# Interaction Between Dietary Iron Intake and Genetically Determined Iron Overload: Risk of Islet Autoimmunity and Progression to Type 1 Diabetes in the TEDDY Study

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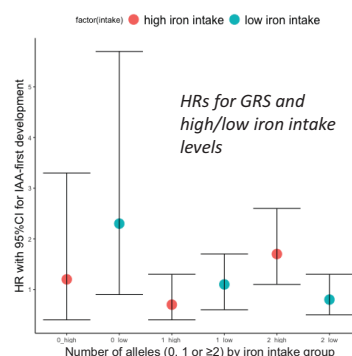
Iron intake plus genetically determined iron overload and risk of islet autoimmunity
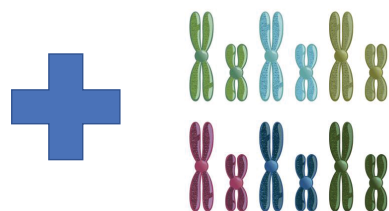
Genetic Risk Score (GRS): Number of alleles involved in iron metabolism leading to increased iron in the circulation and transferrin saturation e.g. TMPRSS6 (rs855791-G allele)

HRs for GRS and high/low iron intake levels

Iron intake sources

There is indication of nonlinear relation between iron intake and GAD antibody as first autoantibody and type 1 diabetes progression. In subjects with a GRS≥2 iron risk alleles, high iron intake was associated with increased risk of islet autoimmunity with insulin as first autoantibody (adjusted hazard ratio [HR] 1.71 [95% CI 1.14; 2.58]) compared with moderate iron intake.

ARTICLE HIGHLIGHTS

- A nonlinear relationship was found between GAD antibody first and progression to type 1 diabetes.
- Having a minimum of two risk alleles associated with increased plasma iron together with high iron intake increases the risk of insulin autoantibody development.
- Together with high iron intake, genetic variation in the key cellular iron transporter ferroportin showed a stepwise increase in risk of progression to type 1 diabetes.

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OBJECTIVE

To examine whether iron intake and genetically determined iron overload interact in predisposing to the development of childhood islet autoimmunity (IA) and type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

In The Environmental Determinants of Diabetes in the Young (TEDDY) study, 7,770 genetically high-risk children were followed from birth until the development of IA and progression to T1D. Exposures included energy-adjusted iron intake in the first 3 years of life and a genetic risk score (GRS) for increased circulating iron.

RESULTS

We found a U-shaped association between iron intake and risk of GAD antibody as the first autoantibody. In children with GRS ≥2 iron risk alleles, high iron intake was associated with an increased risk of IA, with insulin as first autoantibody (adjusted hazard ratio 1.71 [95% CI 1.14; 2.58]) compared with moderate iron intake.

CONCLUSIONS

Iron intake may alter the risk of IA in children with high-risk HLA haplogenotypes.

Childhood type 1 diabetes (T1D) is a chronic multifactorial immune-mediated disease with an increasing incidence (1). There is increasing evidence that a β-cell stress response to environmental factors contributes to the loss of immunological tolerance and triggers β-cell autoimmunity (2,3).

Iron is essential for β-cell function and insulin secretion (4). However, iron overload is toxic for β-cells, as iron catalyzes the formation of reactive oxygen species (5). Balanced iron homeostasis is important for maintaining both β-cell and immunological health (6,7). Under normal circumstances, elevated iron levels stimulate hepcidin secretion from the liver. Hepcidin then inhibits iron export through the cellular iron transporter ferroportin from iron storage sites such as liver, gut, and macrophages. Genetic iron overload can be caused by mutations in *HFE* (HighFE2^{+}) and *TMPRSS6*

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(rs855791-G allele) (8,9), which regulate hepcidin, and in *SLC40A1* (rs11568351-C allele), which codes for ferroportin 1.

Therefore, we investigated the association between energy-adjusted iron intake and development of persistent islet autoimmunity (IA), its initiation with either insulin autoantibodies (IAA-first) or GAD antibodies (GADA-first), and progression to T1D in The Environmental Determinants of Diabetes in the Young (TEDDY) study (10). Furthermore, we investigated whether relationships were modified by *1*) a genetic risk score (GRS) based on three single nucleotide polymorphisms (SNPs) with the strongest association with high iron status (increased ferritin and transferrin saturation levels) in adult genome-wide association studies and *2*) preselected SNPs located in iron metabolism genes.

RESEARCH DESIGN AND METHODS

Study Sample and Design
TEDDY is a prospective cohort study in Sweden, Finland, Germany, and the U.S. From 2004 to 2010, TEDDY enrolled 8,676 newborn infants who carried one of the eligible HLA-DR-DQ genotypes with high risk for T1D. The details of screening and follow-up have been previously published (11). In total, 7,770 children were included in our analyses (Supplementary Fig. 1). The study was approved by local institutional review boards or ethics committees and is monitored by an external evaluation committee formed by the National Institutes of Health.

Assessment of Iron Intake
Iron intake was assessed using a 24-h recall and repeated 3-day food records (from 6 to 36 months) filled out before each visit by the caregiver (12) (Supplementary Materials).

Assessment of Persistent IAAs and T1D
Serum samples were drawn every 3 months for the first 4 years of participation and then every 6 months thereafter, unless autoantibodies developed, in which case quarterly visits and blood draws were continued (13). The persistent development of IA was defined as the presence of confirmed positive findings for IAA; GADA, specifically isoform GAD-65; or IA2 autoantibody on two or more consecutive visits (14) (details are provided in the Supplementary Materials).

Genotyping and Polygenic Risk Score
SNPs located in iron metabolism genes were genotyped using the Illumina ImmunoChip (15) (Supplementary Table 1). We created a GRS based on three SNPs associated with circulating iron status (see details in the Supplementary Materials).

Statistical Analysis
Cox proportional hazards regression was used for our main analyses of IA during the first 10 years of life (all TEDDY participants had turned 10 years by 29 February 2020, when we initiated this study) and progression to T1D as outcomes (see details in the Supplementary Materials). Participants with positive tissue transglutaminase autoantibody (TGA+) findings were excluded in a post hoc analysis.

Intake of iron was adjusted for total energy intake by using the residual method (16) stratified by country (i.e., the mean residual was 0 for each country) and visit of food record collection in the first 3 years (Supplementary Fig. 2). Energy-adjusted iron intake was considered as *1*) a continuous variable (mg/day) and *2*) three categories based on first and third quartiles (Q1 and Q3) of energy-adjusted iron intake as follows: low, less than or equal to Q1; moderate, between Q1 and Q3; and high, greater than or equal to Q3. Specifically, the quartiles of residuals were calculated per visit to

Table 1—Association between energy-adjusted iron intake and risk of persistent IAAs and childhood T1D

Outcome	Variable	Adjusted HR (95% CI)	*P* value
IA	Iron intake (per mg/day)	1.01 (0.99; 1.03)[a]	0.30
GADA-first	Iron intake (per mg/day)	**1.03 (1.00; 1.06)[a]**	**0.04**
IAA-first	Iron intake (per mg/day)	1.00 (0.97; 1.04)[a]	0.91
Progression to T1D	Iron intake (per mg/day)	0.99 (0.96; 1.02)[b]	0.64
IA	Low iron intake[c]	1.04 (0.84; 1.27)[a]	0.74
	High iron intake	1.15 (0.94; 1.39)	0.17
GADA-first	Low iron intake	1.25 (0.92; 1.72)[a]	0.16
	High iron intake	**1.43 (1.07; 1.92)**	**0.02**
IAA-first	Low iron intake	0.97 (0.70; 1.36)[a]	0.87
	High iron intake	1.19 (0.88; 1.60)	0.27
Progression to T1D	Low iron intake	1.08 (0.80; 1.44)[b]	0.62
	High iron intake	1.16 (0.88; 1.54)	0.29

Boldface indicates significance at *P* < 0.05. [a]Covariates included in the model: sex, HLA genotype, country, first-degree relative with T1D, and principal components 1 and 2. [b]Covariates included in the model: sex, HLA genotype, country, first-degree relative with T1D, principal components 1 and 2, age at seroconversion, and type of first-appearing autoantibody. [c]Reference is the medium intake group (50% of iron intake values between the low and high groups).

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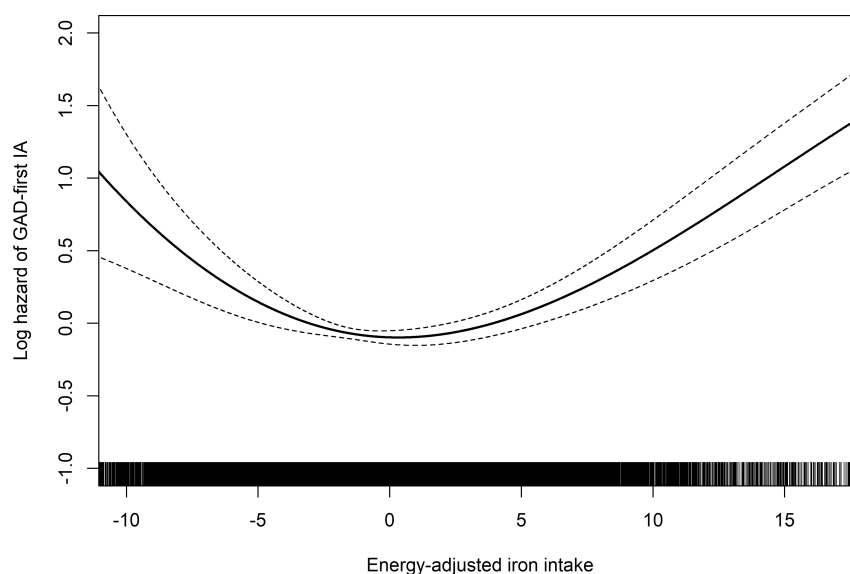
Figure 1—Estimated association of energy-adjusted iron intake with the log hazard of first-appearing GAD-65 autoantibody using smoothing splines to examine a possible nonlinear effect; this was not altered by excluding participants who were TGA+. A solid line represents the estimated effect and is accompanied by pointwise SEs shown with dashed lines. Values on the x-axis represent the energy-adjusted iron intake calculated using the residual method. Participants included in this figure are only the middle 99% of energy-adjusted iron intake values because of dispersed data in the two 0.5% tails and large pointwise SEs.

consider the potential variations of the residuals across the visits. The magnitude of the associations was described by hazard ratios (HRs) with 95% CIs.

Descriptions of iron intake and iron SNP interactions and model adjustments are presented in-depth in the Supplementary Materials.

Data were analyzed using SAS 9.4 statistical software (SAS Institute, Cary, NC). Two-tailed $P < 0.05$ was considered statistically significant.

Table 2—Association between energy-adjusted iron intake and risk of persistent IAAs and childhood T1D stratified by GRS for elevated circulating iron, ferritin, and transferrin saturation

Outcome	Energy-adjusted iron intake	GRS, no. of risk alleles	Adjusted HR (95% CI)	P
IA	Low	0	1.59 (0.90; 2.81)[a]	0.11
		1	0.85 (0.60; 1.21)	0.37
		≥2	1.10 (0.82; 1.47)	0.54
	High	0	0.98 (0.53; 1.82)	0.95
		1	0.94 (0.68; 1.31)	0.72
		≥2	**1.37 (1.04; 1.79)**	**0.02**
IAA-first	Low	0	2.29 (0.92; 5.70)[a]	0.08
		1	1.05 (0.64; 1.74)	0.85
		≥2	0.77 (0.45; 1.31)	0.33
	High	0	1.17 (0.42; 3.28)	0.77
		1	0.74 (0.43; 1.27)	0.27
		≥2	**1.71 (1.14; 2.58)**	**0.01**
GADA-first	Low	0	2.06 (0.76; 5.58)[a]	0.16
		1	0.96 (0.56; 1.66)	0.89
		≥2	1.36 (0.89; 2.08)	0.15
	High	0	2.15 (0.84; 5.47)	0.11
		1	1.40 (0.86; 2.26)	0.17
		≥2	1.32 (0.87; 2.01)	0.19
Progression to T1D	Low	0	0.83 (0.38; 1.82)[b]	0.64
		1	0.94 (0.53; 1.67)	0.84
		≥2	1.34 (0.87; 2.06)	0.18
	High	0	2.79 (0.96; 8.14)	0.06
		1	1.15 (0.74; 1.80)	0.53
		≥2	1.00 (0.66; 1.53)	0.99

The GRS was based on the following risk alleles: *HFE* (rs1800562-A allele) + *HFE* (rs1799945-G allele) + *TMPRSS6* (rs855791-G allele). Boldface indicates significance at $P < 0.05$. [a]Covariates included in the model: sex, HLA genotype, country, first-degree relative with T1D, and principal components 1 and 2. HRs for low and high iron status were estimated from the same model compared with the medium intake group (50% of iron intake values between the low and high groups) and stratified by the number of risk alleles. [b]Covariates included in the model: sex, HLA genotype, country, first-degree relative with T1D, principal components 1 and 2, age at seroconversion, and type of first-appearing autoantibody. HRs for low and high iron status were estimated from the same model compared with the medium intake group (50% of iron intake values between the low and high groups) and stratified by the number of risk alleles.

RESULTS

In the first 10 years of life, 769 (9.9%) children developed IA, representing 291 (3.7%) with IAA-first and 334 (4.3%) with GADA-first. Of those, 1,288 were TGA+. The median (Q1–Q3) age at onset of IA was 3 (1.5–6) years (1.8 [1–3.8] years for IAA-first, 4.4 [2.3–7.3] years for GADA-first). Among the 769 children with IA, 152 were TGA+ and 315 developed T1D. Median (Q1–Q3) age at onset of T1D was 6.3 (3.3–9.3) years (Supplementary Table 2). The median (Q1–Q3) follow-up time was 10.7 (5.3–12.5) years.

Iron Intake and Risk of Persistent IAAs and T1D

Increased iron intake (mg/day) was associated with increased risk of GADA-first (adjusted HR 1.03 [95% CI 1.00; 1.06], P = 0.04). High (greater than or equal to Q3) versus moderate intake (between Q1 and Q3) was associated with increased risk of GADA-first (1.43 [1.07; 1.92], P = 0.02), whereas low (less than or equal to Q1) versus moderate intake was not (Table 1 and Supplementary Table 7). Iron intake (per mg/day or categorical) was not associated with the development of overall IA, IAA-first, or progression to T1D (Table 1). In a sensitivity analysis, iron intake was nonlinearly associated with development of GADA-first (U-shaped association; P value for nonlinearity = 0.03) (Fig. 1) and progression to T1D (P value for nonlinearity = 0.03) with and without TGA+ (Supplementary Fig. 3).

Interaction Between Dietary Iron Intake and Iron Metabolism Genes

The main effects of the associations between SNPs and GRS on the risk of IA, IAA-first, and GADA-first and progression to T1D are shown in Supplementary Table 3. For GRS ≥2 iron risk alleles, the HR for IAA-first was 0.77 (95% CI 0.45; 1.31 [P = 0.33]) for low versus moderate intake, but 1.71 (1.14; 2.58 [P = 0.01]) for high versus moderate iron intake (Table 2). This association was driven by *TMPRSS6* (rs855791-G allele) (1.71 [1.07; 2.75], P = 0.03) for high versus moderate iron intake (Table 3A and Supplementary Table 4B).

There was a stepwise increasing risk for *SLC40A1* (rs11568351-C allele) (adjusted $P_{interaction}$ = 0.02) (Supplementary Table 5) for progression to T1D for high versus moderate iron intake with an HR

of 2.25 (95% CI 1.36; 3.71 [P = 0.01]) for one risk allele and 6.42 (1.59; 25.99 [P = 0.01]) for two risk alleles with and without TGA+ (Table 3B and Supplementary Tables 8 and 9).

Dietary vitamin C interacted with iron intake on the risk of GADA-first ($P_{interaction}$ = 0.02). In children with high iron intake, higher dietary vitamin C intake (1 mg/day increase) was associated with an increased risk of GADA-first (HR 1.002 [95% CI 1.000; 1.004], P = 0.014); vitamin C may, to some degree, enhance nonheme iron absorption (Supplementary Materials).

CONCLUSIONS

This prospective study revealed novel associations between iron intake during the first 3 years of life and the risk of β-cell–specific autoimmunity. Iron intake was associated in a U-shaped fashion with risk of GADA-first. Furthermore, higher iron intake was only associated with IAA-first and progression to T1D when stratified by genetic polymorphisms, which increase intestinal iron absorption and impair cellular iron release.

The effects of early-life iron exposure on childhood T1D risk have been investigated with inconsistent results (17–19).

Compared with previous studies, we investigated a high-risk T1D cohort with more detailed early-life iron exposure with energy-adjusted dietary and supplemental iron intake. These data were collected at multiple visits throughout the first 3 years of life and allowed us to investigate time to autoantibody development and progression to T1D, including gene-diet interactions. Murine models of T1D also have supported gene-diet interactions, where downregulation of early-life hepcidin in pancreatic islets may result in accelerated IA, which is further aggravated if mice are fed a high-iron diet (7).

A strength of this study is that TEDDY is a large prospective multicenter study of children genetically predisposed to T1D with the longitudinal dietary data and development of IA and T1D, as well as immunogenetic data. Another strength is that we were able to investigate IAA-first and GADA-first separately, which is important because they may reflect different disease processes. IAA usually appears during the 1st to 2nd year of life, whereas GADA usually appears at 3–5 years of age or even later (10).

Our results may be confounded by yet-unknown dietary patterns associated with iron intake, (e.g., vegetarian diet, fortified

Table 3—Stratified analyses by the number of risk alleles for SNPs that modified the association of energy-adjusted iron intake with the risk of persistent IAAs and childhood T1D

Outcome	Iron intake	No. of risk alleles	Adjusted HR (95% CI)	P
A: rs855791-G IAA-first	Low[a]	0	1.82 (0.88; 3.78)[b]	0.11
		1	1.12 (0.71; 1.78)	0.63
		2	0.50 (0.24; 1.05)	0.07
	High	0	0.80 (0.33; 1.96)	0.63
		1	1.01 (0.64; 1.59)	0.97
		2	**1.71 (1.07; 2.75)**	**0.03**
B: rs11568351-C Progression to T1D	Low	0	0.83 (0.56; 1.21)[c]	0.33
		1	1.52 (0.90; 2.57)	0.12
		2	5.15 (0.86; 30.71)	0.07
	High	0	0.71 (0.49; 1.03)	0.07
		1	**2.25 (1.36; 3.71)**	**0.001**
		2	**6.42 (1.59; 25.99)**	**0.01**

Boldface indicates significance at $P < 0.05$. [a]Reference is the medium intake group (50% of iron intake values between the low and high groups). [b]Covariates included in the model: sex, HLA genotype, country, first-degree relative with T1D, and principal components 1 and 2. HRs for low and high iron status were estimated from the same model compared with the medium intake group (50% of iron intake values between the low and high groups) and stratified by the number of risk alleles. [c]Covariates were included in the model: sex, HLA genotype, country, first-degree relative with T1D, principal components 1 and 2, age at seroconversion, and type of first-appearing autoantibody. HRs for low and high iron status were estimated from the same model compared with the medium intake group (50% of iron intake values between the low and high groups) and stratified by the number of risk alleles.

food, high-meat diet, processed food, celiac disease); however, to our knowledge, it remains unexamined whether such dietary factors are associated with IA and T1D risk. Currently, the TEDDY study lacks measures of plasma iron parameters, which could have provided insight into endogenous circulating iron concentrations.

In conclusion, our novel findings indicate that iron may contribute to the initiation of IA. However, because the observations were exploratory and made in children with high-risk HLA haplogenotypes only, the data should be interpreted cautiously. Further research will be needed to confirm our findings in population-based cohorts.

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