAAC questionnaire. Information on the duration of breastfeeding was received from the written questionnaire. The diagnoses of food allergies come both from the structured questionnaire and from the Social Insurance Institution registers.

### Statistical methods

Measurements of the same individual tend to be correlated, and to accommodate this, a conditional logistic regression analysis with a generalized estimating equation (GEE) framework to estimate regression coefficients was used to analyze the associations between the longitudinal food intakes and the risk of asthma in this nested case-control data set (17). The analyses were made separately for atopic and non-atopic asthma cases. Interactions between food consumption variables and CMA, CM use, and asthma were assessed using interaction tests. All food variables were  $\log(x + 1)$ -transformed to obtain normality.

Differences in background characteristics between cases and controls were assessed using the conditional logistic regression analysis. When the proportion of food users was  $\geq 25\%$ , median food consumption was calculated separately in children with and without CMA, and the Mann-Whitney *U*-test was applied to examine the differences. When the proportion of food users was  $< 25\%$ , food consumption was categorized to users and non-users, and the chi-square or Fisher's exact test was used to examine the differences.

The following covariates were used as potential confounders in the adjusted models: gestational age, maternal age, maternal smoking during pregnancy, duration of breastfeeding, number of siblings, parental asthma or allergic rhinitis, birth weight, mode of delivery, maternal vocational education, dogs at home

during the first year of life, CMA, and age at introduction of solid foods (rye, wheat, barley, oats, fish, and egg) in thirds. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for the analyses.

### Results

The median age at asthma diagnosis was 3 (range 1–5) yr. Of the background characteristics, full-term pregnancy, introduction of oats, wheat, barley, or rye at the age of 5–5.5 months, that of fish at 6.1–8 months and that of egg at 10 months or earlier were associated with a decreased risk of asthma. Parental asthma or allergic rhinitis and duration of total breastfeeding  $< 9$  months were associated with an increased risk of asthma (Table 2).

The estimated median (range) consumption of breast milk in grams per day was 860 (28–989) and 231 (0–693) at the ages of 3 and 6 months, respectively. At the age of 12 months, 13.5% of the children were breastfed, and among those, the median (range) consumption of breast milk was 344 (170–563) g.

Food consumption between children with and without the diagnosis of CMA differed significantly during the first 4 yrs. At the age of 6 months, children with CMA consumed less CM products and CM-based infant formulas, as expected. In addition, they consumed less oats, wheat, barley, or rye, meat and meat products, fish and fish products, oils and margarines, roots and potatoes, fruits and berries, as well as fruit and berry juices compared to those with no history of CMA (Table 3). At the age of 1 yr, children with CMA consumed less CM products, CM-based infant formulas, oats, wheat, barley, or rye, fish and fish products, eggs, butter and fruit and berry juices. However, they consumed more soy products, other cereals (rice, buckwheat, corn flour, or millets), and vegetables. At the age of 2 yr, the diet of children with or without CMA still differed from each other (Table 3). These differences diminished by the age of three and 4 yr but still at the age of 4 yr, the diet of children with history of CMA contained less fish and fish products and CM products, but more fruits and berries, and fruit and berry juices than the diet of those children with no history of CMA (data not shown).

Higher consumption of breast milk, CM products, oats, wheat, barley, or rye, and fish and fish products was associated with a decreased risk of asthma in the unadjusted model (Table 4). In contrast, higher consumption of soy products, other cereals (rice, buckwheat, corn flour, or millets), and vegetables was associated with an increased risk of asthma. After adjusting for potential confounders including CMA, only a higher consumption of fish and fish products was associated with a decreased risk of asthma. After further adjustment with age at introduction of fish, this association was no longer significant possibly indicating the importance of early consumption.

When stratifying for atopy, even after adjusting for CMA, higher consumption of CM products and wheat, barley, or rye was inversely associated with the risk of atopic asthma. After adjusting for age at introduction of the corresponding cereals, only higher consumption of CM products was inversely

**Table 2** Distribution of background characteristics and their associations with asthma

| Background characteristics                                             | Frequency (%) <sup>*</sup> | OR (95% CI)             | p-value <sup>†</sup> |
|------------------------------------------------------------------------|----------------------------|-------------------------|----------------------|
| Sex                                                                    |                            |                         |                      |
| Boys                                                                   | 492 (61.1)                 |                         |                      |
| Girls                                                                  | 313 (38.9)                 |                         |                      |
| Maternal age, years                                                    |                            |                         |                      |
| <25                                                                    | 136 (16.9)                 | 1                       | 0.46                 |
| 25–29                                                                  | 282 (35.0)                 | 0.88 (0.54–1.42)        |                      |
| 30–34                                                                  | 248 (30.8)                 | 0.92 (0.56–1.52)        |                      |
| >34                                                                    | 139 (17.3)                 | 0.63 (0.35–1.15)        |                      |
| Mode of delivery                                                       |                            |                         |                      |
| Vaginal                                                                | 690 (85.7)                 | 1                       | 0.79                 |
| Cesarean section                                                       | 110 (13.7)                 | 1.06 (0.67–1.70)        |                      |
| Missing information                                                    | 5 (0.6)                    |                         |                      |
| Gestational age (weeks), in quarters                                   |                            |                         |                      |
| 1st <38.9                                                              | 181 (22.5)                 | 1                       | <b>0.02</b>          |
| 2nd 38.9–39.9                                                          | 207 (25.7)                 | 1.02 (0.65–1.60)        |                      |
| 3rd 40.0–40.7                                                          | 214 (26.6)                 | <b>0.54 (0.33–0.88)</b> |                      |
| 4th >40.7                                                              | 198 (24.6)                 | 0.63 (0.38–1.02)        |                      |
| Missing information                                                    | 5 (0.6)                    |                         |                      |
| Number of previous deliveries                                          |                            |                         |                      |
| 0                                                                      | 374 (46.5)                 | 1                       | 0.12                 |
| 1                                                                      | 253 (31.4)                 | 1.24 (0.85–1.83)        |                      |
| 2                                                                      | 108 (13.4)                 | 1.18 (0.71–1.98)        |                      |
| >2                                                                     | 63 (7.8)                   | 0.46 (0.20–1.07)        |                      |
| Missing information                                                    | 7 (0.9)                    |                         |                      |
| Maternal smoking during pregnancy                                      |                            |                         |                      |
| No                                                                     | 710 (88.2)                 | 1                       | 0.60                 |
| Yes                                                                    | 69 (8.6)                   | 0.84 (0.45–1.59)        |                      |
| Missing information                                                    | 26 (3.2)                   |                         |                      |
| Maternal asthma or allergic rhinitis                                   |                            |                         |                      |
| No                                                                     | 373 (46.3)                 | 1                       | <b>&lt;0.001</b>     |
| Yes                                                                    | 405 (50.3)                 | <b>2.28 (1.59–3.26)</b> |                      |
| Missing information                                                    | 27 (3.4)                   |                         |                      |
| Paternal asthma or allergic rhinitis                                   |                            |                         |                      |
| No                                                                     | 445 (55.3)                 | 1                       | <b>&lt;0.01</b>      |
| Yes                                                                    | 316 (39.3)                 | <b>1.81 (1.27–2.58)</b> |                      |
| Missing information                                                    | 44 (5.5)                   |                         |                      |
| Birth weight (g) in quarters                                           |                            |                         |                      |
| 1st <3238                                                              | 200 (24.8)                 | 1                       | 0.16                 |
| 2nd 3238–3589                                                          | 196 (24.4)                 | 0.72 (0.45–1.17)        |                      |
| 3rd 3590–3900                                                          | 208 (25.8)                 | 0.73 (0.46–1.15)        |                      |
| 4th >3900                                                              | 196 (24.4)                 | <b>0.58 (0.36–0.94)</b> |                      |
| Missing information                                                    | 5 (0.6)                    |                         |                      |
| Dogs at home during the 1st year of life                               |                            |                         |                      |
| No                                                                     | 679 (84.4)                 | 1                       | 0.55                 |
| Yes                                                                    | 126 (15.6)                 | 0.87 (0.54–1.39)        |                      |
| Missing information                                                    | –                          |                         |                      |
| Duration of total breastfeeding (months) in thirds                     |                            |                         |                      |
| 1st <5                                                                 | 263 (32.7)                 | <b>1.78 (1.14–2.77)</b> | <b>0.02</b>          |
| 2nd 5–9                                                                | 289 (35.9)                 | <b>1.77 (1.14–2.75)</b> |                      |
| 3rd >9                                                                 | 246 (30.6)                 | 1                       |                      |
| Missing information                                                    | 7 (0.9)                    |                         |                      |
| Age at introduction of rye, wheat, barley, and oats (months) in thirds |                            |                         |                      |
| 1st <5                                                                 | 144 (17.9)                 | 0.72 (0.43–1.19)        | <b>&lt;0.01</b>      |
| 2nd 5–5.5                                                              | 455 (56.5)                 | <b>0.55 (0.37–0.81)</b> |                      |
| 3rd >5.5                                                               | 187 (23.2)                 | 1                       |                      |
| Missing information                                                    | 19 (2.4)                   |                         |                      |

**Table 2.** (Continued).

| Background characteristics                     | Frequency (%) <sup>*</sup> | OR (95% CI)             | p-value <sup>†</sup> |
|------------------------------------------------|----------------------------|-------------------------|----------------------|
| Age at introduction of fish (months) in thirds |                            |                         |                      |
| 1st <6.1                                       | 279 (34.7)                 | 0.66 (0.43–1.01)        | <b>&lt;0.01</b>      |
| 2nd 6.1–8                                      | 234 (29.1)                 | <b>0.45 (0.28–0.72)</b> |                      |
| 3rd >8                                         | 222 (27.6)                 | 1                       |                      |
| Missing information                            | 70 (8.7)                   |                         |                      |
| Age at introduction of egg (months) in thirds  |                            |                         |                      |
| 1st <8                                         | 208 (25.8)                 | <b>0.53 (0.33–0.84)</b> | <b>&lt;0.001</b>     |
| 2nd 8–10                                       | 261 (32.4)                 | <b>0.43 (0.27–0.68)</b> |                      |
| 3rd >10                                        | 250 (31.1)                 | 1                       |                      |
| Missing information                            | 86 (10.7)                  |                         |                      |

<sup>\*</sup>Seventy-six children served as controls for more than one case but were included only once in the total number of controls. Fifteen of the controls became a case at a later date and were counted only as cases.

<sup>†</sup>Conditional logistic regression was used to test associations between background characteristics and asthma.

P<0.05 are indicated as bold.

**Table 3** Median intakes (g) or proportion of users (%)<sup>\*</sup> of different food groups in children with and without cow's milk allergy (CMA) at the ages of 6, 12, and 24 months

| Food group                                    | 6 months          |                |                  | 12 months         |               |                  | 24 months         |               |                  |
|-----------------------------------------------|-------------------|----------------|------------------|-------------------|---------------|------------------|-------------------|---------------|------------------|
|                                               | No CMA<br>n = 650 | CMA<br>n = 104 | p-value          | No CMA<br>n = 602 | CMA<br>n = 96 | p-value          | No CMA<br>n = 440 | CMA<br>n = 63 | p-value          |
| Breast milk                                   | 239               | 0              | 0.70             | –                 | –             | –                | –                 | –             | –                |
| Cow's milk products                           | 246               | 0              | <b>&lt;0.001</b> | 612               | 0             | <b>&lt;0.001</b> | 591               | 108           | <b>&lt;0.001</b> |
| Cow's milk based infant formulas <sup>*</sup> | 133               | 0              | <b>&lt;0.001</b> | 47.8%             | 17.7%         | <b>&lt;0.001</b> | –                 | –             | –                |
| Hydrolyzed infant formulas <sup>*</sup>       | 0.2%              | 18.3%          | <b>&lt;0.001</b> | 0.3%              | 31.3%         | <b>&lt;0.001</b> | 0.2%              | 12.7%         | <b>&lt;0.001</b> |
| Soy products <sup>*</sup>                     | 0.3%              | 1.9%           | 0.09             | 10.0%             | 22.9%         | <b>&lt;0.001</b> | 0                 | 0             | <b>&lt;0.01</b>  |
| Oats                                          | 4.3               | 0              | <b>&lt;0.001</b> | 14                | 8.4           | <b>&lt;0.001</b> | 8.5               | 8.0           | 0.66             |
| Wheat, barley, and rye products <sup>*</sup>  | 57.9%             | 23.2%          | <b>&lt;0.001</b> | 26                | 13            | <b>&lt;0.001</b> | 46                | 46            | 0.13             |
| Other cereals <sup>†</sup>                    | 1.2               | 0.70           | 0.41             | 3.5               | 7.2           | <b>&lt;0.001</b> | 6.6               | 12            | <b>&lt;0.001</b> |
| Meat and meat products                        | 12                | 6.07           | <b>&lt;0.01</b>  | 40                | 42            | 0.53             | 60                | 70            | <b>&lt;0.01</b>  |
| Fish and fish products <sup>*</sup>           | 14.3%             | 3.9%           | <b>&lt;0.01</b>  | 42.4%             | 21.9%         | <b>&lt;0.01</b>  | 0                 | 0             | 0.09             |
| Eggs <sup>*</sup>                             | 3.4%              | 0.9%           | 0.23             | 0.3               | 0             | <b>&lt;0.001</b> | 3.7               | 0.9           | <b>&lt;0.001</b> |
| Butter <sup>*</sup>                           | 5.5%              | 3.9%           | 0.47             | 0.3               | 0             | <b>&lt;0.001</b> | 2.5               | 0.8           | <b>&lt;0.001</b> |
| Oils and margarines                           | 2.1               | 1.13           | <b>&lt;0.001</b> | 4.5               | 4.8           | 0.68             | 5.6               | 7.5           | <b>&lt;0.01</b>  |
| Roots and potatoes                            | 54                | 50.78          | <b>0.04</b>      | 87                | 84            | 0.70             | 73                | 69            | 0.45             |
| Fruits and berries                            | 44                | 27.93          | <b>&lt;0.001</b> | 65                | 71            | 0.44             | 83                | 108           | 0.06             |
| Fruit and berry juices <sup>*</sup>           | 22.3%             | 9.6%           | <b>&lt;0.01</b>  | 45.0%             | 16.7%         | <b>&lt;0.001</b> | 0.7               | 0.2           | 0.55             |
| Vegetables                                    | 5.3               | 4.49           | 0.82             | 21                | 26            | <b>0.03</b>      | 28                | 43            | <b>&lt;0.001</b> |

<sup>\*</sup>When the proportion of food users was  $\geq 25\%$ , median (range) food intakes were calculated separately in children with and without CMA, and Mann–Whitney *U*-test was used to examine the differences. When the proportion of food users was  $< 25\%$ , food intakes were categorized to users and non-users, and chi-square or Fisher's exact test was used to examine the differences.

<sup>†</sup>Other cereals included rice, buckwheat, corn flour, and millets.

P<0.05 are indicated as bold.

associated with the risk of atopic asthma. Among the children with history of CMA, those with atopic asthma consumed less CM products compared to those children with no atopic asthma. Between the ages of 3 months to 3 yr, the median consumption was below 1 g per day. At the age of 4 yr, children with atopic asthma still consumed 30% less CM

products compared to those with no atopic asthma. However, the numbers of subjects in these groups were small (range 3–30), and the differences in CM product consumption were not statistically significant (data not shown). Further, higher consumption of breast milk and oats was inversely associated with the risk of non-atopic asthma (Table 4).

**Table 4** Odds ratios (95% CI) for the risk of asthma associated with food intake during infancy and childhood analyzed longitudinally until the diagnosis of asthma

| Food group                       | All asthma OR (95% CI) unadjusted (182 cases and 728 controls) |                  | All asthma OR (95% CI) adjusted* (154 cases and 636 controls) |             | Atopic asthma OR (95% CI) adjusted* (86 cases and 342 controls) |                 | Non-atopic asthma OR (95% CI) adjusted* (62 cases and 265 controls) |             |
|----------------------------------|----------------------------------------------------------------|------------------|---------------------------------------------------------------|-------------|-----------------------------------------------------------------|-----------------|---------------------------------------------------------------------|-------------|
|                                  |                                                                | p-value          |                                                               | p-value     |                                                                 | p-value         |                                                                     | p-value     |
| Breast milk                      | <b>0.95 (0.91–0.99)</b>                                        | <b>0.03</b>      | 0.96 (0.91–1.02)                                              | 0.21        | 0.99 (0.91–1.07)                                                | 0.71            | <b>0.92 (0.85–0.99)</b>                                             | <b>0.03</b> |
| Cow's milk products              | <b>0.93 (0.88–0.98)</b>                                        | <b>0.01</b>      | 0.95 (0.90–1.00)                                              | 0.07        | <b>0.92 (0.85–0.99)</b>                                         | <b>0.04</b>     | 0.98 (0.91–1.06)                                                    | 0.65        |
| Soy products                     | <b>1.27 (1.09–1.48)</b>                                        | <b>&lt;0.01</b>  | 1.09 (0.94–1.27)                                              | 0.27        | 1.00 (0.81–1.23)                                                | 0.99            | 1.13 (0.86–1.48)                                                    | 0.38        |
| Oats                             | <b>0.86 (0.78–0.95)</b>                                        | <b>&lt;0.01</b>  | 0.92 (0.82–1.03)                                              | 0.14        | 0.95 (0.82–1.10)                                                | 0.52            | 0.87 (0.73–1.05)                                                    | 0.14        |
| Oats†                            |                                                                |                  | 0.92 (0.82–1.04)                                              | 0.19        | 1.00 (0.84–1.18)                                                | 0.96            | <b>0.81 (0.68–0.96)</b>                                             | <b>0.01</b> |
| Wheat, barley, and rye products  | <b>0.74 (0.64–0.84)</b>                                        | <b>&lt;0.001</b> | 0.88 (0.77–1.02)                                              | 0.09        | <b>0.73 (0.61–0.87)</b>                                         | <b>&lt;0.01</b> | 1.28 (0.98–1.67)                                                    | 0.08        |
| Wheat, barley, and rye products† |                                                                |                  | 0.98 (0.83–1.16)                                              | 0.82        | 0.89 (0.71–1.11)                                                | 0.29            | 1.22 (0.92–1.61)                                                    | 0.16        |
| Other cereals‡                   | <b>1.18 (1.07–1.31)</b>                                        | <b>&lt;0.01</b>  | 1.07 (0.96–1.18)                                              | 0.23        | 1.13 (0.98–1.31)                                                | 0.08            | 1.01 (0.84–1.21)                                                    | 0.93        |
| Other cereals‡, †                |                                                                |                  | 0.92 (0.81–1.05)                                              | 0.22        | 1.03 (0.85–1.24)                                                | 0.77            | 0.85 (0.68–1.07)                                                    | 0.16        |
| Meat and meat products           | 0.96 (0.85–1.08)                                               | 0.51             | 0.95 (0.84–1.08)                                              | 0.46        | 0.92 (0.79–1.08)                                                | 0.32            | 0.93 (0.74–1.17)                                                    | 0.53        |
| Fish and fish products           | <b>0.82 (0.73–0.92)</b>                                        | <b>&lt;0.001</b> | <b>0.87 (0.77–0.98)</b>                                       | <b>0.02</b> | 0.84 (0.70–1.01)                                                | 0.07            | 0.99 (0.83–1.17)                                                    | 0.87        |
| Fish and fish products†          |                                                                |                  | 0.93 (0.82–1.05)                                              | 0.26        | 0.89 (0.74–1.07)                                                | 0.20            | 1.03 (0.85–1.25)                                                    | 0.78        |
| Eggs                             | 0.88 (0.77–1.02)                                               | 0.08             | 1.08 (0.89–1.31)                                              | 0.58        | 1.01 (0.79–1.28)                                                | 0.95            | 1.16 (0.97–1.38)                                                    | 0.11        |
| Eggs†                            |                                                                |                  | 1.15 (0.98–1.37)                                              | 0.09        | 1.28 (0.98–1.67)                                                | 0.07            | 1.09 (0.91–1.29)                                                    | 0.34        |
| Dietary fats                     | 1.12 (0.93–1.35)                                               | 0.25             | 1.08 (0.89–1.31)                                              | 0.46        | 1.02 (0.80–1.29)                                                | 0.90            | 1.01 (0.72–1.41)                                                    | 0.98        |
| Butter                           | 0.83 (0.68–1.01)                                               | 0.06             | 0.89 (0.72–1.10)                                              | 0.26        | 0.81 (0.62–1.06)                                                | 0.13            | 1.07 (0.75–1.52)                                                    | 0.72        |
| Oils and margarines              | <b>1.18 (1.00–1.38)</b>                                        | 0.05             | 1.11 (0.93–1.32)                                              | 0.25        | 1.10 (0.88–1.37)                                                | 0.42            | 0.97 (0.73–1.28)                                                    | 0.82        |
| Vegetables                       | <b>1.11 (1.00–1.22)</b>                                        | <b>0.04</b>      | 1.10 (0.98–1.23)                                              | 0.11        | 1.12 (0.96–1.30)                                                | 0.15            | 1.10 (0.92–1.30)                                                    | 0.30        |
| Roots and potatoes               | 0.93 (0.83–1.04)                                               | 0.21             | 0.96 (0.84–1.09)                                              | 0.53        | 0.90 (0.77–1.06)                                                | 0.22            | 0.99 (0.81–1.20)                                                    | 0.91        |
| Fruits and berries               | 0.95 (0.87–1.04)                                               | 0.29             | 0.98 (0.89–1.08)                                              | 0.73        | 0.91 (0.82–1.01)                                                | 0.08            | 1.14 (0.94–1.37)                                                    | 0.18        |
| Fruit and berry juices           | 0.95 (0.88–1.01)                                               | 0.11             | 0.97 (0.89–1.05)                                              | 0.39        | 0.95 (0.85–1.05)                                                | 0.31            | 1.04 (0.90–1.20)                                                    | 0.58        |

\*Adjusted for gestational age, maternal age, maternal smoking during pregnancy, number of siblings, parental asthma or allergic rhinitis, birth weight, mode of delivery, duration of breastfeeding, maternal vocational education, dogs at home during the first year of life, and cow's milk allergy.

†Adjusted in addition for age at introduction of the corresponding food (oats, wheat, barley, rye, other cereals, fish, and egg) in thirds.

‡Other cereals included rice, buckwheat, corn flour, and millets.

P<0.05 are indicated as bold.

## Discussion

This study found that a diagnosis of CMA resulted in significant dietary restrictions continuing until 4 yr of age. Even after adjusting for CMA, higher consumption of CM products remained inversely associated with the risk of atopic asthma. Furthermore, higher consumption of breast milk and oats was inversely associated with the risk of non-atopic asthma. Early consumption of fish was inversely associated with the risk of all asthma.

The presence of asthma and allergic diseases in the family influences the practises of infant feeding. Parents often restrict the diet of the child on the basis of their own allergic diseases (15). Also, the child's own allergic diseases, in particular atopic eczema, can result in extensive elimination of many common allergenic foods from the diet initiated by the parents themselves or even recommended by a physician. In developed countries, 10–20% of children have atopic eczema (18), while only 0.1–6% have food allergy (19). To avoid over diagnosis especially with skin symptoms, food allergy diagnosis should

be carefully considered based on good clinical practise. The results of this study stress the importance of sound clinical judgement before commencing any elimination diets. On the contrary, early diet of infants should be expanded according to nutritional recommendations. In the present study, CMA resulted in dietary restrictions up to 4 yr of age. To analyze the possible disease-related modification in food consumption, CMA was considered as a putative confounder. In earlier studies, children with food allergy were simply excluded from the analysis (20, 21) resulting in biased results, or food allergy was used as a confounding factor (22, 23).

The present study indicates that higher consumption of CM products is inversely associated with the risk of atopic asthma even after adjusting for CMA. In this study, the diagnosis of CMA came from the questionnaire and may overestimate the number of children having CMA and despite using CM products. In earlier studies, consumption of raw or unpasteurized milk has been associated with a reduced risk of allergic diseases and asthma in 4.5-yr-old children (24), in children over 5 yr of age and their parents (25), and in school-aged children. (26) However, those studies reported no information on CMA.

In the current study, fish intake was inversely associated with the risk of asthma. When the age at introduction of fish was included into the same model, the age at introduction of fish was significant ( $p < 0.01$ ) indicating that early consumption of fish may be inversely associated with the risk of asthma. In line with our results, regular fish intake during infancy has been associated with reduced risk of allergic diseases in childhood (20, 21, 23, 26).

In the present study, higher consumption of breast milk was associated with a decreased risk of non-atopic asthma. In accordance, we have previously shown a longer duration of breastfeeding to be inversely associated with the risk of non-atopic asthma (27). Also, in earlier studies, breastfed children had clinically better lung function compared to children fed CM-based infant formulas (1).

The strengths of the present study are a well-defined study population and its prospective nature. Repeated, longitudinally collected food records were used to analyze the associations between long-term dietary data and childhood asthma risk. Food records were checked by trained research staff and entered into the database by a trained nutritionist. The study population was selected before the determination of asthma

and other allergic diseases. The asthma component of the ISAAC-based questionnaire has been validated for epidemiological research (12). Also, we had information on other allergic diseases and special diets and were able to quantitate the BM consumption using detailed growth data and expected energy requirements. To our knowledge, no earlier study has investigated the impact of the quantitative breast milk intake on childhood asthma risk.

The selection of the study population in terms of genetic susceptibility to type 1 diabetes can reduce the applicability of the results to the general population. The evidence of the relationship between atopic diseases and asthma and type 1 diabetes is conflicting (28, 29). The median age of asthma diagnosis was very early (median 3 yr) suggesting that some of the asthma diagnoses could in fact be wheezy bronchitis. However, the prevalence of asthma in our study population (6%) was the same as the prevalence in the general population of the same age group in Finland (30).

In conclusion, dietary intake in early life combined with atopy history is one of the environmental factors associated with the risk of developing asthma. Our results suggest that CMA-associated CM restriction modifies food consumption in early childhood, with significant impact on childhood asthma risk.

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