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1 **Association of gluten intake in the first 5 years with incidence of celiac**
2 **disease autoimmunity and celiac disease among children at increased risk**

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Key Points

Question: Is the amount of gluten intake in the first 5 years associated with the risk of celiac disease autoimmunity and celiac disease in at-risk children?

Findings: In this multinational prospective birth cohort consisting of 6,605 genetically predisposed children, higher gluten intake was associated with a statistically significant increase of celiac disease autoimmunity (HR 1.30, 95% CI 1.22-1.38) and celiac disease (HR 1.50, 95% CI 1.35-1.66), for every gram increase of gluten intake per day.

Meaning: Increased intake of gluten during the first 5 years of life was an independent risk factor of celiac disease autoimmunity and celiac disease in genetically predisposed children.

74 **Abstract**

75 **Importance:** High gluten intake during childhood may confer risk of celiac disease.

76 **Objectives:** To investigate if the amount of gluten intake is associated with celiac disease
77 autoimmunity and celiac disease in genetically at risk children.

78 **Design, Setting, and Participants:** The Environmental Determinants of Diabetes in the
79 Young (TEDDY), a prospective observational birth cohort designed to identify environmental
80 triggers of type 1 diabetes and celiac disease. Participants were followed at six clinical centers
81 in Finland, Germany, Sweden and the US. Between 2004 and 2010, 8,676 newborns carrying
82 HLA-genotypes associated with type 1 diabetes and celiac disease, were enrolled into a
83 longitudinal observational study. In 6,757 children, screening for celiac disease with tissue
84 transglutaminase (tTG) autoantibodies was performed annually from age 2 years. Data on
85 gluten intake were available in 6,605 (98%) children.

86 **Exposure:** Gluten intake was estimated from 3-day food records collected at 6, 9, and 12
87 months and biannually thereafter until age 5 years.

88 **Main Outcomes:** The primary endpoint was celiac disease autoimmunity, defined as positive
89 tTG autoantibodies in two consecutive serum samples. The secondary endpoint was celiac
90 disease confirmed by intestinal biopsy or persistently high tTG autoantibody levels.

91 **Results:** Of the 6,605 children (49% females, median follow-up 9.0 years [interquartile range
92 8.0 to 10.0 years]), 1,216 (18%) developed celiac disease autoimmunity and 447 (7%)
93 developed celiac disease by September 30, 2017. The incidence for both endpoints peaked at
94 age 2 to 3 years. Daily gluten intake was associated with higher risk of celiac disease
95 autoimmunity (HR 1.30, 95% CI 1.22-1.38) and celiac disease (HR 1.50, 95% CI 1.35-1.66)
96 for every 1-gram/day increase. The absolute risk increases corresponding to HR were 6.1%
97 for celiac disease autoimmunity and 7.2% for celiac disease, respectively.

98 **Conclusions and Relevance:** Higher gluten intake in the first 5 years was associated with

99 increased risk of celiac disease autoimmunity and celiac disease among genetically
100 predisposed children.

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122 **Introduction**

123 Gluten is a food antigen found in wheat, rye and barley. It has a high content of proteins rich
124 in gliadin peptides, which are resistant to complete digestion by gastrointestinal enzymes, and
125 may cause an inflammatory response leading to celiac disease in genetically predisposed
126 individuals¹. Celiac disease is an autoimmune enteropathy affecting approximately 1% of the
127 western population and attributable to both genetic and environmental factors². While gluten
128 consumption and certain human leukocyte antigen (HLA) genes are key factors for celiac
129 disease development, not all individuals with a predisposing genetic background develop
130 lifelong intolerance to gluten³, and the risk is likely to be modified by the timing or quantities
131 of gluten consumed as well as other potential pathophysiologic factors^{4,5}.

132 Celiac disease commonly presents early in childhood⁶, highlighting the importance of
133 studying early life events for identifying triggers of the disease⁷. It was initially reported that
134 early or late introduction of gluten to infants increased the risk of celiac disease^{8,9}. The timing
135 of infant gluten exposure has not been consistently associated with celiac disease risk^{10,11}, and
136 this has led to changing recommendations for infant feeding¹². Importantly, it remains unclear
137 whether the amount of gluten consumed triggers celiac disease^{11,13-15}.

138 Gluten intake during the first 5 years of life was assessed from genetically at-risk children
139 followed in the multinational prospective birth cohort the Environmental Determinants of
140 Diabetes in the Young (TEDDY) study. The aim was to investigate whether the amount of
141 gluten in the diet was associated with development of celiac disease autoimmunity and celiac
142 disease, to allow better understanding of the pathogenesis and to inform feeding
143 recommendations to minimize disease burden.

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146 **Methods**

147 *Study population*

148 This prospective cohort study follows children from birth up to 15 years of age at clinical
149 research centers in Colorado, Georgia, Florida, and Washington state in the U.S., as well as
150 Finland, Germany, and Sweden¹⁶. The final date of follow-up for the present study was
151 September 30, 2017.

152 The primary goal was to identify genetic and environmental factors associated with increased
153 risk of type 1 diabetes, celiac disease, or both. Newborn infants were screened for HLA
154 genotypes associated with type 1 diabetes and celiac disease¹⁷. Distribution of the HLA-
155 genotypes in the study is shown in **Table 1**. For all study participants separate written
156 informed consents for genetic screening and participation in the prospective follow-up
157 beginning at birth were obtained from a parent or primary caretaker. Local institutional or
158 regional ethics review boards in all participating countries approved the study. Full details of
159 study design, eligibility and methods have been published previously^{16,18-20}.

160

161 *Dietary assessment*

162 Gluten intake was estimated from 3-day food records collected at ages 6, 9, and 12 months
163 and biannually (i.e. at 18, 24, 30, 36 months) thereafter until 5 years of age. Parents were
164 asked to keep a food record documenting all foods and drinks consumed by the child over the
165 3-day periods (2 weekdays and 1 weekend day) before the scheduled clinic visit. Normal food
166 habits were encouraged during the time of food record collection. Portion sizes were
167 estimated using household measurements, food models, pictures, drawings and shapes of
168 foods as references. A specific booklet was developed and used in all countries to facilitate
169 estimation of food portion sizes. The dietary assessment method used in the study has been
170 described in detail elsewhere^{15,21}.

171 Dietary intake was analyzed using the food composition databases from each participating
172 country. For analyses at the food group level, a harmonized food grouping system was
173 developed with comparable food groups and quantification of food intakes between the
174 databases used in individual countries²². Composite foods and recipes were broken down to
175 ingredients. Mean intake (g/day) was calculated from total intake of gluten-containing flours
176 (wheat, rye, and barley) reported in the 3-day recording period. Vegetable protein content
177 (using country-specific values) was obtained from the daily intake of gluten-containing flours
178 and converted to amount of gluten using a conversion factor of 0.8 (gluten content in wheat
179 protein)²³. The converted amount was analyzed as absolute gluten intake (g/day).

180

181 *Measurement of tissue transglutaminase (tTG) autoantibodies*

182 Testing for serum tTG autoantibodies started from the 24 months clinic visit and continued
183 yearly thereafter. Radiobinding assays were used to measure tTG autoantibody levels in two
184 laboratories as previously described¹⁹. Briefly, samples from US centers were screened for
185 IgA-tTG autoantibodies at the Barbara Davis Center for Childhood Diabetes, University of
186 Colorado (Denver laboratory)²⁴. Samples from European centers were tested at the University
187 of Bristol, UK, (Bristol laboratory), using an assay that detected both IgA and IgG
188 autoantibodies against tTG²⁵. To harmonize results, all samples with tTG autoantibody index
189 >0.01 in the Denver laboratory were sent for quantification of tTG autoantibodies in the
190 Bristol laboratory, the reference laboratory for the study¹⁹. Results were expressed in arbitrary
191 units derived from a standard curve consisting of dilutions of serum taken from a patient with
192 celiac disease. If a sample tested positive from the Bristol laboratory (≥ 1.3 units)²⁵, the child's
193 earlier blood samples were retrospectively analyzed in the Bristol laboratory to determine the
194 age at which tTG autoantibodies first became detectable. Persistence of tTG autoantibodies

195 was confirmed by finding positive results in two consecutive samples at least 3 months
196 apart²⁶.

197 *Outcomes*

198 The primary outcome was celiac disease autoimmunity, defined as positive tTG
199 autoantibodies measured in the Bristol laboratory in two consecutive samples. Children
200 meeting the criteria for persistence of tTG autoantibodies were referred to a gastroenterologist
201 at the clinical discretion of their usual physician. The decision whether to perform a biopsy
202 was not determined by the TEDDY study protocol. The secondary endpoint was celiac
203 disease, which was defined as an intestinal biopsy showing a Marsh score ≥ 2 or, if biopsy was
204 not performed, non-biopsy proven celiac disease was defined by the average of two samples
205 ≥ 100 units²⁶.

206

207 *Statistical analyses*

208 Time to event was defined as the age of the first positive tTG autoantibody sample for
209 children who later fulfilled the criteria for both celiac disease autoimmunity and celiac
210 disease. The right censored time for celiac disease autoimmunity was the age at the last
211 negative tTG autoantibody sample and for celiac disease was the age at the last clinic visit at
212 which celiac disease had not been diagnosed. In order to control for differences in age or body
213 size, we analyzed energy and age adjusted intake using the residual method²⁷, as well as
214 intake per 10 kg bodyweight at a given age, in addition to absolute daily intake.

215 To address concerns regarding missing data and variability in dietary data, joint modeling was
216 selected as the pre-specified analysis, chosen to assess the association between gluten intake
217 over time and the risk of celiac disease autoimmunity and celiac disease^{28,29}. Joint modeling
218 assesses the association by fitting an individual trajectory for the intake over time. Based on

219 the patterns seen in **eFigure 1** and **eFigure 2**, a linear trajectory was assumed for the
220 longitudinal model and the incidence peak in the beginning was considered for the baseline
221 hazard estimation assuming piecewise constant. Seven intervals without weighting were
222 applied per the best model fit based on ΔAIC ³⁰. The longitudinal model was adjusted for
223 energy intake (kcal/day) at the same time, and the time to event model was adjusted for HLA-
224 genotype, sex, country of residence and family history (mother, father, or sibling) of celiac
225 disease. SAS macro JMFit was used for the analyses³¹. From the log-hazard model fitted by
226 joint modeling, absolute risk by 3 years old was estimated as the cumulative hazard, in
227 relation to the average daily gluten intake at 2 years of age. The hazard ratios and absolute
228 risk increases were assessed at 1 unit increase of gluten intake, conditioned on energy intake
229 (kcal/day) at the same time, HLA-genotype, sex, country of residence and family history of
230 celiac disease.

231 In addition, two Cox regression analyses including the most recent intake prior to the event
232 and energy intake at the same time as time dependent covariates were performed as sensitivity
233 analyses: 1) all children, and 2) children with gluten intake available within 1 year prior to
234 each risk-set, to control for various lag times between gluten exposure and the event.

235

236 As a post-hoc analysis, we examined the effects of age-specific gluten intake. The association
237 with subsequent incidence of celiac disease autoimmunity and celiac disease was assessed
238 using Cox regression, focusing on absolute intake reported at the age of each TEDDY visit.

239 For children whose gluten intake at the specific age was the most recent data prior to the
240 event, the standard Cox regression model assessed the effects of gluten intake reported at the
241 specific age as a time constant covariate. For children who had additional gluten intake data
242 available after the specific age, the most recent gluten intake prior to the event needs to be
243 controlled to assess the effects of the intake reported at the specific age (i.e., the primary

244 interest). In order to assess the effects of age-specific gluten intake in addition to the effect of
245 current intake, the model considered the most recent intake prior to the event as a time
246 dependent covariate and the intake at the specific age as a time constant covariate.
247 The proportional hazard assumption was examined using martingale residual analysis with the
248 supremum test. The functional form in the martingale residual plot, as well as change-point
249 analysis based on log-rank test³², suggested a dichotomization for absolute gluten intake at 2
250 years of age.
251 Two-sided p-values are reported. Statistical significance was determined when the p-value
252 was <0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.,
253 Cary, NC).

254

255 **Results**

256 Between September 2004 and February 2010, 424,788 newborn infants were screened for
257 HLA and 21,589 (5%) HLA-eligible infants were identified, of whom 8,676 (40%) were
258 enrolled in this study before the age of 4 months. The most common reasons for failing to
259 enroll to this 15-year follow-up study were related to protocol characteristics (e.g. blood draw,
260 demanding protocol) or family circumstances (e.g. changing contact information)³³. At time
261 of analysis, 6,757 children had been screened for tTG autoantibodies, and 6,605 (97.8%) had
262 submitted at least one 3-day food record during the first 5 years of life or prior to detection of
263 tTG autoantibody positivity (**eFigure 3**). Descriptive characteristics of the study population
264 are presented in **Table 1**. Of 6,605 children in the study, 3,233 (49%) were girls. Data on
265 gluten intake were missing or of inadequate quality in 4,465 visits (8%) of the 52,952 visits
266 for which parallel tTG results were available. In total, 204 (3%) subjects completed at only
267 one food record. Among children with celiac disease autoimmunity, 20 (1.6%) subjects
268 completed one food record more than 3 months prior to their seroconversion.

269 As of September 30, 2017, among the 6,605 children included in the analysis, 1,411 (21%)
270 had tested positive for tTG autoantibodies on at least one occasion. During a median follow
271 up of 9.0 years (range 1.0 – 13.0, interquartile range 8.0 – 10.0) 1,216 (18%) children with
272 celiac disease autoimmunity had seroconverted to positive tTGA autoantibodies at a median
273 age of 3.3 years (range 0.9 - 11.5), and 447 (7%) children fulfilling the criteria for celiac
274 disease had their seroconversion at a median age of 3.0 years (range 0.9 – 11.2). The
275 incidence of seroconversion for both endpoints peaked around 2 to 3 years of age (**eFigure 1**).

276 Children homozygous for DR3-DQ2 were at the highest risk of celiac disease autoimmunity
277 and celiac disease. Swedish residence, female sex, and family history of celiac disease were
278 also associated with increased risk for both endpoints (**eTable 1**).

279 Gluten consumption linearly increased with age with some national differences (**eFigure 2**,
280 **eTable 2**). Higher intake of gluten during the first 5 years of life was associated with
281 increased risk of both celiac disease autoimmunity and celiac disease (**Table 2**). Absolute
282 intake of gluten was associated with higher risk of celiac disease autoimmunity (HR 1.30,
283 95% CI 1.22 -1.38; $p < 0.001$) and celiac disease (HR 1.50, 95% CI 1.35 -1.66; $p < 0.001$)
284 for every per 1-gram/day increase in gluten consumption. Age- and energy adjusted gluten
285 intake was associated with higher risk of celiac disease autoimmunity (HR 1.40, 95% CI 1.30
286 -1.52; $p < 0.001$) and celiac disease (HR 1.43, 95% CI 1.23 -1.68; $p < 0.001$) for every per
287 1-gram/day increase in gluten consumption. In addition, gluten intake per 10 kg bodyweight
288 was associated with higher risk of celiac disease autoimmunity (HR 1.87, 95% CI 1.66 -2.11;
289 $p < 0.001$) and celiac disease (HR 2.18, 95% CI 1.75 -2.71; $p < 0.001$) for every per 1-
290 gram/day/10kg increase in gluten consumption. Sensitivity analysis using Cox regression
291 models supported the statistical significance found from the joint modeling analysis (**Table**
292 **2**).

293 In the country-specific analyses, a higher gluten intake was associated with an increased risk
294 of celiac disease autoimmunity in all countries (**eTable 3**). Absolute gluten intake and age-
295 and energy adjusted intake were associated with increased risk for celiac disease in the U.S.
296 and Sweden.

297 Finally, the absolute risks by 3 years of age in relation to the average daily gluten intake at 2
298 years of age were assessed. The absolute risk difference suggests the risk increase if gluten
299 was 1 unit higher than the average daily gluten intake at 2 years of age. The absolute risk
300 increases were 6 to 18% for celiac disease autoimmunity and 3 to 20% celiac disease,
301 respectively (**Table 3**).

302 *Post-hoc analysis*

303 In view of the early peak incidence of seroconversion to later celiac disease autoimmunity and
304 celiac disease, we focused on the intake reported at 2 and 3 years of age, respectively. Gluten
305 intake reported at the 2-year visit was available for 833 children with celiac disease
306 autoimmunity and intake reported at the 3-year visit was available for 526 children with celiac
307 disease autoimmunity. The analysis showed that gluten intake at 2 years of age had an
308 independent effect on the risk of celiac disease autoimmunity and celiac disease, in addition to
309 the current intake during the first 5 years of life (**eTable 4**).

310 The supremum test showed no indication of violating the proportional hazard assumption, but
311 there was a deviation at >2 g gluten intake per day in the martingale residual plot (**eFigure 4**).

312 In addition, the change point analysis showed a significance risk difference between >2 and \leq
313 2g/day. Based on these analyses, we dichotomized the gluten intake reported at 2 years as >2
314 and ≤ 2 g/day and examined the adjusted HRs with the endpoints (**Table 4**). Children who
315 consumed gluten >2 g/day at 2 years of age had a 50% higher risk of celiac disease
316 autoimmunity (HR 1.49, 95% CI 1.16 – 1.91; $p = <0.002$) and a 75% higher risk of celiac
317 disease (HR 1.75, 95% CI 1.10 – 2.81; $p = <0.019$), compared with those who consumed ≤ 2 g

318 gluten per day. When analyzing absolute gluten intake reported at the 2-year visit and risk for
319 developing celiac disease autoimmunity and celiac disease, using a subsequent increase in
320 gluten intake, a linear increase in hazard ratios were seen for higher intakes (**Table 5**).

321 **Discussion**

322 Higher gluten intake in the first 5 years was associated with increased risk of celiac disease
323 autoimmunity and celiac disease among genetically predisposed children.

324 The incidence of both endpoints peaked around 2 to 3 years of age. In the post-hoc analysis,
325 the association with gluten intake on these risks was significantly increased if the child
326 consumed more than 2 g/day at around 2 years of age, which corresponds to approximately
327 one slice (35 g) of white bread or 1 portion of cooked pasta (150g). Also, hazard ratios
328 increased with subsequent higher gluten intake at the 2 year visit suggesting that higher
329 intakes were associated with higher risk of celiac disease autoimmunity and celiac disease.

330 These findings are in line with a previous retrospective case-control study of gluten intake in
331 Swedish children born during the mid-1980s, which showed that children subsequently
332 diagnosed with celiac disease had been introduced to larger amounts of gluten-containing
333 foods compared with children who did not develop celiac disease¹³.

334 The hypothesis that gluten given in small amounts at 5 to 6 months of age would protect at-
335 risk children from developing celiac disease was furthermore addressed in a randomized
336 placebo-controlled intervention trial, though with null results¹¹. In the same study population,
337 mean daily gluten intake, from 10 months of age when unrestricted gluten consumption was
338 allowed, was not associated with celiac disease up to 3 years of age, except in children
339 carrying the HLA-genotype HLA-DQ2.2/-DQ7¹⁴.

340 In contrast to the randomized placebo-controlled intervention trial, gluten consumption during
341 the first 2 years of life was previously found associated with increased risk of celiac disease in
342 a subset of Swedish children from the present cohort, and furthermore, children in the upper

343 tertile of gluten intake were at a 2-fold increased risk of celiac disease, compared with
344 children with lower gluten intake. This nested case-control study on 146 children with biopsy
345 confirmed celiac disease and 436 matched controls indicated that the amount of gluten
346 consumed could be a risk factor for celiac disease¹⁵.

347 For the current study, food record data from all the participating countries have been
348 harmonized which enabled us to do longitudinal analysis of the full birth cohort. In addition,
349 we have extended the data with gluten intake up to 5 years of age and included another 301
350 children diagnosed with celiac disease and performed time to event analyses. This extended
351 data set yields credible power to do country-specific analysis for celiac disease autoimmunity
352 and celiac disease, except for the German site, which had only 16 cases with celiac disease. In
353 these country-specific analyses, a higher gluten intake was associated with an increased risk
354 of celiac disease autoimmunity in all countries, whereas absolute gluten intake and age- and
355 energy adjusted intake were only associated with increased risk for celiac disease in the U.S.
356 and Sweden.

357 Despite similar dietary assessment methods and calculation of gluten intake, discrepancies in
358 results between the studies are likely attributed to study design and population size. In the
359 randomized controlled study, the gluten introduction was overlooked and gluten amounts
360 were fixed¹¹, which indeed differed from the present observational study consisting of a larger
361 population that reflected the natural variations of gluten intake in real life. Other contributing
362 factors may be differences in exposures to various triggering environmental factors such as
363 gastrointestinal infections or rotavirus vaccination status⁵, which partly could explain why
364 Swedish children are more prone to develop celiac disease as compared to children from other
365 countries.

366 A major strength of this study as compared to the aforementioned the randomized controlled
367 study¹¹, is its prospective study design, enrolling a large cohort of children with the same

368 genetic risk, from four countries with different infant feeding habits and following the same
369 study protocol. Another strength is the dietary assessment method that allowed repeated
370 measurements to capture changes in dietary habits in growing infants and young children over
371 time prior to disease onset. The prospective design also reduced the effect of changes in
372 dietary habits because parents were unaware of their child's autoantibody status at time food
373 records were collected. Our analyses were also adjusted for known confounders for celiac
374 disease (HLA, country, gender, and having a family member with celiac disease)²⁶. Moreover,
375 potential confounders such as socioeconomic status in terms of maternal smoking (during
376 pregnancy), maternal education, and maternal age had previously already been analyzed and
377 were not associated with risk of celiac disease³⁴ and therefore considered less likely to
378 confound the results.

379 *Limitations*

380 This study has several limitations. First, the lack of information of analyzed gluten content in
381 foods in national food composition databases. Therefore, the same conversion factor for
382 estimation of gluten content in wheat, rye and barley was chosen because this method has
383 been used in several previous studies^{10,14,15,35}. Other studies have used cereal specific
384 conversion factors for the estimation of gluten content³⁶. Second, calculations of gluten
385 content are approximate as they are based on self-reported dietary data. Different dietary
386 assessment methods together with differences in methods of estimating gluten content are
387 challenging when comparing results from previous studies. Conclusions should therefore be
388 taken with care. A randomized trial of different amounts during early childhood in genetically
389 at-risk individuals would therefore be warranted to confirm our findings.

390 **Conclusions**

391 Higher gluten intake in the first 5 years was associated with increased risk of celiac disease
392 autoimmunity and celiac disease among genetically predisposed children.

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494 **Table 1.** Descriptive characteristics of the study population, by study endpoint.

	Children always negative for tTG autoantibodies (n = 5,194)	Children with celiac disease autoimmunity (n = 1,216)	Children with celiac disease (n = 447)
Country	n (%)	n (%)	n (%)
USA	2108 (40.5)	444 (36.5)	131 (29.3)
- HLA DR3-DQ2/DR3-DQ2 ^a	391 (18.5)	194 (43.7)	69 (52.7)
- HLA DR3-DQ2/DR4-DQ8 ^b	849 (40.3)	183 (41.2)	50 (38.2)
- HLA others ^c	868 (41.2)	67 (15.1)	12 (9.1)
Finland	1218 (23.5)	251 (20.6)	78 (17.4)
- HLA DR3-DQ2/DR3-DQ2 ^a	124 (10.2)	79 (31.5)	36 (46.2)
- HLA DR3-DQ2/DR4-DQ8 ^b	376 (30.9)	120 (47.8)	30 (38.5)
- HLA others ^c	718 (58.9)	52 (20.7)	12 (15.4)
Germany	314 (6.1)	57 (4.7)	16 (3.6)
- HLA DR3-DQ2/DR3-DQ2 ^a	50 (15.9)	22 (38.6)	9 (56.2)
- HLA DR3-DQ2/DR4-DQ8 ^b	131 (41.7)	19 (33.3)	4 (25.0)
- HLA others ^c	133 (42.4)	16 (28.1)	3 (18.8)
Sweden	1554 (29.9)	464 (38.2)	222 (49.7)
- HLA DR3-DQ2/DR3-DQ2 ^a	225 (14.5)	202 (43.5)	108 (48.6)
- HLA DR3-DQ2/DR4-DQ8 ^b	690 (44.4)	152 (32.8)	66 (29.7)
- HLA others ^c	639 (41.1)	110 (23.7)	48 (21.6)
First degree relative with celiac disease			
Yes	129 (2.5)	126 (10.4)	77 (17.2)
No	5065 (97.5)	1090 (89.6)	370 (82.8)
Sex			
Female	2453 (47.3)	693 (57.0)	281 (62.9)
Male	2741 (52.7)	523 (43.0)	166 (37.1)
Breastfeeding duration, months, median (q1, q3)	7.8 (3.5, 12.0)	8.3 (5.0, 12.0)	8.1 (5.0, 12.0)
Age at gluten introduction, months, mean (SD)	6.2 (1.9)	6.1 (1.8)	5.9 (1.9)

495 **Footnote:** Detailed description of human leukocyte antigen (HLA) genotypes followed in TEDDY.

496 ^a DR3-DQA1*05:01-DQB1*02:01 / DR3-DQA1*05:01-DQB1*02:01

497 ^b DR4-DQA1*03:0X-DQB1*03:02 / DR3-DQA1*05:01-DQB1*02:01

498 ^c DR4-DQA1*03:0X-DQB1*03:02 / DR4-DQA1*03:0X-DQB1*03:02 or DR3-DQA1*05:01-DQB1*03:02 / DR8-DQA1*04:01-DQB1*04:02,

499 DR4-DQA1*03-DQB1*03:02/DR3-DQA1*05:01-DQB1*02:01, DR4-DQA1*03-DQB1*03:02/DR4-DQA1*03-DQB1*03:02, DR4-DQA1*03-DQB1*03:02/DR8-

500 DQA1*04:01-DQB1*04:02, DR3-DQA1*05:01-DQB1*02:01/DR3-DQA1*05:01-DQB1*02:01, DR4-DQA1*03-DQB1*03:02/DR4-DQA1*03-DQB1*02, DR4-DQA1*03-

501 DQB1*03:02/DR1-DQA1*01:01-DQB1*05:01, DR4-DQA1*03-DQB1*03:02/DR13-DQA1*01:02-DQB1*06:04, DR4-DQA1*03-DQB1*03:02/DR9-DQA1*03-

502 QB1*03:03,or DR3-DQA1*05:01-DQB1*02:01/DR9-DQA1*03-DQB1*03:03.

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514 **Table 2.** Daily gluten intake and risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study.

Analysis ^a	Measurements of gluten	Celiac disease autoimmunity		Celiac disease	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Joint modeling, n=1,216	Absolute intake (g/day)	1.30 (1.22 to 1.38)	<0.001	1.50 (1.35 to 1.66)	<0.001
	Residual intake (g/day) ^b	1.40 (1.30 to 1.52)	<0.001	1.43 (1.23 to 1.68)	<0.001
	Intake/10kg body weight	1.87 (1.66 to 2.11)	<0.001	2.18 (1.75 to 2.71)	<0.001
Cox regression, n=1,216	Absolute intake (g/day)	1.14 (1.11 to 1.17)	<0.001	1.14 (1.09 to 1.20)	<0.001
	Residual intake (g/day) ^b	1.12 (1.09 to 1.15)	<0.001	1.07 (1.02 to 1.13)	0.011
	Intake/10kg body weight	1.19 (1.14 to 1.23)	<0.001	1.14 (1.07 to 1.22)	<0.001
Cox regression including only those with gluten consumption available within 1 year prior to time of event, n=905	Absolute intake (g/day)	1.12 (1.08 to 1.16)	<0.001	1.07 (1.02 to 1.13)	0.009
	Residual intake (g/day) ^b	1.09 (1.05 to 1.13)	<0.001	1.04 (0.99 to 1.10)	0.140
	Intake/10kg body weight	1.15 (1.10 to 1.20)	<0.001	1.12 (1.05 to 1.21)	0.002

515 ^a Adjusting for HLA-type, country, sex, FDR with celiac disease, and energy intake

516 ^b Age- and energy adjusted intake using the residual method ^(ref 27).

517 n = Number of children with celiac disease autoimmunity included in each analysis.

518

519 **Table 3.** Absolute risk for developing celiac disease autoimmunity and celiac disease in the TEDDY study, conditioned on HLA-type, country,
 520 sex, FDR with celiac disease, and energy intake. Cumulative hazard from the log-hazard model fit by the joint modeling in Table 2.

Measurements of gluten	Gluten intake (Reference ^a)	Celiac disease autoimmunity			Celiac disease		
		Absolute risk by 3 years of age if gluten was consumed at reference amount (%)	Absolute risk by 3 years of age if 1 unit higher than reference was consumed (%)	Absolute risk difference (%)	Absolute risk by 3 years of age if gluten was consumed at reference amount (%)	Absolute risk by 3 years of age if 1 unit higher than reference was consumed (%)	Absolute risk difference (%)
Absolute intake (g/day)	3.71	28.1	34.2	6.1	20.7	27.9	7.2
Residual intake (g/day) ^b	0.48	18.7	24.6	5.9	7.8	10.7	2.9
Intake/10kg body weight	2.91	51.9	70.2	18.3	35.0	55.0	20.0

521 ^a Average gluten intake reported at the 2-year visit was considered as reference

522 ^b Age- and energy adjusted intake using the residual method ^(ref 27).

523 Abbreviation: FDR; First degree relative

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525 **Table 4.** Daily absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease
 526 in the TEDDY study.

Model		Celiac disease autoimmunity		Celiac disease	
		HR (95% CI)	p-value	HR (95% CI)	p-value
A	≤ 2g/day	1		1	
	>2 g/day	1.49 (1.16 to 1.91)	0.002	1.75 (1.10 to 2.81)	0.019
B	≤ 2g/day	1		1	
	>2 g/day	1.62 (1.29 to 2.03)	<0.001	1.71 (1.12 to 2.60)	0.012

527 A: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake and the most recent gluten intake prior to the event as time dependent covariates

528 B: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2 year TEDDY visit.

529

530 **Table 5.** Daily absolute gluten intake reported at the 2-year visit and risk for developing celiac disease autoimmunity and celiac disease
 531 in the TEDDY study.

Model ^a	Celiac disease autoimmunity		Celiac disease	
	HR (95% CI)	p-value	HR (95% CI)	p-value
≤ 2 g/day	1		1	
> 2 and ≤ 4 g/day	1.52 (1.20 to 1.93)	<0.001	1.57 (1.02 to 2.41)	0.041
> 4 and ≤ 6 g/day	1.77 (1.37 to 2.29)	<0.001	1.96 (1.24 to 3.11)	0.004
> 6 and ≤ 8 g/day	2.43 (1.76 to 3.36)	<0.001	2.69 (1.53 to 4.71)	<0.001
> 8 g/day	1.54 (0.81 to 2.93)	0.70	2.04 (0.68 to 6.08)	0.20

532 ^aAdjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2 year TEDDY visit

533

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552 **Access to Data and Data Analysis**

553 Dr. Hye-Seung Lee had full access to all the data in the study and takes responsibility for the
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555 **Conflict of Interest Disclosures**

556 No disclosures were reported.

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