

# Consumption of differently processed milk products and the risk of asthma in children

Katariina Koivusaari<sup>1,2</sup>  | Essi Syrjäälä<sup>3</sup>  | Sari Niinistö<sup>1</sup> | Suvi Ahonen<sup>1,3,4</sup> |  
 Mari Åkerlund<sup>1,3,4</sup> | Tuuli E. Korhonen<sup>1</sup> | Jorma Toppari<sup>5,6</sup> | Jorma Ilonen<sup>7</sup> |  
 Minna Kaila<sup>8,9</sup>  | Mikael Knip<sup>10,11,12,13</sup>  | Tapani Alatossava<sup>2</sup> | Riitta Veijola<sup>14</sup> |  
 Suvi M. Virtanen<sup>1,3,4,12</sup> 

<sup>1</sup>Public Health and Welfare Department, Finnish Institute for Health and Welfare, Helsinki, Finland

<sup>2</sup>Department of Food and Nutrition, University of Helsinki, Helsinki, Finland

<sup>3</sup>Faculty of Social Sciences, Unit of Health Sciences, Tampere University, Tampere, Finland

<sup>4</sup>Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland

<sup>5</sup>Department of Pediatrics, Turku University Hospital, Turku, Finland

<sup>6</sup>Research Centre for Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland

<sup>7</sup>Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland

<sup>8</sup>Public Health Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

<sup>9</sup>Department of Pediatrics, Tampere University Hospital, Tampere, Finland

<sup>10</sup>Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

<sup>11</sup>Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

<sup>12</sup>Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland

<sup>13</sup>Folkhälsan Research Center, Helsinki, Finland

<sup>14</sup>Department of Pediatrics, PEDEGO Research Unit, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland

## Correspondence

Katariina Koivusaari, Public Health and Welfare Department, Finnish Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland.  
 Email: katariina.koivusaari@thl.fi

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## Abstract

**Background:** Consumption of unprocessed cow's milk has been associated with a lower risk of childhood asthma and/or atopy. Not much is known about differently processed milk products. We aimed to study the association between the consumption of differently processed milk products and asthma risk in a Finnish birth cohort.

**Methods:** We included 3053 children from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study. Asthma and its subtypes were assessed at the age of 5 years, and food consumption by food records, at the age of 3 and 6 months and 1, 2, 3, 4, and 5 years. We used conventional and processing (heat treatment and homogenization)-based classifications for milk products. The data were analyzed using a joint model for longitudinal and time-to-event data.

**Results:** At the age of 5 years, 184 (6.0%) children had asthma, of whom 101 (54.9%) were atopic, 75 (40.8%) were nonatopic, and eight (4.3%) could not be categorized. Consumption of infant formulas [adjusted hazard ratio (95% confidence intervals) 1.15 (1.07, 1.23),  $p < .001$ ] and strongly heat-treated milk products [1.06 (1.01, 1.10),

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$p = .01$ ] was associated with the risk of all asthma. Consumption of all cow's milk products [1.09 (1.03, 1.15),  $p = .003$ ], nonfermented milk products [1.08 (1.02, 1.14),  $p = .008$ ], infant formulas [1.23 (1.13, 1.34),  $p < .001$ ], and strongly heat-treated milk products [1.08 (1.02, 1.15),  $p = .006$ ] was associated with nonatopic asthma risk. All these associations remained statistically significant after multiple testing correction.

**Conclusions:** High consumption of infant formula and other strongly heat-treated milk products may be associated with the development of asthma.

#### KEYWORDS

childhood chronic asthma, infant formula, joint models for longitudinal and time-to-event data, milk products, processing of milk

## 1 | INTRODUCTION

Asthma is the most common noncommunicable disease among children.<sup>1</sup> The growth in the proportion of children with allergic diseases is often explained by improved hygiene, and asthma is less common in children raised on traditional farms.<sup>2</sup> Consumption of raw, unprocessed cow's milk has been associated with a lower risk of childhood asthma or atopy in several studies regardless of exposure to farm environments.<sup>3,4</sup> Studies indicate that the protective association may not be solely linked to the microbes of raw milk but the fat content<sup>5</sup> or native proteins<sup>3,6</sup> of milk. Although processing may destroy the possible asthma protective features of milk, consumption of raw milk cannot be recommended because it can potentially carry several pathogenic bacteria.<sup>3,4</sup>

Due to the potential risks of raw milk, milk sold for consumption is almost always pasteurized or sterilized. However, there are hardly any studies about the differences between the consumption of commercial low-pasteurized milk and strongly heat-treated milk in association with the risk of asthma.<sup>6</sup> Consumption of milk products in general has been associated with a decreased risk of atopic asthma in children.<sup>7</sup> However, formula feeding<sup>8</sup> and intake of any milk other than breastmilk (including soy milk)<sup>9</sup> in infancy have been associated with an increased risk of asthma in 3-year-old children. Considering these conflicting results together with the protective properties of raw milk, more research is needed about differently processed milk products, especially because cow's milk and its products are often consumed in large amounts by children.

We set out to study in a Finnish population-based birth cohort with food consumption data whether the processing of milk plays a role in the association between milk consumption and asthma risk in children using both conventional and heat treatment- and homogenization-based milk product categorizations.

#### Key Message

In this large birth cohort study, consumption of strongly heat-treated milk products was associated with an increased risk of asthma. Previous studies have shown that raw milk has a protective association with asthma, whereas the results of this study show that strongly heat-treated milk may be a risk factor. Further studies are needed to understand the role of strongly heat-treated milk products in the development of asthma by the age of 5 years.

## 2 | METHODS

### 2.1 | Subjects

We used data from the Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study. The participants were born between September 1996 and September 2004 in the University Hospitals of Oulu and Tampere in Finland. The families of newborn infants with a human leukocyte antigen-conferred risk for type 1 diabetes were invited to the follow-up study. Genetic screening was described previously.<sup>10</sup>

The children still taking part in the study at the age of 5 years were asked to participate in the DIPP Allergy Study. Of the 4075 children invited, 3781 children participated.<sup>11</sup> The parents of 3143 children completed an International Study of Asthma and Allergies in Childhood (ISAAC)-based form regarding allergic diseases and asthma in the participants and in the family. We included 3053 children in the analyses performed in this study. The inclusion criteria were having information on whether the child had asthma, the time of asthma diagnosis, and at least one food record from the time before the asthma diagnosis.

## 2.2 | Dietary assessment

The type and amounts of foods consumed by the children were collected by 3-day food records completed at the ages of 3 and 6 months and 1, 2, 3, 4, and 5 years (at the age of 5 years collected only from part of the cohort). The brand names for commercial infant foods and formulas were specified. The food records were entered using the Finnish National Food Composition Database Fineli and the in-house dietary calculation software Finessi at the Finnish Institute for Health and Welfare. The food record collection and processing were described in detail previously.<sup>12</sup> The amount of breastmilk was calculated based on the child's growth and intake of other foods.<sup>7</sup>

Milk products in the database have been classified according to a conventional classification and according to processing (Table 1), as described in detail previously.<sup>13</sup> For the processing-based classification, we classified each milk product according to the adopted heat treatment and homogenization. The classification was done based on the literature and, when needed, by asking additional questions from dairy manufacturers. Hereinafter, we will refer to high-pasteurized milk products at  $\geq 100^\circ\text{C}$  or sterilized milk products such as strongly heat-treated milk products. For example, ultrahigh temperature (UHT)-treated milk belongs to this group, as UHT treatment is performed at temperatures higher than  $100^\circ\text{C}$ .

## 2.3 | Outcomes

We considered three outcomes in this study: asthma, atopic asthma, and nonatopic asthma. The first outcome, "asthma," represents all asthma

cases in total, including both atopic and nonatopic asthma. Based on the Finnish ISAAC questionnaire (filled at the age of 5 years), asthma was defined as doctor-diagnosed asthma plus either wheezing symptoms or use of asthma medication during the preceding 12 months. The age at the diagnosis of asthma was reported by the child's parents.

Atopic asthma was defined as children with asthma who were IgE-positive to at least one of the allergens tested. IgE concentrations were measured with ImmunoCAP fluoroenzyme immunoassays (Phadia Diagnostics) from serum samples obtained from the children at the age of 5 years. Sensitization to eggs, cow's milk, fish, wheat, house dust mites, cats, timothy grass, and birch was tested. If any allergen-specific IgE was  $\geq 0.35$  kU/L, the child was considered atopic. Nonatopic asthma was defined as children with asthma who were IgE-negative. IgE measurements were available for 2949 (96.6%) children.

## 2.4 | Sociodemographic and perinatal characteristics

Information on the child's sex was obtained by a questionnaire completed by the child's parents after delivery. Gestational age was obtained from the medical birth registries of Oulu and Tampere University Hospitals. Information on maternal and paternal asthma and allergic rhinitis and the child's atopic eczema before the age of 6 months was obtained from the Finnish ISAAC questionnaire. Information on cow's milk allergy was obtained from the DIPP nutrition questionnaires and the registers of the Finnish Social Insurance Institution.

**TABLE 1** Conventional and processing-based classification of milk products. The details of the classification were described in a previous study<sup>13</sup>

| Conventional classification  | Milk products included   |
|--|--|
| Cow's milk products  | Nonfermented milk products, fermented milk products, and cheeses   |
| Nonfermented milk products   | Milk products, creams, ice creams, milk-based infant formulas, and powder-like milk-containing preparations  |
| Milk-based infant formulas   | Conventional and partially and extensively hydrolyzed formulas   |
| Fermented milk products  | Fermented milk products (eg, yogurt and buttermilk) and sour creams  |
| Cheeses  | All kinds of cheeses, both fresh and ripened   |
| Processing-based classification  | Examples of classification of some milk products   |
| Heat treatment   |  |
| Low-pasteurized <sup>a</sup> or less heat-treated milk products                        | Standard milk, organic milk, and most ripened cheeses  |
| High-pasteurized milk products at $< 100^\circ\text{C}$                                | Yogurt, buttermilk, sour creams, quark, and butter   |
| High-pasteurized milk products at $\geq 100^\circ\text{C}$ or sterilized milk products | Special milk products (eg, lactose-free milk products), conventional and partially hydrolyzed infant formulas, milk powders, milk-containing porridge, and commercial baby foods |
| Homogenization   |  |
| Homogenized milk products  | Standard milk, special milk products (eg, lactose-free milk products), infant formulas, and yogurt   |
| Nonhomogenized milk products   | Organic milk, most ripened cheeses, and butter   |
| Fat-free ( $\leq 0.5\%$ fat)   | All milk products with $\leq 0.5$ g/100 g or 0.5 ml/100 ml of fat regardless of being homogenized or not   |

<sup>a</sup>Typically 15 s at  $73^\circ\text{C}$  or corresponding conditions where milk alkaline phosphatase is inactivated.

## 2.5 | Ethics

Parents gave written informed consent for genetic testing of their newborn infant from cord blood samples and for participation in the follow-up. The study adhered to the Declaration of Helsinki, and the local ethics committees approved the study protocol.

## 2.6 | Statistical analyses

We analyzed the associations between the amounts of different milk products consumed and the risk of asthma in children using a joint model for longitudinal and time-to-event data with a current value association structure.<sup>14</sup> The use of joint models, adjustments, and sensitivity analyses are described in the Supplementary file. In brief, a linear mixed-effects model determining the milk product consumption (until the diagnosis of asthma) and a relative risk model were fitted simultaneously. We adjusted the models for maternal and paternal asthma and allergic rhinitis, gestational age, sex, atopic eczema before the age of 6 months, cow's milk allergy, and intake of energy. False discovery rate adjustment was used for the adjusted results to control for multiple testing.

## 3 | RESULTS

Of the 3053 children, 184 (6.0%) were diagnosed with asthma by the age of 5 years. Among these, 101 (54.9%) children had atopic asthma, 75 (40.8%) children had nonatopic asthma, and eight (4.3%) children could not be categorized due to lack of IgE results. The median (IQR) age at asthma diagnosis for the children fulfilling the study definition of asthma at the age of 5 years was 3.0 (2.0–3.5) years for atopic children, and 2.0 (1.0–3.0) years for nonatopic children. The characteristics of the participants are presented in Table 2. Children's consumption of different and differently processed milk products is presented in Figures 1 and 2.

Consumption of milk-based infant formulas was associated with an increased risk of all asthma and nonatopic asthma (Table 3). We performed an additional analysis for infant formulas excluding extensively hydrolyzed formulas, which did not change the results. Consumption of strongly heat-treated milk products was weakly associated with an increased risk of all asthma. The evidence strengthened when infant formulas were excluded from the strongly heat-treated milk products (Table 3).

High consumption of all cow's milk products had a borderline association with the risk of all asthma and was associated with an increased risk of nonatopic asthma (Table 3). Additionally, consumption of nonfermented milk products was associated with an increased risk of nonatopic asthma. However, the consumption of nonfermented milk products without infant formulas (including milk products, creams, ice creams, and milk powders) was not associated with nonatopic asthma.

The results of the Cox proportional hazards analyses done separately for each food record collection age point showed an association between consumption of all cow's milk products and an increased risk of nonatopic asthma at the age of 3 and 6 months, and 1 year, but not later. No associations were seen for all asthma or atopic asthma.

## 4 | DISCUSSION

In this cohort study, the consumption of infant formula and other strongly heat-treated milk products was associated with an increased risk of asthma. Consumption of all cow's milk products showed a borderline association with the risk of all asthma. Consumption of all cow's milk products, nonfermented milk products, and infant formulas was associated with an increased risk of nonatopic asthma.

Higher intake of milk-based infant formulas was associated with an increased risk of all asthma and nonatopic asthma, the result being in line with a few previous studies that found a direct association between formula feeding<sup>8</sup> and the introduction of any milk other than breastmilk in infancy<sup>9</sup> and asthma. We found no association between nonfermented milk products and asthma outcomes when infant formulas were excluded. This indicates that the relation between all milk products and nonfermented milk products and nonatopic asthma may reflect the consumption of infant formulas. In the heat treatment-based classification, infant formulas are included in the class of strongly heat-treated milk products, the consumption of which was also associated with an increased risk of nonatopic asthma. Mostly due to infant formulas, products classified into this heat treatment group were consumed in larger amounts than milk products of milder heat treatment classes during the first year of life. Interestingly, the consumption of strongly heat-treated milk products was associated with an increased risk of all asthma also when infant formulas were excluded from the variable. This implies that the association between strongly heat-treated milk products and all asthma stems from the heat treatment, rather than from intake of infant formulas per se.

To the best of our knowledge, no previous studies have evaluated the association between the consumption of strongly heat-treated milk products and the risk of asthma, as it was used as a reference category in studies if it was assessed separately.<sup>6</sup> Most of the existing evidence on the inverse association between raw milk and asthma or atopy is based on comparing the consumption of raw milk with no consumption of raw milk or with the consumption of store-bought (processed) milk,<sup>4</sup> not having observed the amounts of milk products consumed as the present study does. In many central European countries, the use of UHT milk is preferred,<sup>4</sup> but in this Finnish population, low-pasteurized milk products were primarily consumed after the age of 1 year.

The consumption of low-pasteurized or less heat-treated milk products was inversely associated with all asthma and atopic asthma only in the unadjusted analyses. This group also included raw milk, which was, however, rarely consumed in the study population.

TABLE 2 Baseline characteristics of the children and their association with asthma outcomes presented as hazard ratios (HR) with 95% confidence intervals (CIs)

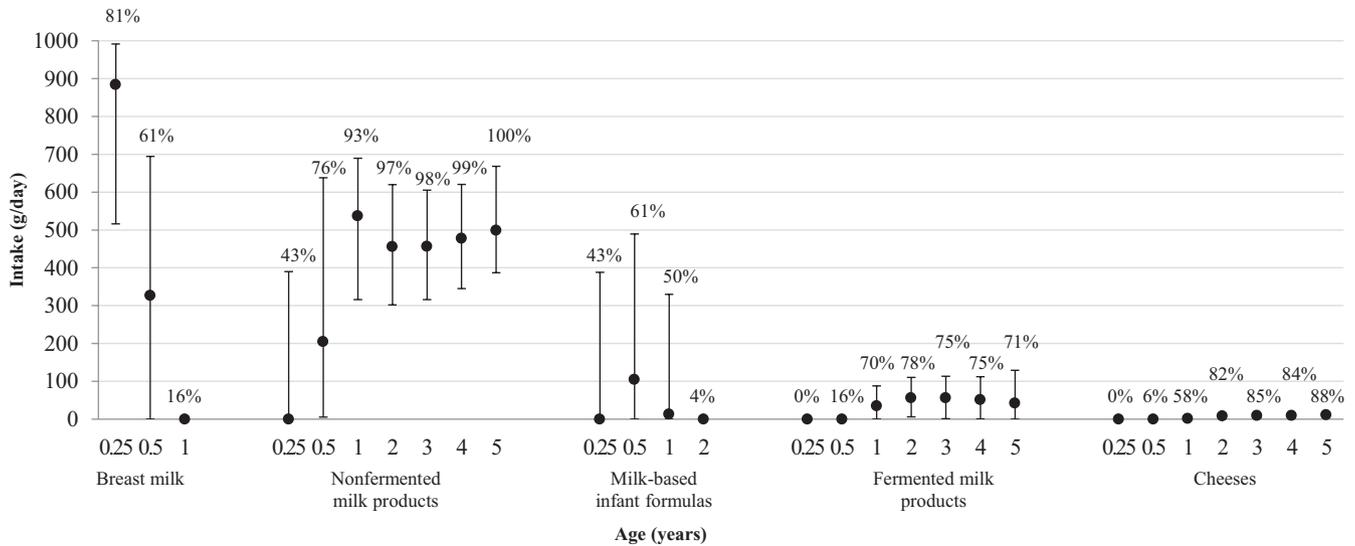
| Characteristics  | All asthma  |                      |       | Atopic asthma |                          |       | Nonatopic asthma |                            |       |
|--|-------------|----------------------|-------|---------------|--------------------------|-------|------------------|----------------------------|-------|
|  | N = 3053    | n = 184 <sup>a</sup> | p     | n = 101       | HR (95% CI) <sup>b</sup> | p     | n = 75           | HR (95% CI) <sup>b,c</sup> | p     |
| <b>Sex</b>   |             |                      |       |               |                          |       |                  |                            |       |
| Male   | 1597 (52.3) | 115 (7.2)            | 1     | 64 (4.0)      | 1                        |       | 46 (2.9)         | 1                          |       |
| Female   | 1456 (47.7) | 69 (4.7)             | .013  | 37 (2.5)      | 0.68 (0.46, 1.03)        | .07   | 29 (2.0)         | 0.67 (0.42, 1.08)          | .10   |
| Gestational age in weeks, mean (SD)                    | 39.7 (1.9)  | 39.3 (2.2)           | .002  | 39.6 (1.7)    | 0.98 (0.88, 1.10)        | .76   | 38.7 (2.7)       | 0.83 (0.77, 0.90)          | <.001 |
| <b>Maternal asthma or allergic rhinitis</b>            |             |                      |       |               |                          |       |                  |                            |       |
| No   | 1607 (52.6) | 57 (3.5)             | 1     | 29 (1.8)      | 1                        |       | 26 (1.6)         | 1                          |       |
| Yes  | 1388 (43.8) | 122 (9.1)            | <.001 | 69 (5.2)      | 2.44 (1.57, 3.79)        | <.001 | 47 (3.5)         | 2.29 (1.40, 3.75)          | .001  |
| Missing information                                    | 108 (3.5)   | 5 (4.6)              | .51   | 3 (2.8)       | 1.69 (0.51, 5.59)        | .39   | 2 (1.9)          | 1.11 (0.26, 4.76)          | .88   |
| <b>Paternal asthma or allergic rhinitis</b>            |             |                      |       |               |                          |       |                  |                            |       |
| No   | 1763 (57.7) | 84 (4.8)             | 1     | 41 (2.3)      | 1                        |       | 38 (2.2)         | 1                          |       |
| Yes  | 1130 (37.0) | 90 (8.0)             | .005  | 56 (5.0)      | 1.82 (1.21, 2.73)        | .004  | 31 (2.8)         | 1.33 (0.82, 2.17)          | .25   |
| Missing information                                    | 160 (5.2)   | 10 (6.2)             | .48   | 4 (2.5)       | 0.96 (0.34, 2.71)        | .94   | 6 (3.7)          | 1.80 (0.75, 4.29)          | .19   |
| <b>Atopic eczema during the first 6 months of life</b> |             |                      |       |               |                          |       |                  |                            |       |
| No   | 2637 (86.4) | 134 (5.1)            | 1     | 65 (2.5)      | 1                        |       | 63 (2.4)         | 1                          |       |
| Yes  | 368 (12.1)  | 48 (13.0)            | .057  | 34 (9.3)      | 1.94 (1.20, 3.14)        | .007  | 12 (3.3)         | 0.87 (0.44, 1.72)          | .68   |
| Missing information                                    | 48 (1.6)    | 2 (4.2)              | .53   | 2 (4.2)       | 1.26 (0.31, 5.16)        | .75   | 0 (0.0)          | -                          | -     |
| <b>Cow's milk allergy</b>                              |             |                      |       |               |                          |       |                  |                            |       |
| No   | 2757 (90.3) | 134 (4.9)            | 1     | 68 (2.5)      | 1                        |       | 60 (2.2)         | 1                          |       |
| Yes  | 296 (9.7)   | 50 (16.9)            | <.001 | 33 (11.2)     | 2.96 (1.84, 4.77)        | <.001 | 15 (5.1)         | 2.21 (1.89, 4.11)          | .012  |

Note: Values are No. (%) unless otherwise indicated.

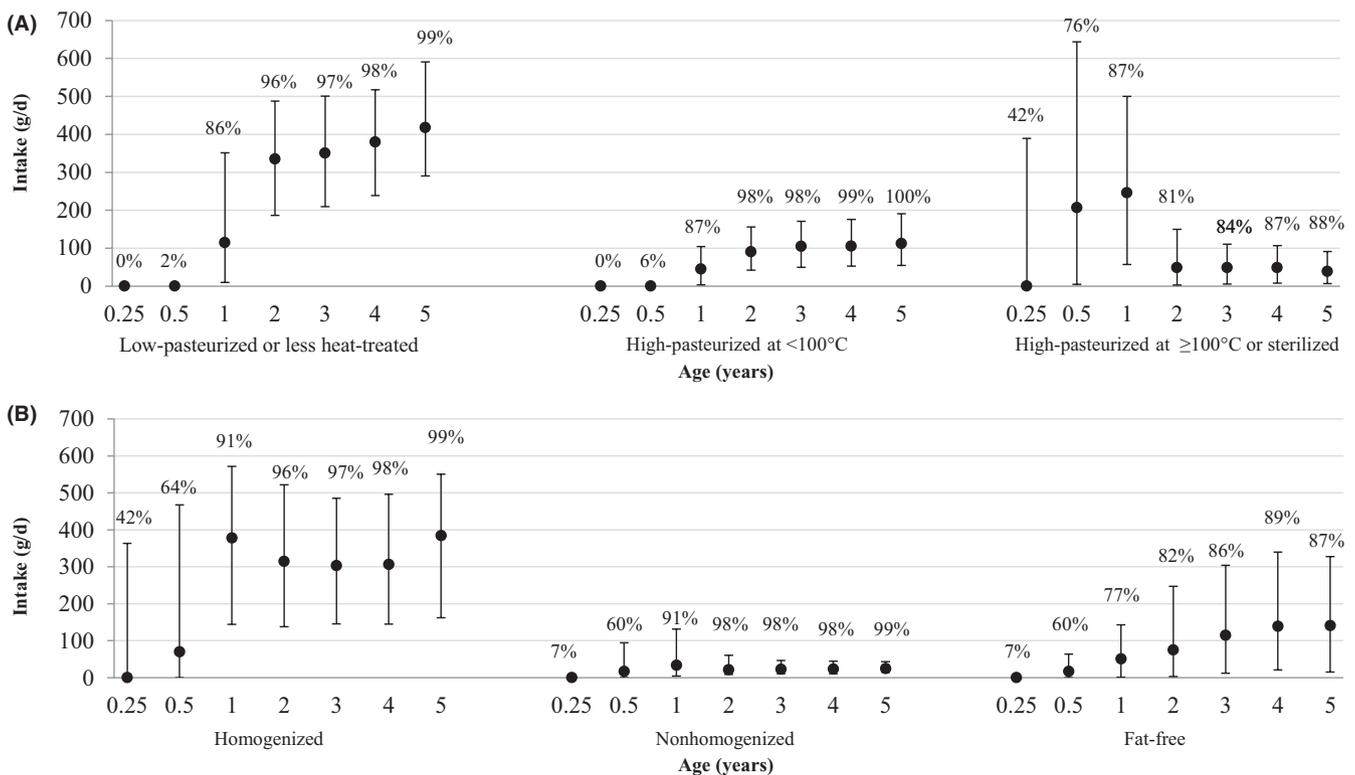
<sup>a</sup>Information on asthma type is missing for eight children (excluded from atopic and nonatopic asthma analyses).

<sup>b</sup>Estimates are hazard ratios from the Cox proportional hazards model including all six baseline factors in the table.

<sup>c</sup>n = 2971 in the Cox proportional hazards model; those with missing class (n = 48) of atopic eczema during the first 6 months of life were excluded from the analyses.



**FIGURE 1** Median intake of breastmilk and different cow's milk products by age. Median and inter-quartile range of consumption of different types of cow's milk products at the age of 3 months ( $n = 2891$ ), 6 months ( $n = 2865$ ), 1 year ( $n = 2761$ ), 2 years ( $n = 2545$ ), 3 years ( $n = 2507$ ), 4 years ( $n = 2416$ ), and 5 years ( $n = 217$ ) using conventional classification. Values are calculated based on all the available data for the 3053 children included in the analyses. The percentages above the lines represent the proportion of children using the particular milk product at that age



**FIGURE 2** Median intake of differently processed (heat treatment and homogenization) cow's milk products by age. Median and inter-quartile range of consumption of different cow's milk products at the age of 3 months ( $n = 2891$ ), 6 months ( $n = 2865$ ), 1 year ( $n = 2761$ ), 2 years ( $n = 2545$ ), 3 years ( $n = 2507$ ), 4 years ( $n = 2416$ ), and 5 years ( $n = 217$ ) using classification based on A) heat treatment and B) homogenization. Values are calculated based on all the available data for the 3053 children included in the analyses. The percentages above the lines represent the proportion of children using the particular milk product at that age

Previous studies including pasteurized milk showed a nonsignificant inverse association between pasteurized milk consumption and asthma risk,<sup>6</sup> or found no associations between pasteurized milk

consumption and asthma.<sup>15</sup> The evidence is still incomplete, but it seems that low-pasteurized milk might not have the same benefits in the prevention of asthma that have been reported for raw milk.<sup>4</sup> We

TABLE 3 Hazard ratios (95% confidence intervals) for the risk of asthma outcomes associated with breastmilk intake and consumption of differently processed milk products

|  | All asthma<br>n (cases) = 184, n (total) = 3053 |   |        | Atopic asthma<br>n (cases) = 101, n (total) = 3045 |   |      | Nonatopic asthma<br>n (cases) = 75, n (total) = 3045 |   |          |
|--|---|---|--------|--|---|------|--|---|----------|
|  | HR<br>unadjusted <sup>a</sup><br>(95% CI)       | HR<br>adjusted <sup>b</sup><br>(95% CI) | p      | HR<br>unadjusted <sup>a</sup><br>(95% CI)          | HR<br>adjusted <sup>b</sup><br>(95% CI) | p    | HR<br>unadjusted <sup>a</sup><br>(95% CI)            | HR<br>adjusted <sup>b</sup><br>(95% CI) | p        |
| Amount of breastmilk <sup>c</sup>                                    | 0.89<br>(0.76, 1.05)                            | 0.93<br>(0.84, 1.03)                    | .17    | 0.92<br>(0.72, 1.19)                               | 0.91<br>(0.75, 1.11)                    | .54  | 0.80<br>(0.60, 1.06)                                 | 0.83<br>(0.64, 1.07)                    | .12      |
| Conventional classification  |   |   |        |  |   |      |  |   |          |
| Cow's milk products  | 0.98<br>(0.92, 1.04)                            | 1.04<br>(1.00, 1.08)                    | .49    | 0.93<br>(0.86, 1.01)                               | 1.01<br>(0.96, 1.07)                    | .07  | 1.08<br>(0.99, 1.17)                                 | 1.09<br>(1.03, 1.15)                    | .10      |
| Nonfermented milk products   | 0.99<br>(0.92, 1.05)                            | 1.04<br>(1.00, 1.08)                    | .67    | 0.94<br>(0.87, 1.02)                               | 1.01<br>(0.96, 1.07)                    | .14  | 1.07<br>(0.98, 1.17)                                 | 1.08<br>(1.02, 1.14)                    | .12      |
| Milk-based infant formulas <sup>d</sup>                              | 1.36<br>(1.24, 1.50)                            | 1.15<br>(1.07, 1.23)                    | <.001* | 1.27<br>(1.06, 1.52)                               | 0.95<br>(0.65, 1.39)                    | .01  | 1.44<br>(1.27, 1.63)                                 | 1.23<br>(1.13, 1.34)                    | <.001*** |
| Other nonfermented milk products                                     | 0.94<br>(0.87, 1.01)                            | 1.05<br>(0.97, 1.12)                    | .07    | 0.92<br>(0.83, 1.01)                               | 1.06<br>(0.97, 1.17)                    | .07  | 0.98<br>(0.88, 1.09)                                 | 1.05<br>(0.95, 1.18)                    | .66      |
| Fermented milk products <sup>e</sup>                                 | 0.86<br>(0.63, 1.18)                            | 1.09<br>(0.83, 1.42)                    | .35    | 0.84<br>(0.58, 1.20)                               | 0.97<br>(0.65, 1.44)                    | .34  | 1.11<br>(0.75, 1.62)                                 | 1.26<br>(0.87, 1.84)                    | .60      |
| Cheeses  | 0.23<br>(0.03, 1.58)                            | 0.49<br>(0.07, 3.56)                    | .14    | 0.08<br>(0.01, 1.14)                               | 0.57<br>(0.04, 7.76)                    | .062 | 0.42<br>(0.02, 7.86)                                 | 0.17<br>(0.00, 6.57)                    | .56      |
| Processing-based classification                                      |   |   |        |  |   |      |  |   |          |
| Heat treatment:  |   |   |        |  |   |      |  |   |          |
| Low-pasteurized or less heat-treated milk products                   | 0.87<br>(0.79, 0.95)                            | 0.99<br>(0.91, 1.07)                    | .002   | 0.88<br>(0.80, 0.96)                               | 0.99<br>(0.89, 1.10)                    | .006 | 0.94<br>(0.84, 1.05)                                 | 1.01<br>(0.89, 1.13)                    | .27      |
| High-pasteurized milk products at <100°C                             | 0.76<br>(0.58, 0.99)                            | 0.99<br>(0.79, 1.24)                    | .04    | 0.79<br>(0.59, 1.06)                               | 0.94<br>(0.69, 1.29)                    | .11  | 0.93<br>(0.67, 1.29)                                 | 1.08<br>(0.78, 1.51)                    | .68      |
| High-pasteurized milk products at ≥100°C or sterilized milk products | 1.12<br>(1.04, 1.20)                            | 1.06<br>(1.01, 1.10)                    | .001   | 1.08<br>(0.99, 1.18)                               | 1.03<br>(0.97, 1.10)                    | .10  | 1.16<br>(1.07, 1.27)                                 | 1.08<br>(1.02, 1.15)                    | <.001    |
| Excluding infant formulas  | 1.16<br>(1.04, 1.28)                            | 1.16<br>(1.06, 1.27)                    | .006   | 1.16<br>(1.01, 1.33)                               | 1.19<br>(1.05, 1.35)                    | .039 | 1.15<br>(0.98, 1.35)                                 | 1.14<br>(0.98, 1.32)                    | .085     |
| Homogenization   |   |   |        |  |   |      |  |   |          |
| Homogenized milk products  | 0.98<br>(0.92, 1.05)                            | 1.02<br>(0.98, 1.06)                    | .54    | 0.96<br>(0.89, 1.03)                               | 1.00<br>(0.94, 1.06)                    | .26  | 1.02<br>(0.94, 1.12)                                 | 1.05<br>(0.98, 1.11)                    | .58      |

(Continues)

TABLE 3 (Continued)

|                              | All asthma<br>n (cases) = 184, n (total) = 3053 |     |   | Atopic asthma<br>n (cases) = 101, n (total) = 3045 |     |   | Nonatopic asthma<br>n (cases) = 75, n (total) = 3045 |     |   |
|------------------------------|---|-----|---|--|-----|---|--|-----|---|
|                              | HR<br>unadjusted <sup>a</sup><br>(95% CI)       | p   | HR<br>adjusted <sup>b</sup><br>(95% CI) | HR<br>unadjusted <sup>a</sup><br>(95% CI)          | p   | HR<br>adjusted <sup>b</sup><br>(95% CI) | HR<br>unadjusted <sup>a</sup><br>(95% CI)            | p   | HR<br>adjusted <sup>b</sup><br>(95% CI) |
| Nonhomogenized milk products | 0.94<br>(0.76, 1.17)                            | .60 | 1.08<br>(0.91, 1.27)                    | 0.94<br>(0.71, 1.24)                               | .39 | 1.07<br>(0.84, 1.35)                    | 1.05<br>(0.81, 1.40)                                 | .71 | 1.12<br>(0.89, 1.41)                    |
| Fat-free                     | 1.01<br>(0.92, 1.10)                            | .85 | 1.07<br>(0.99, 1.15)                    | 0.96<br>(0.85, 1.09)                               | .09 | 1.04<br>(0.93, 1.16)                    | 1.11<br>(0.98, 1.26)                                 | .09 | 1.13<br>(1.02, 1.26)                    |

<sup>a</sup>Hazard ratios (HRs) and confidence intervals (CIs) are presented per 100 g of food items consumed.

<sup>b</sup>Hazard ratios (HRs) and confidence intervals (CIs) are presented per 20 grams/MJ of food item consumed. Adjusted for maternal and paternal asthma and allergic rhinitis, gestational age, sex, atopic eczema during the first 6 months, cow's milk allergy, and intake of energy. n of cases (total) for adjusted analyses: 183 (3027), 101 (3019), and 74 (2971) for all asthma, atopic asthma, and nonatopic asthma, respectively.

<sup>c</sup>n of cases (total) for breastmilk analyses: 180 (2979), 99 (2971), and 73 (2925), for all asthma, atopic asthma, and nonatopic asthma, respectively.

<sup>d</sup>Includes hydrolyzed formulas.

<sup>e</sup>Does not include cheeses. Cheeses are presented separately.

\*p < .05 after false discovery rate correction for the adjusted results; \*\*p < .01 after false discovery rate correction for the adjusted results; \*\*\*p < .001 after false discovery rate correction for the adjusted results.

failed to confirm a protective association between the consumption of all cow's milk products and atopic asthma, as reported previously in a case-control study within the present cohort.<sup>7</sup>

The protective effect of raw milk may be derived from its heat-labile whey proteins, such as  $\alpha$ -lactalbumin,  $\beta$ -lactoglobulin, and bovine serum albumin, which were all inversely associated with asthma,<sup>6</sup> or cytokines, for example, TGF- $\beta$ .<sup>16</sup> Heat treatment and modification of the fat content of milk destroy part of the exosomal microRNAs with possible immunological functions.<sup>4</sup> Furthermore, strong heat treatments induce other chemical modifications in milk. Advanced glycation end products (AGEs) formed during the processing of skim milk powder disturbed spleen and thymus growth and caused intestinal inflammation in rats,<sup>17</sup> and have been hypothesized to be associated with food allergies.<sup>18</sup> Infant formulas have higher concentrations of AGEs than regular milk products.<sup>19</sup>

As far as we know, no studies exist about the association between the consumption of differently processed milk products and gut microbiota in humans. The bacterial composition between different milk products varies. In calves, feeding with UHT milk resulted in different gut microbe compositions than feeding with pasteurized milk.<sup>20</sup> Several studies have shown a correlation between gut microbiota composition and the development of atopic diseases.<sup>21</sup> Gut microbiota seems to differ between formula-fed and breastfed infants.<sup>22</sup>

Unlike the previous survey based on parts of the same data as the present study,<sup>7</sup> we found no associations between the amount of breastmilk and nonatopic asthma (or other outcomes), although the hazard ratios were slightly toward protective. Likewise, in the same cohort study, the total breastfeeding of 9.5 months or less has been associated with an increased risk of nonatopic asthma.<sup>23</sup> The median (IQR) duration of exclusive breastfeeding was 1.4 (0.2–3.5) months and that of total breastfeeding 7.0 (4.0–11.0) months. A short duration of breastfeeding has also been directly associated with nonatopic asthma but not atopic asthma in other datasets.<sup>24</sup> The association between the consumption of infant formula and increased risk of nonatopic asthma should therefore be interpreted with moderation, as breastmilk and infant formula are complementary feeding methods. We found no associations between the consumption of fermented milk products and asthma. The consumption of yogurt (once or more per week) was previously protectively associated with allergic diseases but not asthma.<sup>15</sup>

An important strength of this study is the longitudinal food consumption data. Using food records enabled assessing the amounts of foods and allowed the use of the processing-based milk product classification,<sup>13</sup> for the first time in studying the association between milk and asthma. Another strength is the use of joint modeling as the statistical approach; this, for example, reduces the risk of bias caused by missing food records.<sup>25</sup> A possible limitation to the generalizability of the results is that this study was conducted on subjects with genetic susceptibility for type 1 diabetes, as children with type 1 diabetes may have a decreased risk for asthma.<sup>26</sup> Another limitation is that the classification of milk products is not unambiguous, and in many cases, the type of milk product determines the processing-based

grouping of that particular milk product.<sup>13</sup> This leads to the fact that there are other characteristics, for example, the presence of lactic acid bacteria that might confound the significance of heat treatment or homogenization. Also, the milk consumption patterns may have slightly changed since the collection of the data. However, no major changes in milk processing parameters concerning the manufacture of traditional milk products have taken place in Finland in the last two decades. Furthermore, as is common in observational studies, despite the adjustments carried out in the analyses, there is a risk of residual confounding. We also acknowledge the heterogeneity of asthma, especially in small children, and the problem of classifying asthma into atopic and nonatopic asthma.<sup>27</sup> On the other hand, the results of the current study highlight the importance of considering different subtypes of asthma in epidemiological studies.

This longitudinal study supports the evidence of many previous surveys indicating that heat treatment plays a role in the association between milk consumption and asthma. Previous studies have shown that raw milk has a protective association with asthma, whereas our results show that strongly heat-treated milk may be a risk factor. Based on the current body of evidence, one might infer that the stronger the heat treatment of milk is, the less beneficial/more harmful (future studies should clarify which term is more accurate) the milk is in relation to asthma prevention; however, more studies are still needed to confirm the findings.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Katariina Koivusaari:** Conceptualization (lead); Funding acquisition (equal); Investigation (equal); Methodology (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). **Essi Syrjälä:** Formal analysis (lead); Investigation (supporting); Methodology (equal); Software (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Sari Niinistö:** Conceptualization (lead); Investigation (supporting); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal). **Suvi Ahonen:** Data curation (equal); Project administration (supporting); Supervision (supporting); Writing-review & editing (equal). **Mari Åkerlund:** Data curation (equal); Writing-review & editing (equal). **Tuuli E. Korhonen:** Data curation (equal); Writing-review & editing (equal). **Jorma Toppari:** Data curation (equal);

Funding acquisition (equal); Investigation (supporting); Project administration (equal); Resources (equal); Writing-review & editing (equal). **Jorma Ilonen:** Conceptualization (equal); Data curation (supporting); Funding acquisition (supporting); Investigation (supporting); Methodology (supporting); Project administration (supporting); Resources (equal); Writing-review & editing (equal). **Minna Kaila:** Conceptualization (equal); Funding acquisition (supporting); Investigation (equal); Methodology (equal); Writing-review & editing (equal). **Mikael Knip:** Conceptualization (equal); Data curation (equal); Funding acquisition (equal); Investigation (supporting); Project administration (equal); Resources (equal); Writing-review & editing (equal). **Tapani Alatossava:** Conceptualization (lead); Investigation (supporting); Methodology (supporting); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal). **Riitta Veijola:** Conceptualization (equal); Data curation (equal); Funding acquisition (equal); Investigation (supporting); Project administration (equal); Resources (equal); Writing-review & editing (equal). **Suvi Virtanen:** Conceptualization (lead); Data curation (lead); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (lead); Resources (equal); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (lead).

## ORCID

Katariina Koivusaari  <https://orcid.org/0000-0002-4269-4878>

Essi Syrjälä  <https://orcid.org/0000-0002-5782-3089>

Minna Kaila  <https://orcid.org/0000-0002-9645-4925>

Mikael Knip  <https://orcid.org/0000-0003-0474-0033>

Suvi M. Virtanen  <https://orcid.org/0000-0001-8928-0878>

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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