

Cesarean delivery, preterm birth, and risk of food allergy: Nationwide Swedish cohort study of more than 1 million children

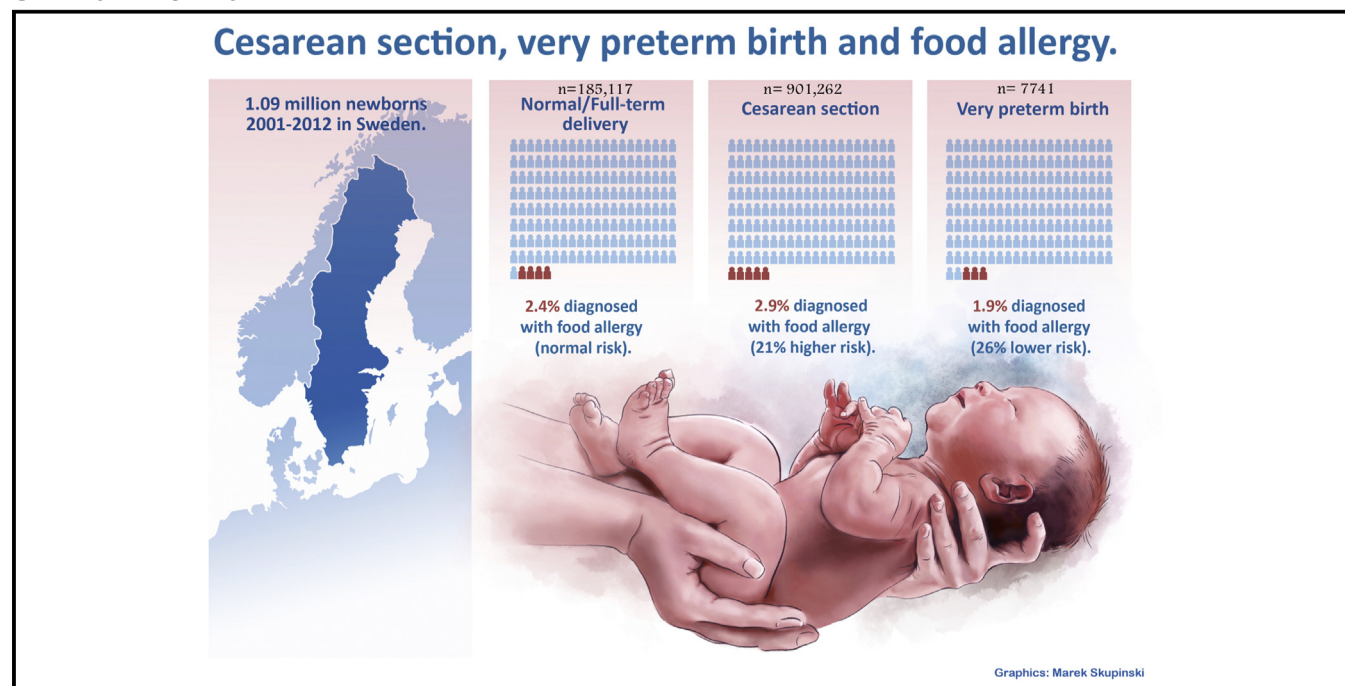
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GRAPHICAL ABSTRACT



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Background: Little is known about early-life risk factors for food allergy in children.

Objectives: We examined the association between perinatal characteristics and future risk of food allergy in offspring.

Methods: This nationwide Swedish cohort study of 1,086,378 children born in Sweden in 2001-2012 used prospectively recorded data from health care registers. Using Cox regression, we estimated hazard ratios (HRs) with 95% CIs for the association between perinatal characteristics (eg, cesarean delivery and preterm birth) and food allergy as defined by diagnoses in the National Patient Register, adjusting for infant sex and maternal factors (age at delivery, country of birth, parity, smoking, body mass index, and asthma/pulmonary disease).

Results: During the 13-year follow-up, 26,732 (2.5%) children were given a diagnosis of food allergy. Food allergy was positively associated with cesarean delivery (HR, 1.21; 95% CI, 1.18-1.25), large for gestational age (HR, 1.15; 95% CI, 1.10-1.19), and low 5-minute Apgar score (HR, 1.22; 95% CI,

1.10-1.36) but negatively associated with very preterm birth (<32 weeks of gestation: HR, 0.74; 95% CI, 0.56-0.98). No association was found between food allergy and moderately preterm birth, low birth weight, or small for gestational age. Risk estimates were similar when the outcome was restricted to 2 records of diagnosed food allergy. In 1,000 children undergoing cesarean delivery, an extra 5 developed food allergy compared with the reference group, suggesting that 17% of food allergy in children born by means of cesarean delivery can be explained by this exposure (attributable fraction).

Conclusions: Cesarean delivery was associated with increased risk of food allergy, whereas very preterm birth decreased risk. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: Food allergy, preterm birth, cesarean delivery, children

Food allergy, defined as a reproducible adverse immune response to food proteins, represents a global public health concern.¹⁻³ The prevalence of food allergy is still increasing,⁴⁻⁶ and although there is an interest in potentially etiological environmental components, very little is known about early-life risk factors, such as perinatal influences.^{7,8}

Two meta-analyses have shown that cesarean delivery is associated with moderately increased risk of asthma and atopic disease.^{9,10} Delayed and altered gastrointestinal microbe colonization has been suggested as a possible etiological factor^{11,12}; however, 1 large register-based sibling study from Sweden proposed that the underlying indications for cesarean delivery might explain this association.¹³ One retrospective study reported an increased risk of allergic rhinoconjunctivitis and asthma after cesarean delivery, yet this association was sex specific and only seen in girls.¹⁴

Preterm birth and low birth weight have also been linked to an increased risk of asthma.¹⁵⁻¹⁸ A meta-analysis of 17 studies reported a 1.46-fold increased risk of asthma or childhood wheeze after preterm birth.¹⁹ Although cesarean delivery and preterm birth can predispose offspring to asthma, there are insufficient and conflicting data on the effect of perinatal factors on the development of food allergy.^{14,20-23} A systematic review suggested that cesarean delivery increases the risk of sensitization to food allergens.²⁴

The aim of this study was to examine the association between cesarean delivery, preterm birth, low birth weight, small for gestational age, large for gestational age (LGA), and low Apgar score (<7) at 5 minutes and future food allergy in more than 1 million children born in Sweden between 2001 and 2012.

METHODS

Study design and population

This nationwide longitudinal cohort study used prospectively recorded data from the Swedish Medical Birth Register (MBR) and the National Patient Register (NPR) to investigate the association between perinatal characteristics and food allergy. Information from the MBR was linked to the NPR by using the unique personal identity number assigned to all Swedish residents.²⁵

We identified 1,232,739 consecutively born children in Sweden between 2001 and 2012 in the MBR, retrieving data on offspring sex, mode of delivery, gestational age, birth weight, and 5-minute Apgar score, and we examined the risk of food allergy up to the year 2013. Among these children, 1,088,990 (88.3%) had complete data on all covariates (listed in Table I). We restricted

Abbreviations used

HR: Hazard ratio
ICD: International Classification of Disease
LGA: Large for gestational age
MBR: Medical Birth Register
NPR: National Patient Register

our cohort to offspring with a follow-up of at least 60 days after birth by excluding subjects who died before that age or had a diagnosis of food allergy in the first 2 months of life (we deemed that a diagnosis <2 months had low validity). In our final analyses 1,086,378 (88.1%) children were included (age range at end of follow-up, 0.2-12.8 years). Follow-up time ended with first diagnosis of food allergy, death, or December 31, 2013, whichever came first.

Covariates

Maternal characteristics analyzed in this study were extracted from the MBR and consisted of age at delivery, country of birth, parity, self-reported smoking habits at first antenatal visit, body mass index in early pregnancy, and maternal asthma/pulmonary disease. We divided our data into 3 calendar periods based on year of birth. Covariates are described in Table E1 in this article's Online Repository at www.jacionline.org.

Exposures

Mode of delivery was categorized as vaginal or cesarean. Cesarean delivery was further divided into elective (before the onset of labor) or emergency. Other exposures are described in the Methods section in this article's Online Repository at www.jacionline.org.

Outcome: food allergy

Through the Swedish NPR, we identified children in our cohort with a diagnosis of food allergy during follow-up. We restricted our study to subjects born in 2001 or later because outpatient care was first included in the NPR in 2001.²⁶ In this study food allergy was defined as having a relevant International Classification of Disease (ICD)-10 code of Z91.0A-E.

Statistical analyses

Cox regression was used to estimate hazard ratios (HRs) for the association between exposures and food allergy diagnosis, adjusting for sex and maternal factors: age at delivery, country of birth, parity, early pregnancy smoking, body mass index, and asthma/pulmonary disease (Tables I and II). We further examined the risk of having at least 2 records of a diagnosis of food allergy (Table I).

In a separate analysis we stratified for years of follow-up (Table II). For instance, the HR for follow-up time of less than 1 year reflects food allergy diagnosed in children aged between 2 and 14 months.

Finally, we calculated excess risks and population attributable fractions (as a percentage) for developing food allergy in children by pregnancy outcomes based on observed and expected incidence rates per 100,000 person-years standardized as regards covariates (Table I).

HRs with 95% CIs that did not include 1.0 were considered statistically significant.

Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr. 2008/1182-31/4).

TABLE I. Perinatal characteristics and risk of food allergy

Perinatal characteristics	Observed events of food allergy/total exposed to perinatal characteristics (%)	Observed events of food allergy/total unexposed to perinatal characteristics (%)	Crude HR (95% CI)	Adjusted HR (95% CI [model 1])*	Adjusted HR (95% CI [model 2])†	Two recorded diagnoses, adjusted HR (95% CI [model 2])‡	Expected events of food allergy§	Excess risk/100,000 person-years	Attributable fraction (%)
Cesarean delivery	5,393/185,117 (2.9)	21,339/901,262 (2.4)	<i>1.24 (1.21-1.28)</i>	<i>1.20 (1.16-1.23)</i>	<i>1.21 (1.18-1.25)</i>	1.21 (1.16-1.26)	4,456	78	17
Elective	2,578/92,220 (2.7)		<i>1.16 (1.12-1.21)</i>	<i>1.16 (1.11-1.21)</i>	<i>1.18 (1.13-1.23)</i>	1.17 (1.10-1.24)	2,184	64	15
Emergency	2,815/90,319 (3.1)		<i>1.33 (1.28-1.39)</i>	<i>1.23 (1.18-1.28)</i>	<i>1.24 (1.19-1.29)</i>	1.25 (1.18-1.32)	2,270	94	19
Gestational age									
Very preterm birth, <32 wk	147/7,741 (1.9)	23,233/949,177 (2.4)	<i>0.78 (0.66-0.91)</i>	<i>0.76 (0.65-0.89)</i>	<i>0.74 (0.56-0.98)</i>	0.62 (0.41-0.93)	199	−102	−35
Moderately preterm, ≥32-36 wk	1,304/52,714 (2.5)		1.01 (0.95-1.06)	0.99 (0.94-1.05)	0.96 (0.90-1.03)	0.95 (0.87-1.04)	1,358	−16	−4
Postterm, ≥42 wk	2,047/76,718 (2.7)		<i>1.07 (1.02-1.12)</i>	1.02 (0.98-1.07)	1.01 (0.97-1.06)	<i>1.07 (1.00-1.13)</i>	2,027	4	1
Low birth weight									
Very low, ≤1,499 g	117/6,093 (1.9)	25,751/1,044,877 (2.5)	<i>0.79 (0.66-0.94)</i>	<i>0.77 (0.64-0.92)</i>	1.17 (0.80-1.69)	1.00 (0.58-1.72)	100	43	15
Moderately low, 1,500-2,499 g	866/35,510 (2.4)		0.99 (0.93-1.06)	0.98 (0.92-1.05)	0.96 (0.88-1.04)	0.95 (0.85-1.06)	902	−16	−4
Fetal growth									
Small for gestational age	2,742/109,313 (2.5)	20,797/858,420 (2.4)	1.04 (1.00-1.08)	1.00 (0.96-1.04)	0.99 (0.95-1.03)	0.98 (0.93-1.04)	2,770	−4	−1
LGA	3,178/118,071 (2.7)		<i>1.10 (1.06-1.14)</i>	<i>1.17 (1.12-1.21)</i>	<i>1.15 (1.10-1.19)</i>	<i>1.19 (1.13-1.26)</i>	2,763	53	13
Low Apgar score (<7) at 5 min	348/11,196 (3.1)	26,282/1,070,413 (2.5)	<i>1.30 (1.17-1.45)</i>	<i>1.23 (1.11-1.37)</i>	<i>1.22 (1.10-1.36)</i>	<i>1.35 (1.17-1.55)</i>	285	90	18

Statistically significant findings are presented in italics.

*Model 1: Adjustment for sex, maternal age at delivery, country of birth, parity, body mass index, early pregnancy smoking, and maternal asthma/pulmonary disease.

†Model 2: Adjustment for all variables in model 1 plus cesarean delivery, gestational age, and birth weight.

‡Model 2: Outcome in this analysis is having at least 2 recorded diagnoses of food allergy.

§Expected events of food allergy were standardized as regards covariates. The attributable fraction is the proportion of all cases of food allergy exposed to a risk factor that could be prevented if the exposure was eliminated (eg, 17% of all food allergies in children exposed to cesarean delivery might be due to mode of delivery).

RESULTS

Among the 1,086,378 children included in this study during the 13-year follow-up, 26,732 (2.5%) had food allergy; of these, 14,534 (1.3%) had at least 2 hospital-based diagnoses of food allergy. The median age at first diagnosis of food allergy was 1.6 years (range, 0.2-12.8 years). The median follow-up was 6.4 years (range, 0.2-13 years). Food allergy was more likely to occur in female children, children of Swedish mothers, and children of mothers with asthma/pulmonary disease (see [Table E1](#)).

Adjusted HRs were calculated to estimate the association between perinatal characteristics and risk of future food allergy ([Tables I and II](#)). Food allergy was positively associated with cesarean delivery (HR, 1.21; 95% CI, 1.18-1.25), both elective (HR, 1.18; 95% CI, 1.13-1.23) and emergency (HR, 1.24; 95% CI, 1.19-1.29). Inversely, food allergy was negatively associated with very preterm birth (HR, 0.74; 95% CI, 0.56-0.98) but not with moderately preterm (HR, 0.96; 95% CI, 0.90-1.03) or post-term (HR, 1.01; 95% CI, 0.97-1.06) birth. The risk of future food allergy increased in infants born at LGA (HR, 1.15; 95% CI, 1.10-1.19) and infants with a low Apgar score (HR, 1.22; 95% CI, 1.10-1.36). No association was found between low birth weight or small for gestational age and future food allergy ([Table I](#)). Adjusting for calendar period did not change the association between cesarean delivery and food allergy (HR, 1.20; 95% CI, 1.17-1.24).

When the outcome was restricted to offspring with at least 2 recorded diagnoses of food allergy, we found similar risk estimates

for all but 1 exposure: a borderline positive association between postterm birth and food allergy (HR, 1.07; 95% CI, 1.00-1.13; [Table I](#)). The results did not change more than marginally when we stratified for follow-up (<1 year, 1-4.99 years, and ≥5 years). The risk of food allergy in offspring born by means of cesarean delivery and a 5-year or greater follow-up was still 21% higher than those born by means of vaginal delivery (HR, 1.21; 95% CI, 1.12-1.30). Moreover, the HR point estimate for food allergy related to very preterm birth was unchanged, although it was no longer statistically significant and had a wide CI (HR, 0.74; 95% CI, 0.38-1.43). No difference was found in HRs for food allergy in LGA infants, infants with low 5-minute Apgar scores, and infants with the other exposures among the 3 subgroups (<1 year, 1-4.99 years, and ≥5 years) during the follow-up or in risk estimates between boys and girls ([Table II](#)). We found no difference in HRs when we divided our data into 3 calendar periods of birth (2001-2004, 2005-2008, and 2009-2012).

Excess risks of future food allergy per 100,000 person-years (adjusted for covariates) and population attributable fractions were calculated. Per our findings, in 1,000 children exposed to cesarean delivery, an extra 5 had food allergies during the follow-up period compared with the reference group. The population attributable fraction was 17% for cesarean delivery, suggesting that 17% of all food allergy in children born by means of cesarean delivery might be due to this exposure. The excess risks and population attributable fractions for the other exposures are shown in [Table I](#).

TABLE II. Perinatal characteristics and risk of food allergy according to follow-up time and sex

Perinatal characteristics	<1 y, HR (95% CI)	1-4.99 y, HR (95% CI)	≥5 y, HR (95% CI)	Boys, HR (95% CI)	Girls, HR (95% CI)
Cesarean delivery	1.27 (1.21-1.34)	1.17 (1.12-1.22)	1.21 (1.12-1.30)	1.22 (1.17-1.27)	1.20 (1.15-1.26)
Elective	1.23 (1.14-1.32)	1.15 (1.08-1.22)	1.15 (1.04-1.27)	1.16 (1.10-1.23)	1.19 (1.12-1.27)
Emergency	1.30 (1.22-1.39)	1.18 (1.12-1.26)	1.27 (1.15-1.40)	1.26 (1.20-1.32)	1.21 (1.13-1.29)
Gestational age					
Very preterm birth, <32 wk	0.80 (0.50-1.27)	0.69 (0.45-1.05)	0.74 (0.38-1.43)	0.80 (0.57-1.13)	0.58 (0.34-1.98)
Moderately preterm, ≥32-36 wk	0.92 (0.82-1.03)	1.03 (0.94-1.13)	0.87 (0.74-1.03)	0.93 (0.86-1.02)	1.01 (0.91-1.11)
Postterm, ≥42 wk	1.01 (0.94-1.10)	1.01 (0.95-1.08)	1.03 (0.92-1.14)	1.04 (0.98-1.10)	0.98 (0.91-1.06)
Low birth weight					
Very low, ≤1499 g	1.26 (0.70-2.30)	1.21 (0.71-2.04)	0.83 (0.27-2.50)	1.03 (0.58-1.80)	1.28 (0.78-2.11)
Moderately low, 1500-2499 g	0.91 (0.79-1.05)	0.96 (0.86-1.08)	1.03 (0.85-1.26)	0.96 (0.86-1.08)	0.95 (0.84-1.06)
Fetal growth					
Small for gestational age	0.99 (0.92-1.07)	1.05 (0.99-1.11)	0.89 (0.80-0.99)	1.02 (0.96-1.08)	0.98 (0.92-1.05)
LGA	1.29 (1.21-1.37)	1.12 (1.06-1.18)	1.06 (0.96-1.16)	1.16 (1.10-1.22)	1.17 (1.10-1.24)
Low Apgar score (<7) at 5 min	1.41 (1.19-1.68)	1.25 (1.08-1.46)	1.00 (0.74-1.34)	1.26 (1.10-1.44)	1.27 (1.07-1.52)

All models were adjusted for maternal age at delivery, country of birth, parity, body mass index, early pregnancy smoking, maternal asthma/pulmonary disease plus cesarean delivery, gestational age, and birth weight.

Statistically significant findings are presented in italics.

DISCUSSION

In this population-based study of more than 1 million children, we found that cesarean delivery (elective and emergency) increased the risk of food allergy in offspring. In addition, children born at LGA or with low 5-minute Apgar scores were more likely to have a diagnosis of food allergy. Inversely, very preterm birth was associated with lower risk.

The increased risk of food allergy observed in children born by means of cesarean section is consistent with most previous research^{24,27,28} but contrasts with data from Renz-Polster et al,¹⁴ yet the proportion of children with food allergy was low in their study (0.37% compared with 2.5% in ours). Furthermore, a second study of 512 Norwegian children did not demonstrate an association between cesarean delivery and food allergy.²³ However, that study included a very high proportion of children born preterm (31.5%). Considering that half of these children were born by means of cesarean delivery, this might have influenced the study's findings.

It is noteworthy that our study suggests that both elective and emergency cesarean deliveries predispose to food allergy. This positive association strengthens the theory that exposure to vaginal microflora might reduce the risk of offspring atopic manifestations. It has previously been implied that mode of delivery is a significant determinant of postpartum adaptation of the immune system.²⁹ Moreover, the hygiene hypothesis stipulates that intestinal microbiota composition influences oral tolerance and the immune response to allergens in children. Van Nimwegen et al¹¹ found that cesarean delivery is strongly associated with *Clostridium difficile* colonization, which consequently increases the risk of wheeze, eczema, and sensitization to food allergens in childhood. Cesarean delivery seems to delay and alter the development of the offspring's immune system, subsequently increasing the risk of atopic disease.^{11,12}

Our results also suggest that very preterm birth is negatively associated with food allergy. In contrast, Liem et al²⁰ found no association between low birth weight or preterm birth and risk of food allergy. Our cohort was substantially larger, and hence a further examination of the hypothesis that an immature gastrointestinal tract leads to increased permeability and food antigen uptake and predisposes to early food sensitization³⁰ is needed.

The observed negative association between very preterm birth and food allergy indicates that either very preterm birth *per se* or associated neonatal care initiated in very preterm-born children (including early introduction of foods orally) might be involved in induction of tolerance to foods. These findings are in accordance with observations that the risk of atopy is influenced by factors operating during early stages of development.³¹ Our findings are intriguing in view of the results from recent trials on early introduction of allergenic foods and current discussions worldwide on strategies to prevent food allergy in children.^{7,32}

The strengths of the present study include its longitudinal population-based design and large size of more than 1 million births. Through nationwide registers, we could include virtually all births in Sweden between 2001 and 2012, minimizing the selection bias typically seen in studies from tertiary centers.³³

The main methodological concern in this study relates to potential confounding factors. We controlled for a broad range of covariates but were unable to investigate the role of breastfeeding or antibiotic use. Another limitation is the lack of nutritional information. Early nutrition might differ between preterm and full-term-born infant children.

In this study the diagnosis of food allergy was based on relevant ICD-10 codes. Such codes can have low sensitivity, and thus there is a risk that mild food allergy has not been captured. We chose to use a narrow definition of food allergy. A drawback with a specific definition is that we might have missed some cases of food allergy and that absolute risks for food allergy might therefore be underestimated. We are unaware of any validation study of the specificity of ICD-10 codes for food allergy in the NPR, but the positive predictive value for most diagnoses ranges from 85% to 95%.^{26,34} However, to increase specificity, we examined the risk of having at least 2 diagnoses of food allergy during the follow-up. This sensitivity analysis demonstrated similar risk estimates, except for a slightly higher risk of food allergy in children born postterm.

In conclusion, using a large population database, we found an increased risk of food allergy in children born through elective or emergency cesarean delivery compared with those delivered vaginally. In contrast, children born very preterm were at a lower risk of food allergy.

Key messages

- Cesarean delivery, LGA, and low 5-minute Apgar score increased the risk of food allergy.
- Inversely, very preterm birth was associated with lower risk of later food allergy.

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METHODS

Mode of delivery was categorized as *vaginal* or *cesarean*. *Cesarean delivery* was further divided into *elective* (before the onset of labor) or *emergency*.

Preterm birth was defined as less than 37 completed weeks of gestation, *very preterm* was defined as less than 32 weeks of gestation, and *moderately preterm* was defined as 32 to 36 weeks of gestation or greater. *Postterm birth* was defined as 42 gestational weeks or greater.

Low birth weight was defined as less than 2500 g (*very low* as <1500 g and *moderately low* as 1500-2499 g).

Small for gestational age was defined as birth weight of less than the 10th percentile according to sex and gestational age and *LGA* as birth weight greater than the 90th percentile.

Low Apgar score was defined as a score of less than 7 at 5 minutes.

TABLE E1. Maternal and pregnancy characteristics

Characteristics	Children without food allergy, no. (%)	Children with food allergy, no. (%)
Total births	1,059,646	26,732
Infant sex		
Female	542,693 (51.2)	15,254 (57.1)
Male	516,953 (48.8)	11,478 (42.9)
Calendar period of birth		
2001-2004	312,698 (29.5)	6,805 (25.5)
2005-2008	315,687 (33.2)	8,656 (32.4)
2009-2012	395,361 (37.3)	11,271 (42.2)
Maternal age at delivery (y)		
≤24	152,066 (14.4)	3,515 (13.1)
25-29	315,823 (29.8)	8,143 (30.5)
30-34	371,067 (35.0)	9,595 (35.9)
≥35	220,690 (20.8)	5,479 (20.5)
Country of birth		
Sweden	840,395 (79.3)	20,614 (77.1)
Other Nordic (not Sweden)	17,499 (1.7)	399 (1.5)
Non-Nordic	201,752 (19.0)	5,719 (21.4)
Parity		
Nulliparous	465,445 (43.9)	13,224 (49.5)
1-2 Children	532,374 (50.2)	12,304 (46.0)
≥3 Children	61,827 (5.8)	1,204 (4.5)
Body mass index (kg/m ²)		
<20	562,948 (53.1)	14,371 (53.8)
20 ≤ BMI < 25	103,529 (9.8)	2,852 (10.7)
25 ≤ BMI < 30	268,916 (25.4)	6,573 (24.6)
≥30	124,253 (11.7)	2,936 (11.0)
Early pregnancy smoking habits		
Nonsmoker	977,615 (92.3)	25,152 (94.1)
1-9 Cigarettes/d	61,710 (5.8)	1,209 (4.5)
≥10 Cigarettes/d	20,321 (1.9)	371 (1.4)
Maternal asthma/pulmonary disease		
No	979,649 (92.5)	23,326 (87.3)
Yes	79,997 (7.5)	3,406 (12.7)

BMI, Body mass index.