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Maternal iron supplement intake during pregnancy and risk of celiac disease in children

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Abstract

Objective—The aim was to study whether maternal use of iron supplements during pregnancy was associated with the risk for celiac disease in the offspring.

Methods—In the prospective Norwegian Mother and Child cohort study (MoBa), cases of celiac disease were identified by questionnaires and linkage to the Norwegian Patient Register (NPR). Complete data were available for 78 846 children (mean age 5.9, range 2–12 years), and 314 children were identified with celiac disease. Use of iron-containing supplements, diet, anaemia and haemoglobin values were reported through questionnaires during pregnancy.

Results—Celiac disease was diagnosed in 4.65/1000 of the children exposed to iron supplementation compared to 3.15/1000 of those without. After adjusting for age and sex, age of gluten introduction and maternal celiac disease, iron supplementation during pregnancy remained a significant predictor (OR 1.33, 95 % CI 1.05 – 1.68, p=0.019), whereas no association was found with the estimated intake of iron from foods (adjusted OR 1.00, 95% CI 0.97–1.03). Anaemia before or in early pregnancy was not significantly associated with the risk of celiac disease in the offspring (adjusted OR 1.24, 95% CI 0.84–2.00, p=0.24). Maternal use of iron supplement during pregnancy remained significantly associated with celiac disease in the child also after adjustment

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Author Contributions:

Ketil Størdal conceptualized the study, drafted the initial manuscript, performed the main data analysis, and approved the final manuscript as submitted.

Margaretha Haugen and Anne Lise Brantsæter developed and validated the methods for analyses of food and supplement intake in MoBa. They critically reviewed the drafts and approved the final manuscript as submitted.

Knut E.A. Lundin contributed in drafting of the manuscript, critically reviewed the manuscript for important intellectual content and approved the final manuscript as submitted.

Lars Christian Stene supervised the writing of the paper, with contributions on the methods applied and critically reviewed the drafts. He is also the principal investigator of the sub-study of type 1 diabetes and celiac disease in MoBa, and approved the final manuscript as submitted.

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for use of iron supplements by the child at age 18 months, which by itself was associated with celiac disease.

Conclusion—We found an increased risk of celiac disease in children whose mother used iron supplements during pregnancy which was apparently not explained by maternal anaemia.

Introduction

The interplay between genes and environment is depicted in the current knowledge on the pathophysiology of celiac disease ¹. A strong genetic predisposition through the presence of HLA haplotypes encoding the DQ2.5- or DQ8-molecules ² and detailed understanding of how the HLA-molecules present modified deamidated gluten to reactive T-cells ³ are the pillars of the current understanding of how celiac disease develops. The 70–75 % disease concordance found in monozygotic twins compared to 10 % in dizygotic twins and 30 % in HLA-identical siblings illustrates the importance of genetic factors ⁴. The >20% frequency of the haplotypes encoding the high-risk HLA-DQ molecules in the general population demonstrates the role of non-HLA genes and environmental factors ¹. Recently, genome-wide association studies have identified SNPs with significant but weak effects on celiac disease, which are located mainly in regulatory elements for genes involved in immunity ^{5, 6}.

Changing environmental factors are suggested by a doubled prevalence with 20 years interval ⁷ and a four-fold increase in 50 years ⁸ using the same screening methods in population-based samples. In addition to the required presence of gluten in the diet to develop celiac disease, several lines of evidence point to timing of gluten introduction and dose of gluten in the weaning diet to impact on disease risk ⁹. A lower risk associated with breastfeeding during gluten introduction has been found in case-control studies and summarized in a meta-analysis ¹⁰. The role of infant feeding may, however, be limited to celiac disease with early onset: A protective effect of breast-feeding has been observed only when celiac disease is diagnosed < 2 years of age, suggesting a delay more than actual prevention of the disease ⁹.

Infections and interactions between infections at the time of gluten introduction have been associated with the risk of celiac disease in some studies ^{11, 12}, but not all ¹³. Rotavirus infections in genetically predisposed individuals have been associated with development of celiac disease-associated autoimmunity ¹⁴.

The recognition of conditions during the fetal period and early life as predictors for later health and disease, has led to an immune programming hypothesis underlining the plasticity of the developing immune system modified by maternal nutrition, micronutrients and gut microbiota ^{15–17}. Iron is important for the development and function of the immune system ¹⁸, and has recently been shown to influence adaptive immune responses and macrophage function ¹⁹.

The aim of this study was to test in a prospective cohort study whether maternal iron supplement intake during pregnancy is associated with the risk of celiac disease in childhood.

Material and methods

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health ²⁰. Participants were recruited from all over Norway from 1999–2008, and 91 000 mothers (39% of invited women) participated with one or more pregnancies. Follow-up is conducted

by questionnaires at regular intervals and by linkage to national health registries. In the current study we use information from seven questionnaires; three completed during pregnancy, two at the age of 6 and 18 months and two at the age of seven and eight years. Written informed consent was obtained, and the sub-study and linkage to the patient register was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway. The current study is based on version VII of the quality-assured data files released for research in June 2012.

Case identification

Cases of celiac disease were identified from the Norwegian Patient Register and from parental questionnaires. The questionnaires administered when the children were seven and eight years old contain a specific question of celiac disease diagnosed in the child. The Norwegian Patient Registry is an administrative database containing activity data from all Norwegian government-owned hospitals and outpatient clinics. Reporting data to the NPR is mandatory and linked to the governmental reimbursement system for funding of health services. Diagnoses are reported as ICD-10 codes, and individual patient files or histology reports were not available. The 11-digit personal identification number unique to every Norwegian citizen was included in the NPR files from 2008 onward, making individual-level research data available.

Health care is free of charge for children up to age 16 years in Norway. All hospitals for children and most child outpatient clinics are owned by the government. In addition, there are currently 29 paediatricians with private practices. Private practices receiving government reimbursements are obliged to report their data to the NPR similar to the government-owned institutions. However, the reporting of personal identification numbers from private practices is not yet complete, and private practice data were not included in the data file used for this study.

The ESPGHAN diagnostic criteria from 1991, which were in use during this period, require a small-bowel biopsy for diagnosis of celiac disease ²¹. As biopsies are performed in government-owned hospitals only, all children with biopsy-proven celiac disease have been diagnosed at facilities reporting to NPR. However, as the registration started 1.1.2008, cases diagnosed before this date, and not seen regularly as recommended in the outpatient clinic, would not be registered in the NPR. For this study, the NPR provided data from 2008 through 2011.

Because blood samples are not collected from the children in MoBa after birth, we could not test for antibodies to screen for undiagnosed celiac disease as part of the study.

Case definition

Children subjected to intestinal biopsy on suspicion of celiac disease may be registered in the NPR on discharge before a final histological report and a confirmed diagnosis. To reduce the possibility of including false positive cases without final diagnosis based on biopsy results, we restricted the case definition in NPR to individuals registered at a minimum of two occasions in the NPR (n=326).

The cases identified from parental questionnaires without NPR registrations (n=67) were added to the ones identified twice in the registry, giving a total of 393 cases of celiac disease (245 females, 62%) among 106 917 live births. After exclusion of participants with missing information on iron supplement use or gluten introduction, the final analysis included 78 846 subjects with complete data, of which 314 were identified with a celiac disease diagnosis (Fig 1).

For validation of the cases identified by two or more entries in the NPR, we reviewed the 92 cases where parental forms also had been completed after the first entry in NPR. All cases except one were confirmed.

Supplements, dietary intake and definition of variables

Pregnant mothers completed a questionnaire at enrolment around week 15–17 of pregnancy, including detailed information on use of dietary supplements, stating the frequency and amount used as well as nutrient content in the supplement for each month of pregnancy. The questionnaire also included questions of diagnosis and treatment of anaemia before or during pregnancy (all questionnaires available at www.fhi.no/moba).

A similar questionnaire with monthly intervals for supplement use was completed at week 30 of pregnancy. This questionnaire also contained haemoglobin measurement results to be transferred from the maternity record (lowest, highest and latest measurement).

The information about iron supplement use was combined into a variable denoting months of iron supplement use during pregnancy ranging from 0 (non-users) to 8 months. For the main analysis, iron supplement use was coded as a dichotomous variable separating non-users and users (one month). A calculation of cumulative iron supplement dose was performed combining estimated daily dose of iron supplement in week 22 of pregnancy and duration of supplement use.

A detailed food frequency questionnaire (FFQ) was completed at week 17–22 of pregnancy concerning dietary intake from the beginning of pregnancy until the date of completion²². A validity study in 119 participants showed that the correlation between dietary iron intake according to the FFQ used in the whole cohort, and that estimated using a weighed 4-day food diary as a reference, was 0.42 (95% CI 0.26, 0.56) after energy adjustment²³. Sixty-six per cent were classified in the same or adjacent quintile with the two methods²³.

From questionnaires administered when the child was 6 months and 18 months old, use of iron supplements was recorded by the mother, father or other primary caregivers. At six months of age the questionnaire contained information on breastfeeding for each month since birth (yes/no). The age at introduction of solid foods (subtypes of cereals, vegetables, fruits) was similarly reported for each month up to 6 months' age. The questionnaire at 18 months contained separate fields for presence of breastfeeding in three-month intervals (6–8, 9–11, 12–14, 15–18), and the midpoint of the reported interval was used in the analysis.

Information about maternal age at delivery, parity, mode of delivery and sex of the child were based on information from the Medical Birth Registry of Norway²⁴, and information about maternal celiac disease and education were based on answers to the pregnancy questionnaires.

Statistical analysis

Analyses were performed using the SPSS 20.0 statistical software package (IBM SPSS inc., Chicago, IL, USA). The main analysis was conducted using logistic regression. Multiple regression models included potential confounding variables with $p \leq 0.1$ in unadjusted analyses. Sensitivity analyses were performed for the main exposure with single iron supplement use or iron in multivitamin/mineral products, and with other supplements commonly used in pregnancy.

Results

The mean age of the cohort at the end of 2011 was 5.9 years (range 2–12 years). At the age of 6 months, 78% were still breastfed and gluten had been introduced to 53% of the children (Table 1).

Maternal iron supplements during pregnancy and risk of celiac disease in children

A total of 56.6 % of the expecting mothers reported use of iron supplements before week 30 of pregnancy, with highest prevalence after 25 weeks of gestation and in women reporting anaemia during pregnancy (Supplementary Table 1).

Celiac disease was diagnosed in 4.65/1000 of the children whose mother reported use of any iron supplements during pregnancy compared to 3.15/1000 of those who did not. After adjustment for age and sex of the child, timing of gluten introduction and maternal celiac disease, maternal iron supplementation during pregnancy was significantly associated with celiac disease in the child with an odds ratio of 1.33 (95 % CI 1.05 – 1.68, $p=0.019$, Table 2). Maternal age and parity, mode of delivery, education and breastfeeding at 6 months were not associated with the risk of celiac disease in this cohort, and did not change the estimated odds ratios (not shown). The adjusted OR per month use of iron supplementation was 1.05 (95 % CI 1.01 – 1.09, p for trend=0.018, supplementary Figure 2a and b). The cumulative iron supplement dose during pregnancy was analysed in quartiles among users as compared with non-users, with the highest OR of 1.67 (95% CI 1.21–2.31, $p=0.002$) for the upper quartile (supplementary Fig 2c; p for trend = 0.001).

Maternal anaemia or low haemoglobin and risk of celiac disease in children

Details of association between use of iron supplements in different parts of pregnancy and questionnaire-reported diagnosis of anaemia as well as reported haemoglobin levels are found in Supplementary Table 1.

A reported diagnosis of anaemia before or during first 17 weeks of pregnancy was not associated with the risk of celiac disease in the offspring (Table 2). Adjusting for maternal anaemia did not materially change the estimated odds ratio for maternal iron supplementation during pregnancy and risk of celiac disease (OR adjusted for maternal anaemia 1.31, 1.03–1.66). Reported haemoglobin of less than 10.5 g/dL before week 30 was not associated with the risk of celiac disease (Table 2).

Association with other dietary supplements

To assess whether the association was mainly driven by iron-containing multivitamin/mineral supplements (often used by health conscious women) or pure iron supplements, we analysed these separately. The association was similar and significant for both types of supplements (Table 2).

To assess for the possibility of iron supplement users being more attentive to recommendations and biased towards seeking health-care, we also analysed the association between celiac disease and use of other supplements frequently used during pregnancy. Use of folic acid, vitamin- or mineral supplements without iron, or fish oil supplements by the mother during pregnancy were not associated with the risk of celiac disease in the offspring (Table 2).

Maternal intake of dietary iron from foods during pregnancy

The median estimated iron intake from foods at week 17–22 of pregnancy was 10.7 mg/d, and the median intake from supplements was 14.0 mg/d among those who took supplements

(Supplementary Table 2). Iron intake from foods analysed as a continuous variable was not associated with the risk of celiac disease (unadjusted OR 0.99, 95% CI 0.96–1.02, adjusted OR 1.00, 95% CI 0.97–1.03). Stratifying the latter analyses by use of iron supplements gave similar results (data not shown).

Children's use of iron supplement and risk of celiac disease

Postnatal supplementation with iron is recommended up to 6 months age in infants with birth weight < 2500 g. Among children reported to use iron supplements at 6 months of age (Table 3), 48% had a birth weight of <2500 g, while the corresponding number was 15% for those given iron supplements at 18 months.

The risk of celiac disease was not associated with iron supplement use in infancy, whereas use of iron supplements at 18 months was associated with a more than three-fold increase in the risk of celiac disease (Table 3). Restricting the analysis to infants with birth weight above 2500 g did not change the association (data not shown).

The main analysis of the relation between maternal iron supplement use and the risk of celiac disease in the children did not change materially after adjusting for iron use at 6 and 18 months (adjusted OR 1.36, 1.05–1.75).

Discussion

We found an increased risk for celiac disease in children whose mothers had taken iron supplements during pregnancy. To our knowledge, this has not been investigated before.

Among the major strengths of the study are the large sample size, and the fact that maternal diet and use of supplements were prospectively collected when the mothers were still pregnant. The exposures studied are consequently expected to be more accurate and the risk of recall bias is minimised compared to studies with retrospective registration after the disease has been diagnosed in case-control designs.

Basing the diagnosis on register data or parental reporting introduces some risk of misclassification. Access to clinical, biochemical and histological information would likely add a proportion of the cases with single entries in the NPR to the celiac group. Additional screening for celiac disease in all the participants to find additional cases of celiac disease would similarly identify more cases, primarily with silent disease or low-grade symptoms^{25, 26}. The relatively strict case definition with two or more entries in the NPR was chosen to avoid false positives among the celiac cases at the expense of false negatives in the control group. False positives are a bigger threat to validity than are false negatives, because in a random sample of the population not defined as cases the chance that a given subject has celiac disease is probably less than 1–2%. In sensitivity analyses to assess the potential influence of incomplete registration of children diagnosed with celiac disease, 10 and 20% of the cases were randomly assigned status as non-celiac individuals. Since this had minimal impact on the observed associations, our simulations suggest that underreporting of the diagnosis in the population did not have any substantial influence on our results..

In the current cohort 323/78846 (0.41 %) of the mothers reported to have celiac disease diagnosed before or in early pregnancy. With a higher likelihood of iron malabsorption and low ferritin levels, mothers with celiac disease are likely to more often take iron supplements. Even though offspring of mothers with celiac disease would have increased genetic risk, the group of mothers with undiagnosed celiac disease is probably too small to have any material influence on our observed results. In a model with a 2% prevalence of

undiagnosed celiac disease in supplement users and 0.3% in non-users, similar to a recent study ²⁷, the association is still significant with an OR of 1.30 (1.03–1.65, $p=0.031$).

This was also supported by adjustment in our main analysis for reported celiac disease in the mothers. Furthermore, the lack of significant association with maternal anaemia before or in early pregnancy makes undetected maternal celiac disease less likely as a major explanation for the observed association.

Similarly, iron supplement use could be more common among mothers more likely to seek health care for their children. The lack of association with other types of supplements makes this less likely.

Iron intake from foods was not associated with the risk of celiac disease, and this could be due to the low range of variation in dietary intake; the median total daily dose among users of iron supplements was 2.3 times higher compared to median intake among non-users.

We did not have biochemical markers for iron metabolism except self-reported haemoglobin and anaemia. National recommendations regarding iron supplementation during pregnancy were until 2005 based on serum ferritin levels ²⁸, and a negative correlation between ferritin and total iron intake has been observed in a subgroup of the cohort (unpublished results from ²⁹). Measurements of ferritin could consequently not be used as a marker of iron excess in this study. From 2005 measurement of haemoglobin (early and in week 28 of pregnancy) has been recommended to guide iron supplementation in Norway ³⁰. The inclusion of pregnancies in the current study from before and after a change in the recommendations reflects this change, with a reduction in the proportion using iron from 62 % in 2000–2005 to 50 % after 2005. As all the estimates were adjusted for year of birth, the change in iron recommendation did not influence the associations.

A high proportion of the pregnant women in this study used iron supplements during pregnancy apparently without having anaemia or borderline haemoglobin. Markers of iron excess would be of interest but, as iron uptake in the gut is strictly controlled; such markers are not necessarily sensitive to assess iron intake and potential local effects of iron in the intestinal lumen.

Iron requirements increase three-fold in a normal pregnancy ³¹. In parallel to the increased requirement, the intestinal iron uptake in the third trimester is increased to a similar extent ³². The active transport of iron across the placenta protects the foetus from low iron availability in cases of maternal iron deficiency ³³. In a global context, iron deficiency in fertile women and during pregnancy is a major health threat, with increased morbidity, risk of miscarriage and stillbirth, low birth weight and impaired development in the infant ^{34, 35}. However, routine supplementation is not recommended during pregnancy in high-income countries with low prevalence of iron deficiency as in the UK and Norway due to the risk of adverse effects ^{30, 36}. The Nordic Nutrition Recommendations for iron intake in pregnancy is 15 mg/d ³⁷, and 27 mg/d is recommended in the recent UK guidelines ³⁶ and in the US ³⁸.

Potential mechanisms for the association with maternal iron supplement use

Several potential mechanisms could be hypothesized in the observed association between maternal iron supplementation and celiac disease in the child. A programming effect on the developing immune system is possible, through direct effects or through epigenetic mechanisms ³⁹.

Direct effects of iron on the innate and adaptive immune system could be involved in modelling immune responses to food antigens ⁴⁰. Accumulation of iron in macrophages has

been demonstrated to activate these into a pro-inflammatory M1 phenotype, with a putative role of iron in chronic inflammatory and autoimmune conditions¹⁹.

Excess of iron in the gut with increased oxidative stress may increase inflammatory activity in the intestinal mucosa^{41, 42} with increased crypt proliferation in animal models^{41, 43}. Markers of oxidative stress in placental tissues has been found after iron supplementation during pregnancy⁴⁴, but adverse clinical effect on the offspring has, to our knowledge, not been reported.

Interestingly, a transcellular transport of intact gliadin peptides bound to IgA across the enterocyte partly mediated through the transferrin receptor CD71 has been demonstrated in celiac disease⁴⁵. In iron deficient states, the transferrin receptor is up-regulated on intestinal epithelial cells⁴⁶, and we can speculate that the aforementioned mechanism of transcellular uptake of iron in the intestine may increase the presence of intact gliadin peptides in the lamina propria. This mechanism is, however, of potential importance only after delivery, when the gut is exposed to gliadin peptides.

Restriction of iron influx to gut pathogens as part of the innate immune system can control multiplication⁴⁷. Changes in the maternal gut microflora caused by iron intake should also be considered, but stool samples for such investigations were not collected in this study. Both in animal⁴⁸ and in human studies⁴⁹ iron excess favours multiplication of bacteria dependent on iron (i.e. *enterobacteriaceae*) at the expense of iron-independent bacteria (i.e. *lactobacillae*). The effect of iron supplements on gut flora in healthy, non-anaemic pregnant women and their offspring is, to our knowledge, unknown. A growing body of evidence links the maternal microflora to long-term outcomes regarding tolerance and immunity in the child⁵⁰.

To study an association between iron supplement use and celiac disease presenting at later ages will require longer observation time as our cohort is still young. Use of iron supplements reported at 18 months of age was associated with a threefold higher risk of celiac disease. Possibly, iron deficiency anaemia as an early symptom of celiac disease or iron supplementation prescribed early after diagnosis could explain this observed association, but this observation could be explored in future studies.

Interestingly, an association between celiac disease and hemochromatosis has recently been reported in a large population-based study⁵¹ as previously described in several case reports. Surveillance bias in celiac patients and shared genetic susceptibility are possible explanations for the association; however, we speculate based on this observation and our findings that iron could be involved in the pathogenic pathways contributing to celiac disease.

As for any novel observation, future replication in independent cohorts are warranted, ideally with biochemical and clinical indicators of iron metabolism and including screening detected celiac disease and full family history. The size necessary for prospective birth cohort studies to replicate these findings limits future replicative studies in the next few years. The observed associations in the current study are of modest magnitude, and we cannot exclude residual confounding or unobserved common root causes of iron supplement use and celiac disease in the offspring. However, iron used to treat anaemia as a consequence of undiagnosed coeliac disease has been considered in simulation studies and found unlikely to be a major confounder. If the association is confirmed, iron supplements during pregnancy should be used with caution unless iron deficiency is present, and routine use discouraged as indicated in the revised guidelines in Norway and in the UK^{30, 36}. If

replicated, the result may have implications for recommendations regarding use of iron supplements in pregnancy.

To conclude, we observed an increased risk of celiac disease in children whose mother had used iron supplements during pregnancy. Maternal anaemia was not associated to celiac disease in the offspring, and the increased risk of celiac disease with iron supplement use in pregnancy was not driven by maternal anaemia or iron supplementation in childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CD	celiac disease
CI	confidence interval
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
HLA	human leukocyte antigen
ICD-10	International Classification of Diseases
MoBa	The Norwegian Mother and Child cohort study
NPR	The Norwegian Patient Register
OR	odds ratio
SNP	single nucleotide polymorphism

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Fig 1.

Flow chart of selection for study of celiac disease in the Norwegian Mother and Child cohort study (MoBa). NPR: Norwegian Patient Register, Qu=Questionnaire at 7 and 8 years age.

Table 1

Description of the study population. (*p<0.05)

	Celiac disease	
	Yes (n=314)	No (n= 78 532)
Mean age at end of follow-up (range)*	6.8 (3–11)	5.9 (2–11)
Female sex (%)*	196 (62.4)	38 265 (48.7)
Parity (%)		
0	45.4	46.6
1	35.5	34.9
2 +	19.1	18.5
Mean maternal age at delivery (SD)	30.0(4.4)	30.2 (4.5)
Caesarean section delivery (%)		
Total	13.1	14.1
- Planned	3.8	5.1
- Emergency	8.9	7.8
- Not specified	0.3	1.2
Maternal education (%)		
12 years	30.0	32.1
13–16 years	38.7	40.3
17 years	24.6	22.9
Missing	6.7	4.8
Duration of any breastfeeding (%)		
< 6 months	16.3	16.8
6–12 months	33.2	34.7
>12 months*	39.0	32.1
Incomplete information	11.5	16.4
Age at gluten introduction (%)		
4 months	8.3	7.9
5–6 months	42.2	45.4
7 months*	49.5	46.7
Maternal celiac disease (%)*	13 (4.2)	310 (0.39)
Birth weight mean (SD)	3574 (554)	3598 (522)
< 2.5 kg	2.2	3.0
2.5–3.5 kg	40.4	37.7
3.5–4.5 kg	53.8	54.8
>4.5 kg	3.5	4.5

	Celiac disease	
	Yes (n=314)	No (n= 78 532)
Gestational age (%)		
< 37 weeks	5.8	5.0
37–40 weeks	69.5	67.2
>40 weeks	24.7	27.8

Table 2

Association of maternal iron supplementation during pregnancy, maternal anaemia and other types of dietary supplements, with risk of celiac disease in the offspring.

Type of supplement used during pregnancy ^{**}	Celiac disease		Unadjusted odds ratio (95% CI)	Adjusted [*] odds ratio (95% CI)	p-value (adjusted model)
	Yes 314 (%)	No 78532 (%)			
Use of any iron supplement during pregnancy	207 (66.1)	44458 (56.6)	1.48 (1.17–1.87)	1.33 (1.05–1.68)	0.019
Iron not combined preparation (%)	129 (41.1)	26498 (33.7)	1.55 (1.20–2.00)	1.32 (1.02–1.72)	0.035
Iron in multivitamin/mineral product (%)	78 (24.8)	17960 (22.9)	1.38 (1.03–1.85)	1.34 (1.00–1.80)	0.051
Maternal anaemia (%)	23 (7.3)	3863 (4.9)	1.52 (0.99–2.32)	1.24 (0.84–2.00)	0.24
Haemoglobin < 10.5 (%)	40 (15.6)	8535 (13.9)	1.13 (0.81–1.60)	1.10 (0.78–1.54)	0.59
Vitamin or mineral supplement without iron (%)	181 (57.6)	42563 (54.2)	1.15 (0.92–1.44)	1.18 (0.94–1.48)	0.15
Folic acid (%)	266 (84.7)	66551 (84.7)	1.00 (0.73–1.36)	1.21 (0.88–1.66)	0.23
Fish oil (%)	216 (68.8)	56280 (71.7)	0.87 (0.69–1.11)	1.03 (0.81–1.32)	0.80

* Adjusted for maternal celiac disease, female gender, age of the child and gluten introduction after 6 months' age.

** reported at around 30 weeks of pregnancy

Table 3

Child's use of dietary iron supplements at 6 and 18 months and the risk of celiac disease.

	Non-celiac	Celiac	Unadjusted odds ratio, 95 % CI	Adjusted odds ratio *, 95 % CI
No use	62458	262	Reference	Reference
6 months only	2333	5	0.51, 0.21 – 1.24	0.54, 0.22 – 1.32
18 months only	673	9	3.2, 1.6–6.2	3.0, 1.5–6.0
6 and 18 months	171	2	2.8, 0.7–11.3	3.1, 0.77–12.7

* Adjusted for maternal celiac disease, gender, age of child, age at gluten introduction and maternal use of iron supplement during pregnancy.