British Journal of Nutrition (2017), **117**, 466–472
doi:10.1017/S0007114517000332

Maternal use of dietary supplements during pregnancy is not associated with coeliac disease in the offspring: The Environmental Determinants of Diabetes in the Young (TEDDY) study

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(Submitted 19 August 2016 – Final revision received 17 January 2017 – Accepted 25 January 2017 – First published online 2 March 2017)

Abstract

Perinatal exposure to nutrients and dietary components may affect the risk for coeliac disease (CD). We investigated the association between maternal use of vitamin D, *n*-3 fatty acids (FA) and Fe supplements during pregnancy and risk for CD autoimmunity (CDA) and CD in the offspring. Children at increased genetic risk were prospectively followed from birth in The Environmental Determinants of Diabetes in the Young (TEDDY) study. CDA was defined as having persistently positive tissue transglutaminase autoantibodies (tTGA). Diagnosis of CD was either biopsy-confirmed or considered likely if having persistently elevated levels of tTGA > 100 AU. Of 6627 enrolled children, 1136 developed CDA at a median 3·1 years of age (range 0·9–10) and 409 developed CD at a median 3·9 years of age (range 1·2–11). Use of supplements containing vitamin D, *n*-3 FA and Fe was recalled by 66, 17 and 94 % of mothers, respectively, at 3–4 months postpartum. The mean cumulative intake over the entire pregnancy was 2014 μg vitamin D (SD 2045 μg), 111 g *n*-3 FA (SD 303 g) and 8806 mg Fe (SD 7017 mg). After adjusting for country, child's human leucocyte antigen genotype, sex, family history of CD, any breast-feeding duration and household crowding, Cox's proportional hazard ratios did not suggest a statistically significant association between the intake of vitamin D, *n*-3 FA or Fe, and risk for CDA or CD. Dietary supplementation during pregnancy may help boost nutrient intake, but it is not likely to modify the risk for the disease in the offspring.

Key words: Coeliac disease: Dietary supplements: Maternal consumption: Offspring

Coeliac disease is an autoimmune disorder that is triggered by the ingestion of gluten[(1)], a protein found in cereals such as wheat, rye and barley. Coeliac disease has a multifactorial aetiology involving a complex interplay between genetics, gluten intake and infections[(1)]. *In utero* exposure to nutrients and dietary components may affect disease risk by influencing

Abbreviations: CDA, coeliac disease autoimmunity; FA, fatty acids; HLA, human leucocyte antigen; HR, hazard ratio; TEDDY, The Environmental Determinants of Diabetes in the Young; tTGA, tissue transglutaminase antibodies.

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the development of the immune system and intestinal microbiota. For example, vitamin D is suggested to affect the control of intestinal inflammation[2–4]. *n*-3 Fatty acids (FA) are found to have anti-inflammatory and immunomodulatory functions[5–7]. Previous animal, as well as human, studies also demonstrated that Fe supplementation may induce changes in the maternal gut microbiota that can be transferred to the infant and may induce a less-favourable bacterial colonisation of the newborn's digestive system[8,9].

The role of maternal diet in the risk for coeliac disease in the offspring has been far less studied, but a recent study demonstrated a positive association between use of Fe supplements during pregnancy and development of coeliac disease in children in a large Norwegian prospective cohort[10]. However, no other prospective birth cohort study has yet confirmed these aforementioned associations.

The Environmental Determinants of Diabetes in the Young (TEDDY) is an international multicentre observational study that prospectively follows children from birth until the age of 15 years in the search for environmental factors involved in both type 1 diabetes and coeliac disease. Exposure to environmental factors during pregnancy, infancy and early childhood is closely monitored. In a previous report from the TEDDY study, we demonstrated that, despite strong associations between human leucocyte antigen (HLA)-risk genotypes and coeliac disease, there are differences in disease risk between the participating countries that cannot be explained by genetic factors[11], suggesting the need to investigate the impact of dietary and other exposures on disease development.

The aim of the current study was to examine whether maternal use of dietary supplements during pregnancy confers a risk for coeliac disease in the TEDDY birth cohort. More specifically, we set out to examine the association between maternal supplementation of vitamin D, *n*-3 FA and Fe during pregnancy and the risk for coeliac disease autoimmunity (CDA) and coeliac disease in genetically at-risk children prospectively followed up from birth.

Methods

Study population

The TEDDY study is a longitudinal prospective observational study of type 1 diabetes and coeliac disease that takes place at six clinical research centres located in Colorado, Georgia and Washington in the USA, and in Finland, Germany and Sweden[12,13] (www.clinicaltrials.gov, registration no. NCT00279318). This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by local ethics or Institutional Review Boards. The study was monitored by an External Evaluation Committee formed by the National Institutes of Health.

Between September 2004 and February 2010, 424 788 newborn infants were screened, of whom 21 589 infants met the inclusion criteria based on HLA genotyping (online Supplementary Table S1). These infants and their parents were invited to join the study, and 8676 of them were accepted and enrolled into a 15-year follow-up. Written informed consent was obtained for all study participants from a parent or primary caregiver for both the infant's genetic screening and for participation in the prospective follow-up study. Detailed study design and methods have been published previously[12,13].

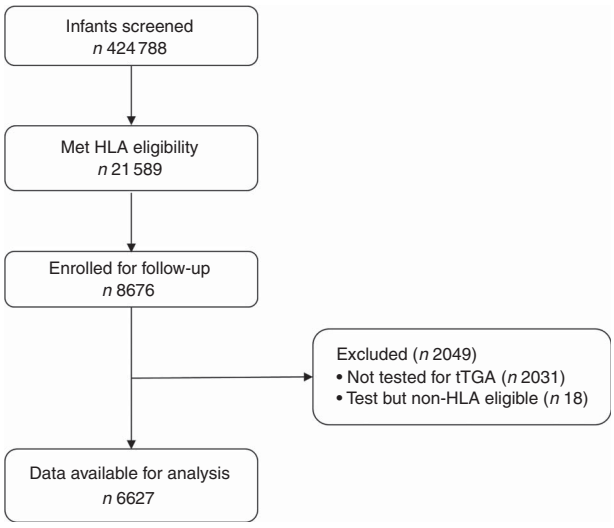

Fig. 1. Study population of the Environmental Determinants of Diabetes in the Young study. HLA, human leucocyte antigen; tTGA, tissue transglutaminase autoantibodies.

Screening for coeliac disease autoimmunity and coeliac disease

Annual screening for coeliac disease with tissue transglutaminase antibodies (tTGA) started at 2 years of age using radioligand binding assays[14]. Children who were tTGA positive in two consecutive serum samples drawn at least 3 months apart were defined as having CDA. Children testing positive for tTGA at the 2-year visit had their previous serum samples analysed retrospectively in order to identify the time point of tTGA seroconversion. All children with CDA were referred to a paediatric gastroenterologist at the local hospital for further evaluation of coeliac disease. In children investigated with intestinal biopsy, all histological specimens were scored by the local pathologist according to the Marsh classification, and having a Marsh score ≥2 was defined as biopsy-proven coeliac disease[11]. Children who had no intestinal biopsy results but had a mean tTGA level of 100 AU or greater in two consecutive samples were also considered as having coeliac disease for the purpose of this study[11]. As of 29 February 2016, 6627 children had been screened for tTGA (Fig. 1). Of them, 1136 (17 %) developed CDA at a median 3·1 years of age (range 0·9–10·0) and 409 (6·2 %) were diagnosed with coeliac disease at a median 3·9 years of age (range 1·2–11·0).

Maternal and child characteristics

Maternal characteristics included mother's age at delivery (maternal age) and whether she smoked or consumed alcoholic

https://doi.org/10.1017/S0007114517000332

drinks during pregnancy. Smoking and alcohol consumption were defined as 'yes' if reported, regardless of frequency and duration. Maternal education attainment was recorded on a ten-category scale designed to account for different education systems in each country. In order to achieve comparability across countries, the education variable was categorised into basic primary education (primary school through trade school) and higher education (completed trade school or higher).

Child characteristics included HLA genotype, country, sex, whether the child has a first-degree relative (i.e. mother, father and/or sibling) diagnosed with coeliac disease (coeliac FDR), birth order (first child or not), gestational age in weeks, mode of delivery and birth weight (g). Season of birth was determined on the basis of birth month – that is, winter (December–February), spring (March–May), summer (June–August) and fall (September–November). Household crowding was included and measured as the number of persons in the household divided by the number of rooms in the house. Because the crowding variable was skewed, it was re-scored to normalise the distribution (1 = 0–0·49; 2 = 0·50–0·59; 3 = 0·60–0·75; 4 = 0·76–1·00; 5 = > 1·00). Information about the durations of exclusive and any breast-feeding (in months) and time of introduction to gluten-containing and gluten-free cereals (in months) was collected every 3 months in a booklet given to the parents at study entry, which has been previously described in detail[15].

Maternal use of dietary supplements

Mothers recalled their use of dietary supplements during pregnancy at the first TEDDY visit between 3·0 and 4·5 months postpartum. Information about the brand, frequency, amount and duration of every supplement was recorded on a questionnaire. The TEDDY study kept track of dietary supplements containing one or any combination of the following nutrients or constituents: vitamin, mineral, FA, probiotics and antioxidant compounds[16]. Fibre, herbal, homoeopathic, amino acid and protein supplements were excluded. A vitamin or other nutrient administered intra-muscularly or subcutaneously was considered a medication and excluded. Upon receipt of the questionnaire, the research staff checked for thoroughness of the information and contacted the caretakers for missing or ambiguous data. When needed, the staff would reach out to the manufacturer or distributor to ascertain the ingredient composition.

Every supplement was categorised into one of the thirty-seven mutually exclusive subgroups based on nutrient profile (twenty-seven single and ten multivitamin/mineral subgroups; see online Supplementary Table S2). A dietary supplement user was defined as anyone who reported taking at least one supplement at least once during the pregnancy. If more than one supplement was reported within the same subgroup, the maximum duration was used in the analysis. The cumulative intakes of vitamin D, *n*-3 FA and Fe from the supplements were calculated on the basis of the dosage listed on product labels and duration of use. The Fe in supplements may exist in different ferrous compounds, and hence the amount of Fe was converted to elemental Fe for all products. There were a small number of mothers who indicated vitamin use without providing information on the specific products. In those cases, the country-specific median was imputed for their cumulative intake.

Statistical methods

The Cox proportional hazards regression model was used to determine factors associated with the risk for CDA and coeliac disease. Each endpoint was analysed separately. With the observed number of 1136 children with CDA and 409 with coeliac disease, the Cox proportional hazards analysis should have approximately 80 % power to detect hazard ratios (HR) of 1·19 for CDA and 1·32 for coeliac disease. The country variable was included as a stratification factor in the analysis. Another eighteen potential covariates described in the 'Maternal and child characteristics' section (excluding dietary supplements) were screened by backward selection (cut-off level of $P < 0·01$) for each endpoint for inclusion in the Cox model. The choice of covariates was done before analysis of dietary supplementation to protect against bias in the selection of a model. After the covariates were chosen, the association between cumulative intake of supplemental vitamin D, *n*-3 FA and Fe, and risk for CDA and coeliac disease were examined in separate regression models. As the relationship between supplement use and the risk for either CDA or coeliac disease is unknown, the cumulative intake of each nutrient was examined in three ways as an approach of sensitivity analysis. First, the actual cumulative amount was analysed as a continuous variable. Second, the cumulative amount was categorised as an ordinal variable (0, no use; 1, less than the median amount over population of supplement users; and 2, more than the median amount over the population of supplement users). Third, the cumulative amount was categorised as a binary variable (0, no use; 1, any use). Statistical significance was accepted at $P < 0·05$. Analyses were performed using Statistical Analysis Software (version 9.4; SAS Institute).

Results

Among 6608 mothers with complete supplement use data, 4369 (66 %), 1107 (17 %) and 6216 (94 %) reported taking single and/or multivitamin/mineral supplements that contained vitamin D, *n*-3 FA and Fe, respectively, during pregnancy (Table 1). The mean cumulative intake of vitamin D was lowest in mothers from Germany and Sweden, whereas German mothers had the lowest median intake of *n*-3 FA and Finnish mothers had the lowest median intake of Fe (Table 1).

HLA genotype, coeliac FDR, sex, duration of any breast-feeding, household crowding and the interaction of HLA and sex were significantly associated with CDA or coeliac disease (Table 2), and were therefore included in the Cox proportional hazards models as covariates. The specific covariates for each endpoint are shown in Table 2. Adjusting for the aforementioned covariates, the cumulative vitamin D intake, when added to the model as a binary variable ('no use' *v.* 'any use' during pregnancy), yielded a small increased risk for CDA (HR 1·15; 95 % CI 1·00, 1·32; $P = 0·04$) (Table 3). However, this result was

https://doi.org/10.1017/S0007114517000332

Table 1. User proportions of dietary supplements containing vitamin D, *n*-3 fatty acids (FA) and iron during pregnancy in the Environmental Determinants of Diabetes in the Young study and the amount of cumulative intakes among users
(Medians and interquartile ranges (IQR))

	All (*n* 6608)		USA (*n* 2637)		Finland (*n* 1502)		Germany (*n* 403)		Sweden (*n* 2066)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Vitamin D	4369	66	2178	82	1104	73	87	22	1000	48
Median (μg)*	1540		2800		1200		1050		1050	
IQR*	1000–2800		2030–2800		695–1400		600–1400		600–1120	
n-3 FA	1107	17	377	26	138	9	138	34	154	7
Median (g)*	62		67		82		38		73	
IQR*	35–92		42–84		28–153		24–56		29–130	
Fe	6216	94	2579	97	1274	85	316	78	2047	99
Median (mg)*	7728		7840		3150		9625		9200	
IQR*	4200–11 410		5040–7840		2030–9702		3500–21 715		4200–16 000	

* Refer to cumulative intake over the entire pregnancy among supplement users.

Table 2. Underlying covariates used in the Cox proportional hazards model when analysing the risk for coeliac disease autoimmunity and coeliac disease in the Environmental Determinants of Diabetes in the Young study
(Hazard ratios (HR) and 95 % confidence intervals; mean values and standard deviations)

	All countries		Coeliac disease autoimmunity			Coeliac disease		
Variables*	*n*	%	HR	95 % CI	*P*	HR	95 % CI	*P*
HLA					<0·001†			<0·001
DR3-DQ2/DR3-DQ2	1366	21				1 (Ref.)		
DR3-DQ2/DR4-DQ8	2621	40				0·33	0·26, 0·41	
DR4-DQ8/DR4-DQ8	1301	20				0·25	0·19, 0·35	
DR4-DQ8/DR8-DQ4	1109	17				0·05	0·02, 0·09	
Other	230	2				0·12	0·04, 0·33	
Sex					<0·001‡			<0·001
Male	3389	51				1 (Ref.)		
Female	3238	49				1·99	1·63, 2·44	
Coeliac FDR								
No	6299	95		1 (Ref.)			1 (Ref.)	
Yes	217	3	2·12	1·71, 2·63	<0·001	3·47	2·60, 4·62	<0·001
Missing	111	2						
Household crowding‡			0·71	0·57, 0·89	0·003		NS	
Mean	0·75							
SD	0·32							
Months of any breast-feeding			1·01	1·00, 1·02	0·007		NS	
Mean	8·7							
SD	6·8							
HLA genotype × sex					0·003		NS	
Female of DR3-DQ2/DR3-DR2			1·96	1·63, 2·35				
Female of DR3-DQ2/DR4-DQ8			1·28	1·05, 1·55				
Female of DR4-DQ8/DR4-DQ8			1·85	1·33, 2·57				
Female of DR4-DQ8/DR8-DQ4			1·16	0·62, 2·15				
Female of all others			0·49	0·17, 1·43				

HLA, human leucocyte antigen; Ref., referent value; coeliac FDR, coeliac disease first-degree relative.
* These variables were identified after eighteen potential covariates were screened by backward selection (cut-off level of $P<0·01$) for each endpoint for inclusion in the Cox model. The eighteen covariates were mother's age at delivery, whether the mother smoked during pregnancy, whether the mother consumed alcoholic drinks during pregnancy, maternal education attainment, child's HLA genotype, child's sex, whether the child has a first-degree relative (i.e. mother, father and/or sibling) diagnosed with coeliac disease, birth order (first child or not), gestational age in weeks, mode of delivery, birth weight (g), season of birth, household crowding, breast-feeding history (yes/no), duration of exclusive breast-feeding (months), duration of any breast-feeding (months), time of introduction to gluten-containing cereals (months) and time of introduction to gluten-free cereals (months).
† HR not meaningful in the presence of an HLA genotype and sex interaction.
‡ Household crowding was included and measured by the number of persons in the household divided by the number of rooms in the house. Because the crowding variable was skewed, it was re-scored to normalise the distribution (1 = 0–0·49; 2 = 0·50–0·59; 3 = 0·60–0·75; 4 = 0·76–1·00; 5 = >1·00).

not replicated when the analysis was repeated using either the continuous actual cumulative intake tested in 1000 μg of increase (HR 0·98; 95 % CI 0·94, 1·02; $P=0·32$) or the ordinal variable (0, none; 1, <1540 μg (61 600 IU); 2, ≥1540 μg; HR 1·07; 95 % CI 0·98, 1·17; $P=0·15$) (Table 3). Neither *n*-3 FA nor Fe intake was associated with risk for either CDA or coeliac disease (Table 3). In all, 6 % of the mothers did not take Fe supplements and this low percentage in the 0 category might have posed a statistical problem; therefore, the analysis was repeated using the first and third quartiles of Fe intake over the entire cohort as the cut-off points. The results yielded an HR of 0·98 ($P=0·63$) for the CDA endpoint and 1·02 ($P=0·77$) for the coeliac disease endpoint, which were similar to the results from the original ordinal categorisation analysis.

https://doi.org/10.1017/S0007114517000332

Table 3. Association between cumulative intakes of vitamin D, *n*-3 fatty acids and iron from supplementation during pregnancy and the risk of coeliac disease autoimmunity and coeliac disease in the Environmental Determinants of Diabetes in the Young participants (Hazard ratios (HR) and 95 % confidence intervals)

	Coeliac disease autoimmunity*			Coeliac disease†		
Cumulative intakes	HR	95 % CI	*P*	HR	95 % CI	*P*
Vitamin D						
Actual value (per 1000 µg increase)‡	0·98	0·94, 1·02	0·32	0·98	0·90, 1·06	0·55
Ordinal (0, <1540 µg, ≥1540 µg)	1·07	0·98, 1·17	0·15	1·09	0·94, 1·27	0·26
Binary (no use, any use)	1·15	1·00, 1·32	0·04	1·16	0·93, 1·44	0·18
n-3 Fatty acids						
Actual value (per 100 g increase)§	0·98	0·92, 1·04	0·45	0·94	0·78, 1·13	0·50
Ordinal (0, <62 g, ≥62 g)	0·94	0·84, 1·05	0·26	0·94	0·78, 1·15	0·56
Binary (no use, any use)	0·89	0·74, 1·06	0·19	0·90	0·66, 1·22	0·48
Fe						
Actual value (per1000 mg increase)‖	0·99	0·98, 1·00	0·10	1·00	0·99, 1·02	0·76
Ordinal (0, <7728 mg, ≥7728 mg)	0·98	0·88, 1·09	0·69	1·10	0·92, 1·32	0·30
Binary (no use, any use)	0·98	0·74, 1·28	0·86	1·27	0·74, 2·16	0·39

* Adjusted for child's sex, human leucocyte antigen (HLA) genotype, coeliac first-degree relative, household crowding, duration of any breast-feeding, and an interaction of HLA genotype and sex. Stratified by country.
† Adjusted for child's sex, HLA genotype, and coeliac first-degree relative. Stratified by country.
‡ The unit of increase referred to cumulative intake. Assuming vitamin D supplements were taken daily during a full-term pregnancy (40 weeks), 1000 µg of cumulative intake would equal 3·57 µg vitamin D/d.
§ The unit of increase referred to cumulative intake. Assuming *n*-3 fatty acid supplements were taken daily during a full-term pregnancy (40 weeks), 100 g of cumulative intake would equal 0·36 g of fatty acids/d.
‖ The unit of increase referred to cumulative intake. Assuming Fe supplements were taken daily during a full-term pregnancy (40 weeks), 1000 mg of cumulative intake would equal 3·57 mg Fe/d.

Discussion

Data from the TEDDY study suggest that maternal use of vitamin D, *n*-3 FA and Fe supplements during pregnancy did not increase the risk for CDA and coeliac disease in their children by 6 years of age. This is in contradiction to a recent study from Norway, which suggested that use of Fe supplements during pregnancy might confer an increased risk for CDA and coeliac disease in the offspring[10]. The null finding of maternal supplementation of vitamin D or *n*-3 FA and CDA or coeliac disease is consistent with the Norwegian population study[10].

Several differences between the Norwegian and TEDDY cohorts may have contributed to these inconsistent findings. First, children in the aforementioned study came from the Norwegian Patient Register and from parental reporting, whereas the TEDDY participants came from the general population of four countries. Second, Norwegian children suspected of coeliac disease may be registered in the Patient Register before a final histological report and a confirmed diagnosis, and hence the cases in the Norwegian study were restricted to those registered at least twice in order to minimise the possibility of false positivity. The cases in the TEDDY study, in contrast, were identified on the basis of repeated screening for coeliac disease. Third, different methods were used to determine supplement users and the cumulative intake of Fe over the entire pregnancy. The Norwegian study limited the users to be those who took supplements for at least 1 month during pregnancy, but in TEDDY, mothers reporting any duration or any amount of supplementation were considered as users. The cumulative intake of Fe was estimated on the basis of inquired daily dose in week 22 of pregnancy in the Norwegian study, whereas in the TEDDY study it was calculated from the duration of every reported Fe-containing supplement in case mothers changed products or paused supplementation during pregnancy.

Mothers giving birth to children developing coeliac disease were found to have different pregnancy serum cytokine profile than mothers of healthy children[17], suggesting that the prenatal environment may have an impact on the autoimmunity status in the offspring. During pregnancy, women are encouraged to optimise their diet to meet increased needs for most nutrients. Those with poor diet quality, Fe-deficiency anaemia, vegans, smokers and women carrying two or more fetuses are recommended to boost their intake with a dietary supplement[18]. The nutrients absorbed from maternal supplements not only participate in the programming of the immune system in the offspring[19,20] but also affect the composition of their gut microbiota[3,8]. Still, the hypothesis that dietary supplements act on the fetus's immune system and induce tolerance to food antigens during infancy remains unknown.

The analysis from the current study captured the cumulative intakes of selected nutrients over pregnancy, which has not been frequently reported in the literature. Our data furthermore aligned with the country-specific recommendations on prenatal vitamin D, FA and Fe supplementation during the TEDDY screening period (2004–2010). The median cumulative intake of vitamin D in Finland was 4·29 µg/d (171·6 IU/d) under the daily use assumption, which was close to the '10 µg/d during winter months' recommendation in Finland prior to 2011[21]. In Germany, pregnant women without fish consumption have been recommended to take 200 mg/d DHA (22 : 6*n*-3) since 2008[21]. The assumed daily intake of *n*-3 FA among German mothers (140 mg) was slightly lower than the recommendation, which may be related to the relatively late establishment of this recommendation during the TEDDY screening period. In Sweden, the same 200 mg/d DHA recommendation was started in 2008[21], and the assumed daily intake of *n*-3 FA seen in Swedish mothers was 260 mg. Pregnant women in the USA were recommended to take 27 mg/d Fe at that time, and our

https://doi.org/10.1017/S0007114517000332

observed median cumulative intake of Fe in the USA was 28·0 mg/d if a daily consumption was assumed throughout pregnancy[18]. The recommendation for Fe intake during pregnancy was established in 2005 in Finland. Women with Hb level <110 g/l during the first trimester or <100 g/l during the second or third trimester were recommended to take 50 mg/d Fe, and such supplementation must start after the 12th week of pregnancy[22]. This recommendation might have explained the lowest accumulative Fe intake seen in our Finnish mothers (3150 mg), which equalled an assumed daily amount of 11·25 mg. Sweden also had a '100 mg/d Fe in the second-half of pregnancy' recommendation until 2008[21], which might have contributed to the observed 32·86 mg assumed daily Fe intake among the Swedish mothers.

We have previously reported that being pregnant with the first child was a strong predictor for any supplement use in TEDDY, whereas younger maternal age (<25 years), higher education and smoking during pregnancy were factors associated with vitamin D and/or FA supplementation[21]. None of these sociodemographic and behavioural factors changed the results from the Cox proportional hazards analysis when incorporated into the models as a new covariate individually, which indicated they could not explain the lack of association between supplementation and disease risk. We have also previously reported country differences in maternal exposure to gluten during late pregnancy and age at first introduction to gluten-containing cereals in children, but neither of these two potential risk factors had been associated with increased risk for coeliac disease in the TEDDY birth cohort and were therefore not considered as confounding factors in the present study[15,23].

The strengths of our study included the prospective multicentre study design and a large population of participants. The supplement data were self-reported by mothers soon after delivery before disease onset, which helped minimise recall bias. Moreover, the data were checked by research dietitians and trained personnel for completeness during the first study visit. Self-reported supplement use may be subject to under- or over-reporting, but a high correlation between biomarker concentrations and intake estimated by self-reported methods has been reported in a large population-based study[24]. This study was limited in the availability of nutrient intake data from foods during pregnancy because the mothers joined the study at least 3 months postpartum and collecting data retrospectively at that point regarding food consumption in the entire pregnancy was likely to be compromised by recall bias. Our analysis did not address Fe supplementation by children during childhood as done in the Norwegian study. However, we are confident that the maternal vitamin D and *n*-3 FA intakes were adequately reported when compared with the national recommendations in Finland, Germany, Sweden and the USA. Therefore, the Fe intake also seems applicable in our study population.

In conclusion, the results from the TEDDY birth cohort found no indication that use of vitamin D, *n*-3 FA and Fe supplements during pregnancy confers risk for coeliac disease in children. Supplementation of these nutrients during pregnancy may be helpful in boosting overall nutrient intake, but it is not likely to modify the risk for coeliac disease in the offspring.

Acknowledgements

The authors thank the participation of all families and the work of the TEDDY study group.

The TEDDY study is funded by U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836 and UC4 DK95300, and contract no. HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF) and Centers for Disease Control and Prevention (CDC). This work was supported in part by the National Institutes of Health/National Center for Advancing Translational Sciences (NIH/NCATS) Clinical and Translational Science Awards to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR001082). The NIDDK, NIAID, NICHD, NIEHS, JDRF and CDC had no role in the design, analysis or writing of this article.

J. Y. supervised the acquisition of data, drafted the manuscript and critically revised the manuscript for important intellectual content; R. N. T. analysed and interpreted data and critically revised the manuscript for important intellectual content; C. A. A., U. M. U., J. M. N. and S. M. V. supervised the acquisition of data, and critically revised the manuscript for important intellectual content; A. L., M. R., W. A. H., J.-X. S., J. T., A. G. Z., B. A. and J. P. K. obtained funding and designed the project; D. A. drafted the manuscript, critically revised the manuscript for important intellectual content, and have primary responsibility for the final content.

The authors have no conflict of interest to disclose.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517000332

References

1. Lebwohl B, Ludvigsson JF & Green PHR (2015) Celiac disease and non-celiac gluten sensitivity. *BMJ* **351**, h4347.
2. Assa A, Vong L, Pinnell LJ, *et al.* (2014) Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation. *J Infect Dis* **210**, 1296–1305.
3. Cantorna MT, McDaniel K, Bora S, *et al.* (2014) Vitamin D, immune regulation, the microbiota, and inflammatory bowel disease. *Exp Biol Med (Maywood)* **239**, 1524–1530.
4. Abreu-Delgado Y, Isidro RA, Torres EA, *et al.* (2016) Serum vitamin D and colonic vitamin D receptor in inflammatory bowel disease. *World J Gastroenterol* **22**, 3581–3591.
5. Alvarez-Curto E & Milligan G (2016) Metabolism meets immunity: the role of free fatty acid receptors in the immune system. *Biochem Pharmacol* **114**, 3–13.
6. Jenmalm MC & Duchén K (2013) Timing of allergy-preventive and immunomodulatory dietary interventions – are prenatal, perinatal or postnatal strategies optimal? *Clin Exp Allergy* **43**, 273–278.

7. Iwami D, Nonomura K, Shirasugi N, *et al.* (2011) Immunomodulatory effects of eicosapentaenoic acid through induction of regulatory T cells. *Int Immunopharmacol* **11**, 384–389.
8. Zimmermann MB, Chassard C, Rohner F, *et al.* (2010) The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Côte d'Ivoire. *Am J Clin Nutr* **92**, 1406–1415.
9. Dostal A, Chassard C, Hilty FM, *et al.* (2012) Iron depletion and repletion with ferrous sulfate or electrolytic iron modifies the composition and metabolic activity of the gut microbiota in rats. *J Nutr* **142**, 271–277.
10. Størdal K, Haugen M, Brantsæter AL, *et al.* (2014) Association between maternal iron supplementation during pregnancy and risk of celiac disease in children. *Clin Gastroenterol Hepatol* **12**, 624–631.e2.
11. Liu E, Lee H-S, Aronsson CA, *et al.* (2014) Risk of pediatric celiac disease according to HLA haplotype and country. *N Engl J Med* **371**, 42–49.
12. Hagopian WA, Lernmark A, Rewers MJ, *et al.* (2006) TEDDY – The Environmental Determinants of Diabetes in the Young: an observational clinical trial. *Ann N Y Acad Sci* **1079**, 320–326.
13. The TEDDY Study Group (2007) The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. *Pediatr Diabetes* **8**, 286–298.
14. Vehik K, Fiske SW, Logan CA, *et al.* (2013) Methods, quality control and specimen management in an international multicentre investigation of type 1 diabetes: TEDDY. *Diabetes Metab Res Rev* **29**, 557–567.
15. Aronsson CA, Lee H-S, Liu E, *et al.* (2015) Age at gluten introduction and risk of celiac disease. *Pediatrics* **135**, 239–245.
16. Moyers S, Richesson R & Krischer J (2008) Trans-atlantic data harmonization in the classification of medicines and dietary supplements: a challenge for epidemiologic study and clinical research. *Int J Med Inform* **77**, 58–67.
17. Lindehammer SR, Bjorck S, Lynch K, *et al.* (2011) Early human pregnancy serum cytokine levels predict autoimmunity in offspring. *Autoimmunity* **44**, 445–452.
18. Kaiser L & Allen LH (2008) Position of the American dietetic association: nutrition and lifestyle for a healthy pregnancy outcome. *J Am Diet Assoc* **108**, 553–561.
19. Amarasekera M, Prescott SL & Palmer DJ (2013) Nutrition in early life, immune-programming and allergies: the role of epigenetics. *Asian Pac J Allergy Immunol* **31**, 175–182.
20. Palmer AC (2011) Nutritionally mediated programming of the developing immune system. *Adv Nutr* **2**, 377–395.
21. Aronsson CA, Vehik K, Yang J, *et al.* (2013) Use of dietary supplements in pregnant women in relation to sociodemographic factors – a report from The Environmental Determinants of Diabetes in the Young (TEDDY) study. *Public Health Nutr* **16**, 1390–1402.
22. National Institute for Health and Welfare, National Nutrition Council (2016) *Eating Together: Food Recommendations for Families with Children. KIDE 28.* Tampere, Finland: Juvenes Print (Suomen Yliopistopaino Oy).
23. Uusitalo U, Lee H-S, Aronsson CA, *et al.* (2015) Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort. *Am J Clin Nutr* **102**, 1216–1221.
24. Brantsæter AL, Haugen M, Hagve TA, *et al.* (2007) Self-reported dietary supplement use is confirmed by biological markers in the Norwegian Mother and Child Cohort Study (MoBa). *Ann Nutr Metab* **51**, 146–154.

British Journal of Nutrition

https://doi.org/10.1017/S0007114517000332