

ORIGINAL ARTICLE

Risk of asthma and allergic outcomes in the offspring in relation to maternal food consumption during pregnancy: A Finnish birth cohort study

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Abstract

Background: Epidemiological and immunological studies suggest that maternal diet during pregnancy might affect the development of allergic diseases in the offspring. The authors set out to study the effect of maternal food consumption during pregnancy on the emergence of the International Study of Asthma and Allergies in Childhood (ISAAC)-based allergic outcomes: asthma, allergic rhinitis, and wheeze by the 5 yr of age.

Methods: Data from 2441 children at 5 yr of age were analyzed within the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study, a population-based birth cohort study. Maternal diet was assessed with a validated food frequency questionnaire.

Results: In multiple regression models adjusted for known confounders, low maternal consumption of leafy vegetables (adjusted odds ratio [aOR]: 1.55; 95% CI: 1.21, 1.98), malaceous fruits (aOR: 1.45; 95% CI: 1.15, 1.84), and chocolate (aOR: 1.36; 95% CI: 1.09, 1.70) were positively associated with the risk of wheeze in children. High maternal consumption of fruit and berry juices was positively associated with the risk of allergic rhinitis (aOR: 1.40; 95% CI: 1.03, 1.90) in children. No associations were observed between maternal food consumption and asthma.

Conclusions: Development of allergic diseases in preschool children may be influenced by intrauterine exposure to maternal diet.

Increased susceptibility to immune-mediated disorders may originate in early life, with long-lasting structural or functional changes to the developing organs or organ systems (1). The immunological processes related to the development of allergic diseases and asthma are thought to be the result of an induced shift in the balance between the Th1 and Th2 cytokines that favors Th2 dominance (2). The fetal environmental factors supporting this proposition are not well-defined. Epidemiological and immunological studies suggest that dietary modification in fetal life could affect the development of allergic diseases, while fetal undernutrition could detrimentally affect the 'programming' of the fetal lung and

immune system (3, 4). Somewhat conflicting findings imply that there might be critical time windows of exposure to foods and nutrients during pregnancy.

Earlier studies have variously reported associations between maternal intake of fish (5–8), fruits and vegetables (5, 8, 9, 10), dairy foods (11), nut products (12), meat (13), margarines, and spreadable fats (5, 6, 13, 14) during pregnancy and the risk of asthma, wheeze, allergic rhinitis, and/or eczema. The inconsistent results and novel findings, however, remain to be confirmed. The recent systematic review and meta-analyses found the body of epidemiologic evidence in relation to maternal dietary factors for the prevention of

asthma and allergic disorders in the offspring weak but nonetheless suggestive in relation to fruits and vegetables (10). Studies in this field are faced with the methodological challenges of eliminating biases and adequately adjusting for potentially important confounding factors.

We set out to assess the effect of maternal food consumption during pregnancy on the emergence of asthma, allergic rhinitis, and wheeze by the 5 yr of age within a large cohort of children with HLA-DQB1-conferred susceptibility to type 1 diabetes. In order to add to the reported literature and to make the results well comparable with earlier studies, a wide set of exposures and outcomes were used.

Subjects and methods

Subjects

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, which started in 1994, is a multidisciplinary population-based prospective cohort study that examines potential means to predict and prevent progression to overt type 1 diabetes (15). Infants born with HLA-DQB1-conferred susceptibility to type 1 diabetes are recruited from three university hospitals in Finland (Turku, Oulu, and Tampere) and monitored at 3- to 12-month intervals for diabetes-associated antibodies, growth, and environmental exposures. The study procedures were approved by the local ethics committees and they are in accordance with the Helsinki Declaration of 1975 as revised in 1983.

In September 1996, the DIPP Nutrition Study was started within the framework of the DIPP study in Oulu (Northern Finland) and Tampere (Southern Finland), (15). The study examines the relationship of maternal diet during pregnancy and lactation, and the child's diet during infancy to the development of type 1 diabetes in childhood. At the 5 years of age, 3523 children who were still participating in the dietary follow-up (born between October 20, 1997, and February 29, 2004) were invited to take part in the allergy study by completing a questionnaire on the child's history of allergic symptoms. Altogether 3253 children (49% of those invited to the study base) participated in the allergy study. For the present analysis, complete information on maternal diet during pregnancy and history of allergic outcomes was available for 2441 children. Distribution of the background characteristics by participation in the allergy study are presented in our earlier paper (16).

Dietary assessment

Maternal food consumption during pregnancy was assessed by means of a self-administered, semi-quantitative 181-item food frequency questionnaire (FFQ), designed specially for the DIPP nutrition study and reflecting the diet of Finnish women of child-bearing age (17). The FFQ was validated against 10-day food records in a sample of pregnant Finnish women. The validity of the FFQ for foods was, in general, good: an average of 70% (52–94%) of the women was classified by both methods into the same or adjacent quintiles according to their food intake. The greatest misclassifications

were found among the most infrequently consumed food items (high-fat milk and offals).

Mothers received the FFQ by mail after delivery and retrospectively recorded the foods they had eaten during the month preceding their pregnancy leave, that is, the 8th month of pregnancy. The FFQ assessed the use of foods and food groups and their consumption frequency (less than once per month, number of times per month, week, or day). The FFQ was returned to the study center at the child's 3-month visit and was checked by a trained study nurse and later by a trained nutritionist. If there were ≥ 10 food items with missing frequency, the FFQ was rejected. Food consumption data were split into ingredients using information of the recipe composition for composite dishes and foods in the Finnish food composition database (18). Software of the National Institute for Health and Welfare, Helsinki, Finland, was used to convert the food consumption data to each mother's daily nutrient intake, taking into account women's individual choices of fats used in food preparations and baking, and oils used for salad dressing (17). The detailed content of the FFQ and data processing have been described elsewhere (19).

Asthma, allergic rhinitis, and wheeze

At the 5 yr of age, the participating families completed a questionnaire modified from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire on the child's history of allergic symptoms and asthma (19, 20). The modification consisted of additional questions on background characteristics of the family. Asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom during the preceding 12 months or use of asthma medication during the preceding 12 months. Age of the child at asthma diagnosis was determined by the question: 'At what age was asthma diagnosed?'. Allergic rhinitis was defined as sneezing, nasal congestion, or rhinitis other than with respiratory infections, accompanied by itching of the eye and tearing during the previous 12 months. Age of onset of rhinitis was indicated by the parents. Wheezing was defined as parental 'yes' answer on whether the child has had any of the following during the last 12 months: wheezy sound in respiration; wheezy sound in respiration in connection with physical activity; difficulties in respiration in the morning on waking up; wheezy respiration without having the sniffles or respiratory infection; dry cough at nights not associated with common colds or respiratory infections.

Sociodemographic and prenatal characteristics of mother-child pairs

Information on the child's sex, maternal age, maternal educational level (comprehensive school education and upper secondary general education), and the number of siblings was recorded in a structured questionnaire completed by the parents after the delivery. Information on place of residence, duration of gestation, mode of delivery, and maternal smoking during pregnancy was received from the Medical Birth Registries of Oulu and Tampere University Hospitals.

Statistical methods

To assess the degree of selection, we compared maternal food consumption (using *T*-test) and background characteristics (using χ^2 test) of those women whose child entered the DIPP study, but who did not participate in the allergy arm of the DIPP study ($n = 270$) with the mothers of participating children in the DIPP allergy study ($n = 3253$). Cox proportional hazards regression was used to analyze the association between maternal diet and confounders and asthma and allergic rhinitis end-points. Logistic regression was used for wheeze end-point. The standardized *Z*-score of maternal food intake categorized in quarters was used, which were then adjusted for total energy intake in the analysis. Intakes between the first and the fourth quarters were combined and used as a reference group in the regression models. First, we used unadjusted and adjusted models separately for each food variable in relation to the end-points. Then, all dietary variables that were significantly associated with each end-point at the unadjusted level were studied together.

Selection of confounding covariates was based on their relations with the exposure and/or the outcome and, in respect of some foods, on earlier findings. The adjusted models included sex, place of birth (Southern Finland; Northern Finland), duration of gestation (in quarters), maternal age at delivery (<25 yr, 25–29 yr, 30–34 yr, ≥35 yr), maternal basic education (less than high school, high school graduate), maternal smoking during pregnancy (no, yes, no information: as the number of quitters was small, they were aggregated with smokers), mode of delivery (vaginal, forceps or suction, cesarean section), number of siblings at the time of the child's birth (none, one, two, or more), parental asthma (no, yes, no information), parental allergic rhinitis (no, yes, no information), eczema by 6 months of age (no, yes), pets at home by 1 yr of age (no, yes), duration of breastfeeding (continuous), and day care at 1 yr of age (no, yes). All analyses were computed using SPSS version 15.0 (SPSS Inc, Chicago, IL).

Results

Baseline characteristics

The cumulative incidence of asthma, allergic rhinitis, and wheeze in the study population at the 5 yr of age was 6%, 15%, and 27%, respectively (Table 1). The coexistence of all three outcomes was identified in 24 (1%) children. Most commonly, there was coexistence of allergic rhinitis and wheeze (in 53 [2.2%] children). Wheeze and allergic rhinitis coexisted in 53 (2.2%), and 33 (1.4%) of the asthmatic children, respectively.

Frequencies of allergic outcomes and baseline characteristics of the 2441 mother–child pairs participating in the DIPP allergy study are presented in Table 1. Season of birth was not related to any of the outcomes (data not shown). Participants in the allergy study were generally not systematically different from non-participants with regard to the background characteristics of the study population (16), and to the average consumption of foods and food groups (data not

shown). Food consumption of the mothers with history of allergy did not differ from that of the mothers with no history of allergy with the exception of the average consumption of cereals (193 [SD 68] vs. 204 [SD 68] g/day, respectively).

Maternal food consumption and allergic outcomes in children by 5 yr of age

Asthma

No statistically significant associations were found between maternal food consumption during pregnancy and asthma in children by age 5 (Table 2).

Allergic rhinitis

High maternal total consumption of fruit and berry juices was positively associated with allergic rhinitis in the offspring in the adjusted model (Table 2). No other statistically significant associations were found.

Wheeze

Low maternal total consumption of vegetables and low consumption of leafy vegetables, roots, potatoes, malaceous fruits (a combination of apple, pear, peach, apricot, and prune/plum), and chocolate were positively associated with wheeze in the offspring (Table 2). After confounder adjustment, the associations between total vegetable consumption, and roots and potatoes and wheeze lost its statistical significance. In a separate adjusted model having all significant and borderline significant ($0.05 < p < 0.1$) variables in the same model, the findings for leafy vegetables, malaceous fruits, and chocolate remained significant whereas all other findings either lost their significance or remained non-significant (data not shown). In an adjusted model including leafy vegetables, malaceous fruits, and chocolate, all findings remained significant (data not shown).

Additional subgroup analyses

When excluding the women with history of allergy from the analysis, the results remained the same (data not shown). All results remain also similar when the children with eczema by 6 months of age were excluded from the analysis (data not shown).

Discussion

In the present Finnish prospective birth cohort of 2441 mother–child pairs, low maternal consumption of leafy vegetables, malaceous fruits, and chocolate during pregnancy were positively associated with the risk of wheeze. High consumption of fruit and berry juices was positively associated with the risk of allergic rhinitis. These associations were independent of several potential confounders. None of the foods was associated with the risk of asthma in the offspring.

Our finding on the possible protective effect of malaceous fruits against wheeze is in agreement with the previous observation by Willers et al. (8) in a similar birth cohort. They reported beneficial associations between maternal apple intake and childhood wheeze and asthma at 5 yr of age. However, earlier findings on the role of maternal total intake

Table 1 Frequencies of allergic outcomes at 5 yr of age and baseline characteristics of the 2441 mother-child pairs in the Type 1 Diabetes Prediction and Prevention (DIPP) allergy study*

	Distribution of variable	Asthma	Allergic rhinitis	Wheeze
	n	n of endpoints	n of endpoints	n of endpoints
Characteristic	(% of all)	(%)	p†	(%)
<i>All children</i>	2441 (100)	143 (6)	359 (15)	650 (27)
Sex			0.029	0.004
Boys	1272 (52)	87 (7)	212 (17)	358 (28)
Girls	1169 (48)	56 (5)	147 (13)	292 (25)
Season of birth			0.252	0.221
Winter (December–February)	637 (26)	38 (6)	100 (16)	167 (26)
Spring (March–May)	610 (25)	45 (7)	99 (16)	167 (27)
Summer (June–August)	978 (40)	49 (5)	126 (13)	264 (27)
Autumn (September–November)	216 (9)	11 (5)	34 (16)	52 (24)
Place of residence			0.718	0.419
Northern Finland	855 (35)	52 (6)	119 (14)	212 (25)
Southern Finland	1586 (65)	91 (6)	240 (15)	438 (28)
Number of siblings at home			0.345	0.377
None	1122 (46)	61 (5)	177 (16)	314 (28)
One	750 (31)	51 (7)	101 (13)	181 (24)
Two or more	546 (22)	28 (5)	79 (14)	150 (27)
Atopic eczema before the age of 6 month			<0.001	<0.001
No	2007 (82)	99 (5)	239 (12)	489 (24)
Yes	384 (16)	43 (11)	118 (31)	147 (38)
Pets at home before the age of 1 yr			0.459	0.288
No	1647 (68)	101 (6)	252 (15)	458 (28)
Yes	783 (32)	42 (5)	107 (14)	192 (25)
Maternal age			0.296	0.756
<25 yr	361 (15)	29 (8)	57 (16)	117 (32)
25–29 yr	871 (36)	46 (5)	127 (15)	227 (26)
30–34 yr	751 (31)	43 (6)	114 (15)	179 (24)
≥35 yr	458 (19)	25 (5)	61 (13)	127 (28)
Maternal basic education			0.272	0.262
Less than high school	834 (34)	54 (6)	132 (16)	219 (26)
High school graduate	1558 (64)	84 (5)	220 (14)	414 (27)
Maternal smoking during pregnancy			0.149	0.420
No	2177 (89)	126 (6)	325 (15)	581 (27)
Yes	29 (1)	0 (0)	6 (21)	8 (28)
No information	194 (8)	16 (8)	24 (12)	4 (2)
Duration of gestation			0.011	0.562
1. quartier: ≤38.9 wk	597 (25)	49 (8)	79 (13)	171 (29)
2. quartier: 39.0–39.9 wk	565 (23)	37 (7)	85 (15)	153 (27)
3. quartier: 40.0–40.7 wk	614 (25)	27 (4)	99 (16)	152 (25)
4. quartier: >40.7 wk	646 (27)	29 (4)	95 (15)	170 (26)
Mode of delivery			0.735	0.076
Vaginal delivery	1959 (80)	112 (6)	279 (14)	508 (26)
Forceps or suction	158 (7)	9 (6)	33 (21)	46 (29)
Caesarean section	309 (13)	21 (7)	47 (15)	94 (30)
Maternal asthma			<0.001	<0.001
No	2195 (90)	105 (5)	298 (12)	543 (25)
Yes	230 (9)	36 (16)	56 (24)	100 (43)
No information	8 (0.3)	1 (13)	3 (38)	3 (38)
Maternal allergic rhinitis			<0.001	<0.001
No	1303 (53)	47 (4)	127 (10)	264 (20)
Yes	1046 (43)	91 (9)	220 (21)	359 (34)
No information	85 (4)	5 (6)	12 (14)	27 (32)

Table 1 Continued

Characteristic	Distribution of variable	Asthma		Allergic rhinitis		Wheeze	
	n (% of all)	n of endpoints (%)	p†	n of endpoints (%)	p†	n of endpoints (%)	p†
Breastfeeding			0.037		0.093		0.153
1st third	677 (28)	52 (8)		116 (17)		194 (29)	
2nd third	787 (32)	47 (6)		112 (14)		214 (27)	
3rd third	945 (39)	44 (5)		126 (13)		230 (24)	
Day care at 1 yr of age			0.685		0.612		0.183
No	2132 (87)	127 (6)		317 (15)		579 (27)	
Yes	298 (12)	16 (5)		41 (14)		70 (23)	

*Missing information: Number of siblings at home 23(0.9%); atopic eczema before age 6 months 50(2.0%); pets at home before age 1 yr 11(0.5%); maternal basic education 49(2.0%); maternal professional education 31(1.3%); maternal smoking during pregnancy 41(1.7%); duration of gestation 19(0.8%); mode of delivery 15(0.6%); maternal asthma 8(0.3%); maternal allergic rhinitis 7(0.3%); breastfeeding 32(1.3%); day care at 1 yr of age 11(0.5%).

†Based on χ^2 test.

of vegetables and fruits have been rather controversial (5, 6, 9, 10, 21). The earlier context of evidence offers some support to the association that we demonstrated between low maternal consumption of leafy vegetables and the increased risk of wheeze in the offspring. In the French E3N study including 68 535 women, higher intake of leafy vegetables was associated with a lower prevalence of asthma (22). Overall, the majority of fruit and vegetable studies are indicative of a protective effect (10).

A positive association between high maternal consumption of fruit and berry juices and the risk of allergic rhinitis in the offspring is a novel one. Dietary exposures can act at least partly as proxies for other life style characteristics. Earlier study among the same cohort of pregnant women showed that smoking during pregnancy, having no vocational education, and young age were the strongest sociodemographic determinants of high juice consumption whereas highest consumption of fruits and vegetables were found in well educated, older (< 30 yr), and non-smoking pregnant women (23).

The finding on the possible protective effect of maternal chocolate consumption against wheeze is also a novel one. The detected association may be attributed to nutritional factors with powerful antioxidant capacities, such as flavonoids, a subgroup of polyphenolic compounds. Some polyphenolic compounds can influence the balance between the Th1 and Th2 cytokines by promoting the secretion of the Th1 cytokine interferon-gamma and inhibiting the secretion of the Th2 cytokine interleukin 4 (24). There are some significant sources of flavonoids and other polyphenols in the food groups of malaceous fruits, leafy vegetables, and chocolates. Cocoa has been shown to have an effect on innate and acquired immune function both in *in vitro* and in *in vivo* experiments (25). Studies suggest that high-dose cocoa intake in young rats favors the Th1 response and increases the intestinal gamma/delta T lymphocyte count, whereas the antibody-secreting response decreases. Intake of apples as a significant source of flavonoids and other polyphenols has been beneficially associated with asthma and lung function in adults (22, 26, 27).

There is substantial heterogeneity in respiratory symptoms among children under the age of 3 yr. In the current study, the end-point 5 yr of age was selected to exclude younger children having transient respiratory symptoms related to viral infections. The natural history of allergic symptoms may follow a sequence, an atopic march that begins with atopic dermatitis in infancy, followed by allergic rhinitis and asthma later in life (28). The diagnosis of asthma is challenging in young children. There is always the possibility that some of the asthma cases had transient wheezing symptoms or persistent wheeze rather than true asthma. By including wheeze as a separate outcome, we aimed to rule out that possibility. In the present study, the coexistence of wheeze and asthma was identified only in 2% of children. If the difference in definition of wheeze and asthma reflect the severity of the disease, the findings could imply that optimal maternal diet during pregnancy can suppress only the mild case, but not the more severe case of asthma.

The "time-window hypotheses" is becoming a key aspect in the study of allergic diseases characterized by a long developmental phase. Immunomodulating benefits may be greater during critical stages of early immune development before an allergic response is even established (29). In the present study, most findings were observed for wheeze. This could imply that critical time windows for exposures differ between the allergic outcomes or that at the 5 yr of age, we were able to note the impact of maternal diet only in a certain phenotype of the allergic march.

We can neither completely rule out that our findings might have occurred by chance. An extensive search for associations always carries a high likelihood of statistically significant associations arising by chance, and therefore, demonstration of reproducibility is needed. The complex relationship between early nutrition and allergic outcomes emphasizes the need for consistent and thorough assessment of women's diets throughout the duration of pregnancy and the children's diet throughout early years. Concentrating only on single foods at a single time point will inevitably lead to oversimplifying the relationship under study, and the

Table 2 Association between maternal food consumption during pregnancy and allergic endpoints in the offspring at 5 yr of age among the 2441 mother-child pairs in the Type 1 Diabetes Prediction and Prevention (DIPP) allergy

Food variables in quarters, cut off values g/d	Hazard ratio (95% confidence interval)* for asthma n = 143 (6%)		Hazard ratio (95% confidence interval)* for allergic rhinitis n = 359 (15%)		Odds ratio (95% confidence interval)† for wheeze n = 650 (27%)	
	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
Vegetables, total	p = 0.616	p = 0.512	p = 0.532	p = 0.827	p = 0.035	p = 0.094
Lowest, <149.1	0.94 (0.59–1.51)	0.92 (0.58–1.48)	1.14 (0.86–1.50)	0.94 (0.67–1.33)	1.39 (1.08–1.78)	1.31 (1.02–1.67)
Mid half, 149.1–315.1	1	1	1	1	1	1
Highest, 312.1–2532.2	0.78 (0.47–1.29)	0.75 (0.46–1.22)	1.13 (0.87–1.47)	1.07 (0.78–1.47)	1.12 (0.88–1.42)	1.14 (0.90–1.45)
Leafy vegetables	p = 0.394	p = 0.456	p = 0.916	p = 0.617	p = 0.033	p = 0.008
Lowest, <9.6	0.90 (0.60–1.35)	0.96 (0.61–1.56)	1.03 (0.79–1.33)	0.87 (0.78–1.23)	1.35 (1.08–1.68)	1.48 (1.15–1.89)
Mid half, 9.6–36.1	1	1	1	1	1	1
Highest, 36.1–260.7	0.74 (0.48–1.14)	0.74 (0.46–1.19)	1.05 (0.82–1.35)	1.06 (0.78–1.44)	1.08 (0.87–1.35)	1.05 (0.83–1.34)
Vegetable fruits	p = 0.469	p = 0.484	p = 0.342	p = 0.701	p = 0.308	p = 0.600
Lowest, <49.5	0.88 (0.58–1.33)	0.80 (0.49–1.35)	1.20 (0.93–1.54)	0.87 (0.83–1.22)	1.12 (0.90–1.40)	1.12 (0.87–1.43)
Mid half, 49.5–138.7	1	1	1	1	1	1
Highest, 138.7–749.0	0.78 (0.52–1.16)	0.75 (0.56–1.22)	1.12 (0.87–1.45)	0.93 (0.68–1.27)	1.17 (0.94–1.46)	1.09 (0.86–1.38)
Roots and potatoes	p = 0.258	p = 0.324	p = 0.239	p = 0.687	p = 0.032	p = 0.096
Lowest, <117.8	0.91 (0.61–1.37)	1.07 (0.66–1.72)	1.24 (0.97–1.59)	1.14 (0.83–1.56)	1.33 (1.07–1.65)	1.29 (1.02–1.64)
Mid half, 117.8–207.5	1	1	1	1	1	1
Highest, 207.5–788.5	1.38 (0.88–2.17)	1.52 (0.88–2.64)	1.08 (0.83–1.42)	0.97 (0.69–1.37)	1.18 (0.94–1.49)	1.14 (0.89–1.47)
Fruits	p = 0.714	p = 0.957	p = 0.679	p = 0.652	p = 0.268	p = 0.274
Lowest, <32.2	1.20 (0.77–1.85)	1.07 (0.64–1.79)	0.89 (0.68–1.16)	0.85 (0.61–1.20)	0.87 (0.69–1.10)	0.84 (0.65–1.08)
Mid half, 32.2–793.9	1	1	1	1	1	1
Highest, 793.9–3908.0	1.02 (0.67–1.55)	0.97 (0.60–1.58)	0.97 (0.74–1.29)	0.95 (0.68–1.34)	1.11 (0.88–1.40)	1.07 (0.83–1.37)
Citrus fruits	p = 0.167	p = 0.215	p = 0.802	p = 0.749	p = 0.570	p = 0.485
Lowest, <7.04	1.14 (0.75–1.71)	1.30 (0.81–2.08)	1.09 (0.85–1.40)	1.13 (0.83–1.54)	1.13 (0.91–1.40)	1.15 (0.91–1.45)
Mid half, 7.04–71.8	1	1	1	1	1	1
Highest, 71.8–778.8	0.75 (0.49–1.13)	0.77 (0.47–1.27)	1.04 (0.81–1.35)	1.03 (0.75–1.42)	1.04 (0.84–1.30)	1.00 (0.79–1.27)
Malaceous fruits	p = 0.979	p = 0.868	p = 0.227	p = 0.513	p = 0.002	p = 0.044
Lowest, <17.7	1.04 (0.70–1.54)	0.97 (0.61–1.55)	1.24 (0.97–1.59)	1.18 (0.87–1.62)	1.47 (1.18–1.83)	1.35 (1.07–1.71)
Mid half, 17.7–97.5	1	1	1	1	1	1
Highest, 97.6–935.0	0.99 (0.65–1.52)	1.12 (0.68–1.85)	1.10 (0.85–1.42)	1.14 (0.83–1.57)	1.11 (0.89–1.39)	1.14 (0.90–1.45)
Berries	p = 0.340	p = 0.199	p = 0.935	p = 0.681	p = 0.578	p = 0.331
Lowest, <6.74	1.15 (0.72–1.84)	1.08 (0.62–1.88)	1.03 (0.79–1.32)	1.10 (0.80–1.52)	0.94 (0.75–1.18)	0.90 (0.70–1.15)
Mid half, 6.74–32.7	1	1	1	1	1	1
Highest, 32.7–611.0	1.34 (0.90–2.00)	1.56 (0.96–2.54)	0.97 (0.75–1.25)	1.14 (0.83–1.57)	1.08 (0.87–1.35)	1.12 (0.88–1.42)
Fruit and berry juices	p = 0.409	p = 0.238	p = 0.113	p = 0.046	p = 0.063	p = 0.077
Lowest, <5.67	0.97 (0.64–1.47)	1.08 (0.67–1.74)	0.90 (0.69–1.16)	0.96 (0.70–1.33)	0.98 (0.79–1.21)	0.97 (0.77–1.23)
Mid half, 5.67–145.7	1	1	1	1	1	1
Highest, 145.7–1700	0.77 (0.52–1.15)	0.71 (0.45–1.13)	1.20 (0.94–1.54)	1.40 (1.03–1.90)	1.26 (1.01–1.58)	1.27 (1.00–1.61)

Table 2 Continued

Food variables in quarters, cut off values g/d	Hazard ratio (95% confidence interval)* for asthma n = 143 (6%)		Hazard ratio (95% confidence interval)* for allergic rhinitis n = 359 (15%)		Odds ratio (95% confidence interval)† for wheeze n = 650 (27%)	
	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
Cereals						
Lowest, <155.0	p = 0.535	p = 0.165	p = 0.852	p = 0.593	p = 0.367	p = 0.494
Mid half, 155.0–246.2	1	1	0.98 (0.75–1.29)	1.14 (0.81–1.61)	1.08 (0.85–1.37)	1.06 (0.82–1.38)
Highest, 256.2–772.9	0.91 (0.59–1.39)	0.86 (0.52–1.42)	0.92 (0.69–1.23)	0.89 (0.62–1.28)	0.86 (0.67–1.10)	0.87 (0.66–1.13)
Dietary fats	p = 0.755	p = 0.409	p = 0.656	p = 0.599	p = 0.424	p = 0.373
Lowest, <31.0	1.09 (0.71–1.67)	1.34 (0.83–2.17)	1.13 (0.87–1.47)	1.14 (0.82–1.59)	1.10 (0.88–1.38)	1.09 (0.85–1.40)
Mid half, 31.0–57.3	1	1	1	1	1	1
Highest, 57.3–264.8	0.88 (0.56–1.39)	0.92 (0.54–1.56)	1.03 (0.78–1.37)	1.14 (0.81–1.62)	0.90 (0.70–1.15)	0.86 (0.66–1.12)
Fish	p = 0.936	p = 0.732	p = 0.466	p = 0.888	p = 0.566	p = 0.854
Lowest, <10.9	0.94 (0.63–1.40)	0.87 (0.53–1.43)	1.17 (0.91–1.50)	0.97 (0.70–1.33)	1.12 (0.90–1.39)	1.06 (0.84–1.35)
Mid half, 10.9–33.27	1	1	1	1	1	1
Highest, 33.28–254.8	1.01 (0.67–1.54)	1.09 (0.66–1.78)	1.02 (0.79–1.32)	0.92 (0.67–1.28)	0.99 (0.79–1.24)	0.99 (0.78–1.25)
Meat	p = 0.408	p = 0.412	p = 0.498	p = 0.616	p = 0.111	p = 0.180
Lowest, <119.2	1.23 (0.78–1.94)	1.25 (0.72–2.17)	0.86 (0.65–1.12)	0.85 (0.60–1.19)	0.91 (0.72–1.14)	0.94 (0.73–1.20)
Mid half, 119.2–197.7	1	1	1	1	1	1
Highest, 197.7–764.7	0.84 (0.55–1.27)	0.79 (0.48–1.32)	1.02 (0.78–1.33)	0.95 (0.67–1.33)	1.22 (0.97–1.55)	1.23 (0.96–1.58)
Milks	p = 0.887	p = 0.997	p = 0.265	p = 0.607	p = 1.000	p = 0.938
Lowest, <214.0	0.95 (0.63–1.42)	1.02 (0.62–1.68)	1.01 (0.79–1.29)	0.92 (0.67–1.25)	1.00 (0.81–1.25)	0.96 (0.76–1.22)
Mid half, 214.0–766.4	1	1	1	1	1	1
Highest, 766.4–2756.3	1.08 (0.69–1.69)	1.00 (0.59–1.69)	0.81 (0.62–1.06)	0.85 (0.61–1.19)	1.00 (0.80–1.26)	0.98 (0.77–1.25)
Fermented milk products	p = 0.925	p = 0.427	p = 0.942	p = 0.785	p = 0.131	p = 0.112
Lowest, <100.0	0.99 (0.66–1.48)	1.21 (0.76–1.93)	1.04 (0.80–1.39)	1.00 (0.72–1.38)	1.06 (0.85–1.33)	1.09 (0.85–1.38)
Mid half, 100.0–309.6	1	1	1	1	1	1
Highest, 309.6–3326.8	1.09 (0.69–1.71)	1.38 (0.81–2.36)	1.04 (0.81–1.34)	0.89 (0.65–1.24)	0.82 (0.66–1.03)	0.81 (0.64–1.03)
Cheese	p = 0.361	p = 0.205	p = 0.359	p = 0.156	p = 0.713	p = 0.448
Lowest, <30.3	0.73 (0.47–1.13)	0.62 (0.36–1.05)	0.85 (0.65–1.11)	0.79 (0.56–1.12)	0.91 (0.73–1.14)	0.86 (0.67–1.10)
Mid half, 30.3–85.8	1	1	1	1	1	1
Highest, 85.8–380.9	0.92 (0.60–1.40)	0.96 (0.60–1.56)	1.06 (0.82–1.37)	1.17 (0.86–1.60)	0.97 (0.77–1.21)	0.93 (0.73–1.18)
Chocolate	p = 0.418	p = 0.433	p = 0.722	p = 0.361	p = 0.039	p = 0.042
Lowest, <7.14	1.36 (0.84–2.22)	1.37 (0.85–2.22)	1.12 (0.85–1.46)	1.18 (0.85–1.63)	1.37 (1.07–1.74)	1.36 (1.07–1.74)
Mid half, 7.14–26.7	1	1	1	1	1	1
Highest, 26.7–250.4	0.99 (0.60–1.65)	1.09 (0.66–1.81)	1.05 (0.80–1.38)	1.24 (0.90–1.70)	1.11 (0.87–1.42)	1.12 (0.88–1.43)

*Assessed with Cox regression analysis. Significant associations marked bold.

†Assessed with logistic regression analysis. Significant associations marked bold.

‡Adjusted for sex, place of birth, duration of gestation, maternal age at delivery, maternal basic education, smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental allergic rhinitis, atopic eczema by 6 months of age, pets at home by 1 yr of age, duration of breast feeding, and day care at 1 yr of age.

information obtained will likely be incomplete or, in some cases, even false. More studies on maternal dietary patterns and their possible impacts on the risk of allergy outcomes in the offspring are needed. The recent finding from a Japanese cohort study suggests that maternal Western pattern during pregnancy, characterized by high intake of vegetable oil, salt-containing seasonings, beef and pork, processed meat, eggs, chicken, and white vegetables, may be preventive against wheeze in the offspring (30). The possible effectiveness of a Mediterranean diet during pregnancy for the prevention of sensitization and asthma has also been discussed (10).

The major virtues of our study are the large, population-based cohort, use of a validated FFQ (17) that is specially targeted for the population group and a broad selection of explanatory and outcome variables. Furthermore, the definitions of the end-points were based on a standardized and validated questionnaire (19) adapted for the Finnish population (20). Validation of the asthma component of the ISAAC questionnaire gave 98% sensitivity and specificity (31). The collection of dietary data before the development of end-points may minimize bias related to the dietary assessment. In the validation study using 10-day food records as the reference method, the FFQ overestimated food consumption (17). However, the quintile notation was acceptable for most of the foods. Apart from duration of breastfeeding, the child's own food consumption was not examined alongside maternal food intake in the present study. Consequently, the reported associations might have been modified by the diet of the children during the first 5 yr of life. Some familial dependence between dietary clusters of mother-child pairs participating in the DIPP study was observed in 6-year-old children but not in younger children (32). It is, therefore, unlikely that maternal food consumption frequencies were a surrogate marker of child food consumption frequencies in early years.

The families participating in the allergy study tended to have characteristics associated with an overall healthier life-style. This could have led to minimized dietary exposure contrasts, and consequently, to decreased informativeness of the study. The study subjects carry HLA-conferred susceptibility to type 1 diabetes, representing about 15% of all newborn infants. The cumulative incidences of asthma, allergic rhinitis, and wheeze in our study, however, were comparable to other Finnish studies (33). Type 1 diabetes is associated with Th1 cell types, whereas allergic disorders are related to Th2 cell types (34). In addition to the complexities surrounding the

various components in the immune system that relate to the production of Th1 and Th2 cytokines, it is inconclusive on how type 1 diabetes and allergies may be associated (35). It is, therefore, possible that our results may not be completely generalizable to the general population.

In conclusion, within the limitations of the present study, the results of this prospective birth cohort study suggest that maternal consumption of leafy vegetables, malaceous fruits, and chocolate during pregnancy may protect from the development of wheeze in the offspring at 5 yr of age. Together with previous studies, the results support the hypothesis that dietary modification in fetal life could affect the development of allergic diseases. An independent effect of maternal flavonoid intake against allergic diseases deserves to be studied.

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Authors' contribution

ME and SMV designed the study and planned the statistical analyses. ME wrote the first draft of the manuscript and had primary responsibility for final content. BIN performed the statistical analyses. MKa contributed to the conception and design of the study. CK-K participated in the preparation of the data. JI, OS, MKn, and SMV designed the DIPP study. BIN, MKa, CK-K, JI, OS, RV, MKn, and SMV participated in the critical revision of the manuscript and approved the final version. The funding sources had no role in the study design, the writing of the report, or the collection, analysis, or interpretation of the data. None of the authors had a conflict of interest.

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