IMPORTANCE  Dietary proteins, such as gluten, have been suggested as triggers of the disease process in type 1 diabetes (T1D).

OBJECTIVE  To study the associations of cereal, gluten, and dietary fiber intake with the development of islet autoimmunity (IA) and T1D.

DESIGN, SETTING, AND PARTICIPANTS  The prospective birth cohort Finnish Type 1 Diabetes Prediction and Prevention Study recruited children with genetic susceptibility to type 1 diabetes from September 1996 to September 2004 from 2 university hospitals in Finland and followed up every 3 to 12 months up to 6 years for diet, islet autoantibodies, and T1D. Altogether 6081 infants (78% of those invited) participated in the study. Dietary data were available for 5714 children (94.0%) and dietary and IA data were available for 5545 children (91.2%), of whom 3762 (68%) had data on islet autoantibodies up to age 6 years. Information on T1D was available for all children. Data were analyzed in 2018 and end point data were updated in 2015.

EXPOSURES  Each child’s intake of cereals, gluten, and dietary fiber was calculated from repeated 3-day food records up to 6 years.

MAIN OUTCOMES AND MEASURES  Islet autoimmunity was defined as repeated positivity for islet cell antibodies and at least 1 biochemical autoantibody of 3 analyzed, or T1D. Data on the diagnosis of T1D were obtained from Finnish Pediatric Diabetes Register.

RESULTS  Of 5545 children (2950 boys [53.2%]), 246 (4.4%) developed IA and of 5714 children (3033 boys [53.1%]), 90 (1.6%) developed T1D during the 6-year follow-up. Based on joint models, the intake of oats (hazard ratio [HR], 1.08; 95% CI, 1.03-1.13), wheat (HR, 1.09; 95% CI, 1.03-1.15), rye (HR, 1.13; 95% CI, 1.03-1.23), gluten-containing cereals (HR, 1.07; 95% CI, 1.03-1.11), gluten without avenin from oats (HR, 2.23; 95% CI, 1.40-3.57), gluten with avenin (HR, 2.06; 95% CI, 1.45-2.92), and dietary fiber (HR, 1.41; 95% CI, 1.10-1.81) was associated with the risk of developing IA (HRs for 1 g/MJ increase in intake). The intake of oats (HR, 1.10; 95% CI, 1.00-1.21) and rye (HR, 1.20; 95% CI, 1.03-1.41) was associated with the risk of developing T1D. After multiple testing correction, the associations with IA remained statistically significant.

CONCLUSIONS AND RELEVANCE  A high intake of oats, gluten-containing cereals, gluten, and dietary fiber was associated with an increased risk of IA. Further studies are needed to confirm or rule out the findings and study potential mechanisms.
Although type 1 diabetes (T1D) has a substantial genetic component, environmental factors, including dietary factors, are likely to explain the marked increase in the incidence of T1D during the last decades in several countries. To our knowledge, there are currently no means to prevent or delay the disease.

Cereals are the world’s most important source of human food. Consuming whole grain cereals is generally considered a good dietary choice because of their potentially beneficial associations with the composition of the gut microbiota and inflammation and their high content of dietary fiber, minerals, polyphenols, phytosterols, and vitamins. However, the cereal protein gluten has been suggested to increase the risk of T1D.

The evidence from human studies on the association between cereals and the disease process of T1D is scarce. Age at the introduction of gluten-containing and other cereals has been inconsistently associated with islet autoimmunity (IA). Maternal consumption of cereals during pregnancy was not associated with offspring risk of IA, but a large study based on the Danish National Birth Cohort reported that maternal gluten intake during pregnancy was associated with the risk of T1D in the offspring. Small intervention studies with gluten-free diets among infants or islet autoantibody-positive children have not been able to confirm or rule out the association of a gluten-free diet with the disease process.

Information on the association between child’s intake (amount) of cereals, gluten, and dietary fiber with IA were not analyzed. To our knowledge, the associations between children’s intake of gluten-containing cereals, gluten, and dietary fiber was associated with the risk of IA and T1D. The associations between IA and T1D have not been reported in a prospective cohort setting previously.

The aim of this study was to examine the associations of cereal, gluten, and dietary fiber intake with IA and T1D. We hypothesized that a high intake of gluten-containing cereals and gluten is associated with an increased risk of IA and T1D.

### Methods

#### Study Design and Population

The DIPP Study is a large population-based birth cohort study of children with human leukocyte antigen (HLA)-conferred susceptibility to T1D. Children carrying the genotypes HLA-DQB1*02/*03:02 and DQB1*03:02/ x / x (x indicates alleles other than DQB1*02 or DQB1*0602/3) until March 1997 and other than DQB1*02 or DQB1*06:02 thereafter) were eligible for the follow-up (15% of those screened). In the nutrition study within the DIPP Study, 54350 children born in the Tampere and Oulu University hospitals between September 1996 and September 2004 were screened, 8293 (15.2%) were eligible, 7782 (14.3%) were invited, and 6081 children (78% of those invited) participated in the follow-up. At the time of the screening, 99% of the Finnish population was white and children with 2 parents of color, severe diseases, or anomalies were excluded. The children were invited to follow-up visits at study clinics at intervals of 3 to 12 months up to age 6 years for food consumption and up to age 15 years for islet autoantibodies and T1D. In the main analyses of this article, the follow-up was limited to 6 years. The inclusion criteria for this article included at least 1 autoantibody assessment and at least 1 completed food record day in a 3-day food record before the autoantibody assessment (IA cohort) and at least 1 completed food record day (T1D cohort). Parents gave their written informed consent for genetic testing of their newborn infant from the cord blood sample and another one for participation in the follow-up. The study adheres to the Declaration of Helsinki, and the ethical committees of Oulu and Tampere University Hospitals approved the study protocol.

#### Assessment of Dietary Exposures

Each participant’s diet was assessed with 3-day food records (including 1 weekend and 2 weekdays) at 3, 6, and 12 months and 2-, 3-, 4-, and 6-year visits. The collection of food consumption data has been described previously. The collection included the training of the study nurses and research nutritionists, written instructions to families to write down all foods and drinks (with portion sizes, recipes, preparation methods, and brand names) before filling the food record, as well as checking and completing the food records at return and probing for missing items.

The cereal calculations are based on the regularly updated national food composition database Fineli (National Institute for Health and Welfare, Finland) and described in detail in the eMethods in the Supplement. The amounts (dry weights in grams) of wheat, barley, and rye separately and grouped as gluten-containing cereals, as well as the amount of oats and rice, were used as exposures. The amount of protein from wheat, rye, barley, and oats was calculated as 12.57, 9.78, 8.77, and 13.55 g of protein per 100 g of cereal intake, respectively, based on the Fineli database. The amount of gluten in wheat, rye, barley, and oats was calculated by multiplying the amount of protein with 0.8 for wheat, 0.65 for rye, 0.5

### Key Points

**Question** Is childhood cereal, gluten, and dietary fiber intake associated with the risk of developing islet autoimmunity and type 1 diabetes?

**Findings** In this large birth cohort study, the intake of oats, gluten-containing cereals, gluten, and dietary fiber was associated with an increased risk of islet autoimmunity in children with increased genetic risk of type 1 diabetes.

**Meaning** Further research is needed to understand the role of dietary cereals and their components in the development of type 1 diabetes.
for barley, and 0.8 for oats. The amount of gluten was calculated in 2 ways: “gluten without avenin” included gluten from wheat, rye, and barley and “gluten with avenin” included gluten from wheat, rye, barley, and oats. This was done because prolamines of oats may be less immunogenic than those in wheat, rye, and barley; in the literature, both ways have been used. Dietary fiber was calculated as the total intake from all foods. Total energy intake was calculated based on food records. For those who were breastfed, we estimated the total energy intake based on age, body weight, and the expected energy deposition needed for growth.

IA and T1D

Children were screened for islet cell antibodies (ICA) at intervals of 3-12 months as described before. After seroconversion for ICA for the first time, all preceding and subsequent samples from that participant were analyzed for insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), and islet antigen-2 antibodies (IA-2A). Islet cell antibodies were quantified by a standard indirect immunofluorescence method, IAA, GADA and IA-2A with specific radiobinding assays. Islet autoimmunity was defined as repeated positivity for ICA and at least one biochemical autoantibody (IAA, GADA, IA-2A), or having T1D. Date of diagnosis of T1D was obtained in May 2015 from Finnish Pediatric Diabetes Register, which covers approximately 92% of children diagnosed with T1D by age 15 years in Finland. In the present study, children not found in the register were considered T1D-free.

Genetic Methods and Background Characteristics

Human leukocyte antigen DQ was genotyped using panels of sequence-specific oligonucleotide probes. Genotypes HLA-DQBI*(02/*03:02) represented “high” and HLA-DQBI*03:02/x (x ≠ 02, 03:01, 06:02) represented “moderate” risk for T1D. Information on familial diabetes (type not specified) among first-degree relatives and offspring sex was collected with a questionnaire completed in the delivery hospital.

Statistical Methods

We used a joint model with a current value association structure for longitudinal and time-to-event data to analyze the association of dietary intake with IA and T1D. The joint model finds continuous cereal consumption profiles based on the dietary data collected during the whole follow-up time for each child using individual, daily food record data (individual days separately) (eFigure 1 in the Supplement); therefore, it considers individual variations of intake and reduces the bias associated with missing data. The joint model allowed us to reconstruct a complete exposure profile for each participant even with incomplete series of repeated measurements of diet. Those with more frequently observed dietary data contributed more to the analysis. The profiles were estimated by a linear mixed-effects model that was coupled with a relative risk model. The linear mixed-effects model fitted an individual specific cubic polynomial spline function. The baseline hazard of the relative risk model was set as a piecewise constant, with knots at ages 1.99 and 3.99 years. The detailed formulation of the used joint models is presented in the eMethods in the Supplement.

Dietary data were used up to 6 years or until the child developed IA or T1D. Based on the basic structure of the joint model, time-to-event data were also used up to 6 years. The joint models were run separately for the intake of oats, rice, wheat, rye, barley, gluten-containing cereals, dietary fiber, gluten without avenin, gluten with avenin, and total energy. The models were adjusted for sex (boy or girl), HLA genotype (high or moderate risk), and familial diabetes (yes or no), as these variables have been previously found to be potential confounders. The confounders were used in the survival parts of the models. Energy adjustment was done by dividing the intake of each cereal in grams by the total energy intake in MJ and by using this variable instead of the original consumption in the models. Statistical significance was set at P < .05. Multiple testing was controlled for using the false discovery rate (FDR) method (a step-up procedure using a .05 level as the criterion) for the energy-adjusted results.

To study the role of body weight on the associations, we used the consumption of oats and gluten-containing cereals divided with body weight (grams/kilograms of body weight) as separate exposure variables. To study whether the HLA genotype (moderate/high-risk) modifies the association between cereal consumption and IA, we added an interaction term between genotype and consumption to the joint model for oats and gluten-containing cereals separately.

As a secondary analysis, we investigated whether cereal, gluten, and dietary fiber intake during the first 6 years of life were associated with the risk of developing IA after age 6 years. We used Cox regression models with the cumulative consumption of the different cereals as a time-independent covariate. Cumulative consumption was calculated as the area under the curve based on the individual estimates of the longitudinal submodels for the consumption of the different cereals. Children who experienced the end point before age 6 years were excluded from these analyses.

Results

Of the 6081 participants enrolled for the follow-up, 5545 children (91.2%) had food record and autoantibody data available. During the 6-year follow-up, 246 children (4.4%) developed IA at a median (interquartile range [IQR]) age of 2.5 (1.3-3.6) years. Of the 5714 children (94.0%) with food record data available, 90 children (1.6%) developed T1D during the 6-year follow-up at a median (IQR) age of 3.8 (2.9-4.8) years. The dropout rates among the 5545 participants at 1-, 2-, and 6-year follow-up were 8%, 16%, and 32%, respectively. The total number of food record days from 3 months to 6 years was 80 170. Characteristics regarding outcomes and diet by sex, genetic risk, and familial diabetes are presented in Table 1.

Oats was the most used cereal up to age 1 year and wheat thereafter (Figure). The consumption of rice and barley was...
low. The intake of wheat, rye, gluten, and dietary fiber increased by age (Figure). The median (IQR) consumption of oats and gluten-containing cereals by outcome status is presented in eFigures 2 and 3 in the Supplement. More than half (52%–56%) of the dietary fiber was derived from cereals in other age points except 6 months (32%).

A high intake of oats, wheat, rye, gluten-containing cereals, gluten (without and with avenin), and dietary fiber was associated with an increased risk of IA (Table 2). The associations did not change when adjusted for sex, HLA genotype, and familial diabetes, or for total energy intake or after correction for multiple testing with the FDR method (Table 2). The intake of rice and barley (Table 2) and total energy (hazard ratio [HR], 1.16; 95% CI, 0.97–1.38 per 1 MJ increase; \( P = .02 \)) was not associated with the risk of IA. The intake of oats per body weight (HR, 1.23; 95% CI, 1.09–1.40; \( P = .001 \)) and gluten-containing cereals per body weight (HR, 1.18; 95% CI, 1.07–1.30; \( P = .001 \)) per 1 g/kg increase were associated with IA.

We observed no interaction between HLA genotype and the consumption of oats (\( P \) for interaction = .72) or HLA and gluten-containing cereals (\( P \) for interaction > .99) with the risk of IA. An additional 102 children (1.8%) of the 5545 developed IA after age 6 years at a median (IQR) age of 8.7 (7.1–10.5) years. The cereal, gluten, or dietary fiber intake during the first 6 years of life was not associated with developing advanced IA after age 6 years (data not shown).

A high intake of oats, rye, gluten-containing cereals, gluten with avenin, and dietary fiber was associated with an increased risk of T1D in unadjusted models (Table 2). Adjustment for sex, HLA genotype, and familial diabetes did not markedly change the results, but after energy-adjustment, only the intake of oats and rye showed statistically significant associations with T1D (Table 2). After multiple testing correction, neither of the associations with T1D were significant (Table 2). The intake of rice and barley was not associated with the risk of TID (Table 2). Total energy intake was associated with an increased risk of T1D (HR, 1.43; 95% CI, 1.06–1.94 per 1 MJ increase; \( P = .02 \)). The intake of oats (HR, 1.33; 95% CI, 1.06–1.67; \( P = .02 \)) and gluten-containing cereals per body weight (HR, 1.28; 95% CI, 1.04–1.58; \( P = .02 \)) per 1 g/kg increase was associated with TID.

### Discussion

In this large prospective birth cohort of children with an increased genetic risk for T1D, the energy-adjusted intake of oats, wheat, rye, gluten-containing cereals, gluten, and dietary fiber was associated with an increased risk of developing IA. The energy-adjusted intake of oats and rye was associated with the risk of developing TID, but these associations did not hold after controlling for multiple testing.

### Strengths and Limitations

The strengths of this study include a large study population, carefully collected data on cereal intake at up to 7 points, the use of a well-maintained food composition database, and a regular assessment of autoantibodies. Another strength is the use of the joint model, which enables the analysis of individual food record days, including children with missing data, and generates the most likely continuous exposure profile for each child while simultaneously accounting for exposure and survival processes.

A limitation is that despite the careful data collection and statistical methods, the complexity and variability of human diets cannot be perfectly modeled. In addition, this...
The study cannot identify which components of the cereals or fractions of dietary fiber are associated with the disease process or conclude whether the observed associations reflect causality.

About 60% of individuals with T1D in Finland carry genotypes included in this study. Our joint model analyses were restricted to children who developed IA and/or T1D by age 6 years because our dietary follow-up ended at that time. There are country-specific features in infant and child cereal consumption. Specific features to the present Finnish study population are the frequent consumption of oats and rye and a low consumption of rice. Whether the findings can be generalized to children living in other parts of the world, noncarriers of moderate or high HLA risk genotypes, or for cereal consumption at an older age remains unknown.

Our findings partially support our initial hypothesis; a higher intake of gluten-containing cereals and gluten were associated with an increased risk of IA. In our previous smaller report from the DIPP study, the direction of the association between gluten-containing cereals and IA in children was similar as in this study, but not statistically significant. In the DAISY Study, gluten intake was not associated with IA or the progression to T1D. Differences with the DAISY Study might be explained by different outcome variables, dietary data collection methods, and study population, whereas differences with our previous study may be explained by a more careful categorization of foods containing cereals, the study of individual cereals, cohort design, improvements in the statistical methods, and increased statistical power.

We also observed that a high intake of oats and dietary fiber was associated with an increased risk of IA, which is somewhat surprising given their various presumed beneficial health effects. A high intake of oats was also associated with the risk of TID, but after multiple testing correction, this association was not statistically significant. To our knowledge, no previous studies exist on the association between oat intake and the risk of IA or TID. Two previous prospective studies found no association between children's total and soluble dietary fiber intake and IA. Differences in the results compared with this study may be explained by different outcome variables, food

Figure. Median Intake of Cereals, Gluten, and Dietary Fiber by Age

**A** Cereals

- **Oats**
- **Rice**
- **Wheat**
- **Rye**
- **Barley**

**B** Gluten and dietary fiber

- **Gluten without avenin**
- **Gluten with avenin**
- **Dietary fiber**

Medians and interquartile ranges (IQRs) were calculated for all individual food record days in 5714 children for cereals (A), gluten, and dietary fiber (B). Numbers of food record days were 14,644, 13,102, 10,752, 10,152, 9,078, and 6,790 at 6 months, 1, 2, 3, 4, and 6 years, respectively. The percentage of users varied from 75.4% at 6 months to 92.6% at 1 year for oats; 52.7% at 6 months to 75.3% at 6 years for rice; 56.2% at 6 months to 98.9% at 6 years for wheat; 33.8% at 6 months to 92.1% at 6 years for rye; and 31.8% at 6 months to 60.1% at 1 year for barley.
Association of Cereal, Gluten, and Dietary Fiber Intake With Islet Autoimmunity and Type 1 Diabetes by Age 6 Years

<table>
<thead>
<tr>
<th>Dietary Factor</th>
<th>Unadjusted HR (95% CI) a,b,c</th>
<th>P Value</th>
<th>Adjusted HR (95% CI) a,d</th>
<th>P Value</th>
<th>Energy-Adjusted HR (95% CI) a,d</th>
<th>P Value</th>
<th>BH Critical Value a,b,c,d</th>
<th>Type 1 Diabetes</th>
</tr>
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<tbody>
<tr>
<td>Oats</td>
<td>1.19 (1.08-1.31)</td>
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<td>1.19 (1.07-1.31)</td>
<td>&lt;.001</td>
<td>1.08 (1.03-1.13)</td>
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<td>.02</td>
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<td>Rice</td>
<td>0.98 (0.79-1.22)</td>
<td>.89</td>
<td>0.96 (0.77-1.20)</td>
<td>.72</td>
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<td>Wheat</td>
<td>1.12 (1.01-1.24)</td>
<td>.02</td>
<td>1.12 (1.01-1.24)</td>
<td>.03</td>
<td>1.09 (1.03-1.15)</td>
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<tr>
<td>Rye</td>
<td>1.22 (1.00-1.47)</td>
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<td>1.20 (0.99-1.45)</td>
<td>.07</td>
<td>1.13 (1.03-1.23)</td>
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<tr>
<td>Barley</td>
<td>1.38 (0.67-2.84)</td>
<td>.39</td>
<td>1.28 (0.61-2.68)</td>
<td>.51</td>
<td>0.97 (0.68-1.39)</td>
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<td>1.11 (1.03-1.20)</td>
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<td>.005</td>
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<td>3.21 (1.34-7.68)</td>
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<td>2.23 (1.40-3.57)</td>
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<td>Gluten with avenin h</td>
<td>3.48 (1.80-6.71)</td>
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<td>3.44 (1.78-6.68)</td>
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<td>Dietary fiber</td>
<td>1.94 (1.21-3.10)</td>
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<td>1.83 (1.14-2.94)</td>
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<td>1.41 (1.10-1.81)</td>
<td>.01</td>
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</table>

Abbreviations: BH, Benjamini-Hochberg; HR, hazard ratio; NA, not applicable.

* Values are hazard ratios with 95% confidence intervals in parentheses from the joint model.

* Hazard ratios are presented per 10-g increase of the consumption of the particular food item.

* Adjusted for sex of the child, human leukocyte antigen genotype, and familial diabetes.

* Food consumption is in grams divided by the total energy intake in megajoules. Thus, the HRs stand for 1-g/MJ increase of consumption of the particular dietary item. The number of children eligible for the energy-adjusted analyses was 5506 for islet autoimmunity and 5652 for type 1 diabetes.

* Multiple testing was controlled for using the false discovery rate method (a step-up procedure using a .05 level as the criterion). If the original P value was smaller than the BH critical value, the finding was considered to be a discovery.

* Statistically significant after correction for multiple testing.

* Gluten-containing cereals include wheat, rye, and barley.

* The amount of gluten without avenin was calculated based on wheat, rye, and barley.

* The amount of gluten with avenin was calculated based on wheat, rye, barley, and oats.

To our knowledge, this is the first study to report direct associations between children’s intake of specific cereals and IA; therefore, the associations need to be retested in another high-quality large study. The magnitude of the observed risk seems clinically relevant: for example, a 10-g increase in oats corresponds to 5 tablespoons of oatmeal per day and is associated with a 19% higher risk of IA. If the associations are confirmed, it is important to consider whether the observed associations could be explained by gluten, components of dietary fiber, or other factors. Theoretically, gluten could act as an antigen and trigger the disease process directly or indirectly by modifying gut microbiota and/or by promoting inflammation and intestinal permeability. Dietary fiber could act by modifying the gut microbiota. Other factors could include α-amylase/trypsin inhibitors, advanced glycation end products, cereal mycobiota and toxins, heavy metals, or remnants of pesticides and fertilizers, all of which are commonly found in cereal products.

Conclusions

This study’s findings indicate that among children with a genetic susceptibility to the risk of T1D, a high intake of oats, wheat, rye, gluten-containing cereals, gluten, and dietary fiber is associated with an increased risk of IA. Given that these cereals are eaten by most children daily and are important sources of many essential nutrients, further studies are warranted to confirm or rule out the findings. To understand potential mechanisms, randomized clinical trials exploring the effects of cereals, dietary fiber, and their components on the immune system and its development, intestinal microbiota, and inflammation in young children are needed.
Association of Cereal, Gluten, and Dietary Fiber Intake With Islet Autoimmunity and Type 1 Diabetes

Original Investigation Research

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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