

Maternal Food Consumption during Pregnancy and the Longitudinal Development of Childhood Asthma

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Rationale: Maternal diet during pregnancy has the potential to affect airway development and to promote T-helper-2-cell responses during fetal life. This might increase the risk of developing childhood asthma or allergy.

Objectives: We investigated the influence of maternal food consumption during pregnancy on childhood asthma outcomes from 1 to 8 years of age.

Methods: A birth cohort study consisting of a baseline of 4,146 pregnant women (1,327 atopic and 2,819 nonatopic). These women were asked about their frequency of consumption of fruit, vegetables, fish, egg, milk, milk products, nuts, and nut products during the last month. Their children were followed until 8 years of age. Longitudinal analyses were conducted to assess associations between maternal diet during pregnancy and childhood asthma outcomes over 8 years.

Measurements and Main Results: Complete data were obtained for 2,832 children. There were no associations between maternal vegetable, fish, egg, milk or milk products, and nut consumption and longitudinal childhood outcomes. Daily consumption of nut products increased the risk of childhood wheeze (odds ratio [OR] daily versus rare consumption, 1.42; 95% confidence interval [95% CI], 1.06–1.89), dyspnea (OR, 1.58; 95% CI, 1.16–2.15), steroid use (OR, 1.62; 95% CI, 1.06–2.46), and asthma symptoms (OR, 1.47; 95% CI, 1.08–1.99).

Conclusions: Results of this study indicate an increased risk of daily versus rare consumption of nut products during pregnancy on childhood asthma outcomes. These findings need to be replicated by other studies before dietary advice can be given to pregnant women.

Keywords: asthma; children; diet; pregnancy

The chance of developing asthma and allergy might be determined during fetal life because there are potential mechanisms by which environmental factors, such as maternal diet and lifestyle, can influence the development of the airways and immune system of the child *in utero* (1). Adherents of the fetal programming theory or Barker hypothesis pose that adverse

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several studies have provided evidence on associations between maternal diet during pregnancy and asthma and allergy in childhood. However, most studies have used cross-sectional statistical analyses to investigate this relationship.

What This Study Adds to the Field

This study provides evidence on the relationship between maternal diet during pregnancy and longitudinal development of childhood asthma. Daily consumption of nut products increased the risk of asthma outcomes during the first 8 years of life.

events during pregnancy, such as undernutrition, smoking, and infections, can result in impaired growth in the fetus and long-term physiologic or metabolic changes (2). This concept, which was established by David Barker, who found that low birth weight was associated with elevated blood pressure and increased risk of cardiovascular mortality (3), has been postulated to play a role in the origin of asthma and allergy as well (4, 5). Several studies have found associations between low birth weight or head circumference and asthma, respiratory symptoms, or atopy (6–8). Maternal nutrient status during pregnancy may have the potential to impair fetal airway development or to promote neonatal T-helper (Th)-cell responses to allergens being biased toward Th2-cell responses, which increase the risk of developing asthma or allergic disease in childhood (1).

Another possible mechanism is that *in utero* allergen exposure exerts an effect on the developing fetal immune system. Research has shown fetal immune responses to allergens from 22 weeks of gestation (9). Maternal intake of allergenic foods during pregnancy may thus increase the risk of sensitization in the fetus and subsequent allergic disease. However, the evidence of the effectiveness of maternal dietary allergen avoidance during pregnancy for the prevention of childhood allergic disease is inconclusive (10).

Previous studies investigating the relationship between maternal diet during pregnancy and asthma or allergic disease in the offspring have found beneficial effects of higher intake of vitamin E (11–14), vitamin D (15, 16), zinc (13), selenium and iron (17), and higher consumption of fish (18–23) and apples (22). The study of Sausenthaler and colleagues (20) has found associations between maternal intake of allergenic foods during pregnancy and sensitization against inhalant and food allergens in childhood.

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The prospective studies mentioned previously have mostly assessed associations between maternal diet during pregnancy and asthma at one specific age of the child. To our knowledge, the present study is the first to use longitudinal statistical techniques to investigate this relationship over a longer period. The aim of this study was to investigate longitudinally the influence of maternal diet during pregnancy on the prevalence of symptoms of childhood asthma from 1 to 8 years of age.

Some of the preliminary findings of this article have been reported in the form of an abstract (24).

METHODS

Study Population and Design

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study, set up in 1996, consisted of a natural history part and an intervention part. Details of the study design have been published previously (25). Briefly, 10,232 pregnant women completed a validated screening questionnaire at their prenatal health care clinic (26). Based on this screening, 7,862 women were invited to participate, of whom 4,146 women agreed and gave informed consent. Follow-up of the children took place at 3 months of age and yearly from 1 to 8 years of age. The Medical Ethical Committees of the participating institutes approved the study, and all participants gave written informed consent. More details of the selection and follow-up of the participants can be found in the online supplement.

Assessment of Maternal Diet during Pregnancy

The pregnancy questionnaire contained questions about diet. Expectant mothers were asked "How often did you consume vegetables, fresh fruit, fish, egg, milk, milk products, nuts, and nut products such as peanut butter during the last month?" Answer options were (1) never, (2) one to three times a month, (3) once a week, (4) two to four times a week, (5) more than four times a week, (6) once a day, or (7) several times per day. These frequency values were combined into three categories: rarely (value 1 and 2), regularly (value 3, 4, and 5), and daily (value 6 and 7).

A variable dairy consumption was constructed by taking the average of milk and milk product consumption. In the Dutch general population, tree nuts, peanuts, almonds, Brazil nuts, cashews, macadamia nuts, pistachios, and so forth, are commonly regarded as nuts.

If the prevalence of rare or daily consumption was less than 5%, it was combined with the category "regularly" consumption. For vegetables, fruit and dairy, daily consumption was compared with regular plus rare consumption. For fish, egg, and nuts, daily plus regular consumption was compared with the reference category rare consumption. For nut products, all categories contained sufficient observations, so daily and regular consumption were compared with rare consumption as a reference category.

Assessment of the Child's Diet at 2 Years of Age

Questionnaires administered from 1 to 8 years of age contained questions about the child's diet. Parents were asked to indicate from the following five options regarding how often in the previous month the child had consumed a number of different foods and drinks: not at all; a few times but less than once a week; 1 or 2 days/week; 3 to 5 days/week; or 6 or 7 days/week. The child's dietary data on fruit, vegetables, fish, egg, full cream milk, butter, and peanut butter consumption at 2 years of age were used to check for potential confounding by the child's diet.

Child's Health Outcomes

The yearly follow-up questionnaires contained the International Study of Asthma and Allergies in Childhood (ISAAC) core questions on asthma, rhinitis, and eczema (27). The main outcomes of interest for longitudinal analyses were wheeze, dyspnea, prescription of inhaled corticosteroids for respiratory problems, and the composite variable "asthma symptoms" in the last 12 months. Data on wheeze were available from 1 to 8 years of age, data on dyspnea, and steroid use from 3 to 8 years of age. The composite variable "asthma symptoms" from 3 to 8 years of age was based on the wheeze, dyspnea, and steroid use outcomes. A child was defined as having asthma symptoms when the parents reported one or more attacks of

wheeze and/or one or more events of dyspnea and/or prescription of inhalation steroids for respiratory problems in the last 12 months. A child who had none of these characteristics was defined as not having asthma symptoms. Other outcomes that were investigated longitudinally were wheeze and dyspnea without a cold and doctor-diagnosed asthma in the last 12 months.

The wheeze data from 1 to 8 years of age was used to categorize the children as never wheezers, early transient wheezers, late-onset wheezers, or persistent wheezers according to Martinez and coworkers (28) (see the online supplement).

IgE data at 8 years of age were present for a subgroup of 1,657 children. The methods used for IgE measurements are described in the online supplement.

Statistical Analyses

All analyses were performed using SAS for Windows version 8.2 (SAS Institute, Cary, NCS). Generalized estimating equations (GEEs) were used to assess the associations between maternal diet during pregnancy and childhood symptoms of asthma during the first 8 years of life simultaneously. GEEs take into account that repeated measurements in the same individual are correlated to derive correct standard errors and *P* values of the estimates. A working correlation structure was used to correct for this within-subject correlation (29). Potential confounders adjusted for in the final longitudinal models were sex, maternal education, parental allergy, maternal smoking during pregnancy, smoking in the home at 8 years of age, breast feeding, presence of older siblings, birth weight, maternal overweight 1 year after pregnancy (body mass index > 25 kg/m²), maternal supplement use during pregnancy, region, and study arm (intervention or natural history study).

The associations between maternal intake of different food groups during pregnancy and the different wheezing phenotypes were calculated by polytomous logistic regression analyses. The final models were adjusted for the same set of confounders as used for the GEE analyses.

Multivariate logistic regression analyses were used to investigate the associations between maternal diet during pregnancy and sensitization to inhalant and food allergens at 8 years of age.

RESULTS

Study Population, Maternal Food Consumption during Pregnancy, and Prevalence of Symptoms of Asthma from 1 to 8 Years of Age

The initial study population consisted of 4,146 pregnant women, of whom 4,112 filled in the pregnancy questionnaire. Around 80% of these mothers completed this questionnaire between the 30th and 36th week of gestation. Dietary consumption frequencies for the different foods of these mothers and mothers who completed the questionnaire before the 30th week (~10%) or after the 36th week (~10%) were comparable.

Of the baseline population of 4,146 mothers, 183 (~4.5%) were lost to follow-up before data on the child had been collected. The study therefore started with 3,963 newborn children. Questionnaire data from age 1 to 8 years were obtained for 3,817, 3,740, 3,694, 3,563, 3,518, 3,473, 3,373, and 3,320 children, respectively. Characteristics of the study population at baseline (*n* = 3,963) and of the participants with complete data (pregnancy questionnaire, at least one of the outcome time points, and all confounders) (*n* = 2,832) included in the analyses are described in Table 1. Participants with complete data were more likely to have a high educational level, to have daily fruit and dairy intake during pregnancy, and to have breast fed their child, compared with participants who did not have complete data. Furthermore, they were less likely to have maternal atopy or maternal asthma, a low educational level, smoked during pregnancy or in the house at baseline, be from a southwestern region (Rotterdam and surrounding municipalities), and participate in the intervention study. Yet, the magnitude of the differences between the populations was small (<10%). The characteristics of study population at baseline compared with the population with questionnaire

TABLE 1. CHARACTERISTICS OF THE POPULATION AT BASELINE AND COMPLETE CASES AT 8 YEARS OF AGE

Maternal Characteristic	Respondents at Baseline (n = 3,963)	Complete Cases at 8 Years* (n = 2,832)
Atopy, [†] n (%)	1,237 (31.2)	788 (27.8)
Partner atopic, n (%)	1,217 (30.7)	856 (30.2)
Asthma ever, n (%)	314 (7.9)	184 (6.5)
Partner ever asthmatic, n (%)	302 (7.6)	208 (7.3)
Educational level low, n (%)	894 (22.6)	577 (20.4)
Educational level high, n (%)	1,331 (33.6)	1,073 (37.9)
Partner's educational level low, n (%)	973 (24.6)	666 (23.5)
Partner's educational level high, n (%)	1,493 (37.7)	1,188 (42.0)
Smoking during pregnancy, n (%)	696 (17.6)	444 (15.7)
Supplement use during pregnancy [‡] , n (%)	3,285 (82.9)	2,372 (83.8)
Smoking in the house by mother, father, or others at baseline [§] , n (%)	970 (24.5)	591 (20.9)
Region North, n (%)	1,231 (31.1)	886 (31.3)
Region Central, n (%)	1,586 (40.0)	1,190 (42.0)
Region Southwest, n (%)	1,146 (28.9)	756 (26.7)
Participates in intervention study	781 (19.7)	450 (15.9)
Age when having child, mean (SD)	30.3 (3.9)	30.6 (3.8)
Body mass index , kg/m ² , mean (SD)	23.3 (3.6)	23.3 (3.5)
Food intake during pregnancy		
Daily vegetable intake, n (%)	2,217 (55.9)	1,621 (57.2)
Daily fruit intake, n (%)	3,025 (76.3)	2,221 (78.4)
Daily + regular fish intake, n (%)	973 (24.6)	694 (24.5)
Daily + regular egg intake, n (%)	2,631 (66.4)	1,894 (66.9)
Daily dairy intake, n (%)	3,335 (84.2)	2,453 (86.6)
Daily + regular nuts intake, n (%)	1,322 (33.4)	984 (34.8)
Daily nut product intake, n (%)	243 (6.1)	169 (6.0)
Regular nut product intake, n (%)	1,452 (36.6)	1,062 (37.5)
Child's characteristics		
Female, n (%)	1,911 (48.2)	1,380 (48.7)
Birth weight, g, mean (SD)	3,507.2 (546.1)	3,526.0 (533.92)
Older siblings present, n (%)	1,994 (50.3)	1,414 (49.9)
Ever breast fed, n (%)	3,200 (80.8)	2,365 (83.5)

* Participants with data on pregnancy questionnaire, at least one of the outcome time points, and all confounders.

[†] Assessed by validated screening questionnaire at recruitment.

[‡] Vitamin A or D, vitamin B, vitamin C, multivitamin, folic acid, calcium, iron, or other vitamins.

[§] At age 3 months.

^{||} Reported 1 year after pregnancy.

follow-up data (n = 3,320) and IgE data (n = 1,657) at 8 years of age are shown in Table E1 of the online supplement.

Table 2 shows the frequencies of rarely, regularly, and daily consumption for the different foods eaten during pregnancy. More than 50% of the pregnant woman daily consumed vegetables, fresh fruit, milk, and milk products and rarely ate fish, nuts, and nut products. We also investigated possible avoidance of potentially allergenic foods. Less than 1% of the mothers reported to have never consumed milk or milk products during

TABLE 2. FREQUENCY OF MATERNAL FOOD CONSUMPTION DURING PREGNANCY

	Rarely*		Regularly [†]		Daily [‡]	
	n	%	n	%	n	%
Vegetables	29	0.7	1,700	42.9	2,217	55.9
Fruit	64	1.6	853	21.5	3,025	76.3
Fish	2,949	74.4	972	24.5	1	0.0
Egg	1,296	32.7	2,625	66.2	6	0.2
Dairy	52	1.3	476	12.0	3,335	84.2
Nuts	2,587	65.3	1,267	32.0	55	1.4
Nut products	2,216	55.9	1,452	36.6	243	6.1

* Never or one to three times a month.

[†] Once a week to more than four times a week.

[‡] Once a day or more.

the last month, and approximately 11% never ate nuts or nut products. Almost 30% of the mothers never ate fish, and almost 5% never ate eggs according to the pregnancy questionnaire data.

The prevalence rates of childhood symptoms of asthma from 1 to 8 years of age are shown in Table 3. The prevalence of wheeze and dyspnea strongly decreased, whereas the prevalence of steroid use stayed quite constant over time. The composite variable "asthma symptoms" based on these three outcomes decreased from approximately 23% at 3 years of age to approximately 13% at 8 years. The prevalence rates of wheeze without cold, dyspnea without a cold, and doctor-diagnosed asthma were lower and more constant over time. From the children who provided complete wheeze data from 1 to 8 years of age (n = 3,043), 1,866 (61.3%) were classified as never wheezers, 731 (24.0%) as early transient wheezers, 132 (4.3%) as late-onset wheezers, and 314 (10.3%) as persistent wheezers.

Associations between Maternal Food Consumption during Pregnancy and Childhood Asthma Outcomes from 1 to 8 Years of Age

Overall estimates derived with univariate and multivariate GEE analyses of the associations between maternal diet during pregnancy and childhood wheeze, dyspnea, steroid use, and the composite variable "asthma symptoms" from 1 or 3 to 8 years of age are shown in Table 4. There were no overall associations between maternal vegetable, fish, egg, milk and milk products, and nut consumption during pregnancy and childhood wheeze, dyspnea, steroid use or asthma symptoms.

Children of mothers who daily ate fresh fruit had a crude decreased risk of wheeze versus children of mothers who did not eat fruit on a daily basis. This changed to borderline significant after adjustment for confounders in the multivariate analysis. There were no significant overall associations between fruit consumption and the other childhood outcomes. Figure 1 shows the course of the associations between maternal fruit consumption during pregnancy and childhood outcomes over time. These plots show that the significance of the crude overall association between fruit and wheeze is strongest determined by the (borderline) significant associations at 1, 2, and 5 years of age. Furthermore, we can see occasional significant associations at certain ages, whereas overall associations are nonsignificant (e.g., for fruit and steroid use at 6 years of age).

Daily consumption versus rare consumption of nut products during pregnancy was significantly positively associated with childhood wheeze, dyspnea, steroid use, and asthma symptoms. Regular consumption versus rare consumption of nut products during pregnancy was not associated with any of the outcomes. *P* values for trend (daily-regular-rare consumption) were not statistically significant (data not shown). Adjustment for potential confounders and stratification by maternal allergy did not consistently alter the magnitude or significance of the results. Plots of the course of the associations between maternal daily nut product consumption versus rare nut product consumption during pregnancy and childhood symptoms of asthma over time are shown in Figure 2. These plots show that the adverse associations are consistent over time.

Table E2 shows the additional results of the overall associations of the different food groups with wheeze without cold, dyspnea without cold, and doctor-diagnosed asthma from 3 to 8 years of age. Daily versus rare nut products consumption during pregnancy was strongly positively associated with these additional childhood outcomes as well.

Results of the analyses of maternal food consumption during pregnancy and the different wheezing phenotypes at 8 years of

TABLE 3. PREVALENCE OF CHILDHOOD SYMPTOMS OF ASTHMA FROM 1 TO 8 YEARS OF AGE

Symptoms	Age (yr)							
	1	2	3	4	5	6	7	8
Number*	3,817	3,740	3,694	3,563	3,518	3,473	3,373	3,320
Wheeze, n (%)	780 (20.4)	668 (17.9)	578 (15.7)	421 (11.8)	334 (9.5)	271 (7.8)	198 (5.9)	221 (6.7)
Wheeze without cold, n (%)	—	—	182 (4.9)	150 (4.2)	136 (3.9)	132 (3.8)	108 (3.2)	115 (3.5)
Dyspnea, n (%)	—	—	564 (15.3)	466 (13.1)	436 (12.4)	370 (10.7)	258 (7.7)	303 (9.1)
Dyspnea without cold, n (%)	—	—	217 (5.9)	179 (5.0)	208 (5.9)	188 (5.4)	146 (4.3)	173 (5.2)
Steroid use, n (%)	—	—	287 (7.8)	273 (7.7)	278 (7.9)	263 (7.6)	229 (6.8)	211 (6.4)
Asthma symptoms†, n (%)	—	—	854 (23.1)	676 (19.0)	624 (17.7)	515 (14.8)	419 (12.4)	437 (13.2)
Doctor-diagnosed asthma, n (%)	—	—	154 (4.2)	147 (4.1)	139 (4.0)	134 (3.9)	95 (2.8)	119 (3.9)

* Number of participants followed-up at specific time points.

† Composite variable of wheeze, dyspnea, or steroid use.

age show a strong positive association between daily nut product consumption and persistent wheeze, which is in line with the consistently positive associations over the entire period as shown by the GEE analyses (Table E3).

Sensitivity Analyses

IgE data were present for a subgroup at 8 years of age. We investigated if maternal nut product consumption during pregnancy was associated with sensitization to food allergens (one or more specific IgE $\geq$ 0.35 IU/ml to milk or egg), sensitization to inhalant allergens (one or more specific IgE $\geq$ 0.35 IU/ml to house dust mite, cat, dog, dactylis, birch, or alternaria), or a high total IgE level (total IgE $\geq$ 100 IU/ml) in these children. This was not the case.

Maternal diet during pregnancy and the child's diet at 2 years of age were strongly associated. However, including the child's consumption of fruit, vegetables, fish, egg, and peanut butter at 2 years of age in the models did not change the results. Neither did inclusion of the child's full-fat milk and butter consumption, which have been associated with doctor-diagnosed asthma and wheeze in earlier cross-sectional analyses of the same cohort (30).

Maternal food allergy could be a reason to avoid consumption of certain foods and could therefore bias the results. We have compared the dietary intake of atopic and nonatopic mothers and found that there were no significant differences in frequencies of consumption of the investigated food groups. Exclusion of mothers who never ate fish, egg, or nuts and nut products during the last month did not change the results. We also checked whether mothers who daily consumed nut products during pregnancy differed from mothers who regularly or rarely consumed nut products regarding characteristics listed in Table 1. This was not the case, except that the daily consumers were more likely to be from region north.

Food consumption frequencies were initially classified into easily interpretable categories: rare, regular, and daily consumption. These categories were condensed if one of them contained $<5\%$ of the observations, which made some of them quite large. We have checked whether a different classification of the food groups into more categories changed the results. The results of these additional analyses were similar to the previous results when using the more condensed classification.

Supplements were used by almost 83% of the pregnant women. About 50% used folic acid and/or iron. The use of the

TABLE 4. OVERALL ASSOCIATIONS OF MATERNAL FOOD CONSUMPTION DURING PREGNANCY AND CHILDHOOD ASTHMA OUTCOMES FROM 1 TO 8 YEARS OF AGE

	n		Wheeze	Dyspnea	Steroid Use	Asthma Symptoms*
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vegetables†	2,830	Crude	0.97 (0.85–1.12)	1.01 (0.86–1.19)	0.93 (0.75–1.15)	0.98 (0.85–1.13)
		Adjusted‡	0.97 (0.83–1.12)	0.99 (0.84–1.17)	0.96 (0.76–1.20)	0.98 (0.84–1.14)
Fruit†	2,828	Crude	0.82 (0.70–0.96)	0.87 (0.72–1.06)	0.84 (0.65–1.09)	0.87 (0.73–1.04)
		Adjusted‡	0.89 (0.75–1.04)	0.90 (0.74–1.10)	0.89 (0.68–1.16)	0.91 (0.77–1.09)
Fish§	2,811	Crude	1.15 (0.99–1.35)	1.11 (0.92–1.33)	0.86 (0.67–1.12)	1.03 (0.88–1.23)
		Adjusted‡	1.10 (0.94–1.29)	1.07 (0.89–1.29)	0.85 (0.66–1.10)	1.01 (0.85–1.20)
Egg§	2,818	Crude	0.97 (0.84–1.12)	1.10 (0.92–1.31)	0.99 (0.79–1.25)	1.02 (0.87–1.19)
		Adjusted‡	0.96 (0.84–1.12)	1.12 (0.94–1.34)	1.01 (0.80–1.28)	1.03 (0.88–1.20)
Dairy†	2,788	Crude	0.84 (0.68–1.03)	0.90 (0.71–1.16)	0.99 (0.72–1.36)	0.89 (0.72–1.10)
		Adjusted‡	0.88 (0.71–1.09)	0.92 (0.72–1.19)	1.03 (0.74–1.43)	0.92 (0.74–1.15)
Nuts§	2,806	Crude	0.96 (0.83–1.12)	1.00 (0.82–1.19)	0.95 (0.75–1.19)	0.96 (0.82–1.11)
		Adjusted‡	0.99 (0.86–1.15)	1.04 (0.88–1.23)	1.03 (0.81–1.29)	1.00 (0.86–1.17)
Nut products	2,812	Crude	1.04 (0.90–1.21)	0.99 (0.84–1.18)	0.94 (0.74–1.18)	0.99 (0.85–1.15)
		Adjusted‡	1.01 (0.88–1.18)	0.98 (0.82–1.16)	0.94 (0.74–1.19)	0.98 (0.84–1.14)
		Crude	1.39 (1.05–1.86)	1.52 (1.12–2.06)	1.48 (0.98–2.22)	1.41 (1.05–1.89)
		Adjusted‡	1.42 (1.06–1.89)	1.58 (1.16–2.15)	1.62 (1.06–2.46)	1.47 (1.08–1.99)

Boldface type indicates P -value < 0.05 .

* Composite variable of wheeze, dyspnea, or steroid use.

† Daily consumption was compared with regular plus rare consumption.

‡ Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region, and study arm (intervention study or natural history study).

§ Daily plus regular consumption was compared with the reference category rare consumption.

|| Regular and daily consumption are included separately. Upper associations are for regular versus rare consumption, and lower associations are for daily versus rare consumption.

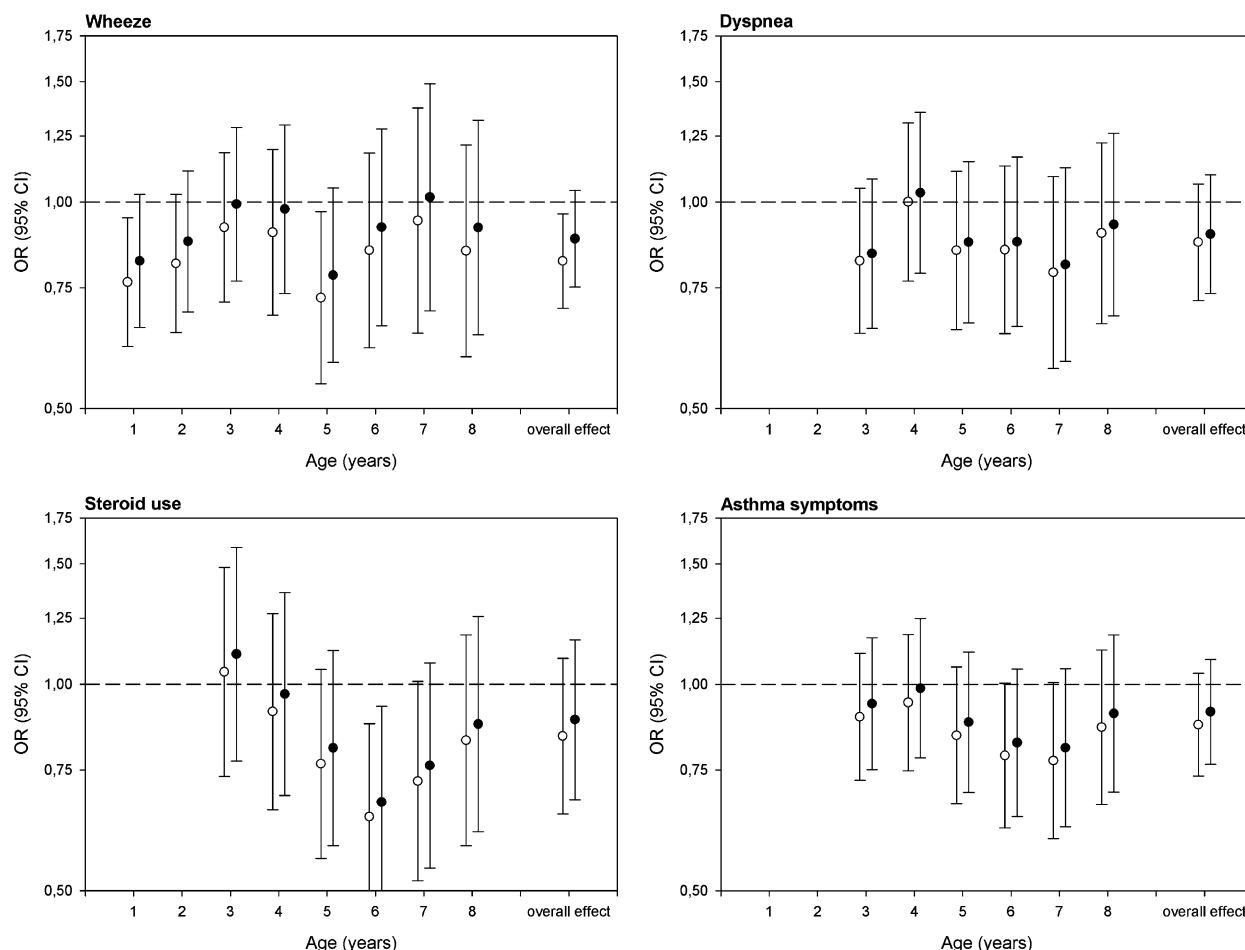


Figure 1. Odds ratios with 95% confidence intervals of the crude (open circles) and adjusted (closed circles) associations of daily versus regular and rare fruit consumption during pregnancy and childhood wheeze, dyspnea, steroid use, and asthma symptoms (composite variable of wheeze, dyspnea, or steroid use) from 1 to 8 years of age. Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region, and study arm (intervention study or natural history study).

other supplements ranged from about 3% for vitamin A/D to about 16% for the use of other supplements, which were mostly multivitamins for pregnant women. We checked if consumption of a certain amount of the specific foods was associated with the use of certain supplements. Positive associations were seen between daily fruit, vegetable, and milk product consumption and folic acid; regular plus daily fish consumption and vitamin B and C; and regular plus daily nuts consumption and vitamin A/D, vitamin B, multivitamin, folic acid, and calcium. Negative associations were seen between daily fruit consumption and vitamin C and iron, daily milk consumption and calcium and iron, and daily milk products consumption and iron. All multivariate analyses were adjusted for maternal supplement use; however, this did not alter the results.

DISCUSSION

We have investigated the associations between maternal consumption of fresh fruit, vegetables, fish, egg, dairy, and nuts and nut products (e.g., peanut butter) during pregnancy and childhood symptoms of asthma longitudinally from 1 to 8 years of age. Our results showed no consistent associations between the maternal intake of the investigated food groups during pregnancy and childhood asthma symptoms until 8 years of age, except for

nut products. Daily versus rare nut products consumption during pregnancy was consistently significantly positively associated with childhood wheeze, and wheeze without cold, dyspnea, and dyspnea without cold, steroid use, doctor-diagnosed asthma, and the composite variable "asthma symptoms."

An important issue when studying the effect of dietary intake on asthma or allergy is whether the effects we find can be attributed to specific nutrients, to specific foods, or to aspects of a healthy diet or lifestyle (31). In this study, the crude association between maternal fruit intake during pregnancy and childhood wheeze lost statistical significance after adjustment for maternal education, maternal smoking during pregnancy, smoking in the home at 8 years of age, breast feeding, presence of older siblings, birth weight, overweight of the mother, and region. This suggests that there may be confounding by socioeconomic and lifestyle factors. The Dutch national food consumption surveys performed in the last two decades have confirmed that socioeconomic status (based on education, occupation, and occupational position) and factors such as region and alcohol consumption were associated with fruit, fruit juice, and vegetable consumption (32, 33). Besides confounding by socioeconomic and lifestyle factors, there is the issue of health consciousness. Daily fruit consumption during pregnancy was associated with the use of folic acid, which might be an indication that mothers who daily eat fruit are more health

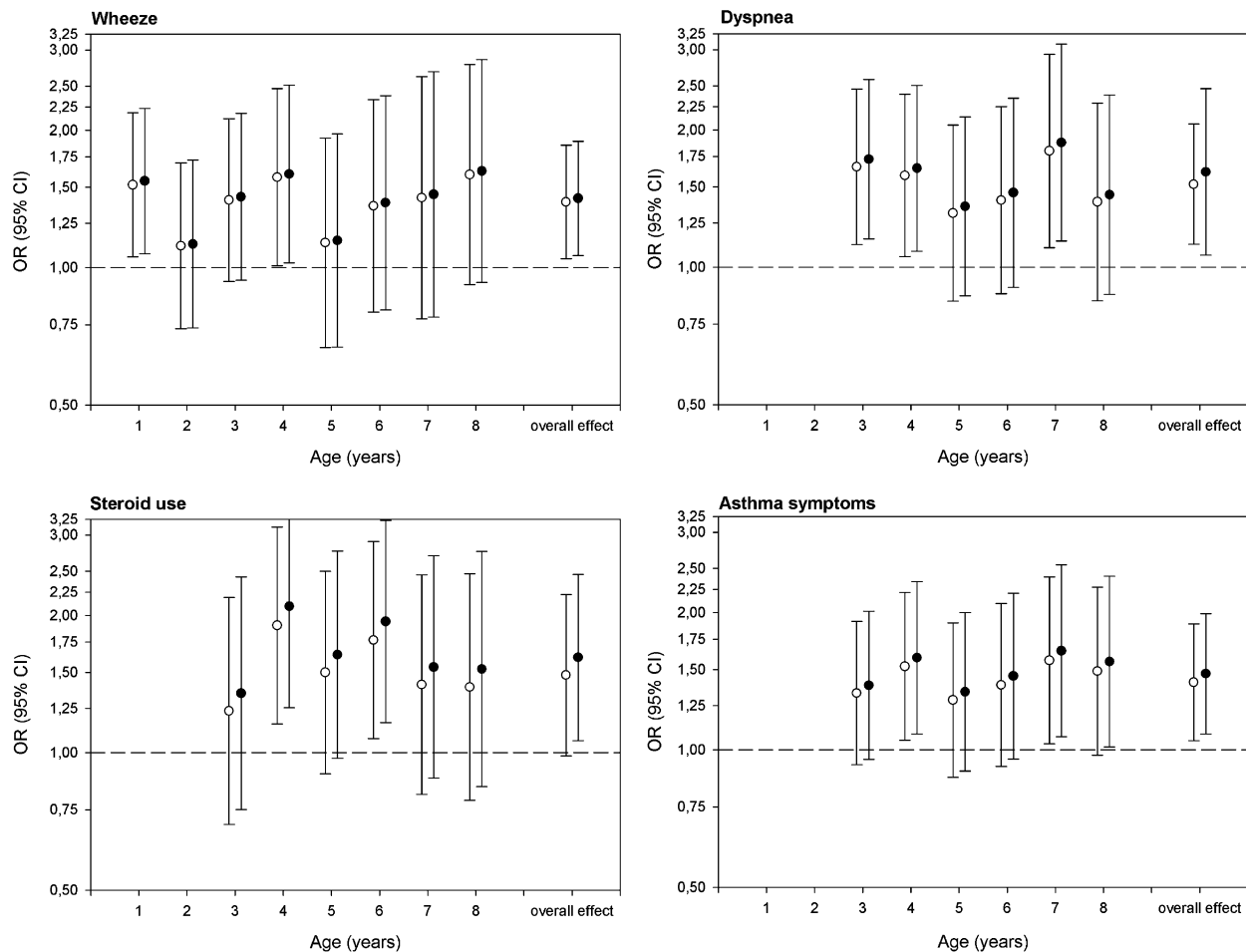


Figure 2. Odds ratios with 95% confidence intervals of the crude (open circles) and adjusted (closed circle) associations of daily versus rare nut product consumption during pregnancy and childhood wheeze, dyspnea, steroid use, and asthma symptoms (composite variable of wheeze, dyspnea, or steroid use) from 1 to 8 years of age. Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region, and study arm (intervention study or natural history study).

conscious and might be more likely to report symptoms in their child. This would lead to an increased risk of childhood wheeze, which is not the case in our study.

A limitation of the present study is that we only had information on the frequency of intake of larger food groups. The questionnaire did not contain questions on intake of more specific foods or portion sizes. The limited distribution of the consumption frequency of large food groups makes it difficult to detect effects. In a study conducted in the United Kingdom, Willers and colleagues reported beneficial effects of maternal apple consumption during pregnancy on wheeze and asthma in 5-year-old children but not of maternal total fruit consumption (22). This suggests that there may be effects of fruit-specific nutrients that cannot be found when only analyzing the effect of total fruit consumption. Apples, tangerines, and bananas are the most consumed fruits in the Netherlands (33, 34). The food questions in the pregnancy questionnaire were not validated against other dietary instruments or biomarkers. Although the main food groups associated with asthma were included in our questionnaire, confounding by other foods or nutrients cannot be ruled out. Dietary misreporting could have led to dietary misclassification; however, that seems unlikely to have happened nonrandomly.

We did not find an effect of maternal fish consumption during pregnancy on childhood asthma outcomes. A number of studies

have suggested that higher fish intake in pregnancy might be protective for asthma or allergy (18–23). The current evidence is inconclusive. For instance, the Seaton study found a protective effect of higher fish consumption during pregnancy on eczema but not on wheeze or asthma (22), whereas the study of Salam and colleagues (18) only found an effect in children of mothers with asthma. The effects of childhood fish consumption on childhood asthma/allergy are inconsistent as well (1, 31).

This study shows a consistent increased risk of daily consumption of nut products during pregnancy on childhood asthma outcomes. Because we mentioned peanut butter as an example of nut products in the questionnaire and because peanut butter is a commonly used spread on sandwiches in the Netherlands whereas the use of other nut spreads is not common, we assumed that the largest proportion of nut products is peanut butter. The observed positive associations might thus be due to a high consumption of peanut butter during pregnancy. One possible explanation could be that a higher exposure to peanut allergens in fetuses of mothers who daily consume peanut butter during pregnancy might increase their risk of developing symptoms of asthma. The study of Sausenthaler and colleagues (20) also suggested that intake of allergenic foods during pregnancy may increase the risk of allergic disease in the offspring. Higher intake of celery and citrus fruit during pregnancy increased the risk of

sensitization against food allergens (egg, cow's milk, wheat, peanut, soybean, or codfish), and higher intake of raw sweet peppers and citrus fruit was associated with sensitization against inhalant allergens. Antenatal exposure to allergens can occur through diaplacental transport (35) and transamniotic transfer (36). This may stimulate the fetal immune system, leading to sensitization (9), which might increase the risk of developing atopic disease. However, we did not find associations between daily nut product consumption during pregnancy and sensitization to food (milk, egg) or inhalant allergens at 8 years of age. Data on sensitization to peanut allergens were not available in our study, but we did check for an association with reported peanut allergy. Daily nut product consumption was not associated with ever having doctor-diagnosed peanut allergy reported at 8 years of age.

Studies that have investigated the effect of maternal allergen avoidance during pregnancy on sensitization and atopic disease in children provide conflicting results. Adherence to a low-allergen-content diet during pregnancy and lactation is considered as potentially harmful for possible maternal and fetal malnutrition and is not recommended (10). There might be an exception for peanut. Peanut is a potent allergen, and peanut allergy is associated with anaphylaxis and is less likely to be outgrown than cow's milk or egg allergy (37). Studies by Hourihane and colleagues (38) and Frank and colleagues (39) found that higher peanut consumption during pregnancy and early introduction of peanut to the child's diet was associated with more peanut allergy and that peanut allergy was associated with asthma, eczema, and rhinitis in children. Since 1998, the U.K. government recommends pregnant women with a family history of atopic disease to avoid peanuts during pregnancy or breast feeding and that infants should not be exposed until 3 years of age. Hourihane and colleagues (40) investigated the prevalence of peanut allergy in children at school entry from 2003 to 2005 but found no effect of this advice. In the Netherlands there is no recommendation to avoid peanuts during pregnancy or lactation.

Another explanation for the increased risk of daily nut product consumption during pregnancy on childhood asthma symptoms could be increased intake of linoleic acid. Peanut butter contains approximately 20% linoleic acid (41). Increased intake of linoleic acid may lead to higher levels of cellular arachidonic acid, which increases the capacity to produce prostaglandin E₂. There is evidence that prostaglandin E₂ can alter the balance of Th1 and Th2 cytokines, leading to increased formation of IgE and hence to atopic disease (42, 43). The average intake of linoleic acid by Dutch pregnant women in 1998 was 12 g/day (44). Ten grams of peanut butter contains approximately 2 g of linoleic acid (41), so daily consumption of one or two peanut butter sandwiches may substantially increase the intake of linoleic acid. We did not have data on the consumption of other N6-rich foods (e.g., margarine) during pregnancy.

Nuts are a source of vitamin E. The Dutch obtain 6% of their vitamin E intake through the consumption of nuts and snacks (34). Daily nut product consumption might thus increase vitamin E intake, which was found to be protective for wheeze and asthma in the SEATON study (Study of Eczema and Asthma to Observe the Influence of Nutrition). However, these protective effects were mainly seen for the highest quintile of vitamin E intake (9.17–30.8 mg/d) (13). This level is not necessarily achieved by daily consumption of a peanut butter sandwich (10 g peanut butter contains 0.97 mg vitamin E) (41).

This study adds to the evidence of the effects of fetal exposure on childhood asthma and allergy. The longitudinal analysis method made it possible to study the development of associations between maternal diet during pregnancy and childhood asthma symptoms over time. Cross-sectional associations between ma-

ternal diet during pregnancy and childhood symptoms might be incidental findings. Longitudinal analyses are important to reveal the temporality of effects and to strengthen the evidence of causal relationships between maternal diet during pregnancy and childhood allergic disease. With GEEs, the relationships between the variables of the model at different time points are analyzed simultaneously, which makes chance findings because of multiple testing less likely than when using logistic regression analyses for all the outcomes at different time points separately.

After 8 years of follow-up, around 80% of the population initially recruited was still participating. Like in other prospective studies, participants with a lower socioeconomic status, a less healthy lifestyle, and poorer health were more likely to become lost to follow-up than others (30). This type of response bias can result in underestimated effects of daily fruit consumption because a larger proportion of symptomatic children with mothers who do not daily eat fruit would make the associations stronger. However, in our study, the proportion of mothers who daily ate fruit in the baseline population was similar to the proportion in the population who provided data at 8 years of age (Table E1).

Maternal diet during pregnancy was strongly associated with the child's diet. However, the observed associations between maternal diet during pregnancy and childhood asthma outcomes were independent from the child's diet. Including the child's diet in the models did not change the results.

The results of this study indicate a small beneficial effect of daily fruit consumption on wheeze (borderline significant after adjustment for potential confounding factors) and an increased risk of daily nut product consumption during pregnancy on childhood symptoms of asthma. Further studies are needed to determine if the beneficial effects of maternal fruit consumption during pregnancy can be attributed to specific nutrients, specific kinds of fruit, or that fruit consumption is an indicator of a healthier lifestyle. This can be done by using more extensive food frequency questionnaires to better assess portion sizes and types of fruit that participants consume. More research is needed to study the effect of exposure to nut or nut products or other allergenic foods during pregnancy, not only on the development of food allergy, but also on the development of asthma and other allergic diseases. The findings of this study need to be replicated by other studies before influencing dietary advice given to pregnant women.

Conflict of Interest Statement: S.M.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.H.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.O.H. has received an annual €30,000 for 3 years as an unrestricted research grant from GlaxoSmithKline. J.C.d.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Maternal food consumption during pregnancy and the longitudinal development of childhood asthma

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Online Supplement

ONLINE METHODS

Selection and follow-up of study participants

Before enrollment in the cohort, 10, 232 pregnant women completed a validated screening questionnaire at their prenatal healthcare clinic (E1). Resulting from this screening, 2949 women were defined as atopic, while 7283 were defined as non-atopic. All atopic women (2779), and 5, 083 non-atopic women were invited to participate in the study, of whom 1327 atopic women and 2819 non-atopic women finally agreed to participate. In the intervention part of the PIAMA study only children born to atopic mothers (high-risk children) were enrolled, whereas in the natural history part children of atopic as well as children of non-atopic mothers (low-risk children) were enrolled. The oversampling of non-atopic mothers in the natural history part of the study provides that the proportion of atopic and non-atopic mothers enrolled in the total study is the same as in the screened population. (In both populations the proportion of atopic mothers is ca. 30%). Study children were born between summer 1996 and late fall 1997, questionnaires were administered when the children were 3 months of age, and yearly from 1 to 8 years of age. Children from the intervention part, the ‘high-risk’ natural history part, and a random sample of the ‘low-risk’ natural history part, drawn at the beginning of the PIAMA study, were selected for more extensive follow-up including home visits, medical examination at 4 years of age, and more extensive medical examination at 8 years of age.

Definition of wheezing phenotypes according to Martinez

Children were assigned to four categories (never wheeze, early transient wheeze, late-onset wheeze, or persistent wheeze) based on their wheezing history from 1 to 8 years of age (E2). Children who did not wheeze in the first three years of life and neither from 6 to 8 years of age were classified as never wheezers; children who had at least one attack of wheeze during

the first three years of life but did not wheeze from 6 to 8 years of age were classified as early transient wheezers; children who did not wheeze during the first three years of life but had at least one attack of wheeze from 6 to 8 years of age were classified as late-onset wheezers; and children who wheezed during the first three years of life and also from 6 to 8 years of age were classified as persistent wheezers.

Assessment of IgE at 8 years of age

At 8 years of age, all children who were still participating in the study were invited for a medical examination, either at home or in hospital (more extensive follow-up). During this medical examination, blood samples were drawn for the assessment of total and allergen-specific IgE.

Children were considered to be sensitised against inhalant allergens if one or more allergen specific IgE levels (to house dust mite (*Dermatophagoides pteronyssinus*), cat, dog, birch (*Betula verrucosa*), grass (*Dactylis glomerata*) and fungus (*Alternaria alternata*) were equal to or higher than 0.35 IU/ml. Sensitisation to food allergens was defined as a high level of allergen specific IgE to milk or egg (also ≥ 0.35 IU/ml).

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TABLE E1. Maternal and child's characteristics of the respondents at baseline, those at follow-up 8 years, and those with IgE data at 8 years of age

Maternal characteristic	Respondents at baseline (N=3963)	Respondents at 8 yr (N=3320)	Respondents with IgE data at 8 yr (N=1657)
Atopy ever, n (%)	1237 (31.2)	959 (28.9)*	625 (37.7)*
Partner ever atopic, n (%)	1217 (30.7)	1017 (30.6)	530 (32.0)
Asthma ever, n (%)	314 (7.9)	232 (7.0)*	152 (9.2)
Partner ever asthmatic, n (%)	302 (7.6)	245 (7.4)	140 (8.4)
Educational level low, n (%)	894 (22.6)	713 (21.5)*	338 (20.4)
Educational level high, n (%)	1331 (33.6)	1206 (36.3)*	629 (38.0)
Partner's educational level low, n (%)	973 (24.6)	808 (24.3)*	375 (22.6)
Partner's educational level high, n (%)	1493 (37.7)	1348 (40.6)*	698 (42.1)
Smoking during pregnancy, n (%)	696 (17.6)	523 (15.8)*	249 (15.0)
Supplement use during pregnancy, n (%)	3285 (82.9)	2761 (83.2)	1379 (83.2)
Smoking in the house by mother, father, or others at baseline, n (%)	970 (24.5)	741 (18.7)*	356 (21.5)
Region North, n (%)	1231 (31.1)	1049 (31.6)	439 (26.5)*
Region Central, n (%)	1586 (40.0)	1368 (41.2)	762 (46.0)
Region South-West, n (%)	1146 (28.9)	903 (27.2)*	456 (27.5)
Participates in intervention study	781 (19.7)	571 (17.2)*	398 (24.0)*
Age when having child, mean (SD)	30.3 (3.9)	30.6 (3.8)*	30.7 (3.8)*
Body Mass Index, kg/m ² , mean (SD)	23.3 (3.6)	23.3 (3.6)	23.4 (3.6)
Food intake during pregnancy			
Daily vegetable intake, n (%)	2217 (55.9)	1882 (56.7)	953 (57.5)
Daily fruit intake, n (%)	3025 (76.3)	2572 (77.5)*	1313 (79.2)
Daily + regular fish intake, n (%)	973 (24.6)	800 (24.1)	411 (24.8)
Daily + regular egg intake, n (%)	2631 (66.4)	2231 (67.2)	1127 (68.0)
Daily dairy intake, n (%)	3335 (84.2)	2840 (85.5)*	1434 (86.5)
Daily + regular nuts intake, n (%)	1322 (33.4)	1131 (34.1)	554 (33.4)
Daily nut product intake, n (%)	243 (6.1)	210 (6.3)	88 (5.3)
Regular nut product intake, n (%)	1452 (36.6)	1219 (36.7)	618 (37.3)
Child's characteristic			
Female, n (%)	1911 (48.2)	1615 (48.6)	799 (48.2)
Birth weight, g, mean, (SD)	3507.2 (546.1)	3524.4 (534.8)*	3533.5 (521.2)
Older siblings present, n (%)	1994 (50.3)	1670 (50.3)	863 (52.1)
Ever breast fed, n (%)	3200 (80.8)	2734 (82.4)*	1392 (82.8)

* p<0.01: responders at 8 yr/responders with IgE data at 8 yr vs non-responders at 8 yr/responders at 8yr without IgE data at 8 yr.

Table E2. Overall associations of maternal food consumption during pregnancy and childhood wheeze without a cold, dyspnea without a cold and doctor-diagnosed asthma from 1 to 8 years of age

	N			Wheeze without cold	Dyspnea without cold	Doctor- diagnosed asthma
				OR (95% CI)	OR (95% CI)	OR (95% CI)
Vegetables	2830	daily vs regularly + rarely	Crude	0.96 (0.74-1.23)	1.01 (0.81-1.26)	1.04 (0.82-1.32)
			Adjusted*	0.99 (0.76-1.29)	1.00 (0.80-1.26)	1.00 (0.77-1.29)
Fruit	2828	daily vs regularly + rarely	Crude	0.84 (0.63-1.13)	0.84 (0.65-1.10)	0.95 (0.72-1.26)
			Adjusted*	0.92 (0.69-1.24)	0.87 (0.67-1.15)	0.99 (0.75-1.32)
Fish	2811	daily + regularly vs rarely	Crude	1.16 (0.87-1.55)	1.14 (0.89-1.46)	1.19 (0.90-1.57)
			Adjusted*	1.10 (0.83-1.47)	1.09 (0.85-1.39)	1.11 (0.84-1.48)
Egg	2818	daily + regularly vs rarely	Crude	1.02 (0.78-1.35)	1.04 (0.82-1.33)	1.19 (0.91-1.55)
			Adjusted*	1.05 (0.80-1.38)	1.06 (0.83-1.36)	1.19 (0.91-1.55)
Dairy	2788	daily vs regularly + rarely	Crude	0.74 (0.52-1.04)	0.81 (0.59-1.12)	1.12 (0.75-1.65)
			Adjusted*	0.78 (0.54-1.11)	0.84 (0.60-1.17)	1.11 (0.75-1.66)
Nuts	2806	daily + regularly vs rarely	Crude	0.93 (0.72-1.21)	0.96 (0.76-1.20)	0.99 (0.77-1.28)
			Adjusted*	1.00 (0.77-1.30)	1.02 (0.81-1.28)	1.06 (0.82-1.36)
Nut products†	2812	regularly vs rarely	Crude	0.98 (0.74-1.28)	0.91 (0.72-1.15)	1.10 (0.86-1.42)
			Adjusted*	0.96 (0.73-1.26)	0.89 (0.70-1.13)	1.08 (0.83-2.60)
		daily vs rarely	Crude	1.71 (1.08-2.69)	1.76 (1.22-2.56)	1.49 (0.96-2.33)
			Adjusted*	1.84 (1.16-2.91)	1.89 (1.30-2.75)	1.64 (1.03-2.60)

* Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region and study arm (intervention study or natural history study).

† Regular and daily consumption are included as dummy variables in the models, the reference category is rare consumption.

Table E3. Associations between maternal intake of different food groups during pregnancy and wheezing patterns in children from 1 to 8 years of age

			Early transient wheeze*	Late-onset wheeze†	Persistent wheeze ‡
			OR (95% CI) §	OR (95% CI) §	OR (95% CI) §
Vegetables	daily vs regularly + rarely	Crude	0.85 (0.71-1.02)	0.78 (0.53-1.15)	1.07 (0.81-1.41)
		Adjusted	0.82 (0.67-0.99)	0.78 (0.53-1.17)	1.07 (0.79-1.44)
Fruit	daily vs regularly + rarely	Crude	0.74 (0.59-0.92)	0.63 (0.41-0.96)	0.86 (0.61-1.19)
		Adjusted	0.80 (0.63-1.00)	0.62 (0.40-0.96)	0.95 (0.67-1.34)
Fish	daily + regularly vs rarely	Crude	1.21 (0.98-1.50)	0.77 (0.48-1.25)	1.24 (0.91-1.69)
		Adjusted	1.16 (0.93-1.43)	0.71 (0.44-1.15)	1.16 (0.84-1.60)
Egg	daily + regularly vs rarely	Crude	0.96 (0.79-1.16)	0.88 (0.60-1.31)	0.93 (0.70-1.24)
		Adjusted	0.96 (0.78-1.17)	0.89 (0.60-1.33)	0.93 (0.69-1.25)
Dairy	daily vs regularly + rarely	Crude	0.92 (0.69-1.22)	0.65 (0.39-1.09)	0.69 (0.47-1.02)
		Adjusted	0.98 (0.73-1.32)	0.68 (0.40-1.15)	0.73 (0.48-1.09)
Nuts	daily + regularly vs rarely	Crude	0.95 (0.79-1.16)	0.89 (0.59-1.33)	0.94 (0.70-1.25)
		Adjusted	0.97 (0.79-1.18)	0.92 (0.61-1.38)	1.01 (0.75-1.36)
Nut products	regularly vs rarely	Crude	1.01 (0.83-1.22)	1.08 (0.73-1.60)	1.01 (0.75-1.35)
		Adjusted	0.98 (0.80-1.19)	1.11 (0.75-1.65)	1.00 (0.74-1.36)
	daily vs rarely	Crude	1.09 (0.74-1.62)	0.94 (0.40-2.23)	1.84 (1.12-3.02)
		Adjusted	1.08 (0.72-1.61)	1.03 (0.43-2.46)	2.14 (1.29-3.56)

* Wheeze during the first three years of life but not from 6 to 8 years of age.

† No wheeze during first three years of life but wheeze from 6 to 8 years of age

‡ Wheeze during the first three years of life and from 6 to 8 years of age as well.

§ Reference category is never wheezing