Dietary intake of soluble fiber and risk of islet autoimmunity by 5 y of age: results from the TEDDY study[1,2]

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ABSTRACT

Background: Deficient soluble fiber intake has been suggested to dysregulate the immune response either directly or through alterations of the microbial composition in the gut.

Objective: We hypothesized that a high intake of dietary soluble fiber in early childhood decreases the risk of type 1 diabetes (T1D)–associated islet autoimmunity.

Design: We analyzed 17,620 food records collected between age 9 and 48 mo from 3358 children from the United States and Germany prospectively followed in the TEDDY (The Environmental Determinants of Diabetes in the Young) study. HRs for the development of any/multiple islet autoantibodies (242 and 151 events, respectively) and T1D (71 events) by soluble fiber intake were calculated in Cox regression models and adjusted for potential confounders.

Results: There were no statistically significantly protective associations observed between a high intake of soluble fiber and islet autoimmunity or T1D. For example, the adjusted HRs (95% CIs) for high intake (highest compared with lowest quintile) at age 12 mo were 0.90 (0.55, 1.45) for any islet autoantibody, 1.20 (0.69, 2.11) for multiple islet autoantibodies, and 1.24 (0.57, 2.70) for T1D. In analyzing soluble fiber intake as a time-varying covariate, there were also no short-term associations between soluble fiber intake and islet autoimmunity development, with adjusted HRs of 0.85 (0.51, 1.42) for high intake and development of any islet autoantibody, for example.

Conclusion: These results indicate that the intake level of dietary soluble fiber is not associated with islet autoimmunity or T1D in early life. *Am J Clin Nutr* 2015;102:345–52.

Keywords: TEDDY study, soluble fiber, diet, autoimmunity, type 1 diabetes

INTRODUCTION

Type 1 diabetes (T1D)[16] is an autoimmune disease with dramatically increasing incidence rates in recent years, especially in industrialized countries (1, 2). The environmental causes of T1D are not well understood, although early diet is suspected to be an important factor. In general, Western diets are characterized by a low content of fiber, which is mainly found in fruits, vegetables, and whole grains (3, 4).

A low-fiber diet has been associated with other inflammatory or autoimmune diseases such as colon cancer and irritable bowel syndrome (5–7). In particular, soluble fiber may be important in this respect, because it is converted to the short-chain fatty acids acetate, propionate, and butyrate by bacterial fermentation in the gut. These products have several anti-inflammatory properties such as regulation of immune-related gene expression and cytokine release (8). One possible pathway by which short-chain fatty acids may regulate inflammatory responses is based on their interaction with GPR43 receptors, which are mainly expressed on cells of the innate immune system (9).

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[16] Abbreviations used: HLA, human leukocyte antigen; T1D, type 1 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young.

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Besides a direct effect on immune regulation, soluble fiber intake may also modulate the immune response through alterations of the microbial composition in the gut (10). There is growing evidence that dietary fiber intake directly affects the gut microbiome (11, 12), which may, in turn, interact with the immune system (13). It has been suggested that a low fiber intake may lead to a status of dysbiosis in the gut, increasing an individual's susceptibility to inflammation (9). Case-control studies suggest that the microbiome in children with islet autoimmunity or T1D differs from healthy subjects with respect to diversity, interactions between species, or, interestingly, the abundance of butyrate-producing species (14–16). Supported by promising findings from animal models, manipulation of the gut microbiota by dietary intake has already been discussed as a potential prevention strategy against T1D (17).

We hypothesized that a high intake of dietary soluble fiber in early childhood decreases the risk of developing T1D-associated islet autoimmunity. If so, this would be an important finding both for understanding T1D pathogenesis and for potential prevention strategies. We investigated this association in data from The Environmental Determinants of Diabetes in the Young (TEDDY) study. The TEDDY study is unique in both the number of children with genetically increased T1D risk included followed prospectively and its regular diet records in very early life, which allowed us to investigate time windows of potentially different susceptibility to the effect of soluble fiber intake.

METHODS

The TEDDY study enrolled 8676 children with increased genetic risk of T1D who were recruited in 6 clinical research centers located in the United States, Finland, Germany, and Sweden between 2004 and 2010 shortly after birth. Detailed information on study design, eligibility, and methods has been previously published (18–20). Written informed consents were obtained for all participants from a parent or primary caretaker, separately, for genetic screening and for participation in prospective follow-up. The study was approved by local institutional review boards and is monitored by the External Advisory Board formed by the NIH.

Assessment of study endpoints and covariates

The primary outcome was the development of persistent confirmed islet autoimmunity, which was assessed every 3 mo. Persistent autoimmunity was defined by the presence of a confirmed islet autoantibody (among GADA, IA-2A, mIAA, or ZnT8A) on 2 or more consecutive visits. Date of persistent autoimmunity was defined as the draw date of the first positive sample. The presence of persistent multiple islet autoantibodies was defined by the first date when at least 2 confirmed islet autoantibodies were detected. T1D diagnosis was based on American Diabetes Association criteria (21), using standardized case report forms covering symptoms, height and weight at diagnosis, and laboratory values such as ketones in urine and blood.

Mode of delivery, birth order, maternal prepregnancy BMI, maternal education, and maternal smoking during pregnancy were obtained by either questionnaires or structured interviews during one of the follow-up visits in the first year of the study. To assess the duration of breastfeeding and the age at introduction of new foods, we asked families to record the age at introduction of all new foods in a specific booklet that was given to the parents at study entry.

Assessment of dietary variables

The first dietary assessment from children's primary caretakers was carried out by 24-h recall at the age of 3 mo, by 3-d food record every 3 mo until the child was 12 mo old, and then every 6 mo. Every participating family was instructed to keep a 3-d record of the child's food consumption, ideally including 2 weekdays and 1 weekend day. To facilitate the completion of food records, TEDDY staff provided written instructions and examples on how to indicate meal time, meal location, adequate description of foods and beverages, quantity of intake, and use of dietary supplements. TEDDY developed a food portion size booklet that contained colorful pictorial illustrations of multi-ingredient composite dishes and black-and-white shapes and scales to facilitate portion size estimation. In Germany, parents weighted food when keeping the records; the food portion booklet was only used in addition. The records were reviewed at all clinical visits and entered into country-specific databases to assess intake of various nutrients (22). Assessment of soluble fiber was possible only for data from Germany and the United States because the national food composition databases have been harmonized between countries only for those nutrients that were available from all the food databases and that had originally been hypothesized to be potentially associated with T1D. No such harmonization efforts were made for soluble fiber, because it was not available separately in the original Finnish and Swedish food databases and not considered a nutrient of major importance when the TEDDY study was initiated. The TEDDY study did not provide any recommendations or advice on infant feeding to the families.

Statistical analyses

Data of 4318 children from Germany and the United States were available for this analysis. Further exclusions applied to children who were followed up for less than 1 y or who had indeterminate autoantibody status or no dietary record between age 9 and 48 mo or before last clinic visit. This restricted the sample to 3358 subjects (**Figure 1**)—2912 from the United States and 446 from Germany—with a total of 17,620 food records, of which in 7 records, soluble fiber intake was considered implausibly high (>13 g) and therefore set to missing. As a next step, intake of soluble fiber was standardized to total energy intake by using the residual method (23). This standardization was done separately for each country, because there were slight differences in the analysis method, although the food databases from Germany and the United States both use content data analyzed by enzymatic methods for calculation of soluble fiber (22).

To assess potential attrition bias, we compared subjects with and without any diet record with respect to covariates by using χ^2 and t tests (as appropriate). Soluble fiber intake was explored both as a continuous and a categorical variable (above compared with below mean intake and highest compared with lowest quintile). We fitted Cox regression models to assess HRs of subsequent islet autoimmunity and T1D with intake of soluble

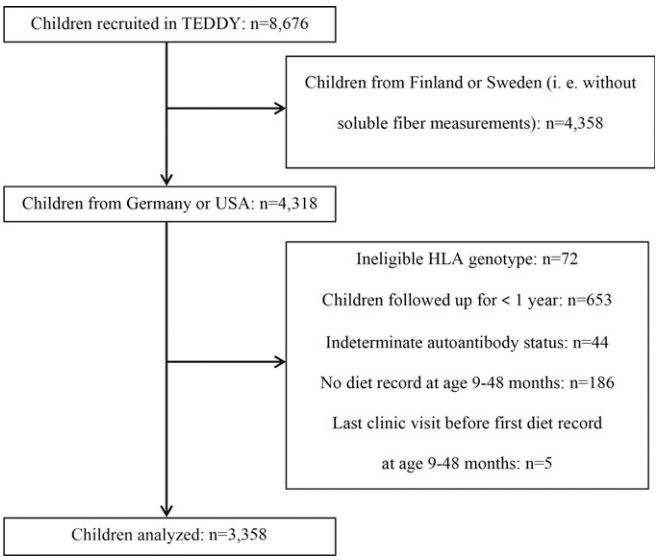

FIGURE 1 Flowchart of children included and excluded. HLA, human leukocyte antigen; TEDDY, The Environmental Determinants of Diabetes in the Young.

fiber at age 12 mo and during the first 2 y of life as predictors. Intake at age 12 mo was defined based on the 12-mo record, if available, or on the 9-mo record otherwise, leaving out subjects who dropped out or developed the respective outcome before age 12 mo. Intake in the first 2 y was defined as mean intake from 9 to 24 mo, and subjects who dropped out or developed the respective outcome before age 24 mo were left out of this analysis. Children with missing values of soluble fiber intake in the respective time intervals were also excluded. We further assessed "short-term" associations (3/6 mo) with islet autoimmunity or T1D by using time-varying covariates of fiber intake at age 9–48 mo according to the counting process method (24). Risk periods were taken as the time between food record collections at consecutive visits with a scheduled dietary assessment where subjects were still deemed at risk of islet autoimmunity seroconversion, meaning that events after age 54 mo did not contribute to the short-term analysis. This calculation was based on real time points of the respective food records or, if a record was missing, on its scheduled time point. Models were adjusted for the potential confounders of sex (female/male), country, human leukocyte antigen (HLA) genotype (HLA-DR3/4 genotype compared with other) and having a first-degree relative with T1D (yes/no), and also birth order (first child in the family, yes/no), maternal prepregnancy BMI, delivery mode (caesarian section, yes/no), maternal smoking in pregnancy (yes/no), maternal education (high school or lower/more than high school), and duration of exclusive breastfeeding or breastfeeding status at the time of the diet record (as appropriate). Interaction terms of the respective predictor variables with time and country were calculated to check the proportional hazards assumption and homogeneity of the association between countries for each model. In sensitivity analyses, we assessed associations in 1353 HLA-DR3/4 genotype carriers, in 497 children with a first-degree relative with T1D, in 182 children with T1D mothers, and with respect to total fiber intake.

For all analyses, the significance level was set to 0.05. All calculations were carried out with SAS 9.3 (SAS Institute) and R 3.0.2 (http://cran.r-project.org).

RESULTS

Median (IQR) follow-up time of the data analyzed was 5.0 (3.8–6.5) y (as of 31 July 2014). In total, 242 children (7.2%) had developed any islet autoantibody during follow-up at a median age of 2.3 (1.3–3.7) y. In 151 children (4.5%) multiple islet autoantibodies were detected at a median age of 2.7 (1.6–4.0) y, and 71 subjects (2.1%) had been diagnosed with T1D at a median age of 3.6 (2.0–4.9) y. The event rates and the proportion of first-degree relatives were higher in Germany than in the United States, whereas both countries were relatively similar with respect to other variables (**Table 1**). Children in Germany were more likely to have a first-degree relative with T1D due to slightly different recruitment strategies between countries.

For a total energy intake of 1000 kcal, mean standardized intake of soluble fiber was 2.8 g (total fiber: 8.9 g), with a lowest quintile of <1.8 g (total fiber: <5.5 g) and a highest quintile of >3.3 g (total fiber: >10.7 g). Standardized values of soluble

TABLE 1
Characteristics of the data analyzed[1]

Variable	United States (n = 2912)	Germany (n = 446)
Duration of follow-up, y	5.0 (4.0–6.5)[2]	5.0 (3.5–7.0)
Maternal prepregnancy BMI, kg/m^2	24.0 (21.4–28.3)	23.1 (20.8–26.4)
Developed any islet autoantibodies, n (%)	198 (6.8)	44 (9.9)
Developed multiple islet autoantibodies, n (%)	118 (4.1)	33 (7.4)
Developed T1D, n (%)	52 (1.8)	19 (4.3)
Male child, n (%)	1418 (48.7)	214 (48.0)
HLA-DR3/DR4 genotype, n (%)	1184 (40.7)	169 (37.9)
Having a first-degree relative with T1D, n (%)	326 (11.2)	171 (38.3)
Maternal T1D, n (%)	101 (3.5)	81 (18.2)
First child in the family, n (%)	1202 (42.0)	219 (50.9)
Born by cesarean delivery, n (%)	1072 (36.8)	158 (35.4)
Maternal smoking in pregnancy, n (%)	256 (8.9)	69 (15.5)
Maternal education less than high school, n (%)	391 (13.6)	45 (10.5)
Child was never breastfed, n (%)	155 (5.3)	12 (2.7)

[1]HLA, human leukocyte antigen; T1D, type 1 diabetes.
[2]Median; IQR in parentheses (all such values).

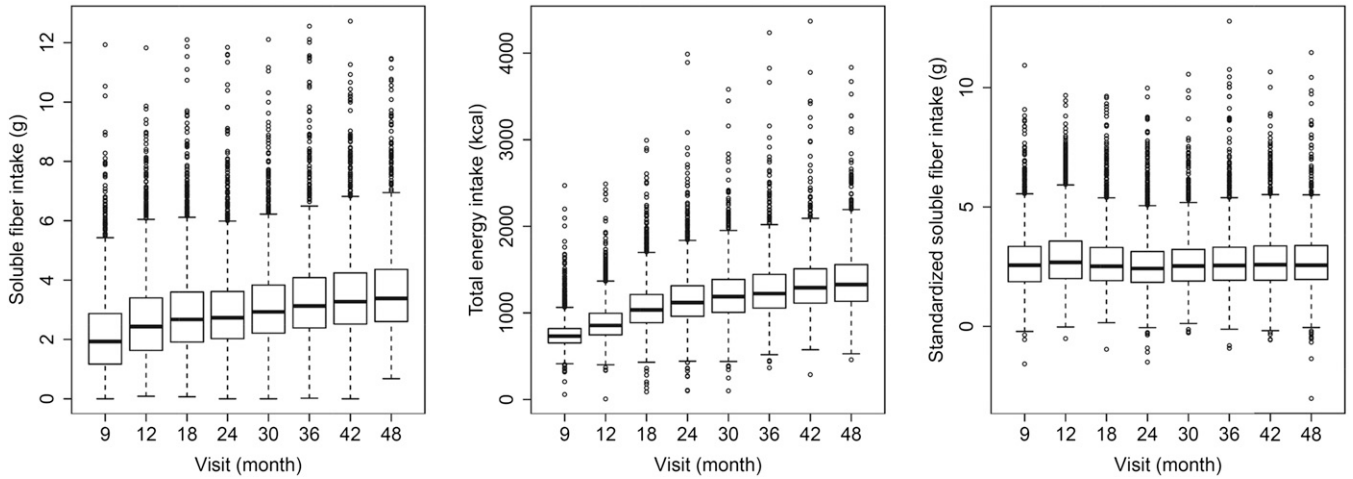

FIGURE 2 Boxplots of soluble fiber intake, total energy intake from food items, and soluble fiber intake standardized to an energy intake of 1000 kcal by diet record visit (n = 3358 subjects). Standardized values of soluble fiber intake were not statistically significantly associated with age (Pearson's $r = -0.01$, $P = 0.12$).

fiber intake were not associated with age (**Figure 2**; Pearson's $r = -0.01$, $P = 0.12$). Children without any food record were more likely to have a mother with lower education (30.5% compared with 13.2%, $P < 0.01$) and younger age (29.1 compared with 30.9 y, $P < 0.01$) but did not differ significantly from children with at least one food record with respect to sex, having a first-degree relative with T1D, birth order, maternal prepregnancy BMI, delivery mode, and duration of exclusive breastfeeding.

There were no statistically significant associations observed between a high intake of soluble fiber and islet autoimmunity (**Tables 2** and **3**). For example, the adjusted HRs (95% CIs) for high intake at age 12 mo were 0.90 (0.55, 1.45) (highest compared with lowest quintile) for development of any islet autoantibodies and 1.20 (0.69, 2.11) for development of multiple islet autoantibodies, respectively. Accordingly, there were also no statistically significant associations found between islet autoimmunity development and soluble fiber intake at age 12 mo as a continuous variable, with adjusted HRs of 0.96 (0.86, 1.08)/1.05 (0.91, 1.19) for single/multiple islet autoantibodies per gram intake, respectively.

Soluble fiber intake during the first 2 y of life was also not associated with reduced islet autoimmunity risk. Soluble fiber intake in the highest compared with the lowest quintile in the first 2 y of life even seemed to be associated with an increased risk of development of any islet autoantibodies [adjusted HR: 2.04 (1.07, 3.88)], with statistically significant differences between countries [adjusted HR in the United States: 3.34 (1.50, 7.41); in Germany: 0.31 (0.07, 1.33)], but no such association was observed for multiple islet autoantibodies [adjusted HR overall: 1.17 (0.60, 2.28); United States: 1.72 (0.78, 3.78); Germany: 0.24 (0.04, 1.29)].

No significant associations were found in analyses with time-varying covariates assessing short-term associations between soluble fiber intake and islet autoimmunity, with adjusted HRs of 0.85 (0.51, 1.42)/0.74 (0.41, 1.34) for intake in the highest compared with the lowest quintile and development of single/multiple islet autoantibodies, for example.

TABLE 2
Development of any persistent autoantibodies according to intake of soluble fiber at age 12 mo only, mean intake at age 9–24 mo, and with respect to short-term associations at age 9–48 mo modeled by time-varying covariates[1]

	Intake at age 12 mo	Mean intake at age 9–24 mo	Short-term associations at age 9–48 mo
Subjects with outcome/at risk, n	207/3252	140/2843	155/3326
Soluble fiber intake as continuous variable, per g			
Basic model	0.98 (0.88, 1.09)[2]	1.16 (0.98, 1.38)	0.95 (0.84, 1.08)
Fully adjusted model[3]	0.96 (0.86, 1.08)	1.14 (0.96, 1.37)	0.93 (0.81, 1.07)
Above vs. below average intake of soluble fiber			
Basic model	1.07 (0.81, 1.41)	1.14 (0.81, 1.60)	0.99 (0.72, 1.37)
Fully adjusted model[3]	1.04 (0.78, 1.39)	1.17 (0.82, 1.67)	0.94 (0.68, 1.32)
Highest vs. lowest quintile of soluble fiber intake			
Basic model	0.92 (0.58, 1.48)	2.02 (1.10, 3.72)[4]	0.87 (0.53, 1.45)
Fully adjusted model[3]	0.90 (0.55, 1.45)	2.04 (1.07, 3.88)[4]	0.85 (0.51, 1.42)

[1]The number of subjects with outcome/at risk differs between models because of different exposure periods. Models were adjusted for sex, human leukocyte antigen–DR3/DR4 status, country, and having a first-degree relative with type 1 diabetes.
[2]HR; 95% CI in parentheses (all such values).
[3]Additionally adjusted for birth order, maternal BMI, delivery mode, maternal smoking in pregnancy, maternal education, and duration of exclusive breastfeeding or breastfeeding status at the time of the diet record (as appropriate).
[4]Test on homogeneity between countries: $P < 0.05$.

TABLE 3
Development of multiple persistent autoantibodies according to intake of soluble fiber at age 12 mo only, mean intake at age 9–24 mo, and with respect to short-term associations at age 9–48 mo modeled by time-varying covariates[1]

	Intake at age 12 mo	Mean intake at age 9–24 mo	Short-term associations at age 9–48 mo
Subjects with outcome/at risk, *n*	142/3278	99/2889	98/3326
Soluble fiber intake as continuous variable, per g			
Basic model	1.05 (0.92, 1.19)[2]	1.13 (0.92, 1.39)[3]	0.92 (0.78, 1.09)
Fully adjusted model[4]	1.05 (0.91, 1.19)	1.14 (0.92, 1.42)[3]	0.92 (0.78, 1.09)
Above vs. below average intake of soluble fiber			
Basic model	1.25 (0.89, 1.76)	1.31 (0.88, 1.97)	1.03 (0.69, 1.53)
Fully adjusted model[4]	1.23 (0.87, 1.74)	1.30 (0.85, 1.98)	1.03 (0.69, 1.54)
Highest vs. lowest quintile of soluble fiber intake			
Basic model	1.22 (0.71, 2.11)	1.18 (0.62, 2.23)	0.76 (0.42, 1.37)
Fully adjusted model[4]	1.20 (0.69, 2.11)	1.17 (0.60, 2.28)	0.74 (0.41, 1.34)

[1]The number of subjects with outcome/at risk differs between models because of different exposure periods. Models were adjusted for sex, human leukocyte antigen–DR3/DR4 status, country, and having a first-degree relative with type 1 diabetes.
[2]HR; 95% CI in parentheses (all such values).
[3]Test on homogeneity between countries: $P < 0.05$. % refers to nonmissing values.
[4]Additionally adjusted for birth order, maternal BMI, delivery mode, maternal smoking in pregnancy, maternal education, and duration of exclusive breastfeeding or breastfeeding status at the time of the diet record (as appropriate).

With respect to T1D outcome, no statistically significant associations were observed for intake at age 12 mo, during the first 2 y of life, or for short-term associations (**Table 4**).

The assumptions of proportional hazards and homogeneity between countries were in most cases not rejected. There were no statistically significant associations in subgroups defined by HLA-DR3/4 genotype carriers or subjects with first-degree relatives or mothers with T1D or between total fiber intake and islet autoimmunity or T1D (data not shown).

DISCUSSION

These results indicate that greater intake of soluble dietary fiber does not protect against the development of islet autoimmunity or T1D in early life, irrespective of whether soluble fiber intake is analyzed as a continuous or categorical variable, the temporal context of intake (age 12 mo/first 2 y of life or short-term associations), and HLA genotype risk. The potentially increased risk of islet autoimmunity by high soluble fiber intake in the first 2 y of life is likely to be a chance finding, because it was different between countries and could not be confirmed for multiple islet autoantibody development. There were also no protective associations observed with respect to intake of total fiber.

Given our results, a direct effect of fiber intake deficiency on inflammatory response seems doubtful as a potential cause of T1D. Furthermore, because fiber intake is assumed to have a major effect on the gut microbiome, these findings seem to challenge the hypothesis that diet-related alterations in the microbiome induce a modulated immune response, which could be relevant for T1D pathogenesis. Specifically, the lack of associations between soluble fiber intake and islet autoimmunity in our data indicates that the proposed mechanism of impaired production of short-chain fatty acids as a cause of immune

TABLE 4
Development of type 1 diabetes according to intake of soluble fiber at age 12 mo only, mean intake at age 9–24 mo, and with respect to short-term associations at age 9–48 mo modeled by time-varying covariates[1]

	Intake at age 12 mo	Mean intake at age 9–24 mo	Short-term associations at age 9–48 mo
Subjects with outcome/at risk, *n*	70/3330	53/2986	32/3358
Soluble fiber intake as continuous variable, per g			
Basic model	1.03 (0.86, 1.24)[2]	0.98 (0.73, 1.32)	1.07 (0.82, 1.39)
Fully adjusted model[3]	0.98 (0.80, 1.19)	0.83 (0.60, 1.14)	0.99 (0.74, 1.31)
Above vs. below average intake of soluble fiber			
Basic model	—[4]	1.35 (0.78, 2.34)	1.11 (0.55, 2.25)
Fully adjusted model[3]	—[4]	1.22 (0.70, 2.13)	0.91 (0.44, 1.89)
Highest vs. lowest quintile of soluble fiber intake			
Basic model	1.41 (0.66, 3.01)	0.78 (0.34, 1.81)	1.15 (0.38, 3.42)
Fully adjusted model[3]	1.24 (0.57, 2.70)	0.61 (0.25, 1.48)	0.80 (0.26, 2.51)

[1]The number of subjects with outcome/at risk differs between models because of different exposure periods. Models were adjusted for sex, human leukocyte antigen–DR3/DR4 status, country, and having a first-degree relative with type 1 diabetes.
[2]HR; 95% CI in parentheses (all such values).
[3]Additionally adjusted for birth order, maternal BMI, delivery mode, maternal smoking in pregnancy, maternal education, and duration of exclusive breastfeeding or breastfeeding status at the time of the diet record (as appropriate)
[4]Test on violation of proportional hazards assumption: $P < 0.05$.

dysregulation and inflammation appears questionable. There may certainly be other genetic or environmental factors influencing the microbiome in a way that increases T1D risk (25), but dietary fiber intake in early life appears unlikely to play a large role in the pathway and therefore not suitable for prevention strategies.

The calculation of nutrients in the TEDDY study is based on established and up-to-date food databases from each country, and the validity of fiber assessment by food records is likely to be high (26). Furthermore, the fiber intake estimates were comparable to those from other studies on young children (27, 28) and stable over children's age if corrected for total energy intake. Unfortunately, we had to exclude the observations from Finland and Sweden from this analysis because the food databases from these countries did not allow an assessment of soluble fiber intake. However, the analysis of the data from Germany and the United States only was still based on a considerable sample size, with more than 17,000 diet records at age 9–48 mo from more than 3300 children. Attrition bias seems unlikely: although children without any diet records were more likely to have younger and lower educated mothers, their proportion appeared negligible, with only 6.5%.

A current study limitation is the relatively short follow-up time. Although most cases of T1D would not yet be apparent in this data set, most incident cases of islet autoimmunity are known to occur in the first 2 y of life (29). Therefore, although our analyses do not suggest an association of soluble fiber intake with islet autoimmunity, the relation between soluble fiber intake and progression of islet autoimmunity to clinical T1D has not been analyzed here and must be updated in the future based on continued observations in the TEDDY cohort.

In summary, this study found no evidence for a protective effect of high dietary soluble fiber intake on T1D-related islet autoimmunity. It is unlikely that encouraging high soluble fiber intake would be a quality prevention strategy.

The TEDDY Study Group is listed in **Appendix A**.

The authors' responsibilities were as follows—AB: analyzed the data and wrote the first and final draft of the manuscript; XL, UMU, A-GZ, and SH: contributed to the interpretation of the results and to subsequent drafts of the manuscript; MH, JMN, KF, SMV, OS, ÅL, WH, and BA: reviewed the manuscript and contributed to subsequent drafts; and MJR, J-XS, OS, ÅL, WH, BA, A-GZ, and JPK: designed the study. The authors declared no conflicts of interest related to this study.

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APPENDIX A

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