Gluten consumption during late pregnancy and risk of celiac disease in the offspring: the TEDDY birth cohort[1,2]

Ulla Uusitalo,[3] Hye-Seung Lee,[3] Carin Andrén Aronsson,[4] Jimin Yang,[3] Suvi M Virtanen,[5–7] Jill Norris,[8] and Daniel Agardh[4] for The Environmental Determinants of the Diabetes in the Young (TEDDY) study group*

[3]Health Informatics Institute, Department of Pediatrics, Morsani College of Medicine, University of South Florida, Tampa, FL; [4]The Diabetes and Celiac Disease Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; [5]Unit of Nutrition, National Institute for Health and Welfare, Helsinki, Finland, Tampere, Finland, [6]Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland, and [7]Science Center of Pirkanmaa Hospital District, Tampere, Finland; and [8]Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO

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ABSTRACT

Background: Maternal diet during pregnancy has been proposed to increase the risk of autoimmune diseases.

Objective: The objective was to investigate the association between maternal consumption of gluten-containing foods during late pregnancy and subsequent risk of celiac disease in the offspring.

Design: Genetically susceptible children prospectively followed from birth were screened annually for tissue transglutaminase autoantibodies (tTGAs). Children testing persistently positive for tTGAs were further evaluated for celiac disease. Diagnosis of celiac disease was confirmed by intestinal biopsy or was considered likely if the mean tTGA concentration was >100 units in 2 consecutive samples. A questionnaire on the mother's diet in late pregnancy was completed by 3–4.5 mo postpartum. Mothers were divided into 3 groups based on the tertiles of their consumption of gluten-containing foods (servings/d). The association between maternal gluten-containing food consumption and the risk of celiac disease was studied by using a time-to-event analysis.

Results: At the time of analysis, 359 (5%) of the 6546 children developed celiac disease. Compared with the middle category of maternal gluten-containing food consumption (servings/d), low (HR: 0.87; 95% CI: 0.67, 1.13; $P = 0.296$) and high (HR: 0.84; 95% CI: 0.65, 1.09; $P = 0.202$) consumption was not associated with risk of celiac disease in the child after adjustment for country, human leukocyte antigen genotype, family history of celiac disease, maternal education, and sex of the child. Median maternal daily consumption frequency of gluten-containing foods was higher ($P < 0.0001$) in Finland (5.3; IQR: 3.9–6.9), Germany (4.3; IQR: 3.1–5.5), and Sweden (3.7; IQR: 2.8–4.9) than in the United States (3.4; IQR: 2.3–4.9). No significant interaction was found between country of residence and the mothers' consumption of gluten-containing foods in relation to risk of celiac disease.

Conclusion: The frequency of gluten-containing food consumption during late pregnancy is not associated with risk of celiac disease in the offspring. *Am J Clin Nutr* 2015;102:1216–21.

Keywords: celiac disease, gluten, maternal consumption, offspring, pregnancy

INTRODUCTION

Celiac disease is an immune-mediated chronic small bowel disorder caused by permanent intolerance to gluten—a storage protein found in wheat, rye, and barley cereals (1). Celiac disease shares many features of an autoimmune disease, e.g., production of autoreactive T cells and production of tissue transglutaminase autoantibodies (tTGAs)[9] in human leukocyte antigen (HLA)–predisposed individuals carrying the DRB1*03-DQA1*05:01-DQB1*02:01 (e.g., DR3-DQ2) or DRB1*04-DQA1*03-DQB1*03:02 (e.g., DR4-DQ8) haplotypes when exposed to gluten (2). Whereas celiac disease is proposed to be a result of an interaction between genetic factors, infant feeding, and infections (3), it is still unresolved why some but not all genetically predisposed individuals develop celiac disease after being exposed to gluten. Age at first introduction of gluten in relation to breastfeeding has shown conflicting results on the risk of developing celiac disease (4–6), and the search for an optimal time point at which to introduce gluten to children has failed to show a window of opportunity for inducing tolerance (7–9).

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[2] Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail: daniel.agardh@med.lu.se.

[9] Abbreviations used: HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young; tTGA, tissue transglutaminase autoantibody.

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The immune system of the fetus is already being developed during pregnancy to distinguish between exposures of self from non-self-antigens. The newborn is being prepared for colonization by the mother's fecal microbiota at birth under protection of transplacental maternal IgG and in addition by secretory IgA and lactoferrin, which are received postpartum from breast milk (10). The infant will then gradually increase its production of IgG antibodies to reach full levels by 3 y of age (11). It has also been shown that there is an imbalance between T cell–mediated cytokines during pregnancy in mothers giving birth to children developing celiac disease by 3 y of age, which indicates that perinatal events may be important for autoimmunity in the offspring (12). Moreover, it has been suggested that maternal diet during pregnancy may affect the risk of islet autoimmunity during childhood (13–15). There is thus a possibility that maternal antibodies to antigens, such as gluten, might be the first innate immunity transferred already during pregnancy to the unborn child. However, it is not known whether maternal gluten-containing food consumption during pregnancy is related to an increased risk of celiac disease in the offspring.

The TEDDY (The Environmental Determinants of the Diabetes in the Young) study is an international multicenter observational study that is prospectively following children from birth until the age of 15 y in the search of environmental factors involved in both type 1 diabetes (16) and in celiac disease (17). Environmental triggers during pregnancy and early diet, such as duration of breastfeeding and timing of introduction of various complementary foods, are closely monitored. The aim of the current study was to examine the association between maternal intake of gluten-containing foods during pregnancy and the risk of celiac disease in genetically at-risk children. We hypothesized that the risk of celiac disease could be associated with maternal exposure to gluten during the prenatal period.

METHODS

Study population

The TEDDY study is approved by local Ethical Institutional Review Boards and is monitored by an External Advisory Board formed by the NIH. It involves 6 clinical research centers located in Colorado, Georgia, and Washington in the United States and in Finland, Germany, and Sweden, all of which follow the same study protocol. The protocol includes scheduled visits every third month until the age of 4 y and every sixth month thereafter (18). Between September 2004 and February 2010, 424,788 newborns were screened, and 21,589 infants fulfilled the inclusion criteria based on HLA genotyping (**Supplemental Table 1**). A total of 8676 children were enrolled in the follow-up study (**Figure 1**). Of this total, 1964 children had not been tested for tTGAs at the time of analysis, 40 children were HLA ineligible, 120 mothers were consuming a gluten-free diet, and another 6 mothers had reported unrealistic cereal consumption in the food-frequency questionnaire (described below) and were thus excluded from the final sample, which left a total of 6546 children for this study (**Table 1**).

Screening for celiac disease

Annual screening for celiac disease with tTGAs starts at 2 y of age, as previously described (19). Children who tested positive for tTGAs at 2 y had their previous serum samples analyzed to find the timing of seroconversion. Children who were tTGA positive in 2 consecutive samples were defined as having celiac disease autoimmunity. All children with celiac disease autoimmunity were recommended to seek consultation with a pediatric gastroenterologist at the local hospital for further evaluation of celiac disease. To diagnose celiac disease, it was recommended that ≥6 biopsy specimens be collected from different parts of the duodenum, including the bulb. All histological specimens were scored by the local pathologist according to the Marsh classification, and having a Marsh score >1 was compliant with biopsy-proven celiac disease (20). Children who had no intestinal biopsy results but had a mean tTGA concentration of >100 units in 2 consecutive samples were also considered to have celiac disease for the purposes of this study (17).

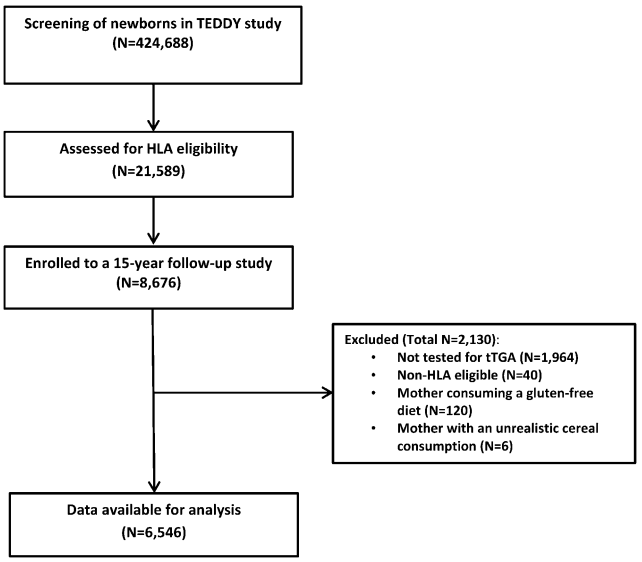

FIGURE 1 Study population. HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young; tTGA, tissue transglutaminase autoantibodies.

Information on maternal characteristics

Information about basic demographic maternal characteristics was derived from the infant screening form. A questionnaire was mailed home to the mothers before the first clinic visit (3–4.5 mo postpartum). This questionnaire contained questions about illnesses, use of medications or dietary supplements, smoking and alcohol consumption, and maternal diet during the last month of pregnancy (in the United States and Sweden) or the eighth month of pregnancy (in Finland and Germany). Information about maternal education was obtained at the 9-mo clinic visit.

Questionnaires on maternal gluten intake

Information on maternal dietary consumption during the eighth or ninth month of pregnancy (depending on country) was collected by using a food-frequency questionnaire (**Supplemental Table 2**). The mother was asked to report how often she ate foods such as cereals, porridge, pastas, and/or bakery products, including all type of breads, sweet and savory pastries, pizza, cookies, and crackers. One portion of each type of food was described in the

TABLE 1
Characteristics of children participating in TEDDY[1]

Child characteristic	*n* (%)
Total	6546
Birth year	
2004–2005	1088 (17)
2006	1135 (17)
2007	1396 (21)
2008	1332 (20)
2009–2010	1595 (25)
Male sex	3352 (51)
FDR with celiac disease	164 (3)
HLA genotype	
DR3/3	1339 (21)
DR3/4	2578 (39)
Others	2629 (40)
Country	
United States	2610 (40)
Finland	1488 (23)
Germany	399 (6)
Sweden	2049 (31)

[1]FDR, first-degree relative; HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young.

questionnaire to help the mother to estimate the consumption frequency per portion; examples of portion sizes are as follows: 1 slice of bread, 2 cookies, and 1 bowl of oatmeal. Consumption frequencies of nongluten-containing foods (i.e., those containing oats, rice, and corn) were asked about separately from the consumption frequencies of foods containing wheat, barley, and rye. All of the gluten-containing food intakes were converted into daily consumption frequencies. Therefore, daily consumption frequencies were used as such, but weekly frequencies were divided by 7 and monthly by 30. Daily consumption frequencies of bread, cookies, savory pastries, sweet pastries, pizza, pasta, and breakfast cereals were summed as mean daily maternal gluten-containing food consumption.

Statistical methods

Fisher's exact test examined the differences in maternal characteristics between countries. Wilcoxon's rank-sum test was used to compare the maternal gluten intake between European countries and the United States. A Cox proportional hazard regression model was used to examine the association between the risk of celiac disease and the maternal gluten consumption frequency during pregnancy. Mothers were divided into 3 equally sized groups based on the tertiles of consumption: low, middle, and high (reference = middle). The time to developing celiac disease autoimmunity was defined as age when the first tTGA-positive blood sample was drawn, and the right-censored time was the age at which the last blood sample was collected for testing of tTGAs. The time to diagnosis of celiac disease was the age of intestinal biopsy, and the right-censored time was the age of the last TEDDY clinic visit at which the participant was confirmed to be free of celiac disease. In children considered to have celiac disease based on high tTGA concentrations, the time of diagnosis was defined as the age at which the first tTGA-positive blood sample was drawn. P values <0.05 were considered to be statistically significant. No multiple testing correction adjustment was considered. All analyses were performed by using SAS software (version 9.4; SAS Institute).

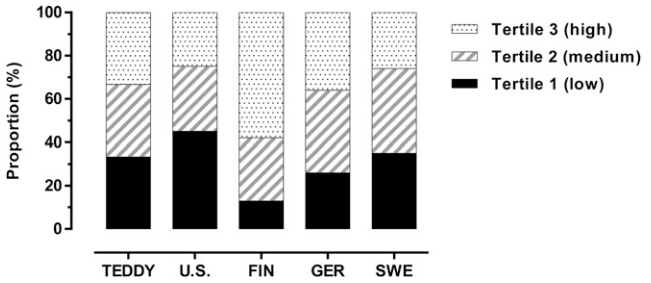

FIGURE 2 Proportion of mothers consuming gluten-containing foods according to tertiles in TEDDY overall and by country: United States (n = 2610), Finland (n = 1488), Germany (n = 399), and Sweden (n = 2049). TEDDY, The Environmental Determinants of Diabetes in the Young.

RESULTS

Maternal consumption of gluten-containing products by country

The median daily maternal consumption frequency of gluten-containing foods (servings/d) during pregnancy was higher ($P < 0.001$) in Finland (5.3; IQR: 3.9–6.9), Germany (4.3; IQR: 3.1–5.5), and Sweden (3.7; IQR: 2.8–4.9) than in the United States (3.35; IQR: 2.28–4.89). The proportions of mothers consuming gluten-containing foods according to tertiles in TEDDY overall and by country are presented in **Figure 2**. Specified per food group, bread was the most consumed gluten-containing source. Finnish mothers had the highest daily bread consumption (**Figure 3**).

Maternal characteristics in relation to the risk of celiac disease autoimmunity and celiac disease in the offspring

The maternal sociodemographic and lifestyle characteristics for TEDDY overall and by each of the participating countries are shown in **Table 2**. The German site had older mothers at delivery (median: 32; IQR: 29–35 y) on average, who more frequently reported smoking (16%) and alcohol use during pregnancy (51%) compared with mothers from the other countries ($P < 0.001$). As previously reported (17), both celiac disease autoimmunity and celiac disease were associated with being female, having celiac disease in the family, having the HLA-DR3 genotype, and being of Swedish residency. After adjustment for all of these factors, mothers who were more educated were also more likely to give birth to a child who later developed celiac disease autoimmunity (HR: 1.33; 95% CI: 1.11, 1.59; $P = 0.002$) or celiac disease (HR: 1.36; 95% CI: 1.01, 1.81; $P = 0.04$) (**Table 3**).

Maternal gluten consumption in relation to known risk factors associated with celiac disease autoimmunity and celiac disease in the offspring

At the time of the study, 1015 of the 6546 (16%) children screened for tTGA had developed celiac disease autoimmunity, and celiac disease was later diagnosed in 359 (5%) of those 6546 children: 345 had biopsy-proven celiac disease and 14 had celiac disease diagnosed based on a mean tTGA concentration >100 units. After adjustment for the child's sex, family history of

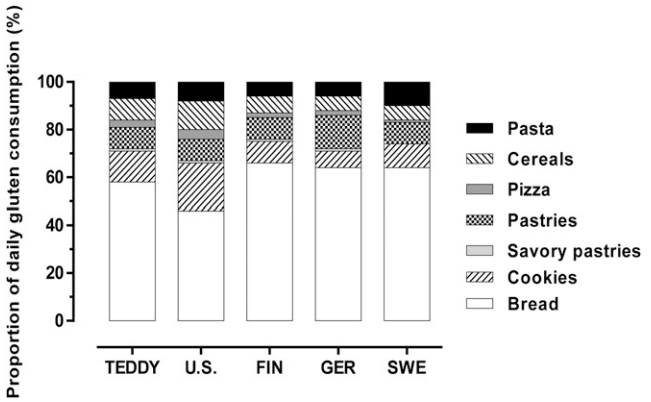

FIGURE 3 Proportion of daily maternal intake of specified gluten-containing foods in TEDDY overall and by country: United States (n = 2610), Finland (n = 1488), Germany (n = 399), and Sweden (n = 2049). TEDDY, The Environmental Determinants of Diabetes in the Young.

celiac disease, HLA genotype, country, and mother's education, maternal consumption frequency of gluten-containing foods during late pregnancy was not associated with risk, neither for celiac disease autoimmunity nor for celiac disease in the offspring (**Table 4**). No significant interaction was found between country of residence and the consumption of gluten-containing foods in relation to celiac disease autoimmunity or for celiac disease. However, a significant interaction between maternal gluten consumption and maternal education was noted for celiac disease autoimmunity (P = 0.028), but not for celiac disease (P = 0.357). Compared to the middle category of consumption, a lower or higher consumption of gluten-containing foods in mothers with a high school education or less showed a trend of increasing the risk of celiac disease autoimmunity in the offspring [lower consumption (HR: 1.50; 95% CI: 0.95, 2.37; P = 0.08); higher consumption (HR: 1.55; 95% CI: 0.98, 2.46; P = 0.06)], whereas mothers with a higher education (more than high school) showed a trend of decreasing risk of autoimmunity in the offspring [lower consumption (HR: 0.84; 95% CI: 0.71, 1.00; P = 0.05); higher consumption (HR: 0.86; 95% CI: 0.72, 1.01; P = 0.06)].

DISCUSSION

In this study, we hypothesized that the risk of celiac disease in the offspring could be associated with maternal exposure to gluten during the prenatal period. Although early-life events have been associated with risk of type 1 diabetes in epidemiologic studies (21, 22) and other prospective studies more specifically have indicated that the maternal diet may modulate the risk of β-cell autoimmunity in offspring (13–15, 23), no study has yet been able to conclude that maternal gluten consumption during pregnancy is related to the development of celiac disease in the child later in life. Apart from the fact that diet might have an immune-modulating effect, we found no indication that the risk of celiac disease during early childhood is influenced by how often mothers consume gluten-containing foods during pregnancy. Whereas we observed differences in the consumption frequencies of gluten-containing foods among pregnant women between the 4 different countries, we found no significant interaction between country and gluten-containing food consumption frequency on the risk of celiac disease. Our findings therefore do not support the avoidance of gluten-containing foods during pregnancy to modify the risk of celiac disease in offspring.

Another observation of unclear significance was the association between maternal sociodemographic and lifestyle characteristics and celiac disease in offspring. In the current study, mothers who were less educated were also less likely to give birth to children developing celiac disease. Previous studies have presented contradicting results. Wingren et al. (21) suggested that a low socioeconomic position was associated with an increased risk of celiac disease in males but not in females, whereas 2 other studies found that lower economic status could protect from celiac disease (24, 25). The results from the 2 latter studies (24, 25) agree with our finding if we regard lower educational level as a proxy for a low economic status. When we adjusted for known risk factors for celiac disease, there was still a weak interaction between maternal gluten consumption and maternal education for celiac disease autoimmunity but not for celiac disease, which suggests that this may be of minor importance for the disease pathogenesis.

TABLE 2
Maternal sociodemographic and lifestyle characteristics of mothers to children participating in TEDDY[1]

Variable	TEDDY (n = 6546)	United States (n = 2610)	Finland (n = 1488)	Germany (n = 399)	Sweden (n = 2049)
Age at delivery, y	31 (27–34)[2]	31 (27–35)	30 (27–33)	32 (29–35)	31 (28–34)
Gluten consumption, servings/d	3.9 (2.7–5.5)	3.4 (2.3–4.9)	5.3 (3.9–6.9)	4.3 (3.1–5.5)	3.7 (2.8–4.9)
Education, n (%)					
>High school	5284 (81)	2235 (86)	1350 (91)	342 (86)	1357 (66)
≤High school	1134 (17)	336 (13)	99 (7)	37 (9)	662 (32)
Missing	128 (2)	39 (1)	39 (2)	20 (5)	30 (2)
Smoking during pregnancy, n (%)					
Yes	712 (11)	215 (8)	192 (13)	63 (16)	242 (12)
No	5828 (89)	2389 (92)	1296 (87)	336 (84)	1807 (88)
Missing	6 (<1)	6 (<1)	0	0	0
Alcohol consumption during pregnancy, n (%)					
Yes	2290 (35)	1046 (40)	457 (31)	203 (51)	584 (29)
No	4253 (65)	1561 (60)	1031 (69)	196 (49)	1465 (71)
Missing	3 (<1)	3 (<1)	0	0	0

[1]TEDDY, The Environmental Determinants of Diabetes in the Young.
[2]Median; IQR in parentheses (all such values).

TABLE 3
HRs and 95% CIs of celiac disease autoimmunity and celiac disease adjusted for child's sex, family history of celiac disease, HLA genotype, and country: Cox proportional hazard regression model[1]

	Celiac disease autoimmunity		Celiac disease	
Risk factor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Maternal age	0.99 (0.99, 1.01)	0.82	0.99 (0.97, 1.02)	0.59
Education				
≤High school	1 (ref)		1 (ref)	
>High school	1.33 (1.11, 1.59)	0.002	1.36 (1.01, 1.81)	0.04
Smoking during pregnancy				
No	1 (ref)		1 (ref)	
Yes	0.85 (0.68, 1.05)	0.12	1.05 (0.74, 1.49)	0.78
Alcohol consumption during pregnancy				
No	1 (ref)		1 (ref)	
Yes	1.12 (0.99, 1.28)	0.08	1.18 (0.95, 1.47)	0.14

[1]United States, n = 2610; Finland, n = 1488; Germany, n = 399; Sweden, n = 2049. HLA, human leukocyte antigen; ref, reference.

Although there are some previous indications that perinatal risk factors may have an effect on the risk of celiac disease (21, 22, 26), many of these epidemiologic studies relied on retrospectively collected data or lacked information before the diagnosis of celiac disease. A major strength of this study was its study design. The data were gathered from one of the largest ongoing prospective birth cohorts to date, including study participants from 6 clinical centers spanning 4 different countries that followed the same study protocol during the same time period. The prospective nature of the study eliminated the possibility of recall bias, because the exposure data were collected before knowledge of outcome status. The study also had limitations. For example, the questionnaire used to collect data on food frequency was not validated and covered only the last month or trimester of pregnancy. It cannot be totally excluded that food intake during the last trimester of pregnancy may have been different from food intake during the first 2 trimesters and thus may have affected the development of the fetus's immune system differently. We also did not study maternal diet during lactation; thus, whether gluten peptides or maternal antibodies to gluten could have been transmitted to the child via breast milk was unknown. Furthermore, we did not take into account those

TABLE 4
HRs and 95% CIs of celiac disease autoimmunity and celiac disease adjusted for child's sex, family history of celiac disease, HLA genotype, country, and maternal education: Cox proportional hazard regression[1]

	Celiac disease autoimmunity			Celiac disease		
Risk factor	*n* (%)	HR (95% CI)	*P* value	*n* (%)	HR (95% CI)	*P* value
Sex						
Male	435 (13)	1 (ref)		133 (4)	1 (ref)	
Female	580 (18)	1.59 (1.40, 1.80)	<0.001	226 (7)	2.02 (1.63, 2.51)	<0.001
Family history of CD						
No	946 (15)	1 (ref)		315(5)	1 (ref)	
Yes	69 (42)	2.23 (1.73, 2.85)	<0.001	44 (27)	3.50 (2.53, 4.84)	<0.001
HLA genotype						
Other	194 (7)	1 (ref)		58 (2)	1 (ref)	
DR3/3	435 (32)	5.49 (4.62, 6.53)	<0.001	184 (14)	6.40 (4.73, 8.66)	<0.001
DR3/4	386 (15)	2.10 (1.76, 2.50)	<0.001	117 (5)	1.98 (1.44, 2.73)	<0.001
Country						
United States	348 (13)	1 (ref)		105 (4)	1 (ref)	
Finland	207 (14)	1.17 (0.97, 1.40)	0.10	58 (4)	0.96 (0.68, 1.34)	0.80
Germany	56 (14)	1.16 (0.87, 1.55)	0.32	14 (4)	1.02 (0.58, 1.79)	0.95
Sweden	404 (20)	1.60 (1.38, 1.86)	<0.001	182 (9)	2.10 (1.63, 2.70)	<0.001
Maternal education						
≤High school	151 (13)	1 (ref)		29 (5)	1 (ref)	
>High school	851 (16)	1.33 (1.11, 1.59)	0.002	297 (6)	1.35 (1.01, 1.81)	0.042
Maternal gluten consumption during pregnancy[2]						
Low	331 (15)	0.92 (0.78, 1.08)	0.28	119 (5)	0.87 (0.67, 1.13)	0.30
Middle	343 (16)	1 (ref)		121 (6)	1 (ref)	
High	341 (16)	0.92 (0.79, 1.08)	0.31	119 (5)	0.84 (0.65, 1.09)	0.20

[1]CD, celiac disease; HLA, human leukocyte antigen; ref, reference.
[2]Cutoffs for categorization: tertile 1 = 3.2 servings per day; tertile 2 = 4.9 servings per day.

mothers who were consuming a gluten-free diet during the study period because of the small number of such mothers. All of these factors could have contributed to the null finding.

The TEDDY study follows children at increased genetic risk of type 1 diabetes and celiac disease. Extensive data from children being collected from all study participants from birth to 15 y of age enables insights on exposures and events before diagnosis of the 2 study outcomes. We previously reported that female sex, a first-degree relative with celiac disease, and the HLA-DR3-DQ2 genotype are established risk factors for celiac disease (17). Age at first introduction to gluten was not an independent risk factor for celiac disease in the TEDDY population (27), which agrees with the findings of other multicenter prospective population studies (7, 8), which is why we did not include this variable in the current analyses. Although we recently found that children carrying the HLA-DPB1*04:01 genotype are protected from celiac disease (28), celiac disease is most likely multifactorial and triggered by co-genetic and environmental factors; however, maternal gluten consumption is likely not one of them.

In conclusion, this study found no indication that consumption frequency of gluten-containing foods during pregnancy is associated with risk of celiac disease in the offspring. Our results therefore do not support the avoidance of gluten-containing foods during pregnancy to modify the risk of celiac disease in offspring.

A list of members of the TEDDY study group is provided in **Supplemental Table 3.**

The authors' responsibilities were as follows—UU, CAA, JY, SMV, JN, and DA: designed the research project conception, developed the overall research plan, and oversaw the study; H-SL: analyzed the data and performed the statistical analysis; UU and DA: wrote the manuscript and had primary responsibility for the final content; and all authors: approved the final version of the manuscript. None of the authors declared a conflict of interest.

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