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Pregnancy outcome and risk of celiac disease in offspring: A nationwide case-control study

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Abstract

Background & Aims—Studies on pregnancy characteristics and mode of delivery and risk of later celiac disease in offspring are inconsistent. In recent decades rates of cesarean delivery and preterm birth survival have increased while at the same time the prevalence of celiac disease has doubled.

Methods—In this population-based case-control study we examine the risk of celiac disease in individuals exposed to cesarean delivery and adverse fetal events (i.e. low Apgar score, small for gestational age, low birth weight, preterm birth, and neonatal infections). Prospectively recorded pregnancy data were obtained from the Swedish Medical Birth Register between 1973 and 2008. Study participants consisted of 11,749 offspring with biopsy-verified celiac disease identified through histopathology reports from Sweden's 28 pathology departments and 53,887 age- and sex-matched controls from the general population.

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Results—We found a positive association between *elective* cesarean delivery and later celiac disease (adjusted odds ratio (AOR) = 1.15; 1.04-1.26; $p = 0.005$), but no increased risk of celiac disease following *emergency* (AOR = 1.02; 0.92-1.13; $p = 0.749$) or *any* cesarean delivery (AOR = 1.06; 0.99-1.13; $p = 0.074$). Infants born small for gestational age were at a 21% increased risk of celiac disease (95% CI = 1.09-1.35; $p = 0.001$), whereas other pregnancy exposures did not increase the risk of future celiac disease.

Conclusions—The positive association with *elective*, but not *emergency*, cesarean delivery is consistent with the hypothesis that the bacterial flora of the newborn plays a role in the development of celiac disease.

Keywords

cesarean section; prematurity; register

INTRODUCTION

Celiac disease is a life-long inflammatory disease prevalent in approximately 1% of the western population¹. In celiac disease the ingestion of gluten leads to villous atrophy and inflammation of the small intestine. Celiac disease is a multifactorial disease in which genetic and environmental factors interplay in triggering the disease. Individuals with celiac disease suffer an increased risk of both lymphoma² and overall mortality³.

In recent decades there has been a marked increase in the number of caesarean deliveries and today, for example, one third of US children are born by cesarean delivery⁴. In the meantime the prevalence of celiac disease has doubled⁵. There has also been an increase in survivors of preterm birth⁶. Cesarean delivery^{7, 8} and adverse fetal events (e.g. preterm birth)^{9, 10} are associated with altered gut microflora colonization in the offspring. Individuals with celiac disease have a different microflora compared with healthy controls^{11, 12}, a condition that may contribute to the impaired oral tolerance and aberrant mucosal immunity seen in celiac disease¹³⁻¹⁵.

In 2010, Decker *et.al*¹⁶ reported an increased risk of celiac disease after cesarean delivery (Odds Ratio (OR) = 1.8) but their study was based on retrospectively collected data. In contrast, Roberts *et.al*¹⁷ found a *decreased* risk of celiac disease after cesarean birth. These contradicting results could be due to methodological restrictions, such as limited study power (less than 200 individuals with celiac disease) and lack of data on potential confounders^{16, 17}. Data is lacking whether there is a difference in risk after elective or emergency cesarean delivery. The distinction between elective and emergency cesarean delivery may be important because it is only in elective cesarean delivery that all children have avoided the birth canal and the maternal vaginal flora. Celiac disease has also been associated with adverse fetal events, e.g. prematurity and low birth weight¹⁸. However, that study¹⁸ was restricted to *inpatients* with celiac disease and therefore potentially susceptible to selection bias.

In this population-based nationwide study we linked histopathology data on individuals with celiac disease and matched controls from the general population to the Swedish Medical Birth Register in order to examine the relationship of cesarean delivery and adverse fetal events with future celiac disease in the offspring.

METHODS

This population-based case-control study used prospectively recorded nationwide Swedish register data.

Study population

Between 2006 and 2008 we searched the computerized registers of Sweden's 28 pathology departments to identify individuals with celiac disease¹⁹. In this study celiac disease is defined by small intestinal villous atrophy (Marsh 3)²⁰. An earlier evaluation has shown that 95% of Swedish individuals with villous atrophy have celiac disease¹⁹. The biopsies had been performed between 1969 and 2008. For each biopsy, we recorded (a) arrival date of the biopsies, (b) personal identity number²¹, (c) morphology, and (d) topography (duodenum or jejunum). In individuals with more than one biopsy available statistics were based on first positive biopsy showing villous atrophy. The data collection process, which included symptoms and signs of a random sample of individuals with villous atrophy, has been described previously¹⁹.

We identified 29,148 individuals with celiac disease (villous atrophy). The government agency Statistics Sweden then matched each individual with celiac disease with five controls from the general population by age at diagnosis, sex, calendar period, and county. We then excluded individuals with a small-intestinal biopsy that could potentially originate from the ileum, those with no matched controls, or other data irregularities (see also our previous paper on mortality³). Individuals with celiac disease and their controls were then linked to the Swedish Medical Birth Register. Through this linkage, we identified 12,738 individuals born in Sweden after 1973 and with a later diagnosis of celiac disease. We restricted our analyses to individuals with complete pregnancy and birth data and so individuals with missing data were censored. Finally, 11,749 individuals with celiac disease and 53,887 controls were included in the study.

Cesarean delivery and adverse fetal events

The Swedish Medical Birth Register, which is of high quality, encompasses prospectively recorded data on more than 98% of all pregnancies since 1973²². The register will only accept gestational age data between 22 and 46 weeks and birth weight data in the range of 300–7000 grams.

We examined the risk of celiac disease in offspring according to mode of delivery categorized into cesarean delivery and vaginal birth. In subanalyses we also divided cesarean delivery into emergency or elective cesarean delivery because only in elective cesarean delivery have all children avoided the birth canal and the maternal vaginal flora. Data on type of cesarean delivery were available in children born 1982-1989 and from 1991 onwards. Because there has been an increase in both cesarean birth rates²³ and the use of celiac disease serology over time, we also examined whether the calendar period of birth (1973-1984, 1985-1996, 1997-2007) influenced the risk of celiac disease after cesarean delivery.

We also examined the influence of adverse fetal events on the risk of future celiac disease. Adverse pregnancy events included low birth weight (1500-2499g)²⁴, very low birth weight (<1500g)²⁴, preterm birth (< 37 gestational weeks)⁶, low Apgar score five minutes after delivery (<7)²⁵ and small for gestational age (weight for sex and gestational age below -2 standard deviations). Finally, we estimated the risk of celiac disease in offspring with neonatal infections as registered in the Medical Birth Register. Neonatal infections were classified according to the international classification of disease (ICD) version 8 to 10 (see supplementary material).

Post-hoc analyses

Childhood-onset celiac disease may be more strongly associated with perinatal characteristics compared with later onset disease, more often diagnosed because of co-

morbidity²⁶. We therefore examined the risk of celiac disease diagnosed before age 2 years and its association with cesarean delivery and adverse fetal events (methods stated above).

Preterm birth is strongly associated with small for gestational age and neonatal infections and have previously been associated with celiac disease¹⁸. We therefore estimated the risk of celiac disease in children with small for gestational age or with a neonatal infection stratified by gestational age (term/preterm birth). Down syndrome increases the risk for both celiac disease²⁷ and small for gestational age²⁸ and may therefore be a confounding factor. Consequently, we identified children with Down syndrome according to ICD codes version 8 to 10 in the Medical Birth Register and estimated the risk of celiac disease following small for gestational age restricted to children without Down syndrome. In two post-hoc analyses we estimated the risk of celiac disease after preterm birth, restricting our sample to children delivered vaginally and with no maternal celiac disease.

We estimated the risk of celiac disease following an infection in the gastrointestinal tract (as opposed to other infections) because gastrointestinal infections may be particularly important in the development of celiac disease²⁹. Gastrointestinal infections were defined according to ICD codes version 8 to 10 in the Medical Birth Register (see supplementary material).

Statistical analyses

We used logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) for the risk of celiac disease by cesarean delivery and adverse fetal events. All analyses were internally stratified (each stratum with one individual undergoing biopsy and his or her five controls were analyzed separately before an OR was calculated). The logistic regression analyses were therefore conditioned on age at first biopsy (and corresponding date in controls), calendar period, sex, and county. However, because of lack of complete strata, we were unable to use conditional logistic regression in two post-hoc analyses restricted to children with small for gestational age or infection and born premature. In these two analyses we instead used logistic regression adjusted for sex and calendar period of birth.

In our main analysis we adjusted for parity, maternal age at delivery, education level, maternal diabetes mellitus, and maternal celiac disease as potential confounders (model I). In an additional multivariate analysis (model II) we also adjusted for smoking (births from 1983 and onward). In a separate analysis of cesarean delivery we also chose to adjust for parental cohabitation (registered from 1982/1983 onwards).

Data on potential confounders

We adjusted for maternal celiac disease and diabetes mellitus in that both convey an increased risk of adverse fetal outcome³⁰ and risk of celiac disease in the offspring.

The Medical Birth Register defines diabetes mellitus as either gestational or chronic. We adjusted for education using seven predefined levels (data from government agency Statistics Sweden) and for the following maternal characteristics: maternal age^{18, 31}; parity^{18, 32}, and smoking in early pregnancy^{18, 33}.

Statistical significance was defined as 95% confidence intervals (CIs) for risk estimates not including 1.0. SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analyses.

Ethics

This study was approved by the Research Ethics Committee of Karolinska Institutet. Before data delivery, Statistics Sweden replaced all personal identity numbers with serial numbers to guarantee the integrity and anonymity of the participants.

RESULTS

A majority of the individuals with later celiac disease were female (Table I) and the average age at diagnosis of celiac disease was 7 years. Most of the infants were born before 1991. Whereas 4.2% of the infants with celiac disease had a history of maternal celiac disease, the percentage was low among controls (0.3%). Characteristics of the mothers to individuals in the study are given in Table I.

Cesarean delivery

Of the 11,749 individuals with celiac disease, 11.1% were born by cesarean delivery, which can be compared with 10.7% in controls (Table II), corresponding to an adjusted OR for later celiac disease of 1.06 (95% CI = 0.99-1.13; $p = 0.074$). Risk estimates did not change more than marginally after adjustments for smoking (adjusted OR = 1.09; 95% CI = 1.02-1.17; $p = 0.012$) and parental cohabitation (adjusted OR = 1.10; 95% CI = 1.03-1.18; $p = 0.006$). The risk estimate for celiac disease after cesarean delivery was similar in the different calendar periods of birth (1973-1984, 1985-1996, 1997-2007) (see supplementary material Appendix Table A1).

In the individuals with celiac disease 5.7% were born by elective cesarean delivery, which can be compared with 5.1% in the controls (adjusted OR = 1.15; 95% CI = 1.04-1.26; $p = 0.005$). Elective cesarean delivery remained statistically significantly associated with later celiac disease after adjustment for smoking (see supplementary material Appendix Table A2). Emergency cesarean delivery was carried out in 5.0% of mothers of the individuals with celiac disease compared with 5.1% of mothers of the controls. Thus, emergency cesarean delivery was not associated with later celiac disease (adjusted OR = 1.02; 95% CI = 0.92-1.13; $p = 0.749$) (Table II).

Adverse fetal events

Infants with small for gestational age were at a 21% increased risk of later celiac disease (95% CI = 1.09-1.35; $p = 0.001$). Risk estimates remained largely unchanged after adjustment for smoking (see supplementary material Appendix Table A2).

In the individuals with celiac disease 4.2% were born preterm as compared with 4.9% in controls, corresponding to an adjusted OR of 0.87 for celiac disease (95% CI = 0.79-0.96; $p = 0.004$). The rate of very preterm birth (< 32 gestational weeks) was low (0.4% in individuals with celiac disease and 0.5% in controls), and was not significantly associated with later celiac disease (adjusted OR = 0.86; 95% CI = 0.64-1.17; $p = 0.334$).

Celiac disease was not associated with low birth weight or very low birth weight (Table III). Nor was a low Apgar score associated with later celiac disease (adjusted OR = 0.82; 95% CI = 0.66-1.03; $p = 0.082$). Neonatal infections occurred in 630 of the 11,749 individuals with celiac disease (5.4%) and in 5.0% of the controls (adjusted OR = 1.05; 95% CI = 0.96-1.14; $p = 0.306$).

Post-hoc analyses

Restricting our sample to individuals with celiac disease diagnosed before the age of 2 years (38% of the study participants) did not influence any of the above risk estimates more than

marginally (e.g., preterm birth: OR = 0.76; small for gestational age: OR = 1.19)(for complete data see supplementary material Appendix Table A3).

Neonatal infections were much more frequent in preterm births (celiac disease = 21.5%; controls = 20.6%) than in term pregnancies (celiac disease = 4.7%; controls = 4.2%). In none of these two strata was neonatal infection associated with later celiac disease (see supplementary material Appendix Table A4).

Full term infants with small for gestational age were at a statistically significant increased risk of later celiac disease (OR = 1.24; 95% CI = 1.11-1.39; $p = 0.001$), whereas preterm small for gestational age children were not (OR = 1.13; 95% CI = 0.83-1.53; $p = 0.444$) (see supplementary material Appendix Table A4).

Restricting our data to vaginal births and to women without celiac disease did not affect the OR for celiac disease in preterm births (see supplementary material Appendix Table A5).

In the 3306 infants with any neonatal infection some 13% of the infections derived from the gastrointestinal tract. Restricting the analyses to gastrointestinal tract infections only marginally changed our risk estimates for celiac disease (adjusted OR = 1.14; 95% CI = 0.89-1.46; $p = 0.305$). Adjusting for smoking as a potential confounder (model II) did not change the risk estimates (data not shown).

Children with small for gestational age were more frequently born by elective cesarean delivery than non-small for gestational age children (small for gestational age = 10.9%; non-small for gestational age = 5.1%). To rule out residual confounding we therefore estimated the association between elective cesarean delivery and celiac disease in small for gestational age and in non-small for gestational age pregnancies. These post-hoc analyses found a positive association with elective cesarean delivery and celiac disease in both groups (in small for gestational age: OR = 1.09; 95% CI = 0.68-1.75; $p = 0.722$; in non-small for gestational age: OR = 1.14; 95% CI = 1.04-1.26; $p = 0.007$).

Excluding children with Down syndrome ($n=183$) from our dataset did not influence the association between small for gestational age birth and celiac disease (data not shown).

DISCUSSION

This is possibly the most comprehensive study to date on neonatal risk factors in celiac disease. We found a positive association with *elective*, but not emergency, cesarean delivery and later celiac disease, indicating that the bacterial flora of the newborn may play a role in the development of celiac disease. In contrast to previous studies using retrospective data, we conclude that cesarean delivery *per se* is not a major risk factor for later celiac disease. Thus, our results should not alter delivery advice (i.e. indication for cesarean delivery). In the current study we also found a 21% increased risk of later celiac disease in children who were small for gestational age.

Interpretation of findings

We found a modest but statistically significant excess risk for celiac disease after *elective*, but not emergency, cesarean delivery. Overall, cesarean delivery *per se* was not a major risk factor for later celiac disease in the offspring, with risk estimates very close to one. While the association with elective cesarean delivery could be due to residual confounding, it could also reflect atypical patterns of initial bowel colonization, which typically occur in the birth canal. Animal data indicate that microbial exposures in the birth canal may be important for the development of homeostasis between host and colonizing flora. This is because perinatal

colonization represents the first major exposure to microorganisms in the gut³⁴. The effect of a disturbed neonatal gut colonization can persist for many years³⁵ and influences the intestinal immune response³⁶ as well as the mucosal barrier function³⁷. This disturbed mucosal barrier function may be important in that translocation of gliadin peptides through the intestinal epithelium is a key element in the pathogenesis of celiac disease³⁸.

Although modest in magnitude, our findings that elective caesarean delivery predisposes to celiac disease are consistent with a similar association for pediatric Crohn's disease observed in two studies^{39, 40}. In contrast to children born by elective cesarean delivery, children born by emergency cesarean delivery (where we found no association with later celiac disease) may have been in contact with the birth canal. By definition in the Swedish Medical Birth Register, elective cesarean delivery must occur before the onset of labor would include ruptures of the membranes, which would limit the possibility of initial contact with microorganisms in the birth canal.

To rule out that the association between elective cesarean delivery and celiac disease was due to a higher frequency of small for gestational age children among mothers with elective cesarean delivery we estimated the association between elective cesarean delivery in celiac disease among small for gestational age pregnancies and non-small for gestational age pregnancies, but with similar risk estimates in both groups.

In 2010, Decker *et.al*¹⁶ reported an increased risk of celiac disease after any cesarean delivery (adjusted OR = 1.80; p = 0.014); however, that study did not distinguish between elective and emergency cesarean delivery. This and other methodological issues may have contributed to the difference between our findings. First, Decker *et.al* used retrospective interview-based data on 123 individuals with celiac disease, as compared with our prospectively recorded data on some 11,000 individuals with celiac disease. Second, we adjusted for maternal celiac disease. This adjustment is very important since mothers with celiac disease have an increased cesarean delivery rate^{30, 41} and convey an increased risk of celiac disease in offspring. The association between cesarean delivery and celiac disease has also recently been examined using British record-based pregnancy data. Although restricted to a limited number of inpatients with celiac disease (n = 90), in this study Roberts *et.al* reported a non-significant *decreased* risk of celiac disease after cesarean delivery (OR = 0.29; p = 0.064)¹⁷. A causal effect between elective cesarean delivery and celiac disease would certainly have the most profound impact in countries with high cesarean delivery rates.

We found a 21% increased risk of celiac disease in children with small for gestational age. Because small for gestational age is a multi-factorial condition, many circumstances could have contributed to this result⁴². Infants born small for gestational age have an altered cell-mediated immunological development^{43, 44}, which may influence the intestinal immunity but separate from the altered immune state associated with prematurity. The association between small for gestational age and celiac disease did not change when we excluded children with Down syndrome.

In contrast to the increased risk of celiac disease in children with small for gestational age, we found a modestly *decreased* risk of later celiac disease following preterm birth. Although this may be a chance finding, it could also reflect the different feeding practices among preterm compared with term infants, as well as compared with children born small for gestational age.

We found no increased risk of celiac disease after neonatal infection. Importantly, these results do not necessarily refute the hypothesis that *infant* infections could influence the

development of celiac disease because infections near the time of gluten introduction may have greater impact on celiac disease development²⁹.

In 2002, Sandberg-Bennich *et.al*¹⁸ reported a statistically significant increased risk of celiac disease after neonatal infection (OR = 1.52), low birth weight (OR = 1.27), and small for gestational age (OR = 1.4), as well as a significantly decreased risk following preterm birth (OR = 0.82). With the exception of preterm birth, we found considerably lower risk estimates (all close to one) than Sandberg-Bennich *et.al*. An important explanation for this discrepancy may be their restriction to *inpatient celiac disease*¹⁸, where selection bias led to inclusion of more complicated celiac disease and comorbidity, possibly inflating risk estimates.

Strengths and limitations

A major strength of our study is the use of prospectively recorded exposure and outcome data, eliminating the risk of recall bias. Further, this is the largest study on neonatal risk factors in celiac disease to date, and the number of individuals with celiac disease (>11,000) greatly exceeds that of all earlier studies in this field combined. The strong statistical power improved the precision of our risk estimates and allowed us to adjust for several potential confounders, including maternal disease.

The use of biopsy data to identify patients with celiac disease enabled us to identify a representative population with celiac disease. In contrast, patients from inpatient registers or referral centers often suffer from surveillance or selection bias that may overinflate risk estimates because of co-morbidity. More than 95% of Swedish gastroenterologists and pediatricians perform a small intestinal biopsy before celiac disease diagnosis¹⁹, implying that biopsy records have a high sensitivity for *diagnosed* celiac disease. The great statistical power allowed for important subanalyses, such as stratification for calendar period of birth and early diagnosed celiac disease (before age 2 years).

We regard the risk of misclassification in celiac disease as low. In an earlier validation study 95% (108/114) of individuals with villous atrophy had celiac disease¹⁹. A manual review of more than 1,500 biopsy reports showed that diagnoses other than celiac disease were rarely the cause of villous atrophy¹⁹ (inflammatory bowel disease was the most common comorbidity mentioned in 0.3% of biopsy reports with villous atrophy). A high specificity is crucial in minimizing the number of false-positive cases, which otherwise would result in a decrease of a true excess risk.

This study has some limitations. In nationwide registers, such as the Medical Birth Register, some of the individual data may be missing or have been erroneously registered. However, validation studies of the Medical Birth Register have concluded that, in general, it holds high-quality data⁴⁵. The proportion of infants with missing diagnosis has varied between 5 % and 15 %²². We cannot rule out the possibility of missing diagnoses in individual infants, but this would only have a marginal effect on our statistical power. More importantly, potential misclassification of pregnancy data should not differ by celiac disease status and therefore not bias our results. With respect to neonatal infectious diseases, the Medical Birth Register foremost monitors severe infectious diseases, thus limiting our ability to study mild neonatal infectious disease and later development of celiac disease.

We adjusted for several potential confounders but not for breastfeeding. Although data on breastfeeding and celiac disease are inconsistent^{46, 47}, infant feeding may influence the development of celiac disease. We cannot exclude that lack of breastfeeding data might have influenced our risk estimates of celiac disease after small for gestational age.

In conclusion, we found a positive association with *elective*, but not emergency, cesarean delivery and later celiac disease, indicating that the bacterial flora of the newborn may play a role in the development of celiac disease. However, the risk of celiac disease was not influenced by cesarean delivery *per se* and therefore our result should not alter delivery guidelines. We also found a 21% increased risk of celiac disease in children born small for gestational age, whereas other pregnancy exposures did not increase the risk of future celiac disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AOR	adjusted odds ratio
CI	confidence interval
ICD	international classification of disease
OR	odds ratio

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Table I

Maternal* characteristics of infants with celiac disease and controls.

	Controls (%)	Celiac disease (%)
Total	53,887	11,749
Maternal age at delivery		
Age ≤19	1,630 (3.0)	353 (3.0)
Age 20-24	11,726 (21.8)	2,882 (24.5)
Age 25-29	20,028 (37.2)	4,541 (38.7)
Age 30-34	14,201 (26.4)	2,851 (24.3)
Age ≥35	6,302 (11.7)	1,122 (9.5)
Parity		
0 #	22,588 (41.9)	4,703 (40.0)
1-2	27,800 (51.6)	6,371 (54.2)
≥3	3,499 (6.5)	675 (5.7)
Infant sex **		
Boys	19,395 (36.0)	4,201 (35.8)
Girls	34,492 (64.0)	7,548 (64.2)
Calendar years		
1973-1984	10,303 (19.1)	2,515 (21.4)
1985-1996	32,896 (61.0)	6,983 (59.4)
1997-2007	10,688 (19.8)	2,251 (19.2)
Maternal diabetes mellitus §	193 (0.4)	84 (0.7)
Maternal celiac disease †	169 (0.3)	493 (4.2)
Maternal preeclampsia ††	686 (1.3)	143 (1.2)

* Mothers may occur more than once in that each pregnancy is counted as one independent event.

"0" indicates no previous children before the birth included in this dataset.

** Similar sex distribution between cases and controls because of matching.

§ Any diabetes or gestational diabetes according to the Medical Birth Register.

† Celiac disease diagnosed by end of January 2008.

†† Preeclampsia according to the Medical Birth Register.

Table II

Risk of celiac disease after cesarean delivery.

	Matched controls (%)	Celiac disease (%)	Odds ratio; 95% CI OR	P-value	Adjusted odds ratio *, 95% CI AOR	P-value
Cesarean delivery	5,766/53,887 (10.7)	1,299/11,749 (11.1)	1.04; 0.98-1.10	0.232	1.06; 0.99-1.13	0.074
<i>Number of participants</i>			65,636		65,493	
Emergency cesarean delivery †	2,136/41,699 (5.1)	444/8,827 (5.0)	0.99; 0.90-1.10	0.857	1.02; 0.92-1.13	0.749
<i>Number of participants</i>			50,526		50,415	
Elective cesarean delivery ‡	2,125/41,688 (5.1)	508/8,891 (5.7)	1.11; 1.01-1.22	0.027	1.15; 1.04-1.26	0.005
<i>Number of participants</i>			50,579		50,471	

* Births with complete data on infant sex, maternal age at delivery, parity, and dates of birth were included in the analysis. We adjusted for maternal age, parity, maternal diabetes, maternal celiac disease, and education level (model I). Accordingly, the number of births differs between the models: Unadjusted model (11,749 individuals with celiac disease and 53,887 controls) and adjusted model (11,738 individuals with celiac disease and 53,755 controls).

§ Birth weight and/or length below two standard deviations according to mean for gestational age.

† Data on emergency versus elective cesarean delivery are restricted to children born between 1982 and 1989 and after 1991 because data on type of cesarean delivery have only been specified during that time.

Table III

Risk of celiac disease after adverse fetal events.

	Matched controls n = 53,887 (%)	Celiac disease n = 11,749 (%)	Odds ratio; 95% CI OR	P-value	Adjusted odds ratio *; 95% CI AOR	P-value
Small for gestational age §	1,463 (2.7)	392 (3.3)	1.20; 1.08-1.34	0.001	1.21; 1.09-1.35	0.001
Low birth weight †	1,528 (2.8)	338 (2.9)	1.01; 0.90-1.14	0.830	1.02; 0.91-1.14	0.799
Very low birth weight #	225 (0.4)	41 (0.3)	0.87; 0.63-1.20	0.387	0.87; 0.63-1.21	0.415
Preterm birth **	2,635 (4.9)	489 (4.2)	0.87; 0.79-0.95	0.003	0.87; 0.79-0.96	0.004
Low Apgar score §§	481 (0.9)	90 (0.8)	0.84; 0.67-1.04	0.108	0.82; 0.66-1.03	0.082
Infection ††	2,676 (5.0)	630 (5.4)	1.05; 0.96-1.14	0.289	1.05; 0.96-1.14	0.306

* Births with complete data on infant sex, maternal age at delivery, parity, and dates of birth were included in the analysis. We adjusted for maternal age, parity, maternal diabetes, maternal celiac disease, and education level (model I). Accordingly, the number of births differs between the analyses: Unadjusted model (11,749 individuals with celiac disease and 53,887 controls) and adjusted model (11,738 individuals with celiac disease and 53,755 controls).

§ Birth weight and/or length below two standard deviations according to mean for gestational age.

† Low birth weight: 1500-2500g.

Very low birth weight: ≤1500g.

** Preterm birth: < 37 gestational weeks.

§§ Apgar score below 7 at five minutes of age.

†† Neonatal infection according to the Medical Birth Register.