

Association of Cereal, Gluten, and Dietary Fiber Intake In Relation to the Risk of Islet Autoimmunity and Type 1 Diabetes

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Abstract

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

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

Design Prospective birth cohort, the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study recruited children with genetic susceptibility to type 1 diabetes from 1996 to 2004 and followed them every 3-12 months up to 6 years for diet, islet autoantibodies and T1D.

Setting Two university hospitals in Finland

Participants Altogether 6081 infants participated in the study (78% of those invited). Dietary data was available on 5714 children, and both dietary and IA data on 5545 children, of whom, 68% had data on islet autoantibodies up to 6 years of age. Information on T1D was available for all children.

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

Main outcome measures IA was defined as repeated positivity for islet cell antibodies and at least one biochemical autoantibody out of three ones analysed, or T1D. Data on diagnosis of T1D was obtained from Finnish Pediatric Diabetes Register.

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

Conclusions and Relevance 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 to study potential mechanisms.

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 prospective birth cohort study, 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.

Introduction

Although type 1 diabetes (T1D) has a significant genetic component,¹ environmental factors, including dietary factors,^{2,3} are likely to explain the fast increase in the incidence of T1D during the last decades in several countries.⁴ Currently, no means exist to prevent or delay the disease.

Cereals are the world's most important source of human food.⁵ Intake of whole grain cereals is generally considered a good dietary choice due to their potentially beneficial effects on the composition of the gut microbiota and inflammation, and because of their high content of dietary fiber, minerals, polyphenols, phytosterols and vitamins.⁶ On the other hand, the cereal protein gluten has been suggested to increase the risk of T1D.⁷

The evidence from human studies on the association between cereals and the disease process of T1D is scarce.⁸ Age at introduction of gluten-containing and other cereals has been inconsistently associated with islet autoimmunity (IA) or T1D in children with genetic susceptibility to T1D.⁹⁻¹² Maternal consumption of cereals during pregnancy was not associated with offspring risk of IA,¹³¹⁴ 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.¹⁵ Small intervention studies with gluten-free diets among infants¹⁶ or islet autoantibody positive children,^{17, 18} have not been able to confirm or rule out the effect of a gluten-free diet on the disease process.

Information on the association between child's intake (amount) of cereals,¹⁹ gluten²⁰ and dietary fiber^{21, 22} with the risk of IA in longitudinal study setting are scarce. A recent prospective cohort study found no association between child's gluten intake and risk of IA or progression to T1D.²⁰ Previously in the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study, in a nested case-control setting, child's intake of gluten-containing and other cereals was not significantly associated with advanced IA.¹⁹ In this previous study, however, the associations between individual cereals, gluten or dietary fiber with islet autoimmunity were not analyzed. Associations between the

child's intake of cereals and risk of clinical T1D have not been reported in a prospective cohort setting previously.

Our aim was to study the associations of cereal, gluten and dietary fiber intake with IA and T1D.

We hypothesized that 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 HLA-conferred susceptibility to T1D.²³ Children carrying the genotypes *HLA-DQB1**02/*03:02 and *DQB1**03:02/x (x stands for 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 the screened). In the nutrition study within the DIPP Study, 6081 children born in the Tampere and Oulu University Hospitals between September 1996 and September 2004, participated in the follow-up (78% of those invited). At the time of the screening, 99% of the Finnish population was Caucasian, and children with two non-Caucasian parents, 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 the age of 6 years for food consumption and up to age of 15 years for islet autoantibodies and T1D. In the main analyses of this report, the follow-up was limited to 6 years. The inclusion criteria for the present report included at least one autoantibody assessment and at least one completed food record day in a 3-day food record before the autoantibody assessment (IA cohort) and at least one 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 have approved the study protocol.

Assessment of Dietary Exposures

The participant's diet was assessed with 3-day food records (including 1 weekend and 2 week days) at 3, 6, and 12 months, and 2, 3, 4, and 6 year visits. The careful collection of food consumption data has been described previously in detail.¹⁹ The careful collection included 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 etc) before filling the food record, as well as checking and completing the food records at return, and probing for missing items.¹⁹

The cereal calculations are based on the constantly updated national food composition database Fineli and described in detail in eMethods. The amounts (dry weights in grams) of wheat, barley and rye separately and grouped as gluten-containing cereals, as well as 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 grams 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 for barley and 0.8 for oats.²⁴ The amount of gluten was calculated in two ways: "gluten without avenin" includes gluten from wheat, rye and barley and "gluten with avenin" includes 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,²⁵ and in the literature, both ways have been used.^{15, 24} 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 total energy intake based on age, body weight and expected energy deposition needed for growth.²⁶

Islet Autoimmunity and Type 1 Diabetes

Children were screened for islet cell antibodies (ICA) at intervals of 3-12 months as described before.²³ 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). ICA was 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. Data 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.²⁷ In the present study, children not found in the register were considered T1D-free.

Genetic Methods

HLA-DQ was genotyped using panels of sequence-specific oligonucleotide probes.²³ Genotypes *HLA-DQB1*(*02/*03:02) represent “high” and *HLA-DQB1**03:02/x (x ≠*02, *03:01, *06:02) “moderate” risk for T1D.

Background Characteristics

Information on familial diabetes (type not specified) among the 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.²⁸ The joint model finds smooth 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) (eFigure1), and therefore takes individual variation of intake into account and reduces the bias related to missing data. The joint model allowed us to reconstruct a complete exposure profile for each subject 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 linear mixed effects model, which 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 the ages of 1.99 and 3.99. The detailed formulation of the used joint models is presented in the supplementary material (eMethods).

Dietary data was 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 was also used up to 6 years. The endpoints occurring after 6 years were treated as censored. Analyses were implemented with R version 3.4.3, by using jointModel function from the JM package.²⁹

The joint models were run separately for 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, girl), HLA-genotype (high, moderate risk), and familial diabetes (yes, 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 intake of each cereal in grams by total energy intake in MJ and by using this variable instead of the original consumption in the models. Multiple testing was controlled for using the false discovery rate (FDR) method³⁰ (a step-up procedure using .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 (g/kg of body weight) as separate exposure variables. To study whether 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 analyses, we investigated whether cereal, gluten and dietary fiber intake during the first 6 years of life was associated with risk of developing IA after 6 years of age. 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 sub-models for the consumption of the different cereals. Children who experienced the endpoint before 6 years of age were excluded from these analyses.

Results

Of the 6081 participants enrolled for the follow-up, 5545 children had both food record and autoantibody data available. During the 6-year follow-up, 246 children (4.4%) developed IA at a median (IQR) age of 2.5 (1.3 to 3.6) years. Of the 5714 children 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 to 4.8) years. The drop-out 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 80170. 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 the age of 1 year and wheat thereafter (Figure 1). The consumption of rice and barley were low. The intake of wheat, rye, gluten and dietary fiber increased by age (Figure 1). The median (IQR) consumption of oats and gluten-containing cereals by outcome status are presented in eFigure 2 and eFigure 3. More than half (52% to 56%) of the dietary fiber was derived from cereals in other age points except 6 months (32%).

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, nor after correction for multiple testing with the FDR method (Table 2). The intake of rice and barley (Table 2), and total energy (HR 1.16 [95% CI: 0.97 to 1.38] per 1 MJ increase, $P=.12$) was not associated with the risk of IA. The intake of oats per body weight (1.23[1.09 to 1.40], $P=0.001$) and gluten-containing cereals per body weight (1.18 [1.07 to 1.30] $P=0.001$) (per 1g/kg increase), were associated with IA.

We observed no modifying effect of HLA genotype on the association between consumption of oats (P for interaction=.72) or gluten-containing cereals (P for interaction=1.00) and IA.

Additional 102 children developed IA after the age of 6 years at a median (IQR) age of 8.7 (7.1 to 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 the age of 6 years (data not shown).

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 intake of oats and rye showed statistically significant association 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 risk of T1D (Table 2). Total energy intake was associated with an increased risk of T1D (HR 1.43 [95% CI: 1.06 to 1.94] per 1 MJ increase, $P=.02$). The intake of oats per body weight (1.33[1.06 to 1.67] $P=0.02$) and gluten-containing cereals per body weight (1.28 [1.04 to 1.58] $P=0.02$) (per 1g/kg increase), was associated with T1D.

Discussion

In this large prospective birth cohort of children with 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. Energy-adjusted intake of oats and rye was associated with the risk of developing T1D, but these associations did not hold after controlling for multiple testing.

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

A limitation is that despite the careful data collection and advanced statistical methods, the complexity and variability of human diet cannot be perfectly modelled. In addition, this 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 the present study³¹. Our joint model analyses were restricted to children who developed IA and/or T1D by the age of 6 years, since our dietary follow-up ended at 6 years of age. There are country-specific features in infant and child cereal consumption.³² Specific features to the present Finnish study population are the frequent consumption of oats and rye, and low consumption of rice. Whether the findings can be generalized to children living in other parts of the world, to non-carriers of moderate or high HLA risk genotypes, or to for cereal consumption at older age, remains open.

Our findings partly support our initial hypothesis; 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 islet autoimmunity in children was similar as in the present one, but not statistically significant.¹⁹ In the DAISY Study, gluten intake was not associated with islet autoimmunity or progression to T1D.²⁰ Differences to the DAISY Study might be explained by different outcome variables, dietary data collection methods, and study population, whereas differences to our previous study may be explained by more careful categorization of foods containing cereals, the study of individual cereals, cohort design, improvements in the statistical methods, and increased statistical power.

We observed that also high intake of oats and dietary fiber was associated with increased risk of islet autoimmunity, which is somewhat surprising, given various presumed beneficial health effects of them.⁶ High intake of oats was also associated with the risk of T1D, 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 risk of islet autoimmunity or T1D. Two previous

prospective studies found no association between the child's total²² and soluble²¹ dietary fiber intake and islet autoimmunity. Differences in the results compared with the present study may be explained by different outcome variables, food data collection and calculation methods, study populations and statistical methods.

This is the first study to report direct associations between the child's intake of specific cereals and islet autoimmunity and 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 gram increase in oats corresponds to 5 tablespoons of oatmeal/day, and is associated with 19% higher risk of IA. If the associations will be 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 permeability⁷. Dietary fiber could act by modifying the gut microbiota.^{6, 33} Other factors could include, α -amylase/trypsin inhibitors,³⁴ advanced glycation end-products,³⁵ cereal mycobiota and toxins,³⁶ heavy metals,³⁷ or remnants of pesticides and fertilizers,³⁸ all of which are commonly found in cereal products.

In conclusion, our findings indicate that among children with genetic susceptibility to risk of T1D, 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 of the children daily and are important sources of many essential nutrients, further studies are urgently warranted to confirm or rule out the findings. To understand potential mechanisms, studies 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.

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Contributions

SMV, LH, MEM and JN were responsible for the current study design, JI, JT, RV, and MK for the DIPP study, and SMV for the Nutrition study within the DIPP. MÅ, H-MT, TEK, and SA participated in dietary data processing, ES and H-MT conducted and are responsible for the data analysis, LH, MEM, ES, JN, and SMV participated in data interpretation, LH performed the literature search and generated the Figure 1, ES generated the eFigure1, LH, MEM, and SMV wrote the first version of the manuscript, and all authors participated in the revision of the manuscript and have read and accepted the final version. LH and SMV had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legend

Figure 1. Median (IQR) intake of cereals (a), and gluten and dietary fiber (b) by age.

Medians and interquartile ranges (IQR) were calculated for all individual food record days in 5714 children. Numbers of food record days were 14644, 13102, 10752, 10152, 9078, and 6790 at 6 months, 1, 2, 3, 4, and 6 years, respectively. Percentage of users varied from 75.4% at 6 months to 92.6% at 1 year for oats; from 52.7% at 6 months to 75.3% at 6 years for rice; from 56.2% at 6 months to 98.9% at 6 years for wheat; from 33.8% at 6 months to 92.1% at 6 years for rye; and from 31.8% at 6 months to 60.1% at 1 year for barley.

Table 1. Distribution of all participating children, children with islet autoimmunity and type 1 diabetes, and their dietary intake by background variables.

	Islet autoimmunity cohort ^a		Type 1 diabetes cohort ^b		Mean dietary intake over the follow-up from 3 months to 6 years N=5714 ^b			
	Total N=5545	Islet autoimmunity N=246	Total N=5714	Type 1 diabetes N=90	Oats, g/day	Gluten- containing cereals, g/day ^c	Gluten without avenin, g/day ^c	Dietary fiber, g/day
	No. (%)	No. (%)	No. (%)	No. (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Sex								
Boys	2950 (53.2)	148 (5.0)	3033 (53.1)	52 (1.7)	9.5 (15.3)	34.0 (38.7)	3.0 (3.5)	6.9 (5.2)
Girls	2595 (46.8)	98 (3.8)	2681 (46.9)	38 (1.4)	8.4 (13.5)	31.5 (35.5)	2.7 (3.2)	6.3 (4.9)
HLA-DQB1–conferred risk ^d								
High	1088 (19.6)	78 (7.2)	1117 (19.5)	35 (3.1)	9.0 (14.3)	31.9 (36.6)	2.8 (3.3)	6.6 (5.1)
Moderate	4457 (80.4)	168 (3.8)	4597 (80.5)	55 (1.2)	9.0 (14.5)	33.1 (37.4)	2.9 (3.4)	6.6 (5.0)
Familial diabetes								
Yes	329 (5.9)	30 (9.1)	335 (5.9)	13 (3.9)	8.1 (13.3)	32.5 (37.6)	2.8 (3.4)	6.5 (4.9)
No	5001 (90.2)	210 (4.2)	5155 (90.2)	75 (1.5)	9.1 (14.5)	33.0 (37.3)	2.9 (3.4)	6.7 (5.1)
Missing information	215 (3.9)	6 (2.8)	224 (3.9)	2 (0.9)				

^aAll children with food record and autoantibody assessment data N=5545. Islet autoimmunity was defined as repeated positivity for islet cell antibodies and at least one biochemical autoantibody out of three ones analyzed.

^bAll children with food record data N=5714.

^cBased on wheat, rye and barley

^dHLA, human leukocyte antigen. High-risk genotype HLA-DQB1(*02/*03:02); moderate risk genotypes HLA-DQB1(*03:02/x); x ≠ *02, *03:01,*06:02).

Mean and standard deviations (SD) were calculated for all individual food record days at age points from 3 months to 6 years in 5714 children.

Table 2. Associations of the cereal, gluten, and dietary fiber intake with the risk of developing islet autoimmunity and type 1 diabetes by the age of 6 years.

	Islet autoimmunity						
	Unadjusted ^{a, b} HR (95% CI)	<i>P</i>	Adjusted ^{a,b,c} HR (95% CI)	<i>P</i>	Energy- adjusted ^{a,d} HR (95% CI)	<i>P</i>	BH critical value ^e
Oats	1.19 (1.08 to 1.31)	<.001	1.19 (1.07 to 1.31)	<.001	1.08 (1.03 to 1.13)	.002 ^f	.02
Rice	0.98 (0.79 to 1.22)	.89	0.96 (0.77 to 1.20)	.72	0.97 (0.87 to 1.09)	.64	
Wheat	1.12 (1.01 to 1.24)	.02	1.12 (1.01 to 1.24)	.03	1.09 (1.03 to 1.15)	.002 ^f	.03
Rye	1.22 (1.00 to 1.47)	.05	1.20 (0.99 to 1.45)	.07	1.13 (1.03 to 1.23)	.008 ^f	.04
Barley	1.38 (0.67 to 2.84)	.39	1.28 (0.61 to 2.68)	.51	0.97 (0.68 to 1.39)	.88	
Gluten- containing cereals ^g	1.12 (1.04 to 1.21)	.005	1.11 (1.03 to 1.20)	.007	1.07 (1.03 to 1.11)	<.001 ^f	.005
Gluten without avenin ^h	3.25 (1.37 to 7.74)	.008	3.21 (1.34 to 7.68)	.009	2.23 (1.40 to 3.57)	<.001 ^f	.01
Gluten with avenin ⁱ	3.48 (1.80 to 6.71)	<.001	3.44 (1.78 to 6.68)	<0.001	2.06 (1.45 to 2.92)	<.001 ^f	.02
Dietary fiber	1.94 (1.21 to 3.10)	.006	1.83 (1.14 to 2.94)	.01	1.41 (1.10 to 1.81)	.006 ^f	.03
	Type 1 diabetes						
	Unadjusted ^{a, b} HR (95% CI)	<i>P</i>	Adjusted ^{a,b,c} HR (95% CI)	<i>P</i>	Energy- adjusted ^{a,d} HR (95% CI)	<i>P</i>	BH critical value ^e
Oats	1.22 (1.06 to 1.40)	.005	1.24 (1.08 to 1.43)	.003	1.10 (1.00 to 1.21)	.04	.01
Rice	1.02 (0.72 to 1.43)	.93	1.00 (0.71 to 1.42)	.98	0.94 (0.72 to 1.24)	.68	
Wheat	1.05 (0.88 to 1.26)	.57	1.06 (0.89 to 1.27)	.51	1.03 (0.92 to 1.16)	.62	
Rye	1.54 (1.16 to 2.05)	.003	1.53 (1.15 to 2.04)	.004	1.20 (1.03 to 1.41)	.02	.006
Barley	1.56 (0.35 to 7.04)	.56	1.44 (0.30 to 6.81)	.65	0.60 (0.11 to 3.32)	.56	
Gluten- containing cereals ^g	1.16 (1.01 to 1.34)	.04	1.16 (1.01 to 1.34)	.04	1.07 (0.98 to 1.17)	.15	
Gluten without avenin ^h	3.94 (0.81 to 19.1)	.09	4.28 (0.87 to 21.0)	.07	1.92 (0.70 to 5.28)	.21	
Gluten with avenin ⁱ	5.13 (1.48 to 17.8)	.01	5.60 (1.58 to 19.8)	.008	2.19 (0.99 to 4.86)	.05	
Dietary fiber	4.25 (1.83 to 9.83)	<.001	4.12 (1.76 to 9.66)	.001	1.67 (0.98 to 2.87)	.06	

^aValues are hazard ratios with 95% CIs in parentheses from joint model.

^bHazard ratios (HR) are presented per 10 grams increase of the consumption of the particular food item.

^cAdjusted for sex of the child, human leukocyte antigen (HLA) genotype and familial diabetes.

^dFood consumption is in grams divided by the total energy intake in MJ. Thus, the hazard ratios stand for 1 gram/MJ increase of consumption of the particular dietary item. Number of children eligible for the energy-adjusted analyses was 5506 for islet autoimmunity and 5652 for type 1 diabetes.

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

^fStatistically significant after correction for multiple testing.

^gGluten-containing cereals include wheat, rye and barley.

^hAmount of gluten without avenin was calculated based on wheat, rye and barley.

ⁱAmount of gluten with avenin was calculated based on wheat, rye, barley and oats.

Supplementary online content

Cereal, Gluten, and Dietary Fiber Intake In Relation to the Risk of Islet Autoimmunity and Type 1 Diabetes

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eMethods

eFigure 1. Examples of individual oat consumption profiles estimated by linear mixed effects model for 4 children.

eFigure 2. Median (IQR) consumption of oats in children with and without islet autoimmunity and with and without type 1 diabetes by age.

eFigure 3. Median (IQR) consumption of gluten-containing cereals in children with and without islet autoimmunity and with and without type 1 diabetes by age.

eMethods

Cereal calculations

The cereal calculations are based on the constantly updated national food composition database Fineli (National Institute for Health and Welfare, Finland, www.fineli.fi) that includes over 8000 food items including cereals as such (e.g. brans), home-made foods, commercial baby foods, and many other commercial foods, and snacks (cereal bars, meal mixes and cereal drinks). The database has been updated regularly for commercial baby foods. The Fineli database includes core dishes and ingredients (e.g. crisp bread and mixed flours) that are not broken down into individual cereals in calculation, and therefore, the in-house software (Finessi) cannot take all sources of cereals into account in the calculation of amounts of individual cereals. The existing food groups in Fineli were manually re-grouped into respective individual cereal food groups, and new coefficients for dry cereal content in foods were created. This new classification and calculation enabled us to study the consumption of individual cereals more precisely than before.

Joint model

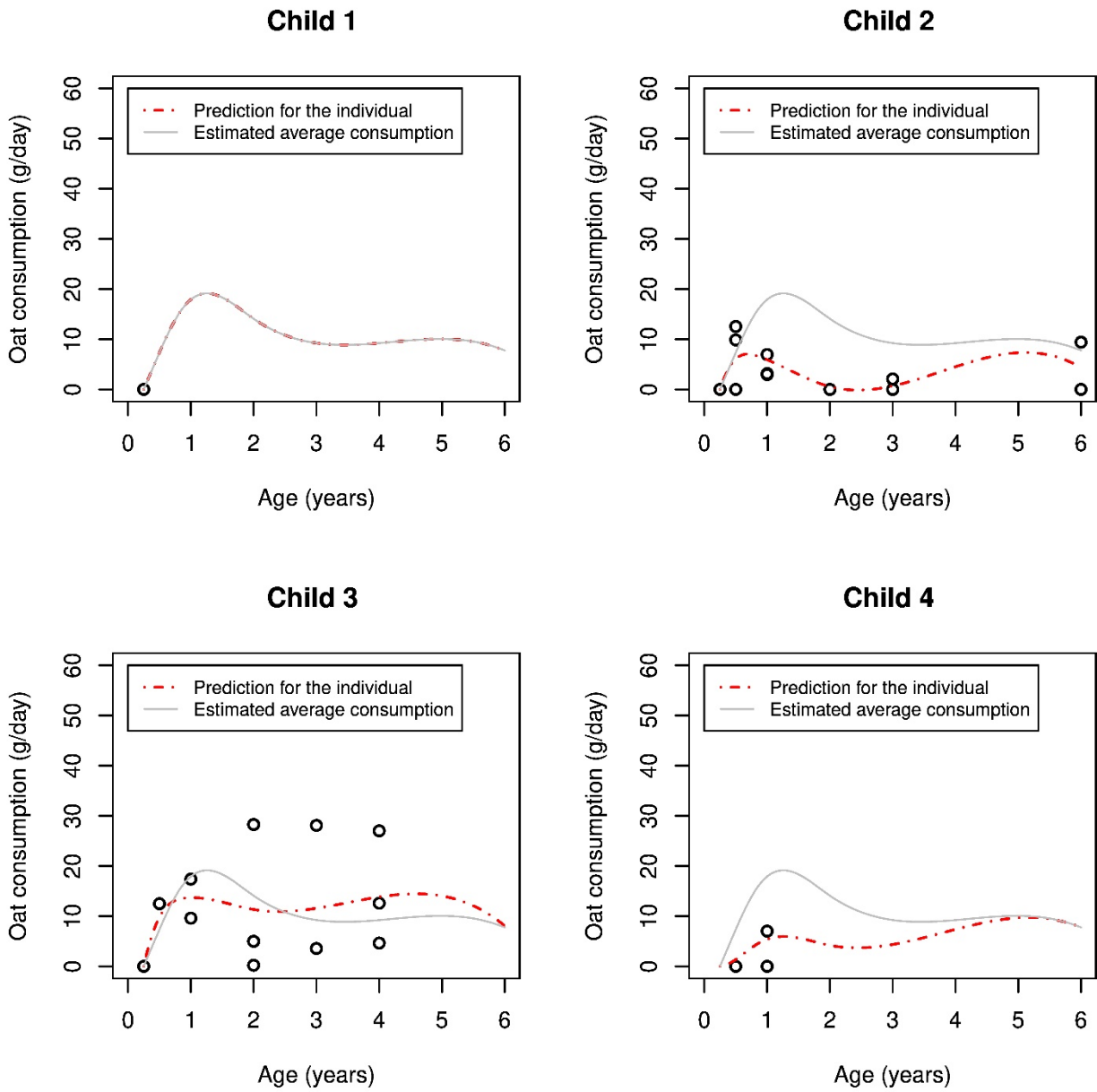
The formula of the joint model for child i were of the form:

$$\begin{cases} y_i(t) = m_i(t) + \epsilon_i(t) = \beta_0 + b_{0i} + \sum_{k=1}^5 (\beta_k + b_{ki}) B_k(t) + \epsilon_i(t) \\ h_i(t|M_i(t), w_i) = e^{\gamma^T w_i + \alpha m_i(t)} h_0(t), \end{cases}$$

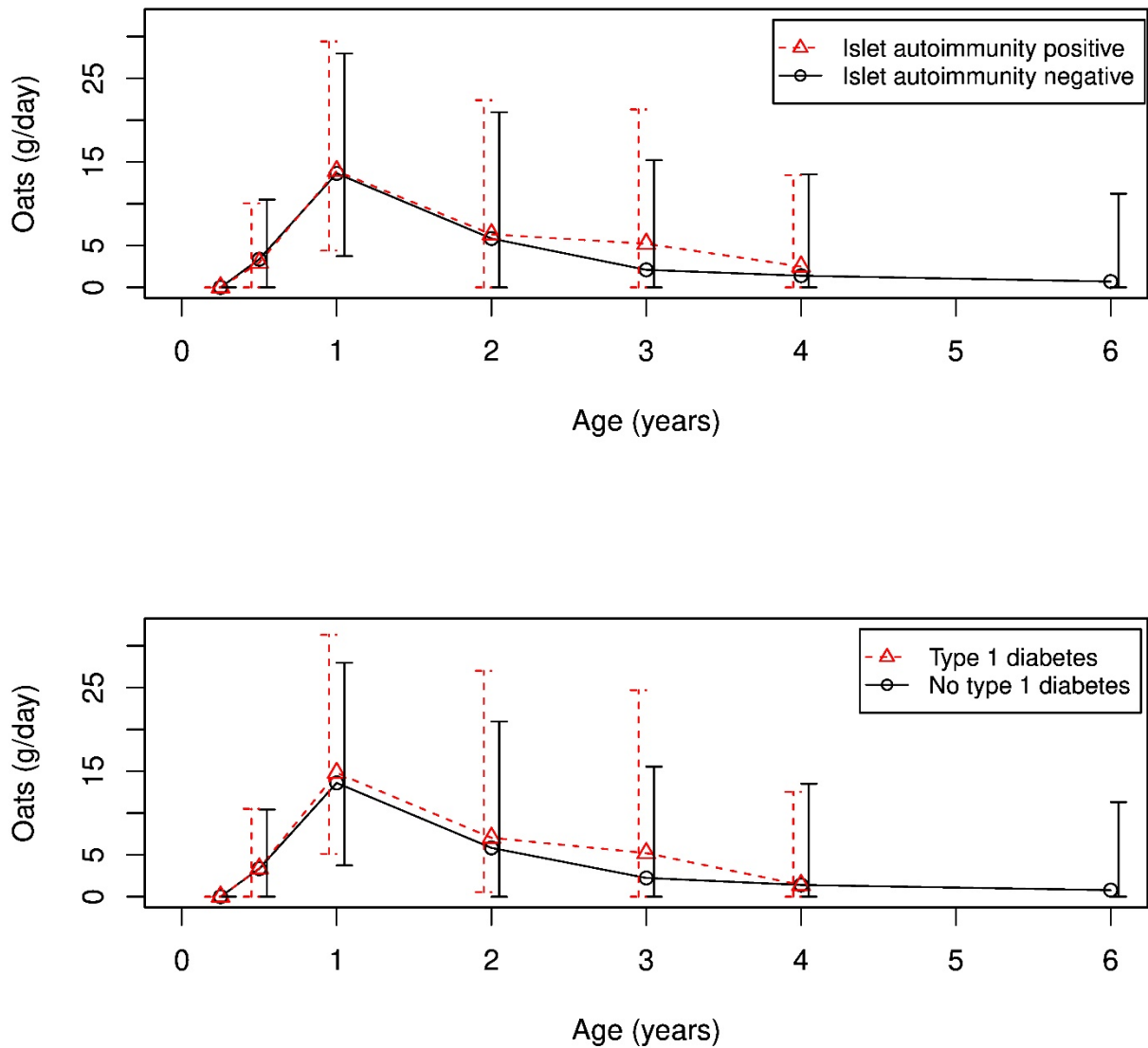
where β denote the fixed part and b denote subject specific random part of the intercepts and regression parameters. $B_k(t)$ is the value of k th B-spline basis function for a spline at age t and $\epsilon_i(t) \sim N(0, \sigma^2)$ are errors. $M_i(t) = \{m_i(s), 0 \leq s < t\}$ denotes the history of the cereal consumption profile until t , w_i is a vector of baseline covariates with a vector of regression parameters γ and $h_0(t)$ is the baseline hazard. The assumed covariance structure for the random effects was a diagonal matrix with unequal diagonal elements (variances). Two knots were used after finding a balance that allowed sufficient flexibility and avoided overfitting. The positions for two knots were selected based on the Bayesian information criterion from all relevant knot combinations.

Times-to-event for children with islet autoimmunity were set to the middle of the time interval between the last measurement, when child was not repeatedly positive for ICA and a biochemical autoantibody, and the measurement when child was repeatedly positive for ICA and at least one biochemical autoantibody.

eFigure 1. Examples of individual oat consumption profiles estimated by linear mixed effects model for 4 children.

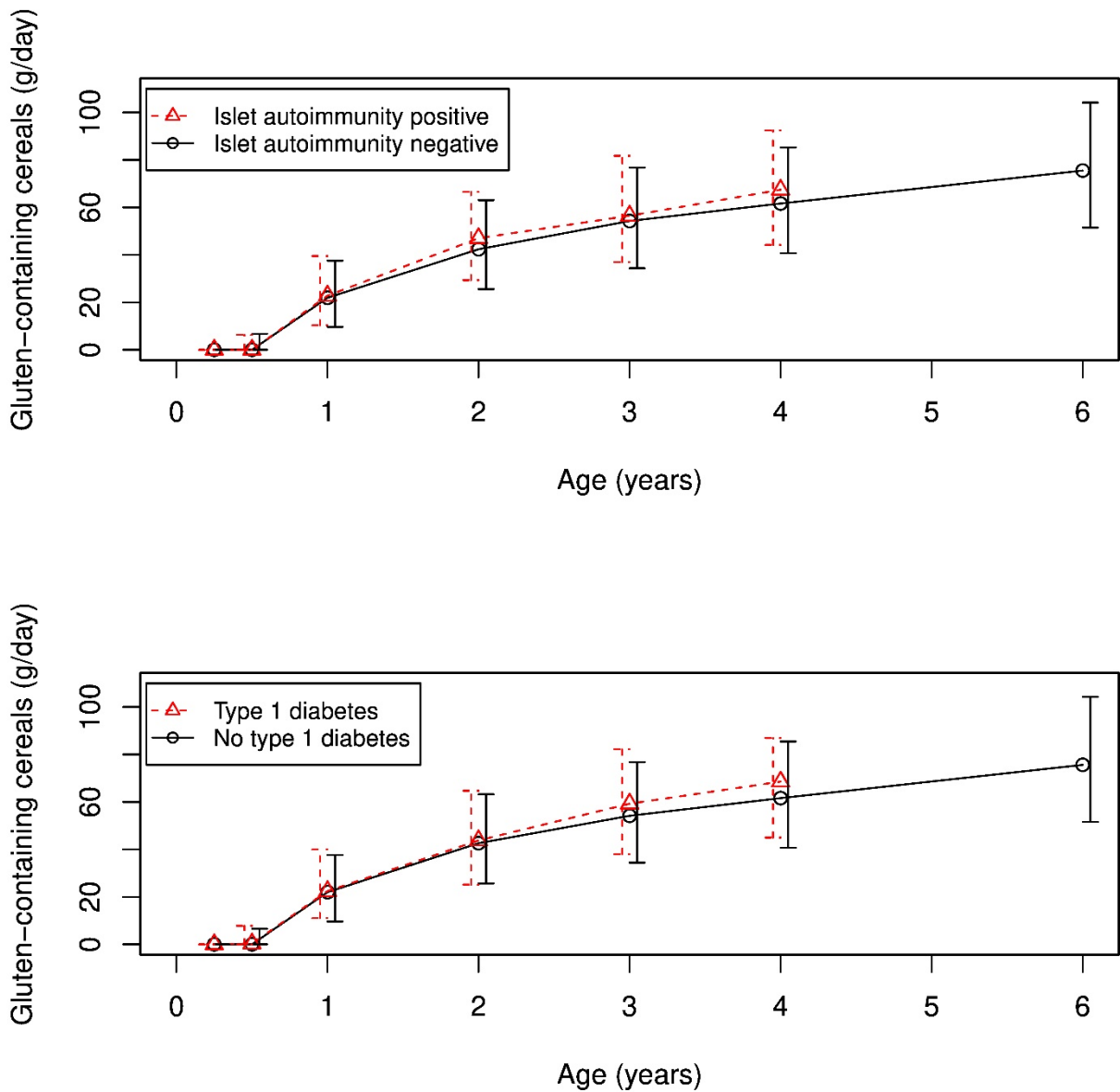


eFigure 2. Median (IQR) consumption of oats in children with and without islet autoimmunity and with and without type 1 diabetes by age.



The medians and interquartile ranges are based in daily oat intake in 246 children with autoimmunity, 5299 children without autoimmunity, 90 children with type 1 diabetes and 5624 children without type 1 diabetes.

eFigure 3. Median (IQR) consumption of gluten-containing cereals in children with and without islet autoimmunity and with and without type 1 diabetes by age.



The medians and interquartile ranges are based in daily intake of gluten-containing cereals (wheat, rye and barley) in 246 children with autoimmunity, 5299 children without autoimmunity, 90 children with type 1 diabetes and 5624 children without type 1 diabetes.