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Longitudinal Micronutrient Exposure Reveals Country-Specific Associations with Risk of Celiac Disease in Genetically Susceptible Children: The Prospective TEDDY Cohort

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Abstract

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Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI and AI-assisted technologies during the preparation of this work.

Background: The role of nutrient intake in celiac disease pathogenesis is poorly understood.

Objective: To examine whether longitudinal childhood intake of selected vitamins and minerals is associated with celiac disease autoimmunity (CDA, primary outcome) and celiac disease (secondary outcome) in genetically at-risk children.

Methods: A total of 6,520 HLA-conferred at-risk children in the observational TEDDY study were prospectively screened for tissue transglutaminase autoantibodies (tTGA) annually from ages 2 to 13 years. CDA was defined as persistent tTGA positivity in two samples ≥3 months apart. Celiac disease was defined by biopsy-confirmed Marsh score ≥2 or mean tTGA ≥100 U/mL in two consecutive samples. Micronutrient intake was assessed via repeated 3-day food records, and adjusted hazard ratios (HRs) were estimated using time-dependent Cox proportional hazards and Bayesian joint models.

Results: Out of 6,520 children, 1,268 (19%) developed CDA and 479 (7.8%) were diagnosed with celiac disease. Results from both models suggested heterogeneity in associations by country as nutrients such as folate showing sporadic associations in the same or opposite direction across ages. Higher vitamin D intake (every 5 μg/1000 kcal) at multiple ages was associated with increased risk of CDA and celiac disease in Sweden, with the strongest at age 5 years for CDA (HR: 1.23, 95%CI: 1.11, 1.37; $p<0.001$) and at age 4 years for celiac disease (HR: 1.20, 95%CI: 1.03, 1.40; $p=0.021$). Higher iron intake (every 5 mg/1000 kcal) was also associated with increased risks of CDA and celiac disease in Sweden, with the highest observed up to age 5 years (HR: 1.70, 95%CI: 1.39, 2.08; $p<0.001$ for CDA and HR:1.80, 95%CI: 1.37, 2.36; $p<0.001$ for celiac disease).

Conclusions: Modest country-specific associations were found between childhood micronutrient intake with the risk of CDA and celiac disease, potentially reflecting influence from regional dietary practices, fortification policies, and host factors in disease pathogenesis.

Keywords

celiac disease; children; vitamin D; iron; supplement; nutrient intake

Introduction

Celiac disease is a systemic autoimmune disorder with a multifactorial etiology involving complex interactions between genetic and environmental factors. Although genetics play a strong role on disease risk, most individuals carrying the HLA-DQ2.5, DQ2.2, or DQ8 risk-genotypes do not develop tissue transglutaminase autoantibodies (tTGA) associated with celiac disease (1).

The Environmental Determinants of Diabetes in the Young (TEDDY) study, one of the largest prospective birth cohorts on celiac disease, has shown that the incidence of tTGA seroconversion and celiac disease peaks before age five (2). Diet in early childhood has been linked to celiac disease development in prospective cohorts, with higher gluten intake (3–5) and lower dietary fiber intake (6) suggesting an increase risk. Data also shows that the associations with celiac disease depend on overall dietary intake in the first few years of life without evidence on whether nutrients may be the driving factors (7–9). Maternal

iron supplementation during pregnancy was not associated with celiac disease in TEDDY (10), but increased risk was reported in the Norwegian Mother, Father and Child Cohort (MoBa) after adjusting for the child's iron intake (11). Findings regarding vitamin D remain inconsistent(12). While the role of gluten is well established, these data highlight the need to investigate whether other early micronutrient exposures contribute to celiac disease pathogenesis. Despite extensive research on micronutrient deficiencies in diagnosed patients, evidence on their role in disease development remains limited and conflicting (12). Moreover, few investigations have explicitly examined whether micronutrient-disease associations prior to diagnosis vary across countries with different culinary cultures, feeding practices, and food manufacturing and fortification policies that may substantially influence nutrient intake levels and bioavailability.

The aim of this study is to examine if the intakes of selected micronutrients during childhood are associated with the risk of developing persistent tTGA, i.e. celiac disease autoimmunity (CDA, primary outcome) and a celiac disease diagnosis confirmed within five years of seroconversion (secondary outcome) independently from other reported risk factors using harmonized dietary data collected and processed with a consistent protocol across TEDDY countries. We hypothesized that intake level of individual nutrients would not be independently associated with the risk of CDA or celiac disease after accounting for known risk factors including gluten intake.

Methods

Study population

TEDDY study is a multinational prospective birth cohort designed to investigate the etiology of type 1 diabetes and celiac disease in children carrying HLA genotypes associated with increased disease risk. Recruitment took place between 2004 and 2010 in the United States (Colorado, Georgia/Florida, Washington) and Europe (Finland, Germany, Sweden)(13, 14). As of April 30, 2023, 7,008 out of 8,676 enrolled children had been screened at least once for celiac disease using tTGA. Written informed consent was obtained from parents or legal guardians for both genetic screening and prospective follow-up. The study was approved by local Institutional Review Boards or Ethics Committees and is overseen by an NIH-appointed External Evaluation Committee. A detailed description of the study design and methodology has been published previously (13, 14).

Screening for celiac disease

Screening for celiac disease were performed with annual measurement of tTGA from age 2 years using radioligand binding assays (15). Both IgA-tTG and IgG-tTG were measured to prevent negligence of IgA-deficient case. For those who tested positive at the 2-year visit, earlier serum samples were analyzed retrospectively to determine the time of seroconversion. Such children also had second serum sample collected after 3 months and before the children reached 3 years of age as well as after 6 months from their 4-year birthday. Children were classified as having CDA if they tested tTGA positive in two consecutive serum samples collected at least three months apart. Children with confirmed CDA were referred to their local health care provider for clinical follow-up. Our

recommendation was to perform intestinal biopsy if tTG levels >30 AU or if presenting symptoms associated with celiac disease regardless of tTGA level. However, the decision whether to perform biopsy or not was outside the TEDDY study protocol. Intestinal biopsies were evaluated locally, and biopsy-proven celiac disease was defined as a Marsh score ≥2 (1). For children who did not undergo biopsy, celiac disease was defined as a mean tTGA level ≥100 AU in two consecutive samples (1). The primary outcome was the development of CDA, with celiac disease diagnosis within five years of CDA confirmation assessed as a secondary outcome.

Nutrient intake assessment

Nutrient intakes from foods, beverages, and dietary supplements were estimated using harmonized, country-specific food composition databases (FCDBs) (16), based on dietary data collected using 3-day food records (two weekdays and one weekend day) at 6, 9, and 12 months of age and semi-annually up to age 13 years(17). Families received standardized instructions, food portion size booklets, and a household measuring cup from trained TEDDY dietitians and nutritionists to ensure consistency in record completion. Continuously updated food product brochures and list of dietary supplements available helped in identification of foods and supplements in research centers. Materials were available in participant's local languages (English, Spanish, Finnish, and Swedish). Dietitians and nutritionists reviewed records for completeness, contacted families to clarify ambiguity and confirm plausibility, and exchanged best practice strategies on data quality control and harmonization during monthly calls and semi-annual in-person meetings. Daily nutrient and energy intakes were averaged across all recorded days within a year to calculate age-specific mean intake for each participant. Data on copper and vitamin K intake were unavailable in the Swedish FCDB, and selenium values were available only in the Swedish and U.S. FCDBs. Folate intake was analyzed separately by country due to methodological differences in estimation across FCDBs. Human milk intake was estimated using an Institute of Medicine algorithm (18). Estimated energy requirements were calculated based on age and weight, and the difference between estimated requirement and recorded energy intake from food and infant formula was attributed to human milk. Human milk quantity (g) was then estimated using energy density conversion factors provided in country-specific FCDBs: 65.3 kcal/100 g (Finland), 68 kcal/100 g (Sweden), and 70 kcal/100 g (U.S.).

Statistical methods

All nutrient intake variables were adjusted for total energy intake (per 1000 kcal). Extreme intake values were identified within country and age strata using the interquartile range method with a scale factor (k=3) where the identified potential outliers were replaced with group-specific medians(19). Nutrient intakes (exposure of interest) were analyzed longitudinally up to 1, 2, 3, 4, 5, and 13 years of age, with outcome status recorded within the first 13 years of follow-up or censored earlier at the time of seroconversion in cases with CDA. Missing observations were regarded as missing at random.

Time-dependent multivariable Cox proportional hazards models and Bayesian joint models were used as main analyses to examine associations between longitudinal nutrient intake and risk of CDA and celiac disease. In the Cox models, the counting process approach (20, 21)

was used to define time-varying risk sets, with censoring at tTGA seroconversion. Adjusted hazard ratios (HRs) were calculated for every 1-unit increase in energy-adjusted nutrient intake for vitamin B6, B12, vitamin C, copper, and selenium and for every 5-unit increase in energy-adjusted nutrient intake for the other nutrients to clearly present the point estimates and 95% confidence intervals (95% CI). The proportional hazards (PH) assumption for the Cox models was evaluated using the Schoenfeld residuals test to assess whether the HRs are constant over time. For continuous variables that violated the PH assumption, we modeled them as time-varying coefficients by including interactions with the logarithm of time. If categorical variables violated the PH assumption, stratified analysis was conducted for those Cox models.

Nutrient intakes up to 13 years of age were also analyzed with Bayesian joint models for longitudinal and time-to-event data in order to estimate associations between intake trajectories and time to CDA or celiac disease. Longitudinal intake was modeled using linear mixed-effects models with random intercepts and slopes, with country-by-nutrient interaction terms. Survival submodels specified proportional hazards linked to the current underlying value of each nutrient trajectory. Results are presented as hazard ratios per 1 SD increase with 95% credible intervals (CrIs).

Both Cox proportional hazards model and Bayesian joint model were adjusted for published TEDDY risk factors, including country, HLA genotype, sex, family history of celiac disease, season of birth, total energy intake, gluten intake, and dietary fiber. Participants in Germany were excluded from all analyses due to non-comparable fiber data. Additional covariate adjustments were made in both models for vitamin D models (total fat intake) and iron models (total milk, total fat, and vitamin C intake) to account for factors that may influence nutrient absorption.

Sensitivity and robust analyses included using time-dependent Cox models with restricted cubic splines to evaluate non-linear associations and assessing country-by-nutrient interactions to determine whether associations varied by country due to the large geographical differences and possible different diet patterns among subjects from different continents. Separate stratification analysis was conducted to compare HRs by HLA genotype within country strata. Cox models were repeated by censoring both exposure and outcome at 4 and 5 years of age to assess the robustness of findings during early life due to the observed early peak of incidence of CDA and celiac disease during this period (Supplementary Figure 1). To address potential reverse causation from anemia-related iron supplementation, an additional sensitivity analysis excluded four children diagnosed with anemia before or shortly after CDA onset.

The nutrients were selected a priori based on biological and clinical evidence, and the primary hypothesis of association between intakes and CDA/CD risk was pre-specified, making these analyses confirmatory rather than exploratory. The different follow-up windows were used to assess the temporal robustness of the same hypothesis, while country interactions were examined to evaluate potential effect modification. In line with recommendations for pre-specified, biologically motivated hypotheses, we did not apply formal multiple-testing corrections.

Statistical analyses were conducted using SAS/STAT version 9.4 (SAS Institute Inc.), Stata version 19 (StataCorp), and R version 4.5.2 (R Core Team, 2025). Bayesian joint models were fitted using Markov chain Monte Carlo methods as implemented in the JMbayes2 package (22), with 10 000 iterations, a burn-in of 1 000, and a thinning interval of 5.

Results

A total of 6,520 children with a median follow-up of 12.96 years (IQR: 4.97 – 13.0) were included in the analysis (Table 1 and Supplementary Figure 2). Persistent confirmed CDA was identified in 1,268 children (19.4%) at a median age of 3.6 years (IQR: 2.3–5.6). Of those with CDA, 479 children (37.8%) were diagnosed with celiac disease within five years of developing CDA, with a median age at diagnosis of 3.3 years (IQR: 2.1–5.2). Longitudinal energy-adjusted daily intakes of the analyzed micronutrients (total intake from foods and supplements) are shown in Supplementary Figure 3. Total vitamin D intake was the highest in Sweden before 2 years of age, and in Finland thereafter. Total folate and iron intake in the U.S. stayed the highest at multiple ages.

Micronutrient intakes and risk of CDA and celiac disease

Higher longitudinal intake of total vitamin D up to age 2 years was associated with an increased risk of both CDA and celiac disease, with HR: 1.09, 95% CI: 1.02, 1.17, p=0.015 for CDA and HR: 1.11, 95% CI: 1.01, 1.23, p=0.039 for celiac disease per 5-unit increase, respectively. The associations persisted through later ages (Figure 1). Higher total intake of iron overtime was associated with an increased risk of CDA (HR: 1.12, 95% CI: 1.01, 1.25, p=0.031 per 5-unit increase) and celiac disease (HR: 1.23, 95% CI: 1.05, 1.43, p=0.009 per 5-unit increase) starting from age 3 years (Figure 2). Bayesian joint model results also suggested heterogeneity in associations by country (Table 2). Longitudinal intakes of other micronutrients were not associated with CDA or celiac disease. Some micronutrients had sporadic associations between their intakes and the risk of CDA and celiac disease. Intake of vitamin E up to ages 4, 5, and 13 years was associated with increased risk of CDA, whereas intake of vitamin K up to 2 years showed an inverse association with celiac disease (HR: 0.93, 95% CI: 0.88, 0.96, p=0.005) (Supplementary Figure 4A). Intake of copper up to age 2 years was associated with an increased risk of CDA (Supplementary Figure 4C). Intake of selenium was associated with a reduced risk of CDA up to 3 and 4 years and associated with reduced risk of celiac disease at 4 years (Supplementary Figure 4C). Intake of folate up to the first year in life was associated with increased risk of celiac disease in the U.S. (HR: 1.01, 95% CI: 1.00–1.03, p=0.042) (Supplementary Figure 4D).

Findings from sensitivity and robustness analysis

When analyzing vitamin D and iron intake from food alone, results were in the same direction as in the main analysis and showed associations from age 3 years and onwards with an increased risk of CDA and celiac disease (Figure 2 and Figure 3). Separate stratified analysis by HLA genotype also showed significant associations with total vitamin D and total iron intakes in the same direction and in similar strength as indicated by p values in the absence of interactions with HLA (data not shown). Interactions were observed between countries and total vitamin D intake and celiac disease risk up to age 3 (p =0.031), age 4

(p=0.005), and age 5 (p=0.009) years. Similar patterns of interaction were observed between longitudinal iron intake and country beginning at age 2 (p=0.041) and increased by age 5 (p<0.001). Subgroup analyses by country of residence revealed that higher vitamin D intake was associated with increased risk of CDA among Swedish participants (Figure 3). Total iron intake in Swedish children was also associated with significantly increased risk of both outcomes (Figure 4). The associations between iron intake and the risk of CDA and celiac disease were almost identical when 4 children with anemia diagnosis were removed from the analysis (Supplementary Figure 5).

Plots from the Cox models based on splines modeling showed that the hazard of CDA and celiac disease had no major non-linear patterns (Figure 5). Nutrient by country interaction figures for iron and vitamin D are presented in Figure 5 (panels A1, B1, C1, and D1).

Results from the sensitivity analysis with both exposure and outcome censored at 4 years and again at 5 years of age were similar in direction of association to the main results for vitamin D and iron intake (Supplementary Figures 6 and 7) and other micronutrients (Supplementary Figures 8 to 11).

Discussion

This prospective analysis from the TEDDY cohort indicates that, overall, the intake of most micronutrients during childhood were not consistently associated with the risk of CDA or subsequent celiac disease within five years of seroconversion. Sporadic associations were observed for vitamins A, C, E, K, B6, B9, B12, copper, and selenium, as confirmed in sensitivity analyses. In contrast, significant associations between higher intakes of vitamin D and iron and increased risks of CDA and celiac disease persisted over multiple age points than the other nutrients, but only in children from Sweden and to a relatively modest extent.

The association between higher vitamin D intake and increased risk of CDA and celiac disease aligns partially with a previous finding of a bell-shaped relationship between 25(OH)D concentrations and CDA risk(23), namely an increased risk was associated with concentrations < 30 nmol/L and > 75 nmol/L compared to 50–75 nmol/L. Mechanistically, excess vitamin D may promote Th2-skewed immune responses(24), and prior case-control work has linked prolonged supplementation in infancy to elevated celiac disease risk(25). TEDDY data showed 67.5% of the participants in the U.S. and 99–100% of the participants in Finland and Sweden were given vitamin D supplements in the first year of life, indicating adherence to national recommendations in the respective countries (26). Interestingly, parents of TEDDY children rarely considered vitamin D supplementation an explicit intent to prevent type 1 diabetes (27). Half of the US vitamin D users lasted longer than a year in comparison to 88.6% of Swedish users (26), and less than 20% of children continued using vitamin D supplements across TEDDY countries after age 6 (unpublished data). Aside from supplements, vitamin D-fortified foods are available in TEDDY countries (28). In Sweden, vitamin D fortification is mandatory milk and fat spreads such as margarine (29). Gruel, a milk cereal drink (a type of follow-on formula composed of skimmed milk powder and flour from different grains) commonly consumed by young Swedish children, is fortified with 0.12–2.0 mcg vitamin D per 100 g across brands regardless of gluten content (per

conversation with Swedish dietitians). Swedish children consumed, on average, 200–410 g/d gruel (0.24 – 8.2 mcg vitamin D) between 6 and 24 months of age per TEDDY food records (30). In Finland, main sources of vitamin D are infant formulas, fortified gruels, and supplements during infancy and fortified milk and supplements for older children (28). Food sources of vitamin D for U.S. children include infant formulas mandated to contain 1–2.5 mcg/100 kcal vitamin D (31) and fortified milk with a targeted final concentration of 10 mcg per quart (1 qt=946.4 mL, approximately 1.02 mcg per 100 g) (32). The potential variations in product formulations and dosage could influence bioavailability of supplemental vitamin D (e.g., ergocalciferol compared with cholecalciferol) and its health effects (31), and the aforementioned varying durations of supplementation may have also contributed to the observed country-nutrient interactions. Given TEDDY participants are genetically at risk for celiac disease and/or type 1 diabetes, the observed association with vitamin D in Sweden cannot be generalized to warrant reconsideration of current vitamin D supplementation recommendation for children (31, 33, 34).

The significant association between iron intake and celiac disease risk echoes a finding from the MoBa study that iron supplement use at 18 months of age was associated with an elevated risk of celiac disease (11). Iron intake in childhood also showed a non-linear relationship with islet autoimmunity in TEDDY (35). In Finland, dietary iron mainly comes from grain and meat products, as well as infant formulas (36, 37). Iron-fortified gluten-containing and gluten-free gruel and porridges are major source of iron for children in Sweden besides meat product (38). Ferrous fumarate is commonly used in Sweden as the fortification compound, while ferrous sulfate is commonly used in Finland and the U.S (per conversations with TEDDY dietitians). The former compound is considered more bioavailable due to its higher percentage of elemental iron than the latter (33% as opposed to 20%), which might affect undesirably the chance of having excessive iron intake or experiencing gastrointestinal side effects. Unfortunately, the amount of heme and non-heme iron in diet cannot be differentiated in the TEDDY FCDBs. Iron supplements were indeed used by less than 5% of TEDDY children between 6 months and 10 years of age in all countries and contributed an average of 6 mg/d or less iron to supplement users (unpublished data). Earlier experimental data showed that iron supplementation in non-anemic infants altered growth trajectories and increased gastrointestinal symptoms(39, 40), and iron overload may induce oxidative stress and changes in gut microbiota that favor pathogenic over commensal strains and may influence immune development(41–43). It is challenging in TEDDY to distinguish the impact of iron from food and from supplements on intestinal health due to the lack of biomarkers related to iron status and intestinal barrier integrity.

Key strengths of this study include the use of repeated, prospective dietary assessments conducted under a standardized protocol, allowing for characterization of nutrient intake trajectories from infancy onward. This design enabled evaluation of nutritional exposures prior to CDA or celiac disease onset, during a time when parents were unaware of their child’s serologic status. Results from the Bayesian joint model indicated the associations were mainly driven by current underlying intake levels with minimal impact from slopes of intake, which suggests cumulative intake during critical developmental windows is more relevant than rapid fluctuations. Data collected prospectively also allowed us to examine

potential reverse causality related to altered iron intake in response to the diagnosis of celiac disease or pre-diagnosis gastrointestinal symptoms. The consistent directions of associations shown across analytic models reinforces that the observed associations were unlikely due to methodological artifacts, as intake estimates were harmonized across countries and adjusted for seasonality and the amount of gluten exposure(3, 4). The time-varying Cox proportional hazards model with robust sandwich variance estimators clustered at the subject level provide robustness to the strength of the association by recomputing the standard errors for within-subject correlation induced by repeated measurements of time-varying covariates. These estimators affect inference through the variance–covariance matrix without altering the regression coefficients. Intra-individual variation was accounted for in the Bayersian joint model, which added robustness to the results.

In conclusion, there were overall no associations between self-reported childhood intake of fat-soluble vitamins, vitamins B6, B9, and B12, copper, or selenium and the risk of CDA and celiac disease. Longitudinal higher intakes of vitamin D and iron were associated with a modestly increased risk of CDA and celiac disease only among Swedish children, starting from 3 years of age (including the ages of peak incidence) and independent of gluten intake. These findings are worth considering, as fortified foods in Sweden and Finland may contribute to higher intakes of vitamin D, iron, and other nutrients. Nevertheless, the absence of circulating biomarker data that indicate bioavailable amount of nutrients (e.g., ferritin level) and factors such as random variation, limited exposure windows, or insufficient power at specific ages call for caution in interpreting the results. Individual variabilities in physiology, metabolic efficiency, and sun exposure could potentially introduce misclassification, and the observed small changes in risk may be confounded by uncaptured but correlated exposures in this observational cohort. Further investigations, including mechanistic studies and well-designed clinical trials integrating intake, biomarker, and multi-omics data, are needed to clarify whether elevated vitamin D and iron exposure plays a role in celiac disease pathogenesis, and should be validated in other populations before any implications for dietary recommendations can be drawn.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability

Data from The Environmental Determinants of Diabetes in the Young (https://doi.org/10.58020/y3jk-x087) reported here will be made available for request at the NIDDK Central Repository (NIDDK-CR) website, Resources for Research (R4R), https://repository.niddk.nih.gov/.

Abbreviations:

CDA	celiac disease autoimmunity
CI	confidence interva
Crl	95% credible interval
FCDB	food composition database
HLA	human leukocyte antigens
HR	hazard ratio
MoBa	Norwegian Mother, Father and Child Cohort

PH	proportional hazards
TEDDY	The Environmental Determinants of Diabetes in the Young (TEDDY) study
tTGA	tissue transglutaminase autoantibodies.

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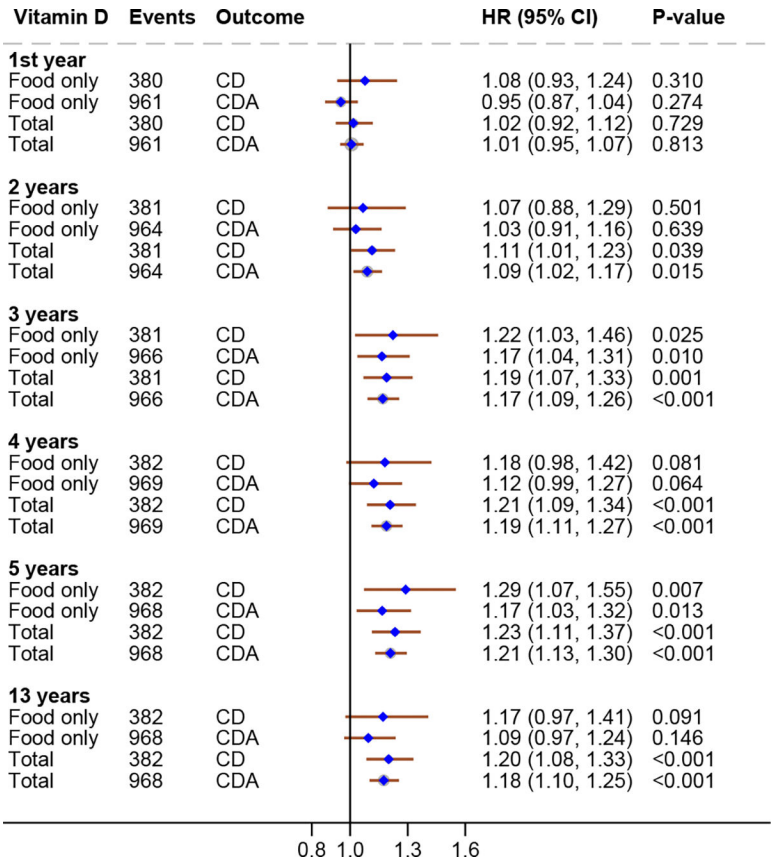


Figure 1.

Associations between longitudinal vitamin D intake (from foods and total intake from foods and supplements) from 6-months of age to various ages and the risk of celiac disease autoimmunity (CDA) and celiac disease (CD). Cox proportional hazard ratios (HRs) reflect the association per 5 mcg/1000 kcal adjusted for country, HLA genotype, sex, family history of celiac disease, season of birth, and intake of energy, gluten, dietary fiber, and total fat.

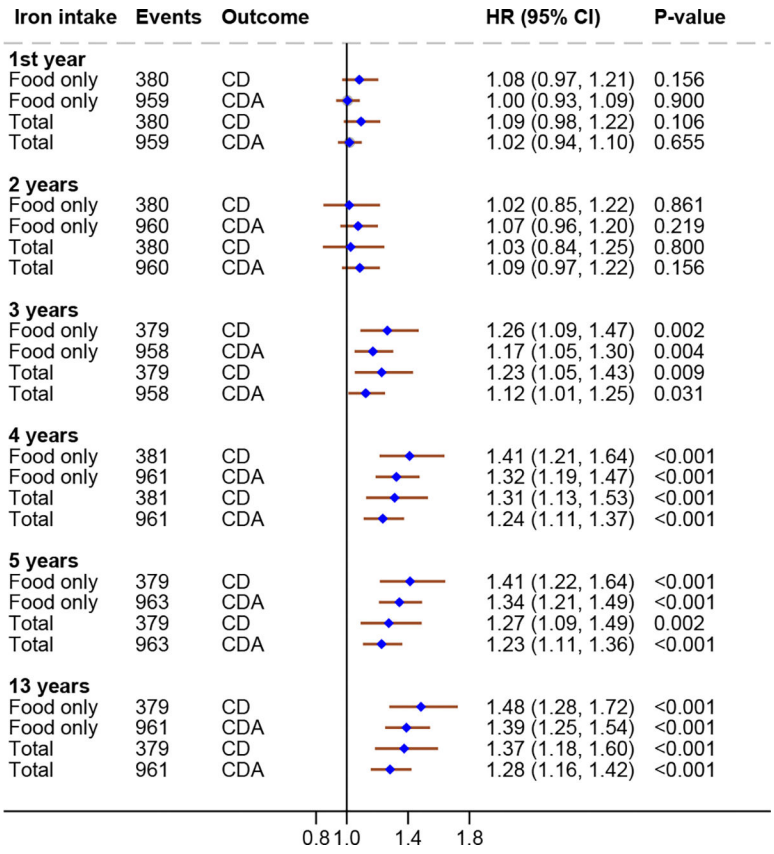


Figure 2.

Associations between longitudinal iron intake (from foods and total intake from foods and supplements) from 6-months of age to various ages and the risk of celiac disease autoimmunity (CDA) and celiac disease (CD). Cox proportional hazard ratios (HRs) reflect the association per 5 mg/1000 kcal adjusted for country, HLA genotype, sex, family history of celiac disease, season of birth, and intake of energy, gluten, dietary fiber, total fat, vitamin C, and total fat.

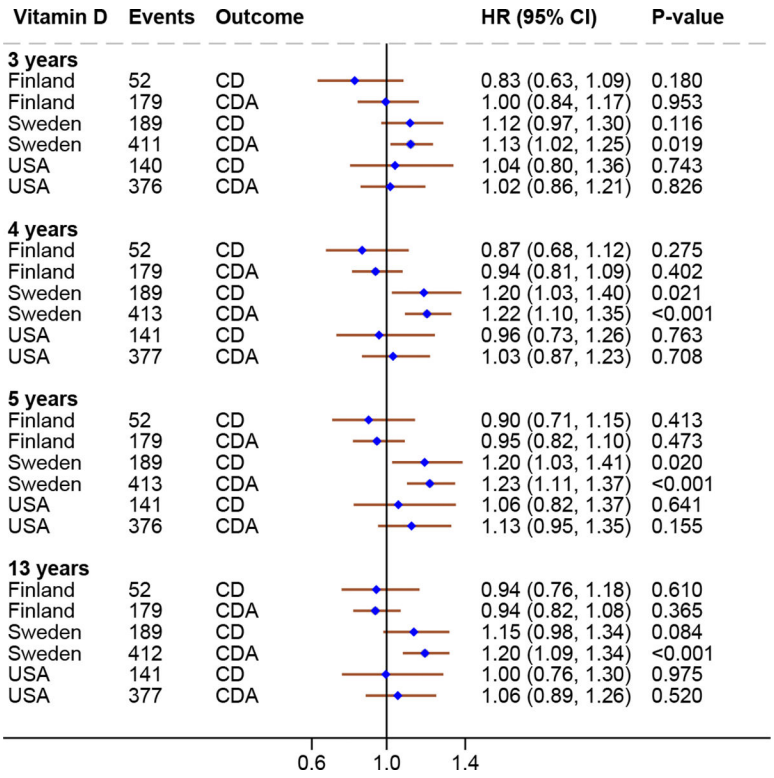


Figure 3.

Associations between longitudinal total vitamin D intake (from foods and supplements) from 6-months of age to various ages and the risk of celiac disease autoimmunity (CDA) and celiac disease (CD) by country. Cox proportional hazard ratios (HRs) reflect the association per 5 mcg/1000 kcal adjusted for country, HLA genotype, sex, family history of celiac disease, season of birth, and intake of energy, gluten, dietary fiber, and total fat.

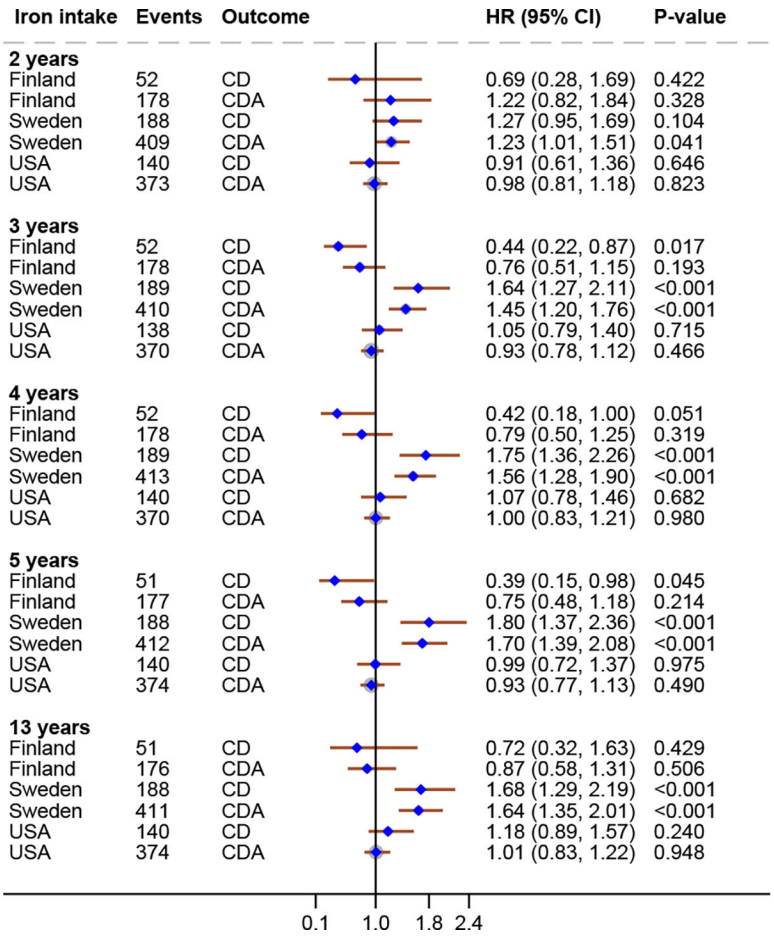
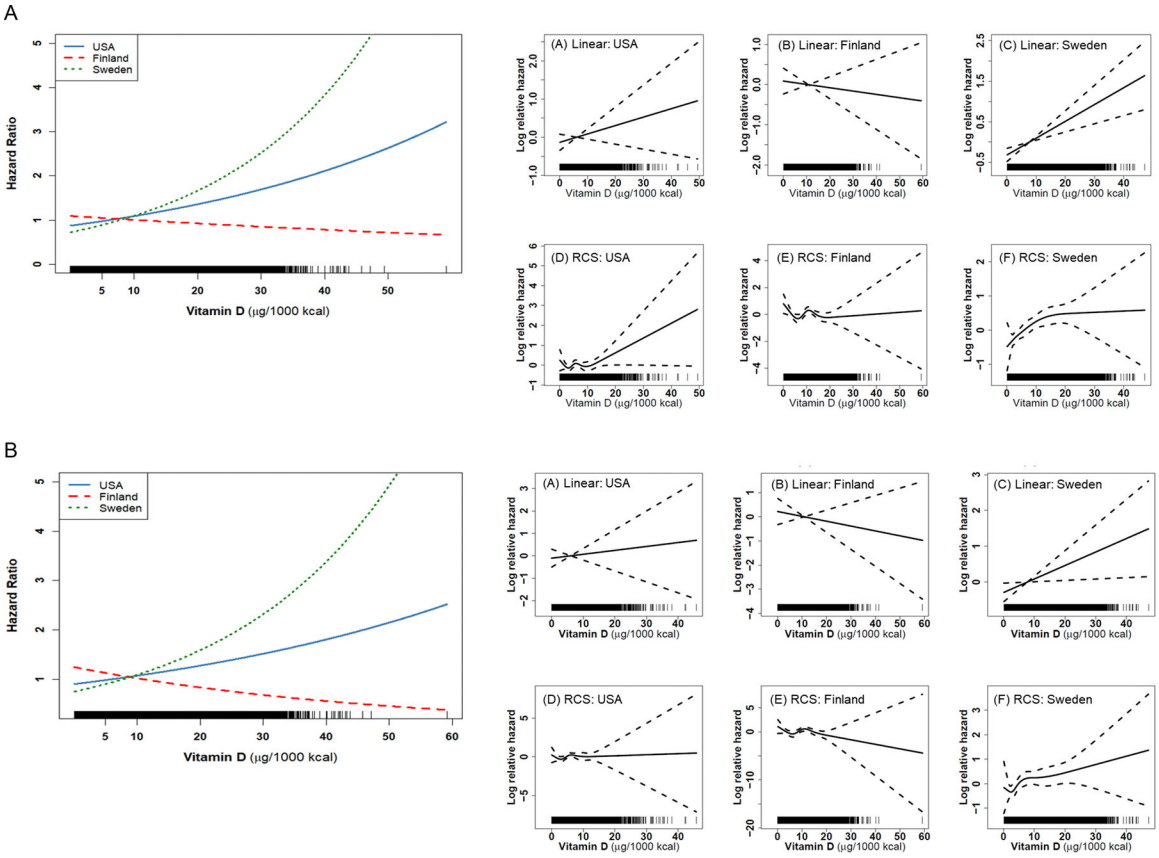


Figure 4.

Associations between longitudinal total iron intake (from foods and supplements) from 6-months of age to various age points and the risk of celiac disease autoimmunity (CDA) and celiac disease (CD) by country. Cox proportional hazard ratios (HRs) reflect the association per 5 mg/1000 kcal adjusted for country, HLA genotype, sex, family history of celiac disease, season of birth, and intake of energy, gluten, dietary fiber, total fat, vitamin C, and total fat.



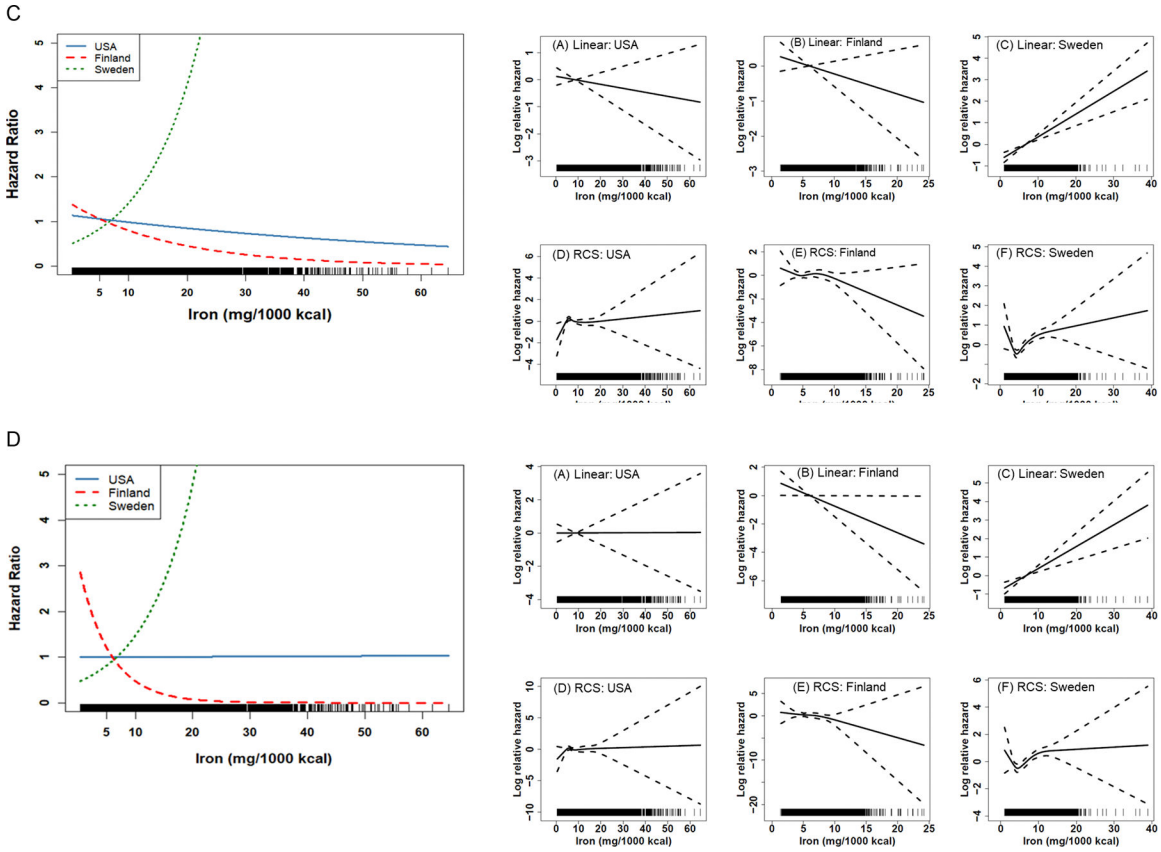


Figure 5.

Linear and restricted cubic spline (RCS) models depicting the risk of developing celiac disease autoimmunity (CDA) or celiac disease and total intake of vitamin D or iron by country. [A] vitamin D intake and risk of CDA, [B] vitamin D intake and risk of celiac disease, [C] iron intake and risk of CDA, and [D] iron intake and risk of celiac disease.

Table 1.

Characteristics of TEDDY[1] participants assessed for the risk of celiac disease autoimmunity (CDA) and celiac disease.

Variable	Subjects included in the analysis (%)	Subjects who developed CDA (%)	Subjects who developed celiac disease within 5 years of CDA (%)
Total	6520 (100%)	1268 (100%)	479 (100%)
Finland	1584 (24%)	280 (22%)	85 (18%)
Sweden	2127 (33%)	495 (39%)	224 (47%)
USA	2809 (43%)	493 (39%)	170 (35%)
HLA[2]			
HLA-DRDQ32/DR9	2561 (39%)	499 (39%)	161 (34%)
HLA-DRDQ32/32	1370 (21%)	514 (41%)	236 (49%)
Others	2589 (40%)	255 (20%)	82 (17%)
Sex			
Male	3321 (51%)	544 (43%)	185 (39%)
Female	3199 (49%)	724 (57%)	294 (61%
Celiac FDR[3]			
No	6409 (98%)	1226 (97%)	457 (95%)
Yes	111 (2%)	42 (3%	22 (5%)
Summer birth			
Yes	3262 (50%)	657 (52%)	272 (57%)
No	3258 (50%)	611 (48%)	207 (43%)

[1]TEDDY, the Environmental Determinants of Diabetes in the Young.

[2]HLA, human leukocyte antigen.

[3]Celiac FDR, celiac disease first-degree relative.

Table 2.

Hazard ratios (HRs) and 95% credible intervals (CrIs) from Bayesian joint models for celiac disease autoimmunity and celiac disease per 1-SD increase in total vitamin D and iron intake. HRs reflect the association per 5 mg/1000 kcal adjusted for country, HLA genotype, sex, family history of celiac disease, season of birth, and intake of energy, gluten, and dietary fiber.

		Celiac Disease Autoimmunity		Celiac Disease	
Nutrient	**Country**	**Rhat[1]**	**HR (95% CrI) per SD**	**Rhat**	**HR (95% CrI) per SD**
Vitamin D[2]	USA	1.09	0.54 (0.37, 0.80)	1.04	0.67 (0.35, 1.16)
Vitamin D	Finland	1.02	1.83 (1.06, 3.27)	1.03	1.53 (0.59, 4.06)
Vitamin D	Sweden	1.09	3.42 (2.28, 4.99)	1.03	3.03 (1.70, 5.65)
Iron[3]	USA	1.02	0.97 (0.79, 1.20)	1.01	0.87 (0.61, 1.21)
Iron	Finland	1.02	1.38 (0.80, 2.23)	1.01	2.01 (0.81, 4.54)
Iron	Sweden	1.02	2.99 (2.30, 3.93)	1.01	3.65 (2.36, 5.66)

[1] Rhat($\widehat{R}$, Gelman–Rubin diagnostic) was used to assess convergence of the Markov chain Monte Carlo chains to the target posterior distribution; values close to 1 indicate adequate mixing and convergence.

[2] Model was also adjusted for daily intake of total fat (g/day).

[3] Model was also adjusted for daily intake of total fat (g/day), total milk (g/day), and vitamin C (mg/day).