Risk of Congenital Malformations Among Offspring of Mothers and Fathers with Celiac Disease: a Nationwide Cohort Study.

Clin Gastroenterol Hepatol 2014 Jul;12(7):1108-1116.e6.
doi: 10.1016/j.cgh.2013.10.012. Epub 2013 Oct 23.

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Background & Aims

Many patients with celiac disease experience malabsorption, weight loss, and anemia; undiagnosed celiac disease during pregnancy has been linked with adverse outcomes. Studies of celiac disease and congenital malformations in offspring have been underpowered. We investigated the risk of congenital malformations among the offspring of parents with celiac disease.

Methods

We performed a nationwide cohort study of data from linked health care registers in Sweden from 1973 through 2009. We collected histopathology data from 28 pathology departments in Sweden to identify individuals with celiac disease (based on the presence of villous atrophy). We estimated the risks of malformations in the offspring of mothers and fathers with and without celiac disease. Logistic regression was used to estimate adjusted prevalence odds ratios (aPORs) with 95% confidence intervals (CIs).

Results

Among 11,382 offspring of mothers with celiac disease, there were 672 cases (5.9%) of malformation compared with 2098 cases (5.1%) among 40,922 offspring of mothers without celiac disease. Similarly, 352 (5.9%) of 6002 offspring of fathers with celiac disease and 1009 (5.1%) of 19,600 offspring of fathers without celiac disease had a malformation. In adjusted analyses, the offspring of mothers or fathers with celiac disease had a slightly increased risk of having children with malformations (for those with mothers with celiac disease: aPOR, 1.15; 95% CI, 1.05–1.26; for those with fathers with celiac disease: aPOR, 1.14; 95% CI, 1.00–1.29). However, these excess risks decreased or vanished entirely when we restricted our data to births since 2000 (for those with mothers with celiac disease: aPOR, 1.11; and 95% CI, 0.79–1.56; for those with fathers with celiac disease: aPOR, 1.01; 95% CI, 0.81–1.26).

Conclusions

In a nationwide study, we found an increased risk for malformation among the offspring of mothers or fathers with celiac disease. However, the excess risk is small; the upper limits of the CIs for malformation indicate a 29% maximum relative increase.

Introduction

Celiac disease (CD) is a chronic immune-mediated disorder characterized by small intestinal inflammation.1

It is triggered by exposure to gluten in genetically susceptible individuals.2

Many patients with CD suffer from malabsorption, weight loss, abdominal distension, and anemia. Further, undiagnosed CD in the pregnant woman has been linked to adverse pregnancy outcomes,3, 4, 5whereas diagnosed CD seems to be associated with adverse pregnancy outcomes in the first few years after diagnosis but not thereafter.5

Folic acid deficiency is common during pregnancy,6 in newly diagnosed CD, 7, 8 but sometimes also after diagnosis of CD9 (perhaps because of a lack of folic acid in the gluten-free diet 10). Folic acid deficiency is a risk factor for neural tube defect (NTD).11,12,13

Consequently, both periconceptional use of folic acid supplements12 and a normal consumption of naturally occurring folic acid14 seem to be protective against NTD. Other malformations, such as oral cleft abnormalities15 and congenital heart defects (CHDs), may be linked to folic acid deficiency.16,17,18

Data on folic acid and limb deficiency in the offspring are conflicting,19,20 though women with a low intake (lowest quartile) of folic acid are reported to have an almost fourfold increased risk of having an offspring with limb deficiency.20

Data on CD and congenital malformations are scarce (Table 1)3, 4, 21, 22,23, 24, 25,26 and mainly derived from underpowered studies in which mothers of infants with malformations have been screened for CD.3,4,21,22, 23,24,25,26

The only cohort study performed reported no cases of NTD in 341 live-born infants to mothers with CD, but the size of the cohort was too small to detect an increased risk of this group of malformations.4

This study aimed to investigate the risk of any congenital malformation and specifically the risk of NTDs, CHDs, orofacial clefts, and limb deficiencies in the offspring of mothers and fathers with CD. We hypothesized that the offspring of women with CD, especially undiagnosed CD, may be at an increased risk of such malformations.

Methods

We linked data on CD from biopsy reports27 to the following registers: the Medical Birth Register,28

the Patient Register,29 the Register of Congenital Malformations30 and the Multi-generation Register.31

We then constructed a cohort of women and men with biopsy-verified CD and disease-free controls. In the offspring of women and men in this cohort, we examined the risk of congenital malformation, comparing those with and without a parental diagnosis of CD before or after the onset of pregnancy.

Data Collection: Celiac Disease

From all Swedish pathology departments (n = 28), we obtained data from biopsy reports in 1969–2008. Because our study was limited to computerized reports, most biopsy reports were from 1990 or later. For each biopsy report, we retained data on personal identity number,32 arrival date of biopsies, morphology, and topography (duodenum and jejunum). In accordance with the Swedish Systematized Nomenclature of Medicine (SnoMed) histopathology classification system, CD was defined as having villous atrophy (VA) equal to Marsh 3 33(Supplementary Table 1).

The current study was based on the same population as our previous paper on mortality in CD (n = 29,096).34

Of the 18,005 women and 11,091 men with CD, we identified those giving birth to a singleton infant in 1973–2009. The analyses were restricted to births from 1973 and onward because this was the year when the Medical Birth Register, one of the sources of data on congenital malformations, was established.28

For each individual with CD, *Statistics Sweden* identified up to 5 reference individuals matched for sex, age, calendar year, and county from all Swedish residents without an earlier duodenal/jejunal biopsy. We excluded reference individuals with data irregularities (eg, when his or her index case with CD had been excluded for any reason or when reference individuals underwent a biopsy during follow-up).

Finally, we restricted our sample to parents who were between 15 and 45 years of age at the time of the infant birth and where data on parental education were available. This criterion was adopted because parental education is associated with the risk of congenital malformation.35

We used the Swedish Multi-generation Register to identify offspring of parents with CD.31

This register lists individuals born since 1932 and who were alive on January 1, 1961.

Outcome Measure

We used relevant *International Classification of Diseases* (*ICD*) codes to identify offspring with any congenital malformation or specific malformation subgroups (NTD, CHD, limb deficiency, or orofacial cleft) from the Patient Register, the Register of Congenital Malformations, and the Medical Birth Register. For the purpose of this study, we excluded offspring with malformation syndromes, chromosomal abnormalities, genetic syndromes, microdeletions, and malformations that were due to maternal infections from the cohort. Potential teratogenic factors, including folate deficiency or inflammation, would not be expected to cause certain changes (eg, genetic changes), and inclusion of infants with genetic syndromes would bias results toward the null. Offspring with malformations that were due to alcohol intake were also excluded. For further details, including *ICD* codes, we refer the reader to Supplementary Table 2.

Covariates

The Medical Birth Register28,36 was set up in 1973. The register records data on more than 98% of all births in Sweden. Data are recorded on structured sheets and contain information on smoking (available since 1982: 0, 1–9 and ≥10 cigarettes per day), civil status (also available since 1982; living with the father of the child: yes vs no) and body mass index (BMI; some data from 1982 and wider coverage from 1992). We used the Total Population Register37 to obtain data on maternal country of birth (Nordic vs other country). Data on parental age (6 categories) at pregnancy onset,

parity (0, 1–2 and ≥3 childbirths), and infant sex were retrieved from the Multi-generation Register.31

Through the national Patient Register,29 we identified mothers with type 1 diabetes, autoimmune thyroid disease, and rheumatoid arthritis (see Supplementary Appendix). Parental education data (highest available education until the end of follow-up) from the National Education Register was classified into 4 categories: ≤9 years of schooling, 2 years of high school (usually programs for manual, clerical, or assistance work), 3 years of high school (theoretical programs), and college/university studies.

Statistics

We conducted 2 sets of analyses. First, to investigate the hypothesis that genetic factors increase the susceptibility to both CD and congenital malformations we examined the rates of congenital malformation (and the 4 prespecified malformation subgroups) in the offspring of both mothers and fathers with and without CD. Second, we wanted to investigate the hypothesis that malnutrition and low levels of eg, folic acid or ongoing inflammation from VA influence fetal development. In our second set of analyses we, therefore, examined congenital malformations in the offspring of mothers with undiagnosed and diagnosed CD at the time of pregnancy (birth date minus 280 days) as compared with women without a CD diagnosis. We expected treatment with a gluten-free diet (starting at CD diagnosis) to reduce the inflammation and malnutrition normally associated with micronutrient deficiency, such as folic acid deficiency.5

Women with undiagnosed CD have lower placental weight than healthy women.5

In the original matching of this dataset,34 parents with CD were matched with controls for age, sex, county, and calendar year of birth. To minimize heterogeneity in the infant birth year distributions between parents with and without CD, we did not keep the original matching but, nevertheless, performed separate analyses for the original matching groups (diagnosed CD vs corresponding matched study participants and parents with undiagnosed CD vs corresponding matched study participants).

We used logistic regression to calculate prevalence odds ratios (PORs) with associated 95% confidence intervals (CIs) for any congenital malformation or specifically for NTD, CHD, orofacial cleft, and limb deficiency.

We performed both crude and adjusted analyses (adjustment for birth year, country of birth, parental age, educational level, parity, type 1 diabetes, autoimmune thyroid disease, and rheumatoid arthritis).

In a post hoc analysis, we stratified for the presence of the above-mentioned autoimmune diseases. Birth year and parental age were modeled by restricted cubic splines with 4 knots. Standard errors for intragroup correlation were adjusted by clustering the multiple births observed on each woman. In a sensitivity analysis restricted to births from 1982 to the present, we adjusted for maternal smoking habits, prepregnancy maternal BMI, and civil status with available data. Finally, we examined the risk of malformations according to calendar period. All statistics were calculated using STATA 11.1 (StataCorp LP, College Station, TX).

Ethics

The study was approved by the Research Ethics Committee of Karolinska Institutet.

Guarantor

JFL had full access to all the data in the study and takes responsibility for the integrity of the data. DZ takes responsibility for the accuracy of the data analyses.

This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institutet, Sweden on June 14, 2006.

Results

Background Data

Of 20,942 offspring of mothers with CD, 70 were excluded because of malformation syndromes, chromosomal abnormalities, genetic syndromes, microdeletions, and malformations that were due to maternal infections from the cohort (see Supplementary Table 2). Of the remaining 20,872 offspring of mothers with CD, 503 were excluded because of twin birth, 13 because their mothers were aged <15 or >45 years at the time of the infant birth, 8934 because they were born before 1973, and 40 because of missing information on parental education. Of the 12,539 offspring of fathers with CD, 6537 were excluded for the reasons given above.

The final study cohort was based on the offspring of 5774 mothers with CD and 3039 fathers with CD and included 11,382 offspring of mothers with CD, 6002 offspring of fathers with CD, who were compared with 40,922 and 19,600 offspring of mothers and fathers, respectively, with no CD. Characteristics of the study participants are given in Table 2.

Any Malformation

Some 672 (5.9%) offspring of mothers with CD and 2098 (5.1%) control offspring had a congenital malformation (Table 3). In fathers, the corresponding figures were 352 (5.9%) CD offspring and 1009 (5.1%) control offspring. Mothers or fathers with CD were at an increased risk of having an

offspring with any malformation (mothers: adjusted POR [aPOR], 1.15; 95% CI, 1.05–1.26 and fathers: aPOR, 1.14; 95% CI, 1.00–1.29) [Table 3]). In absolute terms, this corresponded to 0.8 (95% CI, 0.3–1.3) excess malformation cases per 100 offspring of mothers with CD and 0.7 per 100 offspring of fathers with CD (95% CI, 0.0–1.5).

Restricting our data to births in 2000–2009, neither CD in the mother (aPOR, 1.11; 95% CI, 0.79–1.56) nor CD in the father (aPOR, 1.01; 95% CI, 0.81–1.26) was associated with malformations (Supplementary Tables 5 and 6).

Specific Malformation Subgroups

Twenty-four offspring of mothers with CD had an NTD, 158 had a CHD, 14 had a limb deficiency, and 19 had an orofacial cleft. The number of paternal CD offspring with specific defect subgroups was n = 11 (NTD), n = 72 (CHD), n = 11 (limb deficiency), and n = 20 (orofacial cleft). We found no firm evidence that the offspring of mothers with CD were at an increased risk of NTD (aPOR, 1.09; 95% CI, 0.68–1.74), limb deficiencies (aPOR, 0.96; 95% CI, 0.52–1.75), or orofacial clefts (aPOR, 0.82; 95% CI, 0.49–1.38). However, mothers with CD were at a slightly increased risk of having an offspring with CHD (aPOR, 1.21; 95% CI, 1.00–1.46). We did not detect any statistically significant association between paternal CD and risks of specific malformations (Table 3).

Maternal Celiac Disease: Undiagnosed vs Diagnosed

These analyses included 8186 offspring of mothers with undiagnosed CD and 3196 offspring of mothers with diagnosed CD and were compared with 32,374 and 12,806 offspring of mothers without CD. Some 475 (5.8%) offspring of mothers with undiagnosed CD and 197 (6.2%) offspring of mothers with diagnosed CD presented with a congenital malformation. Undiagnosed and diagnosed CD mothers were at an increased risk of having an offspring with any malformation (undiagnosed CD mothers: aPOR, 1.16; 95% CI, 1.04–1.29; diagnosed CD mothers: aPOR, 1.14; 95% CI, 0.96–1.35). Evidence of an association between maternal undiagnosed CD and risk of CHD (aPOR, 1.32; 95% CI, 1.06–1.66) was observed but no significant association between diagnosed CD and this malformation subgroup (aPOR, 0.94; 95% CI, 0.66–1.34; Table 4). POR estimates in diagnosed women were unreliable for the outcomes of NTDs, oral clefts, and limb defects because of the problem of overfitting related to the low number of observed events.38

Adjustment for Smoking, Civil Status, and Maternal Body Mass Index

After restricting the analyses to the offspring of women with available data on smoking, civil status, and maternal BMI (these data were available in some women from 1982 and in most women after 1992), we estimated PORs for any malformations and specific malformation subgroups. The risk of

any malformation or any of the specific malformation subgroups was not significantly increased. In these sensitivity analyses PORs were similar in crude analyses and in analyses adjusted for smoking, civil status, and BMI (Supplementary Tables 3 and 4). Thus, there was no evidence that the excess risk of malformations observed in the primary analyses could be explained through confounding by these factors.

Post Hoc Analyses

Stratifying for maternal autoimmune disease (type 1 diabetes, thyroiditis, or rheumatoid arthritis), we estimated PORs for any malformation and specific malformation subgroups. In the offspring of CD mothers with autoimmune disease (4.3%), the risk of any malformation or the risks of any specific malformation subgroups were not significantly increased (Supplementary Table 7).

Discussion

In this nationwide Swedish investigation, we found a slightly increased risk of any congenital malformation in the offspring of both mothers and fathers with biopsy-verified CD.

Because we found increased risks of malformations in the offspring of both mothers and fathers with CD and because no folate-dependent malformation subgroup appeared to carry this association in both parental categories, genetic factors may have contributed to the observed association between parental CD and offspring risk of malformations. Our findings of an increased risk of any malformation in the offspring of both diagnosed and undiagnosed mothers with CD suggest that intestinal inflammation and malabsorption had limited influence. On the other hand, while folic acid deficiency is common in newly diagnosed CD,7,8 it is sometimes seen after diagnosis,9 perhaps because of a lack of folic acid in the gluten-free diet.10

If spouses to men with CD are also primarily on a gluten-free diet, this may actually explain the excess risk for congenital malformation in paternal offspring. However, low sperm quality in men with CD39 could potentially influence the risk of malformations.40

In contrast, the offspring of mothers but not fathers with CD were at an increased risk of CHD; this association was restricted to the offspring of mothers with undiagnosed CD. This finding suggests the possibility of influence from intestinal inflammation and malabsorption on the uptake of folic acid. An increased risk of CHDs has been seen in women exposed to folic acid antagonists during early pregnancy,41 and recent Canadian data found that the prevalence of CHD decreased with the introduction of folic acid fortification in that country.42

Van Beynum et al,43 using case-reference individual data from EUROCAT (European surveillance of congenital anomalies), found a protective effect of periconceptional use of folic acid in relation

to the risk of CHD malformations (OR, 0.74; 95% CI, 0.62–0.88). Additionally, variations in certain folate-related genes (MTHFR A1298C) are known to increase the risk of CHD.44

The low number of observed cases in the other malformation subgroups may explain the inability to detect a statistical significance; we, therefore, urge caution when interpreting PORs for specific malformations in this study.

The excess risk for any malformation (or indeed for CHD) was very small but cannot be explained through confounding by smoking and maternal BMI, although admittedly, we had data on these variables in only a subset of the study participants. Adjusting for these confounding variables in a subset of individuals did not influence the PORs for any malformation more than marginally; that PORs for specific malformations differed (in either direction) may merely be a consequence of small numbers of exposed individuals. Further, other concomitant autoimmunity diseases cannot explain the excess risk because we found a positive association between maternal CD and congenital malformation even in women without other autoimmune diseases.

Strengths and Limitations

The main strengths of our study are the large number of exposed pregnancies; the high specificity of biopsy-verified CD; our knowledge of the exact date of diagnosis and, thereby, the start of a gluten-free diet; and our ability to distinguish between mothers and fathers with CD as well as between diagnosed and undiagnosed mothers.

We used biopsy records from all of Sweden's pathology departments to ascertain CD. Because 96%–100% of adult gastroenterologists and pediatricians biopsy at least 9 out of 10 patients with suspected CD before diagnosis, biopsy records have a high sensitivity for CD.27

The positive predictive value for CD in VA is 95%45 (108 of 114 randomly selected patients with VA had CD according to patient charts).27

This said, our lack of data on serology to support the celiac diagnosis is a study limitation. In a subset of individuals with available data, 88% had a positive serology for gliadin, transglutaminase, or endomysium.27

That proportion is similar to data from clinical material in other countries.46

The number of offspring with a congenital malformation in this study was 672 in mothers with CD and 352 in fathers with CD. Our study is the first comparative analysis of population-based data over a long period of time that provides estimates of risk of malformations associated with CD. It expands on previous research, which was unable to estimate malformation risk and totaled only 4 exposed malformation cases (Table 1).3,4,21,22,23,24,25, 26

This study had some other weaknesses that need to be addressed. We did not have access to data on dietary adherence in parents with diagnosed CD. There are little data on the periconceptional use of folic acid supplementation in Sweden,47 and Swedish national health registers do not record folic intake or the presence of malnutrition in the Swedish populace. In 1997, 8% of Swedish women were reported to use periconceptional folic acid, but this is likely an underestimate.48

Periconceptional use of folic acid may dilute differences in malformation risks between CD patients and the general population. Because folic acid deficiency is primarily caused by low absorption rather than low intake, we do not think that supplementation with folic acid affected our risk estimates more than marginally. Besides, given that we found small excess risks for congenital malformations in the offspring of both mothers and fathers, we cannot rule out the possibility that surveillance bias has influenced our risk estimate. Thus, a type 1 error cannot be discounted. Further, we did not have data on congenital malformations in the parents. Parental malformations may lead to surveillance bias in the relevant offspring.

Another study limitation is that a substantial proportion of pregnancies where an NTD was discovered during prenatal screening are likely to have been terminated,49 resulting in falsely low NTD rates and a decreased power to detect differences in the rates of these congenital malformations. Between 1999 and 2009, the proportion of pregnancies terminated because of NTDs out of all pregnancies with NTDs varied from 51% to 93% depending on the specific defect.50

Furthermore, because more severe cases of NTD are more likely to be terminated than less severe cases, the outcome of NTD in our study should be interpreted in the context of less severe NTD. Thus, among NTD cases, we expect that the proportion of spina bifida was higher while the proportion of anencephaly was lower compared with a scenario in which cases terminated during pregnancy were also included. In contrast, the proportions of pregnancies terminated because of CHD50 and orofacial clefts50 were between 2% and 4% and between 0.3% and 1.5% of all terminated pregnancies in 1999 and 2009, respectively. The risk estimates for these malformation subgroups are, therefore, more reliable and so are estimates for limb defects. (Swedish data on proportions of terminations are not available for limb defects, but this proportion is approximately 8% in Europe.51) Yet, a previous study from the United Kingdom found no increased risk of pregnancy termination in women with CD.4

Our study found no increased risk of malformations in births between 2000 and 2009. Over time, symptoms have changed in CD52; it is possible that, with increased use of celiac serology, milder cases of CD are now diagnosed in which there is no association with congenital malformation.

As in any observational study, the possibility of unmeasured confounding cannot be excluded as an explanation of our findings. Given this possibility and the fact that both relative and absolute differences between the offspring with parents with and without CD were small (eg, malformations occurred in 5.9% of pregnancies to mothers with CD vs in 5.1% of control pregnancies), our findings need to be confirmed.

In conclusion, this study found an increased risk of congenital malformation in the offspring of mothers and fathers with CD. However, excess risks were small, with the upper limit of the CIs for any malformation below 1.3 in mothers and fathers with CD. Considering that the excess risk was not seen after 2000 and that we cannot rule out uncontrolled confounding, we encourage the readers to exercise caution in interpreting our findings.

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Table 1 Summary of Previous Studies of Maternal CD and Congenital Malformation

Location, year	Study design	Mothers with CD	Study period
Britain, 1996[22]	CD screening of 60 mothers; offspring had NTD	1 (1.7%)	Not stated
Italy, 2000[3]	12 of 845 mothers had undiagnosed CD; of these 12, 1 offspring had a CHD	Not applicable	Not stated
Britain, 2001[26]	CD screening of 30 mothers Offspring had NTD	0 (0)	1998[b]
Poland, 2001[23]	CD screening of 40 mothers Offspring had NTD	1 (2.5%)[a]	Not stated
Poland, 2001[23]	CD screening of 61 mothers Offspring had orofacial cleft	1 (1.7%)	Not stated
Britain, 2005[4]	0 offspring of 341 mothers with CD had NTD	Not applicable	1987–2002
Brazil, 2009[21]	CD screening of 208 mothers Offspring had NTD	0 (0)	2004–2007

a This mother had positive endomysium antibodies but a normal small intestinal biopsy.
b Oral communication (Dr Haslam), March 22, 2013.

Table 2 Descriptive Characteristics of Offspring of Mothers and Fathers With and Without CD

Characteristics	Mothers with CD, n (%)	Mothers without CD, n (%)	Fathers with CD, n (%)	Fathers without CD, n (%)
Total births	11,382	40,922	6002	19,600
Male	5736 (50.4)	20,885 (51.0)	3006 (50.1)	10,044 (51.2)
Female	5646 (49.6)	20,037 (49.0)	2996 (49.9)	9556 (48.8)
Calendar period				
1973–1977	1736 (15.0)	5115 (12.5)	1145 (19.1)	3327 (17.0)
1978–1982	1426 (12.5)	5453 (13.3)	879 (14.6)	3115 (15.9)
1983–1987	1455 (12.8)	5748 (14.0)	861 (14.3)	3035 (15.5)
1988–1992	1683 (14.8)	6795 (16.6)	942 (15.7)	3238 (16.5)
1993–1997	1526 (13.4)	5956 (14.5)	758 (12.6)	2470 (12.6)
1998–2002	1328 (11.7)	5008 (12.2)	595 (9.9)	2019 (10.3)
2003–2009	2228 (19.6)	6847 (16.7)	822 (13.7)	2396 (12.2)
Maternal age (*y*)				
15–19	431 (3.8)	1378 (3.4)	—	—
20–24	2643 (23.2)	8932 (21.8)	—	—
25–29	4108 (36.1)	14,749 (36.0)	—	—
30–34	2932 (25.8)	11,036 (27.0)	—	—
35–39	1067 (9.4)	4185 (10.2)	—	—
40–45	201 (1.8)	642 (1.6)	—	—
Paternal age (*y*)				
15–19	—	—	38 (0.6)	130 (0.7)
20–24	—	—	608 (10.1)	2003 (10.2)
25–29	—	—	1765 (29.4)	6084 (31.0)
30–34	—	—	2030 (33.8)	6580 (33.6)
35–39	—	—	1156 (19.3)	3606 (18.4)
40–45	—	—	405 (6.8)	1197 (6.1)
Country of birth				
Nordic country	10,552 (92.7)	36,912 (90.2)	5595 (93.2)	17,501 (89.3)
Other country	830 (7.3)	4010 (9.8)	407 (6.8)	2099 (10.7)
Educational level				
9 y or less of primary and secondary school	1527 (13.4)	5222 (12.8)	1300 (21.7)	3922 (20.0)
2 y of high school	3489 (30.6)	12,753 (31.2)	1864 (31.1)	6514 (33.2)
3 y of high school	2224 (19.5)	7492 (18.3)	954 (15.9)	2980 (15.2)
College/university	4142 (36.4)	15,455 (37.7)	1884 (31.4)	6184 (31.6)

Characteristics	Mothers with CD, n (%)	Mothers without CD, n (%)	Fathers with CD, n (%)	Fathers without CD, n (%)
Parity				
0	4831 (42.4)	17,374 (42.5)	2355 (39.2)	7998 (40.8)
1–2	5844 (51.3)	21,088 (51.5)	3192 (53.2)	10,361 (52.9)
≥3	707 (6.2)	2460 (6.0)	455 (7.6)	1241 (6.3)
Maternal smoking during pregnancy [a]				
Nonsmoker	6363 (55.9)	22,784 (55.7)	3080 (51.3)	9810 (50.0)
1–9 cigarettes/d	852 (7.5)	3308 (8.1)	404 (6.7)	1473 (7.5)
≥10 cigarettes/d	424 (3.7)	1866 (4.6)	214 (3.6)	820 (4.2)
Data not available	3743 (32.9)	12,964 (31.7)	2304 (38.4)	7497 (38.2)
Mother civil status				
Married	7208 (63.3)	26,564 (64.9)	3536 (58.9)	11,610 (59.2)
Unmarried	394 (3.5)	1334 (3.3)	142 (2.4)	517 (2.6)
Data not available	3780 (33.2)	13,024 (31.8)	2324 (38.7)	7473 (38.1)
Maternal early BMI [a]				
<18.5	379 (3.3)	875 (2.1)	107 (1.8)	437 (2.2)
18.5–24	4447 (39.1)	14,985 (36.6)	2024 (33.7)	6616 (33.8)
25–29	1035 (9.1)	4684 (11.4)	623 (10.4)	1799 (9.2)
30+	331 (2.9)	1661 (4.1)	195 (3.2)	651 (3.3)
Data not available	5190 (45.6)	18,717 (45.6)	3053 (50.9)	10,097 (51.5)
Mother type 1 diabetes				
No	11,173 (98.2)	40,764 (99.6)	5882 (98.0)	19,516 (99.6)
Yes	209 (1.8)	158 (0.4)	120 (2.0)	84 (0.4)
Mother thyroid disease				
No	10,587 (93.0)	39,977 (97.7)	5879 (97.9)	19,502 (99.5)
Yes	795 (7.0)	945 (2.3)	123 (2.0)	98 (0.5)
Mother rheumatoid arthritis				
No	11,271 (99.0)	40,755 (99.6)	5958 (9.3)	19,553 (99.8)
Yes	111 (1.0)	167 (0.4)	44 (0.7)	47 (0.2)

NOTE. Table 2 refers to the offspring of mothers and fathers with CD. Characteristics are current at pregnancy onset, unless stated otherwise. (For education, we used the highest degree of education until end of the study.) Some parents had more than one child. The number of unique mothers and fathers with CD were 5774 and 3039, respectively.

Table 3 Congenital Malformations in Offspring of Mother or Father With CD vs Those Born to Mothers or Fathers Without CD

Outcome	Mothers				Fathers			
	Mothers with CD, n (%)	Mothers without CD, n (%)	Crude POR; 95% CI	aPOR [a]; 95% CI	Fathers with CD,n (%)	Fathers without CD, n (%)	Crude POR; 95% CI	aPOR [a]; 95% CI
Any malformation								
No	10,710 (94.1)	38,824 (94.9)	Reference	Reference	5650 (94.1)	18,591 (94.8)	Reference	Reference
Yes	672 (5.9)	2098 (5.1)	1.16; 1.06–1.27	1.15; 1.05–1.26	352 (5.9)	1009 (5.1)	1.15; 1.01–1.30	1.14; 1.00–1.29
Heart defects								
No	11,224 (98.6)	40,466 (98.9)	Reference	Reference	5930 (96.2)	19,362 (96.3)	Reference	Reference
Yes	158 (1.4)	456 (1.1)	1.25; 1.04–1.50	1.21; 1.00–1.46	72 (1.2)	238 (1.2)	0.99; 0.75–1.30	0.95; 0.72–1.26
NTD								
No	11,358 (99.8)	40,849 (99.8)	Reference	Reference	5991 (99.8)	19,561 (99.8)	Reference	Reference

Outcome	Mothers				Fathers			
	Mothers with CD, n (%)	Mothers without CD, n (%)	Crude POR; 95% CI	aPOR[a]; 95% CI	Fathers with CD,n (%)	Fathers without CD, n (%)	Crude POR; 95% CI	aPOR[a]; 95% CI
Yes	24 (0.2)	73 (0.2)	1.18; 0.74–1.88	1.09; 0.68–1.74	11 (0.2)	39 (0.2)	0.92; 0.45–1.80	0.87; 0.45–1.69
Limb deficiencies								
No	11,368 (99.9)	40,870 (99.9)	Reference	Reference	5991 (99.8)	19,578 (99.9)	Reference	Reference
Yes	14 (0.1)	52 (0.1)	0.97; 0.54–1.75	0.96; 0.52–1.75	11 (0.2)	22 (0.1)	1.63; 0.79–3.37	1.60; 0.78–3.29
Orofacial clefts								
No	11,363 (99.8)	40,842 (99.8)	Reference	Reference	5982 (99.7)	19,558 (99.8)	Reference	Reference
Yes	19 (0.2)	80 (0.2)	0.85; 0.52–1.41	0.82; 0.49–1.38	20 (0.3)	42 (0.2)	1.56; 0.90–2.70	1.45; 0.83–2.53

a aPOR for birth year, country of birth, maternal age, educational level, parity, maternal type 1 diabetes, maternal thyroid disease, and maternal rheumatoid arthritis.

Table 4 Adjusted PORs of Any Malformation for Offspring of Undiagnosed and Diagnosed Mothers With CD

Outcome	Undiagnosed mother with CD, n (%)	Matched mother without CD, n (%)	Crude POR; 95% CI	aPOR[a]; 95% CI	Diagnosed mother with CD, n (%)	Matched mother without CD, n (%)	Crude POR; 95% CI	aPOR[a]; 95% CI
Any malformation								
No	7711 (94.2)	30,741 (95.0)	Reference	Reference	2999 (93.8)	12,108 (94.5)	Reference	Reference
Yes	475 (5.8)	1633 (5.0)	1.16; 1.04–1.29	1.16; 1.04–1.29	197 (6.2)	698 (5.5)	1.14; 0.96–1.34	1.14; 0.96–1.35
Heart defects								
No	8077 (98.7)	32,034 (98.9)	Reference	Reference	3147 (98.5)	12,625 (98.6)	Reference	Reference
Yes	109 (1.3)	340 (1.1)	1.27; 1.02–1.58	1.32; 1.06–1.66	49 (1.5)	181 (1.4)	1.09; 0.78–1.51	0.94; 0.66–1.34
NTD								
No	8164 (99.7)	32,309 (99.8)	Reference	Reference	3194 (99.9)	12,791 (99.9)	Reference	Reference
Yes	22 (0.3)	65 (0.2)	1.34; 0.82–2.18	1.11; 0.67–1.82	2 (0.1)	15 (0.1)	0.53; 0.12–2.33	0.86; 0.23–3.18
Limb deficiencies								
No	8178 (99.9)	32,328 (99.9)	Reference	Reference	3190 (99.8)	12,794 (99.9)	Reference	Reference
Yes	8 (0.1)	46 (0.1)	0.69; 0.32–1.46	0.66; 0.31–1.41	6 (0.2)	12 (0.1)	2.00; 0.75–5.34	2.57; 0.80–8.27
Orofacial clefts								
No	8170 (99.8)	32,314 (99.8)	Reference	Reference	3193 (99.9)	12,774 (99.7)	Reference	Reference
Yes	16 (0.2)	60 (0.2)	1.05; 0.60–1.84	1.05; 0.60–1.85	3 (0.1)	32 (0.3)	0.37; 0.11–1.23	0.29; 0.09–0.93

a aPOR for birth year, country of birth, maternal age, educational level, parity, maternal type 1 diabetes, maternal thyroid disease, and maternal rheumatoid arthritis.