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Limited risks of major congenital anomalies in children of mothers with coeliac disease: a population-based cohort study

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Objective To examine major congenital anomaly (CA) risks in children of mothers with coeliac disease (CD) compared with mothers without CD.

Design Population-based cohort study.

Setting Linked maternal–child medical records from a large primary care database from the UK.

Population A total of 562 332 live singletons of mothers with and without CD in 1990–2013.

Methods We calculated the absolute major CA risks in children whose mothers had CD, and whether this was diagnosed or undiagnosed before childbirth. Logistic regression with a generalised estimating equation was used to estimate adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs) for CAs associated with CD.

Main outcome measures Fourteen system-specific major CA groups classified according to the European Surveillance of Congenital Anomalies and neural tube defects (NTDs).

Results Major CA risk in 1880 children of mothers with CD was 293 per 10 000 liveborn singletons, similar to the risk in those without CD (282; aOR 0.98, 95% CI 0.74–1.30). The risk was slightly higher in 971 children, whose mothers were undiagnosed (350; aOR 1.14, 95% CI 0.79–1.64), than in 909 children whose mothers were diagnosed (231; aOR 0.80, 95% CI 0.52–1.24). There was a three-fold increase in nervous system anomalies in the children of mothers with undiagnosed CD (aOR 2.98, 95% CI 1.06–8.33, based on five exposed cases and one had an NTD), and these women were all diagnosed with CD at least 4 years after their children were born.

Conclusions There was no statistically significant increase in risk of major CAs in children of mothers with coeliac disease overall, compared with the general population.

Keywords Abnormalities, coeliac disease, congenital epidemiology.

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Introduction

Coeliac disease (CD) is an autoimmune inflammatory disease of the small intestine, and the only treatment is lifelong avoidance of gluten. It is estimated to affect about 1% of the population, based mainly on serology studies, in both North America and Western Europe, with the majority of patients not recognised clinically.[1,2] CD is predominantly diagnosed in women and can potentially cause health damage not only to the women themselves but also to their offspring.[3] It has been reported that women with newly diagnosed CD have increased risks of unfavourable pregnancy and fetal outcomes,[4–9] such as miscarriage and low-birthweight babies, which could possibly be prevented by effective treatment, i.e. by gluten avoidance.[5,7,9]

The villous atrophy present in patients with CD can cause malabsorption, anaemia, and micronutrient deficiencies, which could be a direct mechanism leading to any adverse pregnancy and fetal outcomes.[3] Previous research has shown that micronutrient supplementation is beneficial in reducing low birthweight and small-for-gestational-age births.[10] Folic acid deficiency is associated with neural tube

defects (NTDs) and other congenital anomalies (CAs), and a low level of folic acid has been reported in patients with untreated CD.[11,12] It has therefore been speculated that women with CD may be more likely to give birth to infants with CAs (particularly NTDs) compared with the general population.[12,13] Most previous studies in this area, however, are small clinical studies where mothers having children with various CAs have been screened for CD.[13–16] To date, only three cohort studies have examined the association between women with CD and the risk of CAs in the general population.[6,8,17] Although a Swedish study found a small overall increased risk of CAs in children born to women with undiagnosed CD,[17] this increased risk disappeared after restricting the analysis to children born between 2000 and 2009. The two other studies showed no increased risks; however, they were considerably underpowered.[6,8]

In view of a lack of evidence in this area, we conducted a population-based study to examine the risks of major CA and specific anomalies in children born to women with CD, compared with the general population. We also examined these in pregnant women with diagnosed and undiagnosed CD separately.

Methods

Study population

We included all singleton liveborn children of mothers aged 15–45 years between January 1990 and January 2013 from The Health Improvement Network (THIN), where anonymised medical records for both mothers and children have been linked to provide prospectively recorded information before, during, and after pregnancy. THIN is a nationally representative database of computerised primary care records, and covers nearly 6% of the UK population.[18] THIN contains valid medical diagnoses, events, symptoms, and drug prescriptions, and is widely used for pharmacoepidemiological studies.[19]

Mothers with CD were defined as those with a medical Read code for a diagnosis of CD in their primary care records, with or without a gluten-free prescription record (including Read codes J690.00 CD, J690.13 gluten enteropathy, J690.14 sprue nontropical, J690100 acquired CD, and J690z00 CD NOS). Each woman with CD was assigned a date of diagnosis corresponding to the earliest date of her first diagnostic record of CD or the date of her first record of having a gluten-free prescription. We assessed the timing of the CD diagnosis in relation to pregnancy and defined mothers as having diagnosed CD if their first CD diagnosis was recorded before childbirth. We defined women as having undiagnosed CD if their first CD diagnosis was recorded after childbirth. The comparison cohort consisted of mothers without a medical diagnosis for CD in their entire primary care records. Mothers with a diagnosis of dermatitis herpetiformis or with a record of a gluten-free prescription but with no diagnosis of CD were excluded, representing only 0.1% and 0.8% of the initial study population, respectively.

Defining major CA

We extracted all diagnostic recordings of major CAs from the children's general practice records and classified these into system-specific groups by using Read codes corresponding to the European Surveillance of Congenital Anomalies classification,[20] which is based on the International Classification of Disease (ICD–10). Children with genetic anomalies or anomalies attributed to known teratogens, e.g. anomalies resulting from maternal infections and fetal alcohol syndrome, were excluded from the study population, which represented only 0.1% of the study population.

Defining other variables

We extracted maternal age at childbirth (considered as a continuous variable) and calendar year of childbirth (categorised as years: 1990–1995, 1996–2001, 2002–2007, and 2008–2013). We also extracted other maternal factors, including most recent body mass index (BMI) measurement before pregnancy (classified as normal, underweight, overweight, and obese, according to World Health Organization classification),[21] most recent smoking status before delivery, and socio-economic status, as measured by quintiles of the Townsend Index of Material Deprivation. In addition, women with periconceptional high-dose folic acid supplementation were defined as those with at least one prescription of 5 mg folic acid within the 12 weeks before conception or in the first trimester of pregnancy. Women with other autoimmune disorders including type–1 diabetes, rheumatoid arthritis, and thyroid disorder were also identified, as according to previous research these diagnoses may be potential confounding factors.[17]

Statistical analyses

Absolute risks (per 10 000 live births) of any major CA and 14 system-specific groups were calculated for children of mothers with and without CD separately. Logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs) for any major CA, and 14 system-specific groups where data were available. We also stratified the analyses for children of mothers with diagnosed and undiagnosed CD separately, and compared the major CA risk with that in mothers without CD. The generalised estimating equation approach with exchangeable correlation structure was applied to take account of potential clustering between children born to the same woman in consecutive pregnancies. We adjusted our analysis for maternal age, year of

childbirth, BMI, smoking status, socio-economic status, periconceptional high-dose folic acid supplementation, and maternal autoimmune disorders.

Sensitivity analyses

We undertook three additional analyses to ensure the robustness of the study results. Firstly, to increase the specificity of our CD definition, we repeated our analyses by restricting the group of mothers with CD to those who had received a gluten-free prescription. Secondly, a woman whose first recorded CD diagnosis was in the early postpartum period may have been diagnosed before pregnancy; we thus repeated our analyses reclassifying mothers who had their diagnosis recorded within the first 3 months following childbirth as having diagnosed CD (rather than undiagnosed). Thirdly, to assess whether findings changed for children with only isolated major CAs, we excluded children with a chromosomal anomaly or with more than one major CA. We repeated the main analysis and the first two sensitivity analyses for children with isolated major CA only.

All analyses were carried out using STATA SE 11.0 (Stata Corp., College Station, TX, USA).

Results

Basic characteristics

We identified 562 332 pregnancies resulting in liveborn singletons, of which 1880 (0.3%) were in women with CD either diagnosed before childbirth (909 with diagnosed CD) or after childbirth (971 with undiagnosed CD) (Table 1). Mothers with CD were slightly older, less likely to be from socio-economically deprived areas, and were less likely to be overweight, obese, or smokers, than mothers without

Table 1. Maternal characteristics (n = 562 332)

	Without CD		With CD		Diagnosed CD		Undiagnosed CD	
	n = 560 452		n = 1880		n = 909		n = 971	
	n	%	n	%	n	%	n	%
Maternal age, years								
Median, interquartile range	29	25–33	31	27–34	31	27–35	30	27–33
Year of childbirth								
1990–1995	101 824	18.16	400	21.28	105	11.55	295	30.38
1996–2001	143 103	25.52	519	27.61	184	20.35	334	34.40
2002–2007	169 156	30.16	574	30.53	303	33.33	271	27.91
2008–2013	146 369	26.10	387	20.59	316	34.76	71	7.31
Body mass index (kg/m^2)								
Normal (18.5–24.9)	228 561	40.78	839	44.63	437	48.07	402	41.40
Underweight (<18.5)	16 933	3.02	98	5.21	55	6.05	43	4.43
Overweight (25–29.9)	91 389	16.31	245	13.03	142	15.62	103	10.61
Obese (≥30)	53 211	9.49	114	6.06	55	6.05	59	6.08
Missing	170 358	30.40	584	31.06	220	24.20	364	37.49
Smoking status								
Non-smokers	326 535	58.26	1145	60.90	613	67.44	532	54.79
Smokers	83 212	14.85	221	11.76	122	13.42	99	10.20
Missing	150 705	26.89	514	27.34	174	19.14	340	35.02
Townsend deprivation index								
1 (least deprived)	130 043	23.20	539	28.67	246	27.06	293	30.18
2	106 566	19.01	364	19.36	185	20.35	179	18.43
3	109 863	19.60	375	19.95	182	20.02	193	19.88
4	102 691	18.32	297	15.80	133	14.63	164	16.89
5 (most deprived)	75 899	13.54	199	10.59	108	11.88	91	9.37
Missing	35 390	6.31	106	5.64	55	6.05	51	5.25
Periconceptional high-dose folic acid supplementation*	21 428	3.82	145	7.71	94	10.34	51	5.25
Type–1 diabetes	2767	0.49	54	2.87	24	2.64	30	3.09
Rheumatoid arthritis	4626	0.83	18	0.96	4	0.44	14	1.44
Thyroid disorder	12 142	2.17	99	5.27	69	7.59	30	3.09

*With at least one prescription of 5 mg of folic acid in the 12 weeks before conception or in the first trimester of pregnancy.

CD, yet they were more likely to have type–1 diabetes or thyroid disorder (Table 1). A higher proportion of mothers received 5 mg folic acid supplementation around early pregnancy if they had CD than if not (7.7% versus 3.8%), especially in mothers with diagnosed CD (10.3%). Compared with mothers with diagnosed CD, mothers with undiagnosed CD had more missing data on BMI and smoking status, and they had more pregnancies in the initial years of follow-up (Table 1).

Risks of major CA associated with CD overall

The risk of children with a major CA was broadly similar between mothers with CD (293 per 10 000 liveborn singletons) and without CD (282 per 10 000 liveborn singletons) (Table 2). This corresponds to an OR of 1.04 (95% CI 0.78–1.37), which decreased slightly to 0.98 (95% CI 0.74–1.30) after adjustment for potential confounding factors (Table 3). The risks of most system-specific anomalies such as anomalies of the heart and genital system and cleft lip, with or without cleft palate, were also similar between children of mothers with and without CD (Tables 2 and 3).

In children born to women with CD, five of them had nervous system anomalies and only one had an NTD. The absolute risks of nervous system anomalies were 27 per 10 000 liveborn singletons and 16 per 10 000 liveborn singletons in children of mothers with and without CD, respectively (adjusted OR 1.60, 95% CI 0.57–4.48; Tables 2 and 3).

Risks of major CA associated with diagnosed and undiagnosed CD separately

The risk of major CA was 231 per 10 000 liveborn singletons in the diagnosed CD group, but 350 per 10 000 liveborn singletons in the undiagnosed CD group (Table 4). Compared with children of mothers without CD, the adjusted ORs were 0.80 (95% CI 0.52–1.23) and 1.15 (95% CI 0.80–1.65), respectively (Table 4). For system-specific anomalies, most adjusted ORs included a null risk in both diagnosed and undiagnosed CD, except that children born to women with undiagnosed CD in pregnancy had a statistically significantly increased risk of anomalies of the nervous system (adjusted OR 2.98, 95% CI 1.06–8.33, compared with children of mothers without CD).

The absolute risk of nervous system anomalies in the undiagnosed group was 51 per 10 000 liveborn singletons. This result was based on only five exposed cases (three with microcephaly, one with hydrocephalus, and one with spina bifida). The adjusted OR for NTDs, based on one case with spina bifida, was 4.16 (95% CI 0.59–29.45). There was no specific pattern in the maternal sociodemographic and lifestyle characteristics of the five exposed cases.

Table S7 shows the relative risks of major CAs in children of mothers with CD after restricting the data to mothers with a gluten-free prescription (76.4% of the original CD population). Although the overall number of mothers with CD decreased (443 children of mothers with CD

Table 2. Absolute risks (per 10 000 liveborn singletons) of major congenital anomalies in children born to women with and without coeliac disease in pregnancy (*n* = 562 332)

	Total population		Without CD		With CD	
	n = 562 332		*n* = 560 452		*n* = 1880	
	n	*n*/10 000	*n*	*n*/10 000	*n*	*n*/10 000
Major congenital anomalies overall	15 850	282	15 795	282	55	293
Heart	4516	80	4501	80	15	80
Limb	3025	54	3009	54	16	85
Genital system	2291	41	2283	41	8	43
Urinary system	1470	26	1464	26	6	32
Chromosomal	1069	19	1067	19	2	11
Orofacial cleft	783	14	780	14	3	16
Nervous system	880	16	875	16	5	27
Neural tube defects*	136	2	135	2	1	5
Musculoskeletal system	778	14	776	14	2	11
Digestive system	593	11	593	11	0	–
Eye	620	11	620	11	0	–
Other malformations**	581	10	578	10	3	16
Respiratory system	368	7	368	7	0	–
Ear, face, and neck	145	3	145	3	0	–
Abdominal wall	132	2	132	2	0	–

*Including anencephalus, encephalocoele, and spina bifida.
**E.g. asplenia, situs inversus, and skin disorders.

Table 3. Odds ratios for major congenital anomalies in relation to maternal coeliac disease

	Unadjusted OR		Adjusted OR*	
	OR	95% CI	OR	95% CI
Major congenital anomalies overall	1.04	0.78–1.37	0.98	0.74–1.30
Heart	1.00	0.60–1.66	0.92	0.55–1.53
Limb	1.59	0.97–2.60	1.49	0.91–2.44
Genital system	1.04	0.52–2.08	0.99	0.49–1.99
Urinary system	1.23	0.55–2.75	1.15	0.52–2.58
Chromosomal	0.56	0.14–2.26	0.52	0.13–2.07
Orofacial cleft	1.14	0.37–3.55	1.15	0.37–3.55
Nervous system	1.66	0.59–4.64	1.60	0.57–4.48
Neural tube defects**	2.21	0.31–15.79	2.23	0.32–15.47
Musculoskeletal system	0.76	0.19–3.06	0.75	0.19–3.01
Other malformations***	1.53	0.36–6.51	1.47	0.34–6.28

Comparison group includes children of women without CD; system-specific anomalies with no exposed cases were not presented in the table.
*Adjusted for maternal age, year of childbirth, body mass index, smoking, socio-economic status, periconceptional folic acid supplementation, type–1 diabetes, rheumatoid arthritis, and thyroid disorders.
**Including anencephalus, encephalocele, and spina bifida.
***E.g. asplenia, situs inversus, and skin disorders.

but without a gluten-free prescription were excluded), the adjusted OR remained similar to the main analyses (aOR 1.00, 95% CI 0.73–1.37) and all other 95% CIs included unity (Table S7).

Table S8 shows the relative risks of major CAs after re-classifying mothers whose CD diagnosis was first recorded in the 3 months following childbirth as having diagnosed CD, rather than undiagnosed CD. Compared with the results from the main analyses, the adjusted ORs for the diagnosed and undiagnosed groups remained almost unchanged, and we again found a slightly increased risk of nervous system anomalies in the undiagnosed group (aOR 2.99, 95% CI 1.07–8.37).

There were 1787 children with a chromosomal anomaly or with more than one major anomaly (11.3% of children with any major CA). After repeating the analyses in children with isolated major CA, we found very similar results to the analyses in children with any major CA (Tables S1–S6).

Discussion

Principal findings

Overall, we found no increased risk of major CA in children of mothers with CD, compared with children of mothers without CD. The major CA risk in children of mothers with diagnosed CD was similar to the risk in the general population. Risk estimates for major CA were slightly higher, although not statistically significant, for children born to mothers with undiagnosed CD. This was mainly related to a three-fold statistically significant increase of nervous system anomalies in children of mothers with undiagnosed CD, although this was derived from only five exposed cases (one with a NTD).

Strengths and limitations

Our study is among the very few studies to examine the major CA risk in children of mothers with CD on such a large scale. Besides the overall major CA risk, we have also examined the risk for system-specific anomalies. Although the numbers in some specific anomaly groups are inevitably low (e.g. we have about 60% power to estimate a three-fold increased risk of nervous system anomalies associated with undiagnosed CD, at the 5% significance level, which decreased considerably to just over 30% after using the restricted CD definition), our study is the second largest published study thus far. The THIN database used in this study is broadly representative of the UK population in terms of demographics and chronic disease prevalence,[22] which makes our study findings generalisable to the rest of the UK and likely to wider afield. As data are routinely collected through the general practice, exposures and covariates are prospectively recorded prior to diagnoses of major CA, minimising recall bias.

There could of course be some misclassification in terms of maternal CD in our study. It is likely that some mothers without CD in our study had undiagnosed disease throughout the whole study period. This is likely to have biased our results, if at all, towards the null, i.e. of no increase in risk of major CA. Population screening, however, indicates that only up to 1% of people with no detected symptoms are seropositive for CD,[2] so the degree of misclassification is likely to be very low. Another potential limitation of using large routinely collected data, such as data from THIN, is that we were unable to validate the diagnostic data for each patient; however, when we increased the specificity of our exposure definition by restricting our analysis to only women with a gluten-free prescription, we found similar results to the main analyses.

We assumed that once women were diagnosed with CD they would take a gluten-free diet and thus be reasonably well protected from further damage of the small bowel. This assumption may not always be true; however, complete non-compliance of gluten-free diet among those with CD is uncommon.[23] It is possible that women who we defined as having undiagnosed CD in pregnancy in this study actually had existing CD before or during pregnancy, but this was not recorded until the early postpartum period when there may be increased GP contact related to their newly born child; however, when we reclassified mothers

Table 4. Absolute risks and adjusted odds ratios of major congenital anomalies in children of mothers with undiagnosed and diagnosed coeliac disease

	Diagnosed CD				Undiagnosed CD			
	n = 909				*n* = 971			
	n	*n*/10 000	aOR*	95% CI	*n*	*n*/10 000	aOR*	95% CI
Major congenital anomalies overall	21	231	0.80	0.52–1.24	34	350	1.14	0.79–1.64
Heart	7	77	0.89	0.42–1.87	8	82	0.95	0.48–1.91
Limb	7	77	1.44	0.69–3.04	9	93	1.53	0.79–2.94
Genital system	1	11	0.26	0.04–1.83	7	72	1.66	0.79–3.50
Urinary system	4	44	1.60	0.60–4.29	2	21	0.74	0.18–2.98
Chromosomal	2	22	1.06	0.26–4.24	0	–	–	
Orofacial cleft	2	22	1.67	0.42–6.67	1	10	0.70	0.10–5.01
Nervous system	0	–	–		5	51	2.98	1.06–8.33
Neural tube defects**	0	–	–		1	10	4.16	0.59–29.45
Musculoskeletal system	1	11	0.89	0.13–6.38	1	10	0.62	0.09–4.41
Digestive system	0	–	–		0	–	–	
Eye	0	–	–		0	–	–	
Other malformations***	0	–	–		3	31	2.50	0.58–10.73
Respiratory system	0	–	–		0	–	–	
Ear, face, and neck	0	–	–		0	–	–	
Abdominal wall	0	–	–		0	–	–	

Comparison group includes children of women without CD; empty cells indicated insufficient numbers.
*Odds ratio adjusted for maternal age, body mass index, smoking, socio-economic status, periconceptional folic acid supplementation, type–1 diabetes, rheumatoid arthritis, and thyroid disorders.
**Including anencephalus, encephalocele, and spina bifida.
***E.g. asplenia, situs inversus, and skin disorders.

with CD in the first 3 months after childbirth as having diagnosed CD rather than undiagnosed CD, we found very similar results to the main analyses.

Among the children, we had a median of 4 years of follow-up data after birth and we included major CAs diagnosed up to age 20 years, where available, so we expect to have captured these for live births as completely if not more completely than registry data.[24] We have only assessed the risks for major anomalies, as these have been validated against written primary care records,[25] and the prevalence estimates across all system-specific groups and for specific anomaly diagnoses have been shown to be comparable with those reported in UK registers of the European Surveillance of Congenital Anomalies network.[24] As nearly 90% of children with any major CA had only an isolated anomaly, and as the aetiology between isolated and multiple anomalies can differ, we also conducted a sensitivity analysis excluding children with a chromosomal anomaly or children with more than one anomaly, and found very similar results to the main analyses. Moreover, as stillborn children are not registered with a general practice we only included liveborn children, as is the case in most previous studies. Stillbirth occurs in approximately 0.6% of births in developed countries,[26] and CAs account for only 8–14% of stillbirths,[27,28] so the effect of excluding them on our estimates should be minimal. We were also unable to ascertain CAs in pregnancies ending in miscarriage or termination. It is likely that a considerable proportion of pregnancies where the fetus has a severe major CA, especially an NTD, would end in spontaneous or induced abortion. There are no accurate data sources to ascertain CAs in these cases, as spontaneous abortion is likely to occur in early pregnancy when many women may not know that they are pregnant, and autopsy information on later losses is rarely ascertained. This is similar for induced abortion (or medical termination), as most happen in early pregnancy. The UK registry ascertainment of major CAs among medically terminated pregnancies varies regionally,[29] and national abortion statistics estimate that only 1% are for major CAs.[30] Nevertheless, this would only lead us to underestimate a potentially true teratogenic effect of CD, and no studies thus far have been able to overcome this methodological problem.

We have adjusted our results for maternal sociodemographic factors, folic acid supplementation, and comorbidities. To the best of our knowledge, no population-based studies have assessed intake of folic acid in the risks of CAs associated with CD. Although both 0.4- and 5-mg tablets of

folic acid are sold in the UK market, 5-mg tablets can only be issued with a prescription from a health care professional.[31] In the UK chronic conditions like CD are normally managed in primary care. Therefore, such high-dose folic acid prescriptions should be largely captured in these data. Low-dose folic acid is widely available as an over-the-counter drug, however, and can be purchased directly from pharmacies. We have no information on folic acid intake through diet, although the level of such intake is likely to be minimal (e.g. about 0.2 mg/day according to the UK National Diet & Nutrition Survey),[32] and previous studies have shown folic acid supplementation to be effective in reducing risks of NTDs at a dosage of 0.36–4.00 mg/day.[33–38]

Finally, we acknowledge that mothers with undiagnosed CD had more missing values on BMI and smoking status than mothers with diagnosed CD. We also observed lower proportions of mothers with undiagnosed CD in more recent years, compared with those with diagnosed CD. These represented pregnancies in the undiagnosed group occurring earlier in the data, and vice versa for those with diagnosed CD. We therefore adjusted for the calendar period and included missing values as separate categories in the multivariable analyses. We found the results were roughly similar between unadjusted and adjusted ORs.

Interpretation in the context of previous literature

A study that linked biopsy reports to various national registers from Sweden was published recently,[17] and showed that the risk of overall CAs was slightly higher in children of mothers with undiagnosed CD than in children of mothers without CD (aOR 1.16, 95% CI 1.04–1.29, after adjustment for various maternal sociodemographic factors and comorbidities). Although the Swedish study included a much larger study population than ours, with over 11 000 children of mothers with CD, the similar effect found between our study and theirs is reassuring. The Swedish study also found a small increase in the risk of heart anomalies in the undiagnosed group (OR 1.32, 95% CI 1.06–1.66), but no increase in the risk of NTDs, limb anomalies, or orofacial clefts. The association with heart anomalies, however, disappeared after the authors restricted the analyses to children born after 1982, indicating that there were some unmeasured confounding effects. Similar to our study, a previous UK study using primary care data also identified one child with an NTD in the CD group; however, this study did not present results for other CAs.[8] Other previous studies were small clinical studies, with only one or two exposed cases, and with screening for CD in mothers whose children had various CAs, so they are not directly comparable with our study.[13–16]

In terms of the possible mechanisms that could increase the likelihood of major CAs in children born to women with CD, previous research has shown that compared with healthy controls red cell and serum folate levels are lower in patients with untreated CD, but not in patients with recovered villous atrophy.[39] Folate deficiency can impair the synthesis and replication of deoxyribonucleic acid (DNA), especially when increased blood volume and red cell mass and the growing fetus in pregnancy impose additional demands for folate on the mother.[40,41] This may result in disruption of the growth and differentiation of neural crest cells in early pregnancy, when folate is most essential for the fetus.[41] Mothers with dysregulated folate metabolism therefore have the potential for experiencing severe consequences in pregnancy, such as having an increased risk of NTDs in their offspring compared with the general population.[41,42] Previous clinical trials have shown statistically significant decreases of NTDs, heart, and other CAs in children of mothers taking periconceptional folic acid supplementation, compared with children of mothers without folic acid supplementation.[33–36,43,44] The statistically significant increase of nervous system anomalies, although not specifically NTDs, found for mothers with undiagnosed CD in our study could therefore be explained by such mechanisms; however, we acknowledge that this could be a chance finding because of the number of comparisons we have made.

Conclusion

There was no statistically significant difference in risk of having children with major CA between women with CD and without CD. Although we found a small increased risk of nervous system anomalies in women with undiagnosed CD compared with the general population, this was based on a very small number of exposed cases, and should be regarded cautiously. For women who have been diagnosed with CD, these findings are reassuring and will help doctors and other health care workers to advise women with CD that their risks are similar to those of other women.

Disclosure of interests

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Contribution to authorship

LJT and JW initially proposed the study. LJT obtained data and ethical approval. JW and LJT obtained funding. LJT, JW, and LB designed the study. LB performed the analysis, with guidance from LJT, JW, AAS, NND, and JFL upon its conduct and the interpretation of results. LB wrote and edited the article and LJT, JW, AAS, NND, and JFL commented on the article. LJT is the guarantor. LB, LJT, JW, AAS, NND, and JFL have read and approved the final article.

Details of ethics approval

All data are anonymised, such that individual patients as well as the name and specific location of general practices cannot be identified by researchers. Ethical approval for this research was obtained from the South-East Multicentre Research Ethics Committee (SE-REC), reference 04/MRE01/9.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Maternal characteristics (n = 560 545).

Table S2. Absolute risks (per 10 000 liveborn singletons) of isolated major congenital anomalies in children born to women with and without coeliac disease in pregnancy (n = 560 545).

Table S3. Odds ratios for isolated major congenital anomalies in relation to maternal coeliac disease.

Table S4. Absolute risks and adjusted odds ratios of isolated major congenital anomalies in children of mothers with undiagnosed and diagnosed coeliac disease.

Table S5. Relative risks of isolated major congenital anomalies in children of mothers with a diagnosis of coeliac disease and a gluten-free prescription.

Table S6. Relative risks of isolated major congenital anomalies in children of mothers with undiagnosed and diagnosed coeliac disease.

Table S7. Relative risks of major congenital anomalies in children of mothers with a diagnosis of coeliac disease and a gluten-free prescription.

Table S8. Relative risks of major congenital anomalies in children of mothers with undiagnosed and diagnosed coeliac disease. ■

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