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TITLE PAGE

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Abbreviations:
ATC: anatomical therapeutic chemical coding system. BMI: body mass index. CI: confidence interval. DNBC: the Danish National Birth Cohort. HLA: human leukocyte antigen. MoBa: The Norwegian Mother and Child Cohort Study. N/A: Not available. OR: odds ratio.

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Title: Association Between Antibiotics in the First Year of Life and Celiac Disease

Abstract:
Background & Aims: The intestinal microbiota is thought to be involved in pathogenesis of celiac disease, along with genetic variants and dietary gluten. The gut microbiota is strongly influenced by systemic antibiotics—especially in early life. We explored the association between exposure to a systemic antibiotic in the first year of life and risk of diagnosed celiac disease.

Methods: We performed an observational nationwide register-based cohort study. We included all children born in Denmark from 1995 through 2012 or Norway from 2004 through 2012. Children born in Denmark were followed until May 8, 2015 (age at end of follow-up was 2.3–20.3 years) and children born in Norway were followed until December 31, 2013 (age at end of follow-up was 1–10 years). We collected medical information from more than 1.7 million children, including 3346 with a diagnosis of celiac disease. Exposure to systemic antibiotics was defined as a dispensed systemic antibiotic in the first year of life.

Results: Exposure to systemic antibiotics in the first year of life was positively associated with diagnosed celiac disease in the Danish and in the Norwegian cohort (pooled odds ratio, 1.26; 95% CI, 1.16–1.36). We found a dose-dependent relationship between an increasing number of dispensed antibiotics and the risk of celiac disease (pooled odds ratio for each additional dispensed antibiotic, 1.08; 95% CI, 1.05–1.11). No specific type of antibiotic or age period within the first year of life was prominent. Adjustment for hospital admissions with an infectious disease in the first year of life did not change the estimates; adjustment for the number of maternally reported infections in the child in 2 large sub-cohorts reduced the association slightly (pooled odds ratio, 1.18; 95% CI, 0.98–1.39).

Conclusion: In a nationwide study of children in Denmark and Norway, we found exposure to systemic antibiotics in the first year of life to be associated with a later diagnosis of celiac disease. These findings indicate that childhood exposure to systemic antibiotics may be a risk factor for celiac disease.

KEY WORDS: microbiome; epidemiology; population; autoimmunity

Celiac disease is a chronic immune-mediated enteropathy driven by the ingestion of dietary gluten in genetically predisposed individuals.[1] The presence of one of the human leukocyte antigens (HLA) DQ2 or DQ8 and exposure to dietary gluten are necessary but insufficient causes of celiac disease. Only a few individuals carrying HLA DQ2 or DQ8 develop celiac disease, suggesting that additional factors are involved in disease development. Non-HLA genetic variants associated with celiac disease are thought to account for a proportion of the disease risk.[2] Environmental factors, in addition to gluten, are not well-established and equivocal.

The role of the gut microbiota has attracted increasing interest as a contributing factor in the pathogenesis of autoimmune diseases,[3] including celiac disease.[4] Studies have reported differences in gut microbiota when comparing patients with active celiac disease to healthy controls.[5, 6]

The gut microbiota evolves dramatically in the first years of life[7] and stabilizes at two to three years of age.[8] The gut microbiota in early life influences the maturation of the immune system[9] and plays a role in the degradation of gluten in the gastrointestinal tract and may thereby affect the immunogenicity of gluten peptides.[10] Antibiotic exposure has a strong and sustained impact on the developing and unstable intestinal ecosystem.[11, 12]

The objective of the present study was to study whether use of systemic antibiotics in the first year of life was associated with diagnosed celiac disease in two large independent nationwide cohorts with different prevalence of diagnosed celiac disease.

MATERIALS AND METHODS

This study was an observational register-based study of two independent nationwide cohorts, one from Denmark and one from Norway, using data from administrative and health administrative registers. All registrations were linked at the individual-level. Based on data availability, all children who were born in Denmark from January 1, 1995, to December 31, 2012, and all children who were born in Norway from January 1, 2004, to December 31, 2012 and registered in the medical birth registers were included in the study. In addition, we included data from two large birth cohorts for a subgroup of the included children to examine the effects of adjusting for the number of maternally reported infections in the child and duration of breastfeeding as potential confounders.

Outcome: Diagnosed celiac disease

The outcome was diagnosed celiac disease (International Classification of Diseases 10th Revision (ICD-10) K90.0).

The Danish National Patient Register includes all the inpatients and outpatients seen in Danish hospitals.[13] To identify children with celiac disease, we included all the registrations of celiac disease and confirmed the diagnoses with duodenal biopsies registered in the Danish Pathology Data Bank and celiac disease-specific antibodies from medical records.[14] We considered the diagnosis to be confirmed if a duodenal biopsy compatible with celiac disease i.e. Marsh 2–3[15] (81% of the confirmed cases) or if a measurement of IgA tissue transglutaminase 2 antibodies at 10 or more times the upper limit of normal or a positive IgA endomysial antibody measurement (70% of the confirmed cases) was registered. The end of the follow-up in Denmark was May 8, 2015.[14]

The Norwegian National Patient Register includes diagnoses from Norwegian hospitals and outpatient clinics.[16] We considered all the children with two or more registrations of celiac disease as having diagnosed celiac disease. The use of two or more registrations has been previously validated for participants in the Norwegian Mother and Child Cohort Study (MoBa).[17] The data did not include the exact dates of registration but were available as cumulative data for each year since 2008. Children diagnosed in the period 2004–2008 were registered at the recommended annual hospital follow-up from 2008 onwards, but the exact year of diagnosis was unavailable. The end of follow-up in Norway was December 31, 2013.

Exposure: Dispensed systemic antibiotics

The main exposure was a systemic antibiotic dispensed from a pharmacy in the first year of life. In Denmark and Norway, antibiotics are available by prescription only. All antibiotics dispensed outside of hospitals (90% of antibiotics used in Denmark, and 93% of antibiotics used in Norway) are registered at the individual level in national prescription registers and drugs are classified according to the Anatomical Therapeutic Chemical (ATC) Coding System.[18, 19] We included all systemic antibiotics (ATC J01) dispensed in the first two years of life. The use of antibiotics from one to two years of age was included in sub-analyses.

In the Norwegian Prescription Register, approximately 30% of the prescriptions from the first year of life lacked ID numbers (range, 17–56% per year) (Table S.1) which excluded the individual-level linkage. Prescriptions with missing ID numbers were not included in the study, and thus the exposure to antibiotics was an underestimate and some children exposed to antibiotics may have been misclassified as unexposed. However, there are no reasons to assume that this is dependent on celiac disease diagnosis.

Antibiotic treatment for infections requiring hospitalization is often completed outside of the hospital and in these cases dispensed antibiotics are usually registered. An exception occurs in the cases of neonatal infections, which are typically treated by intravenous antibiotics in the hospital only. In the Danish cohort, we constructed a proxy variable for antibiotic exposure in the neonatal period as admissions in the neonatal period (0–28 days of age) of at least three days duration with an infectious diagnosis, for included diagnoses, please refer to Table S.2. The proxy variable for neonatal exposure in the Danish cohort was only used in the sub-analysis of the age at first exposure. In the Norwegian cohort, we included information on systemic antibiotics administered at the neonatal ward (yes or no) from the Norwegian Medical Birth Register.

Exposure to antibiotics was categorized as any (≥1) dispensed antibiotic and the number of dispensed antibiotics with no dispensed antibiotic in this age period or prior to this age period as a reference. We categorized the types of antibiotics based on the most commonly prescribed groups of antibiotics. See Table S.3 for details.

Other variables

We included information from the Danish Civil Registration System, the Danish National Patient Register, the Danish Medical Birth Register, the Danish Population's Education Register, the Norwegian Medical Birth Register, and Statistics Norway on the following potential confounders: gestational age, birthweight, season of birth, maternal parity, maternal age, maternal educational

level, maternal smoking during pregnancy, maternal pre-pregnancy body mass index (BMI), maternal country of birth, and maternal diabetes diagnosed prior to the birth of the child. We included information from the Danish National Patient Register on the child's hospital admissions for infections in the first year of life, chromosomal and autoimmune diseases known to be associated with celiac disease and diagnosed prior to the first registration of celiac disease, and maternal autoimmune disease diagnosed prior to the birth of the child. From the Danish National Prescription Register, we included dispensed antifungals for topical use (ATC D01A) as a negative control. From the Norwegian National Prescription Register, we included dispensed insulin (ATC A10A) and considered children with two or more registrations to have type 1 diabetes. See the supplementary material (Section 1.1 *Registers and variables* and Table S.2) for additional information.

The Danish National Birth Cohort (DNBC) and the Norwegian Mother and Child Cohort Study (MoBa)

To examine the effect of adjusting for the number of maternally reported infections in the child and the duration of breastfeeding as potential confounders, we included data from two large national birth cohorts with overlapping study periods: the Danish National Birth Cohort (DNBC)[20] and the Norwegian Mother and Child Cohort Study (MoBa).[21]

The DNBC includes approximately 30% (94,000 children) of all children born in Denmark from 1998 to 2003. The mothers answered questionnaires about infectious diseases in the child and infant feeding via computer-assisted telephone interviews (questionnaires) when the child was 6 and 18 months old. The mothers were asked if the child had had a specific symptom or disease during the periods of 0–6 months of age (common cold, diarrhea, acute otitis media, bronchitis or pneumonia) and 6–18 months (common cold, diarrhea, acute otitis media, bronchitis, pseudocroup, tonsillitis, fever, pneumonia or scarlatina) respectively. Fungal infections (oral thrush and other fungal infections) were included as a separate variable. The mothers were asked how often the disease lasted more than three days (common cold, diarrhea, tonsillitis and fever) or how many times they had had the disease (acute otitis media, bronchitis, pneumonia, pseudocroup and scarlatina). The mothers were also asked about infant feeding including the duration of breastfeeding. The questionnaires are available in Table S.4 and at www.dnbc.dk.

The MoBa recruited participants from all over Norway from 1999 to 2008 and the women consented to participation in 41% of the pregnancies corresponding to approximately 114,000 participating children. We included only children born in our study period (2004–2008). The mothers filled in questionnaires about infectious diseases in the child and infant feeding when the child was 6 and 18 months old. The mothers were asked if the child had had specific health problems (common cold, diarrhea, throat infection, ear infection, bronchitis/pneumonia, diarrhea, urinary tract infection or pseudocroup) and the number of times they occurred in the age periods 0–6 months of age (6-month questionnaire), 6–12 months of age, and 12-18 months of age (18-month questionnaire). Mårild et al. have previously reported that the number of infectious episodes is associated with celiac disease in the MoBa.[22] Information on fungal infections was not available in the MoBa. The mothers were also asked about breastfeeding during the first week of life and each

month until 6 months of age and in 3-month intervals from 6 to 18 months of age. The questionnaires are available in Table S.4 and at www.fhi.no/en/studies/moba.
The number of infectious episodes was estimated as the sum of positive indications of infections from the questionnaires at 6 and 18 months of age. In the DNBC, common cold, diarrhea, tonsillitis and fever of less than three days was not included because the mothers were asked only about symptoms lasting more than three days. If the answers for one or more type of infection were missing, the values were set to no infectious episodes of this type and this may also have led to underestimation of the total number of infectious episodes.
The duration of breastfeeding was categorized as 0–3 months, 3–6 months, 6–9 months, 9–12 months, and 12 months or longer. We did not distinguish between exclusive breastfeeding or partial breastfeeding.

Statistics

The data were analyzed using a logistic regression model with robust cluster variance estimation to take into account siblings with the same mother. All the analyses were adjusted for year of birth to take into account differences in follow-up times and the increasing prevalence of celiac disease and the propensity to prescribe antibiotics in the study period. Furthermore, all the analyses were adjusted for sex as a confounding variable because girls are more likely to develop celiac disease[1] and boys are more often treated with antibiotics in early life.[19] In the Danish cohort, we excluded children diagnosed before or in the exposed age period to minimize the risk of reverse causality. This was not possible in the Norwegian cohort because the exact age at diagnosis was not known. The Danish cohort and the Norwegian cohort were analyzed separately. The estimates were pooled using a fixed-effect meta-analysis. The degree of statistical heterogeneity was assessed by the I^2 test.[23]
The main exposure was dispensed systemic antibiotics in the first year of life. As a sensitivity analysis, we examined dispensed antibiotics in the first 3, 6, 9, 12, 18 and 24 months of life both as the age period for the first antibiotic exposure, the cumulative exposure since birth, and any exposure in a given age period regardless of previous exposures.
We examined the effects of adjusting for the following additional potential confounders: hospital contact with an infectious disease in the first year of life, gestational age, weight for gestational age, season of birth, maternal parity, maternal educational level, maternal age, maternal smoking during pregnancy, maternal country of birth, maternal autoimmune disease diagnosed prior to the birth of the child, and maternal pre-pregnancy BMI.
Information in the DNBC and the MoBa was available for the first 18 months of life. For the children participating in the DNBC or the MoBa, we analyzed the association between antibiotic exposure in the first 18 months of life and diagnosed celiac disease and the effect of adjusting for the number of maternally reported infections in the child, the number of fungal infections in the child (DNBC) and duration of breastfeeding.
We stratified the analyses for the age at celiac disease diagnosis (first registration): 1–4 years of age, 5–8 years of age and 9–19 years of age. In the Danish cohort, we stratified the analyses for the presence of associated comorbidity in the child (yes/no). As a post hoc analysis, we stratified the analyses for the mode of delivery (both cohorts), autoimmune disease in the mother or the child

(Danish cohort) and a diagnosis of type 1 diabetes in the mother or the child (both cohorts). We tested for evidence for effect modification by testing for statistical interaction between the potential effect modifier and antibiotic exposure in the first year of life using the log likelihood ratio test.
To examine the effect of the model choice, we analyzed the Danish data using a Cox proportional hazards regression model with follow-up time from one year of age to the first event of diagnosis, emigration, death, or January 1, 2015. We adjusted for year of birth and sex.
To examine potential bias due to missing ID numbers in the Norwegian National Prescription Register, we stratified the analyses according to the proportion of missing ID numbers: 2004–2007 (42% missing), 2008–2009 (26% missing), and 2010–2013 (20% missing). See the supplementary material (Table S.1).
To test the effect of the criteria for diagnosed celiac disease, we conducted the main analysis using one or more registrations of celiac disease in the national patient registers, two or more registrations of celiac disease in the national patient registers (the definition used in the Norwegian cohort) and diagnoses confirmed by a registration of a duodenal biopsy or serology compatible with a celiac disease diagnosis (the definition used in the Danish cohort, only available in the Danish cohort). See the supplementary material (Section 3. *Definition of outcome)*.
A 95% confidence interval (95% CI) for the odds ratio (OR) that excluded 1.00 was considered statistically significant. All the analyses were conducted using Stata version 15 statistical software (StataCorp LP, College Station, TX, USA).

Ethics

The Danish study was approved by the Danish Data Protection Agency. Patient consent from the participants and notification of the regional committees on health research ethics was not required as this was a register-based study not including human biological material. The DNBC was approved by the Committee on Biomedical Research Ethics (KF 01-471/94) and the Danish Data Protection Agency.
The Norwegian study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics (2013/2114-12). The study was exempted from individual consent as it was a register-based study with a low risk of personal identification. The data collection in the MoBa has a license from the Norwegian Data Inspectorate and approval from the Regional Committee for Medical Research Ethics.
Informed consent was obtained from all participants in the DNBC and the MoBa.

RESULTS

For the analyses in the Danish cohort, we included 1,168,656 children after exclusions for inconsistent data in personal identification numbers (n=39). The median age at end of follow-up was 11.6 years (range: 2.3–20.3 years). Celiac disease was registered for 1,427 children (0.12%). Systemic antibiotics in the first year of life were dispensed to 451,196 children without celiac disease (38.7%) and to 622 children with celiac disease (43.6%).
For the analyses in the Norwegian cohort, we included 537,457 children after exclusions for inconsistent data in personal identification numbers (n=3,579). The median age at end of follow-up was 5.4 years (range: 1–10 years). Celiac disease was registered for 1,919 children (0.36%).

Systemic antibiotics in the first year of life were dispensed to 98,538 children without celiac disease (18.4%) and to 390 children with celiac disease (20.3%). In Norway, the proportion of children with a dispensed systemic antibiotic was approximately 30% higher than reported here because prescriptions lacking ID numbers were not included in this study.
Table 1 and Table S.5 show the distribution of the potential confounders according to antibiotic exposure in the first year of life. Antibiotic exposure in the first year of life was less common in girls, children born in autumn, firstborn children, children of mothers with a higher educational level and children who were breastfed for a longer period of time.

Antibiotic exposure and celiac disease
Exposure to systemic antibiotics in the first year of life was positively associated with diagnosed celiac disease in both the Danish and the Norwegian cohort (pooled adjusted OR: 1.26; 95% CI: 1.16–1.36) with a dose-dependent relationship between an increasing number of dispensed antibiotics and the risk of celiac disease (pooled adjusted OR for each additional dispensed antibiotic: 1.08; 95% CI: 1.05–1.11). Adjustment for hospital contacts with an infectious disease in the first year of life (only available in the Danish cohort) (Table 2) and other potential confounders (Table S.6) did not change the estimates substantially.
Analysis of the Danish data using a Cox proportional hazards regression model did not change the association (data not shown).
Table 2 shows the association between antibiotic exposure in the first 6, 12, 18, and 24 months of life and celiac disease. Antibiotic exposure was associated with celiac disease in all age groups except exposure from 0–6 months of age in the Norwegian cohort.
The association between age at first exposure and celiac disease is shown in figure 1A and the association between age at any exposure and celiac disease is shown in figure 1B. The association between exposure to different types of antibiotics in the first year of life and the risk of celiac disease is shown in figure 1C-D. The associations did not appreciably differ by type of antibiotic or age at exposure.

Stratification for age at diagnosis, associated comorbidity and mode of delivery
We found a positive association for all the groups of the age at diagnosis (Table 3).
Stratification for the presence of an associated comorbidity diagnosed prior to celiac disease showed no association between antibiotic exposure and risk of celiac disease in the group of children with an associated comorbidity. Post hoc analyses showed no association between antibiotics and celiac disease in the group with a diagnosed associated autoimmune disease in the mother or the child (Danish cohort) or the groups with diagnosed type 1 diabetes in the mother or the child (Table 3).
Table 3 shows comparable estimates across strata for mode of delivery with no evidence of effect modification.

Maternally reported infections in the child and duration of breast-feeding (DNBC/MoBa)
We included 55,082 children (100 with celiac disease) from the DNBC and 53,257 children (464 with celiac disease) from the MoBa with completed questionnaires about breastfeeding and

infectious diseases 6 and 18 months postpartum. Adjustment for breastfeeding did not change the association. Adjustment for the number of maternally reported infections in the child weakened the association slightly. In DNBC, adjustment for the number of maternally reported fungal infections in the child did not change the association. (Table 4).

Negative control

Antifungal drugs for topical use were dispensed to 118,534 children (10.1%) in the Danish cohort. The children registered with dispensed systemic antibiotics were more likely to be registered with dispensed antifungal for topical use ($p<0.0001$). A dispensed topical antifungal was not associated with celiac disease (adjusted OR: 1.08; 95% CI: 0.91–1.28).

DISCUSSION

In this observational study of two large independent nationwide cohorts of more than 1.7 million children (3,346 diagnosed with celiac disease), a dispensed systemic antibiotic in the first year of life was consistently positively associated with diagnosed celiac disease. We found a dose-dependent relationship with an increasing number of dispensed antibiotics. No specific type of antibiotic in the first year of life or age at exposure were prominent, suggesting no specific vulnerable age at exposure and a similar effect for all the antibiotic types, although the low use of some antibiotics limited the study of these types.

Previous studies have reported conflicting findings on the association between early antibiotic exposure and risk of celiac disease.[24-29] Our main findings agree with those of Canova el al.[25] who found an incidence rate ratio of 1.31 (95% CI: 1.10–1.56) for celiac disease confirmed by pathology reports (510 cases). A Swedish study[24] used parentally reported antibiotics during the first six months of life and diagnosed celiac disease until two years of age in a post hoc analysis without any adjustments and with low power (373 cases). They found no statistically significant association, although the point estimate was comparable to our findings and those of Canova et al. (OR: 1.2; 95% CI: 0.87–1.6). In a recent study from the TEDDY cohort, a multinational cohort of children at high genetic risk of type 1 diabetes and celiac disease, Kemppainen et al.[26] found no association between parentally reported antibiotic exposure and persistently positive celiac disease -specific antibodies at four years of age (783 cases of celiac disease autoimmunity). In contrast to population-based cohort studies that do not include cases of undiagnosed children, screening for celiac disease autoimmunity as the outcome captured all the children with celiac disease and some who never will develop celiac disease. Our findings may be affected if factors related to being diagnosed as opposed to remaining undiagnosed are related to the use of antibiotic.

Previous studies have reported differences in risk factors for children with both type 1 diabetes and celiac disease.[30] When we stratified our analyses for a diagnosis of type 1 diabetes in the mother or the child (post hoc analysis), we found no association between antibiotic exposure and diagnosed celiac disease in the group with type 1 diabetes diagnosed in the mother or the child in accordance with the findings in the TEDDY cohort. However, we found no evidence for effect modification. Mårild et al.[27] reported from a Swedish register-based study that antibiotic exposure up to three years prior to the diagnosis was associated with celiac disease at all ages. This suggests that antibiotic exposure not only in early life but exposure at any age may be associated with celiac

disease. However, caution needs to be taken as these associations are more prone to bias by reverse causation. In our study, the association was at least as strong for exposure from 0-24 months as for 0-12 months. In a sub-analysis, Mårild at al. found that exposure in the first six months of life was associated with celiac disease in accordance with our findings but the study did not have sufficient power for such a sub-analysis (OR: 2.26; 95% CI: 0.55–9.25).

Adjustment for potential confounders did not change the conclusion of our study. The knowledge about risk factors for celiac disease in addition to gluten intake and HLA DQ2/DQ8 is limited. Therefore, it is difficult to select relevant confounders for adjustment. We examined potential confounders also included in other studies and were reassured that adjustments only altered our estimates slightly and did not change our conclusions. We found no evidence for effect modification by mode of delivery. Maternal use of antibiotics during pregnancy,[31] age at gluten introduction and use of proton pump inhibitors may also be effect modifiers but are not included in this study.

Infections in early life have been proposed to contribute to celiac disease development and are thus important potential confounders. Studies have reported an association with specific infectious agents,[32, 33] types of infection,[22, 25] as well as the overall number of hospital admissions for infectious diseases,[25] medically attended infectious diseases,[34] and parentally reported infectious diseases.[22, 35] The association has been reported for both viral[32, 33] and bacterial infections.[22, 25, 34] Infectious diseases may be present without antibiotic treatment, but antibiotic treatment is rarely used in absence of an infectious disease. Infections with severe symptoms are more likely to be treated with antibiotics but assuming that infections treated with antibiotics are bacterial and infections not treated with antibiotics are viral is not tenable. Disentangling the effect of infections and antibiotics is therefore difficult in an observational study lacking details on the infections and indication for antibiotic use. Adjustment for hospital admission with an infectious disease did not change our conclusions; these infections are likely to represent the most severe infectious episodes. We were able to adjust for the number of maternally reported infections in the child for the subgroup of children participating in the DNBC/MoBa. This adjustment weakened the association slightly, indicating that infections may be a confounder, but the association for antibiotic exposure remained. Maternally reported infectious episodes at 6 and 18 months may be an imprecise measure for the actual incidence. The imprecision is probably unrelated to diagnosed celiac disease, but may result in residual confounding in our analysis.

In the Norwegian cohort, some children were misclassified as unexposed to antibiotics when they were in fact exposed because a considerable number of prescriptions to young children lacked the personal identification number. We have no reason to suspect that this misclassification depends on the risk of diagnosed celiac disease or other variables included in the study and expect the misclassification to bias the estimates toward no association (Table S.7 and S.8). In the Norwegian cohort, we found no association between antibiotics and celiac disease in the first 6 months of life. The most likely explanation for the lack of association in this age group that this is the age group with most prescriptions lacking ID number and thus children misclassified as unexposed to antibiotics.

We have previously demonstrated that the registration of celiac disease diagnoses in the national patient registers is prone to misclassification[14] and therefore we used validated diagnoses to ensure

a high validity of the included cases. In the Danish cohort, the prevalence of diagnosed celiac disease was higher than reported for registrations of celiac disease in the Danish National Patient Register until 2010 (0.084%)[36] even though we used a more strict case definition with validation of the diagnosis. This reflects an increased prevalence of diagnosed celiac disease in the Danish pediatric population. In the Norwegian cohort, the prevalence of diagnosed celiac disease was slightly lower than previously reported for registrations of celiac disease in the Norwegian National Patient Register (0.38%).[37] The difference resulted from a more strict definition of celiac disease: two or more registrations in the Norwegian National Patient Register in the present study compared to one or more registrations of celiac disease in the previous study; and a shorter average follow-up time.

It is well-known that celiac disease is underdiagnosed. Factors associated with a diagnosis of celiac disease as opposed to remaining undiagnosed are unclear but are likely to include both symptoms of disease, belonging to a risk group, and parental health-seeking behavior. The propensity to use antibiotics may also be associated with a certain parental health-seeking behavior. Health-seeking behavior may thus be a confounder for the association between antibiotics and diagnosed celiac disease if the two types of health-seeking behavior are related. We expected that the health-seeking behavior leading to increased propensity for an antibiotic prescription was comparable to the health-seeking behavior increasing the propensity for prescriptions for other medications such as antifungals for topical use. We found an association between antifungals for topical use and antibiotics, but no association with the risk of celiac disease. Therefore, we do not find it likely that this health-seeking behavior is an important confounder for this study. Furthermore, we found comparable estimates in both cohorts although the proportion of diagnosed children compared to undiagnosed children, most likely, is higher in the Norwegian cohort reflected in the higher prevalence of diagnosed celiac disease. The true prevalence of celiac disease in the pediatric population of Denmark and Norway is unknown.

The diagnosis of celiac disease may be a long process with significant diagnostic delay. We cannot exclude that our findings are attributable to reverse causality, meaning that the symptoms of celiac disease mimic an infection, exaggerate symptoms of infections, or increase the risk of infectious diseases thereby increasing the propensity for prescriptions for antibiotics. However, we found that the association between antibiotics in the first year of life and celiac disease was comparable across the strata of age at diagnosis, making it less likely that our findings are attributable to reverse causality. Furthermore, studies have reported a very low prevalence of celiac disease-specific antibodies before one year of age.[38]

This study, the largest of its kind on this subject with a long follow-up period including two independent study populations and adjusting for several potential confounders including infections, suggests that antibiotic exposure in early life may be a risk factor for celiac disease. Exposure to antibiotics can by no means be regarded as the main contributing factor for development of celiac disease, but this study suggests that antibiotics is an important candidate maybe in combination with other factors. Future studies should attempt to separate the effect of infections and antibiotics by using more detailed information on indication for use of antibiotics and type of infections preferably by using biomarkers; and to elaborate on types and ages of exposure and interaction between risk factors and if the effect of antibiotic differs between risk groups.

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Figure 1.

Odds ratio for celiac disease with 95% confidence interval adjusted for year of birth and sex when comparing A) age at first exposure to a systemic antibiotic with no exposure prior to this age period B) age at exposure to a systemic antibiotic with no exposure in this age period C) type of antibiotic at first exposure to no antibiotic exposure in the first year of life D) exposure to different types of antibiotic with no exposure to this type of antibiotic in the first year of life.

Table 1. Distribution of selected characteristics and potential confounders by dispensed systemic antibiotic in the first year of life.

	Denmark		Norway	
Characteristic	**No dispensed antibiotics in the first year of life** n=716,838 *Number (%[a])*	**≥1 dispensed antibiotics in the first year of life** n=451,818 *Number (%[a])*	**No dispensed antibiotics in the first year of life** n=438,529 *Number (%[a])*	**≥1 dispensed antibiotics in the first year of life** n=98,928 *Number (%[a])*
Celiac disease				
Yes	805 (0.11)	622 (0.14)	1,529 (0.35)	390 (0.39)
No	716,033 (99.9)	451,196 (99.9)	437,000 (99.7)	98,538 (99.6)
Sex				
Male	347,391 (48)	252,278 (56)	219,677 (50)	56,199 (57)
Female	369,447 (52)	199,540 (44)	218,852 (50)	42,729 (43)
Season of birth				
Winter (December-February)	170,195 (24)	104,680 (23)	102,075 (23)	23,551 (24)
Spring (March-May)	165,286 (23)	129,008 (29)	110,441 (25)	27,891 (28)
Summer (June-August)	189,336 (26)	120,502 (27)	118,382 (27)	25,231 (26)
Autumn (September-November)	192,021 (27)	97,628 (22)	107,631 (25)	22,255 (22)
Parity				
First child	338,728 (47)	174,306 (39)	190,588 (43)	35,876 (36)
Second or more child	371,701 (52)	273,897 (61)	247,941 (57)	63,052 (64)
Missing	*6,409 (0.9)*	*3,615 (0.8)*	*0*	*0*
Maternal educational level[b]				
Compulsory education	134,713 (19)	98,812 (22)	70,334 (16)	17,544 (18)
Medium length	324,113 (45)	214,981 (48)	124,131 (28)	29,823 (30)
Higher education	232,095 (32)	126,330 (28)	226,263 (52)	47,747 (48)
Missing	*25,917 (3.6)*	*11,695 (2.6)*	*17,801 (4.1)*	*3,814 (3.9)*
Maternal age				
<25 years old	96,338 (13)	66,174 (15)	72,274 (16)	16,462 (17)
25-35 years old	494,567 (69)	316,435 (70)	282,095 (64)	64,787 (65)
≥35 years	125,923 (18)	69,200 (15)	84,160 (19)	17,679 (18)
Missing	*10 (-)*	*9 (-)*	*0*	*0*
Associated co-morbidity[c]				
Yes	4,171 (0.58)	2,980 (0.66)	*N/A*	*N/A*
No	712,667 (99.4)	448,838 (99.3)	*N/A*	*N/A*
Type 1 diabetes in the child				
Yes	1,726 (0.24)	1,115 (0.25)	690 (0.16)	151 (0.15)
No	715,112 (99.8)	450,703 (99.8)	437,839 (99.8)	98,777 (99.8)
Type 1 diabetes in the mother				
Yes	3,469 (0.48)	2,567 (0.57)	1,966 (0.45)	609 (0.62)
No	713,369 (99.5)	449,351 (99.5)	436,563 (99.6)	98,319 (99.4)
Hospitalization with infection				
Yes	73,396 (10)	100,192 (22)	*N/A*	*N/A*
No	643,442 (90)	351,626 (78)	*N/A*	*N/A*
Children participating in DNBC/MoBa	**No dispensed antibiotics in the first 18 months of life** (n=21,151) *Number (%[a])*	**≥1 dispensed antibiotics in the first 18 months of life** (n=33,931) *Number (%[a])*	**No dispensed antibiotics in the first 18 months of life** (n=32,185) *Number (%[a])*	**≥1 dispensed antibiotics in the first 18 months of life** (n=21,072) *Number (%[a])*
Maternally reported infections in the child				
0-3 episodes	5,782 (27)	2,932 (9)	6,113 (19)	1,844 (9)
4-6 episodes	7,864 (37)	8,771 (26)	10,653 (33)	4,830 (23)
7-9 episodes	3,686 (17)	7,239 (21)	8,215 (26)	5,673 (27)
≥10 episodes	3,819 (18)	14,989 (44)	7,204 (22)	8,725 (41)
Duration of breastfeeding				
0-3 months	2,449 (12)	5,385 (16)	2,581 (8)	2,165 (10)
3-6 months	3,150 (15)	6,191 (18)	2,596 (8)	1,934 (9)

6-9 months	6,137 (29)	9,607 (28)	5,603 (17)	3,917 (19)
9-12 months	4,472 (21)	6,485 (19)	8,372 (26)	5,282 (25)
≥12 months	4,943 (23)	6,263 (18)	13,033 (40)	7,774 (37)
Maternally reported fungal infections in the child				
0 episodes	13,978 (66)	21,216 (63)	*N/A*	*N/A*
1-2 episodes	6,282 (30)	10,806 (32)	*N/A*	*N/A*
≥ 3 episodes	891 (4)	1,909 (6)	*N/A*	*N/A*

Additional characteristics and potential confounders are shown in Table S.5.

[a] The denominator is the total number of children without or with a registration of a dispensed antibiotic in each country. The percentages may not add up to 100 because of rounding.

[b] The classification of maternal educational levels in Denmark and Norway is not straightforwardly comparable due to differences in the classification of educational levels: Denmark: Compulsory education: 10 years. Medium length: Additional four years of vocational education or 3 years of general education leading to a university admission certification possibly followed by 1-2 years of further education. Higher education: Education beyond medium length. Norway: Compulsory education: 10 years. Medium length: Additional 4 years of vocational education or 3 years of general education leading to a university admission certification. Higher education: Education beyond medium length.

[c] Prior to the first registration of celiac disease, the child was registered in the Danish National Patient Register with a diagnosis of type 1 diabetes (ICD-10 E10 E14), autoimmune thyroid disease (ICD-10 E03.9 E05 E06.3), autoimmune hepatitis (ICD-10 K73.2 K75.4) or juvenile rheumatoid arthritis (ICD-10 M08.0).

Abbreviations:

DNBC: The Danish National Birth Cohort. MoBa: The Norwegian Mother and Child Cohort Study. N/A: Not available.

Table 2. Association between dispensed systemic antibiotics and diagnosed celiac disease.

	Denmark	Norway	Pooled
	n=1,168,656 (1,427 cases[a])	n=537,457 (1,919 cases)	n=1,706,113 (3,346 cases)
	OR (95% CI)[b]	*OR (95% CI)*[b]	*OR (95% CI)*[b]
Antibiotic exposure in the first year of life (0–12 months)			
Any antibiotics (yes/no)	1.32 (1.18–1.47)	1.21 (1.08–1.36)	1.26 (1.16–1.36)[g]
Number of dispensed antibiotics	*1.08 (1.05–1.12)*	*1.09 (1.04–1.15)*	*1.08 (1.05–1.11)*[g]
+adjustment for hospital contact with infection[c]			
Any antibiotics (yes/no)	1.32 (1.18–1.47)	*N/A*	*N/A*
Number of dispensed antibiotics	*1.08 (1.05–1.12)*	*N/A*	*N/A*
Cumulative exposure since birth[d]			
0–6 months			
Any antibiotics (yes/no)	1.26 (1.06–1.49)	0.99 (0.81–1.19)	1.11 (0.97–1.25)[h]
Number of dispensed antibiotics	*1.17 (1.08–1.27)*	*1.00 (0.86–1.16)*	*1.12 (1.04–1.20)*[i]
0–18 months			
Any antibiotics (yes/no)	1.34 (1.20–1.50)	1.27 (1.16–1.39)	1.30 (1.20–1.39)[g]
Number of dispensed antibiotics	*1.08 (1.06–1.10)*	*1.08 (1.06–1.11)*	*1.08 (1.06–1.10)*[g]
0–24 months			
Any antibiotics (yes/no)	1.35 (1.19–1.53)	1.30 (1.19–1.42)	1.32 (1.22–1.41)[g]
Number of dispensed antibiotics	*1.06 (1.04–1.07)*	*1.07 (1.05–1.08)*	*1.06 (1.05–1.08)*[g]
Age at first exposure[e]			
6–12 months	1.30 (1.16–1.46)	1.31 (1.15–1.49)	1.30 (1.19–1.42)[g]
12–18 months	1.18 (1.02–1.37)	1.26 (1.12–1.43)	1.22 (1.11–1.34)[g]
18–24 months	1.18 (0.96–1.46)	1.25 (1.08–1.45)	1.23 (1.08–1.37)[g]
Exposure in specified age periods[f]			
Any antibiotics 6–12 months	1.28 (1.15–1.42)	1.32 (1.16–1.49)	1.30 (1.19–1.40)[g]
Any antibiotics 12–18 months	1.23 (1.10–1.37)	1.34 (1.21–1.49)	1.28 (1.19–1.38)[g]
Any antibiotics 18–24 months	1.20 (1.07–1.34)	1.29 (1.16–1.43)	1.25 (1.15–1.34)[g]

[a] Analyses in the Danish cohort excluded children diagnosed prior to or during the time periods 0–6 months, 6–12 months, 12–18 months, 18–24 months; a maximum of 61 children were excluded.

[b] Odds ratio (OR) with 95% confidence interval (CI) for celiac disease when comparing children with dispensed systemic antibiotics with children with no dispensed antibiotics as a reference; adjusted for year of birth and sex.
Additional adjustment for gestational age, weight for gestational age, season of birth, maternal parity, maternal educational level, maternal age, maternal smoking during pregnancy, maternal country of birth, maternal autoimmune diseases, and maternal pre-pregnancy BMI did not change the conclusions. Details are described in the supplementary material.

[c] Further adjusted for a hospital contact with an infectious disease in the first year of life (see included ICD-10 codes in the supplementary material, Table S.2).

[d] The reference in each analysis was no dispensed antibiotics in this age period.

[e] The reference in each analysis is no dispensed antibiotics prior to this age period. If a child was previously exposed, they were excluded from the analysis.

[f] The reference in each analysis was no dispensed antibiotics in this specific age period.

[g] The I^2 test for heterogeneity: 0.0%.

[h] The I^2 test for heterogeneity: 60%.

[i] The I^2 test for heterogeneity: 76%.

Table 3. Stratification for the presence of an associated comorbidity and age at diagnosis.

		Denmark			Norway		
		Number included in analysis (cases)	*OR (95% CI)*[a]	LRT for statistical interaction[b]	*Number included in analysis (cases)*	*OR (95% CI)*[a]	LRT for statistical interaction[b]
Diagnosed associated comorbidity in the child[c]							
No	Any antibiotics (yes/no)	1,161,500 (1,212)	1.32 (1.17–1.48)	p=0.40		N/A	
	Number of dispensed antibiotics		*1.08 (1.05–1.12)*			N/A	
Yes	Any antibiotics (yes/no)	6,941 (208)	1.07 (0.80–1.42)			N/A	
	Number of dispensed antibiotics		*1.01 (0.92–1.10)*			N/A	
Autoimmune disease in the mother[d] **or the child**[e]							
No	Any antibiotics (yes/no)	*1,144,692 (1,178)*	*1.36 (1.21–1.52)*	p=0.036		N/A	
	Number of dispensed antibiotics		*1.10 (1.06–1.13)*			N/A	
Yes	Any antibiotics (yes/no)	*23,957 (242)*	*1.02 (0.78–1.33)*			N/A	
	Number of dispensed antibiotics		*0.98 (0.89–1.08)*			N/A	
Type 1 diabetes in the mother or the child							
No	Any antibiotics (yes/no)	*1,159,947 (1,242)*	*1.33 (1.19–1.49)*	P=0.27	*534,068 (1,826)*	*1.21 (1.07–1.35)*	P=0.69
	Number of dispensed antibiotics		*1.09 (1.05–1.13)*			*1.09 (1.04–1.15)*	
Yes	Any antibiotics (yes/no)	*8,702 (178)*	*1.14 (0.84–1.56)*		*3,389 (93)*	*1.09 (0.66–1.82)*	
	Number of dispensed antibiotics		*1.01 (0.92–1.12)*			*0.95 (0.73–1.25)*	
Mode of delivery							
Vaginal delivery	Any antibiotics (yes/no)	*843,030 (1,114)*	*1.28 (1.14–1.45)*		*447,329 (1,631)*	*1.23 (1.09–1.40)*	
	Number of dispensed antibiotics		*1.08 (1.04–1.12)*			*1.11 (1.05–1.16)*	
Cesarean section (all types)	Any antibiotics (yes/no)	*196,511 (263)*	*1.34 (1.05–1.71)*	P=0.85 (vaginal delivery and all types of cesarean section)	*90,128 (288)*	*1.14 (0.86–1.50)*	P=0.69 (vaginal delivery and all types of cesarean section)
	Number of dispensed antibiotics		*1.08 (1.01–1.16)*			*1.02 (0.90–1.16)*	
Elective cesarean section	Any antibiotics (yes/no)	*103,358 (145)*	*1.05 (0.75–1.46)*	P=0.12 (vaginal delivery, elective and emergency cesarean section)	*34,728 (116)*	*1.47 (0.96–2.24)*	P=0.31 (vaginal delivery, elective and emergency cesarean section)
	Number of dispensed antibiotics		*1.03 (0.92–1.17)*			*1.13 (1.00–1.27)*	
Emergency cesarean section	Any antibiotics (yes/no)	*92,972 (118)*	*1.81 (1.26–2.60)*		*54,970 (171)*	*0.97 (0.67–1.39)*	
	Number of dispensed antibiotics		*1.13 (1.06–1.20)*			*0.91 (0.74–1.13)*	
Age at diagnosis							
1-4 years of age	Any antibiotics (yes/no)	1,167,691 (462)	1.10 (0.91–1.33)		536,926 (1,388)	1.23 (1.08–1.40)	
	Number of dispensed antibiotics		*1.06 (0.99–1.13)*			*1.08 (1.02–1.14)*	
5-8 years of age	Any antibiotics (yes/no)	1,007,153 (414)[f]	1.49 (1.23–1.81)		291,572 (531)[f]	1.14 (0.88–1.48)	
	Number of dispensed antibiotics		*1.09 (1.03–1.15)*			*1.11 (1.01–1.23)*	
9-19 years of age	Any antibiotics	748,969 (544)[g]	1.34 (1.13–1.60)			N/A	

(yes/no) *Number of dispensed antibiotics*		*1.10 (1.05–1.16)*			N/A	

[a] Odds ratio (OR) with 95% confidence interval (CI) for celiac disease when comparing children with dispensed systemic antibiotics in the first year of life with children with no dispensed antibiotics as a reference; adjusted for year of birth and sex.
[b] Likelihood ratio test (LRT) for statistical interaction between the potential effect modifier and antibiotic exposure in the first year of life.
[c] Prior to the first registration of celiac disease, the child was registered in the Danish National Patient Register with a diagnosis of type 1 diabetes (ICD-10 E10 E14), autoimmune thyroid disease (ICD-10 E03.9 E05 E06.3), autoimmune hepatitis (ICD-10 K73.2 K75.4), juvenile rheumatoid arthritis (ICD-10 M08.0), Down's syndrome (ICD-10 Q90) or Turner's syndrome (ICD-10 Q96).
[d] Before giving birth to the child included in this study, the mother was registered in the Danish National Patient Register with a diagnosis of autoimmune thyroid disease (ICD-10 E05.0, E06.0, O09.92B, O99.2C), rheumatoid arthritis (ICD-10 M05, M06), type 1 diabetes (ICD-10 E10, O24.0) or celiac disease (K90.0).
[e] Prior to the first registration of celiac disease, the child was registered in the Danish National Patient Register with a diagnosis of type 1 diabetes (ICD-10 E10 E14), autoimmune thyroid disease (ICD-10 E03.9 E05 E06.3), autoimmune hepatitis (ICD-10 K73.2 K75.4) or juvenile rheumatoid arthritis (ICD-10 M08.0).
[f] The analyses included only children of 5 years of age or older at the end of follow-up.
[g] The analysis included only children of 9 years of age or older at the end of follow-up.

Table 4. DNBC/MoBa: Effect of adjusting for the number of maternally reported infections in the child and duration of breastfeeding (0-18 months of age).

	Denmark (DNBC) n=55,076 (94 cases)[a] *OR (95% CI)*[b]	**Norway (MoBa)** n=53,257 (464 cases) *OR (95% CI)*[b]	**Pooled** n=108,333 (558 cases) *OR (95% CI)*[b]
Answered questionnaires at 6 and 18 months of age *(complete information on infections and breastfeeding)*			
Any antibiotics	1.41 (0.91–2.19)	1.21 (1.00–1.45)	1.23 (1.02–1.44)[c]
Number of dispensed antibiotics	*1.13 (1.08–1.19)*	*1.09 (1.03–1.16)*	*1.11 (1.07–1.16)*[c]
Additionally adjusted for infectious episodes			
Any antibiotics	1.29 (0.81–2.05)	1.17 (0.97–1.41)	1.18 (0.98–1.39)[c]
Number of dispensed antibiotics	*1.13 (1.06–1.19)*	*1.08 (1.01–1.14)*	*1.11 (1.06–1.15)*[d]
Additionally adjusted for fungal infections			
Any antibiotics	*1.40 (0.90–2.17)*	*N/A*	*N/A*
Number of dispensed antibiotics	*1.13 (1.07–1.19)*	*N/A*	*N/A*
Additionally adjusted for duration of breastfeeding			
Any antibiotics	1.42 (0.92–2.21)	1.22 (1.01–1.46)	1.24 (1.03–1.45)[c]
Number of dispensed antibiotics	*1.14 (1.08–1.19)*	*1.09 (1.03–1.16)*	*1.12 (1.08–1.16)*[e]

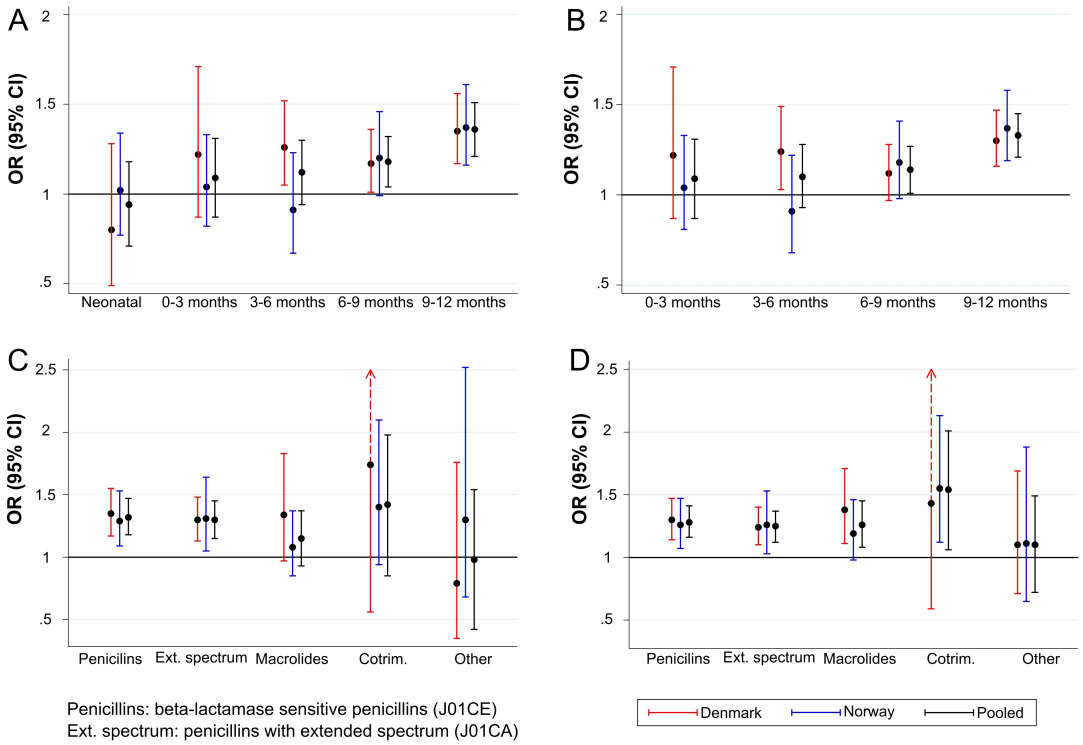
[a] 6 children diagnosed with celiac disease before 18 months of age were excluded from the analyses.

[b] Odds ratio (OR) with 95% confidence interval (CI) for celiac disease when comparing children with dispensed systemic antibiotics from 0 to 18 months of life with children with no dispensed antibiotics as a reference; adjusted for year of birth and sex.

[c] The I^2 test for heterogeneity: 0.0%.

[d] The I^2 test for heterogeneity: 12%.

[e] The I^2 test for heterogeneity: 25%.



Penicillins: beta-lactamase sensitive penicillins (J01CE)
Ext. spectrum: penicillins with extended spectrum (J01CA)
Macrolides: macrolides and lincosamides (J01F)
Cotrim.: sulfonamides and trimethoprim (J01E)
Other: antibiotics not included in the other subgroups (J01*)

Supplementary Material

1. Assessment of potential confounders

1.1 Registers and variables

From the Danish Civil Registration System[1] we included information on date of birth, sex, identity of parents, maternal country of birth and date of death or emigration. Maternal country of birth was registered as the mother's country of birth for immigrants and as the maternal grandmother's country of birth for second-generation immigrants and categorized as Denmark, other Western country, Non-Western country.
From the Danish Medical Birth Register,[2] we obtained variables for birthweight, gestational age, maternal age at birth, maternal parity, maternal smoking during pregnancy, and maternal pre-pregnancy body mass index (BMI) (available from 2004 to 2010). Maternal BMI was categorized as <18.5, 18.5-25, 25-30, or ≥30 kg/m^2.
The Danish Population's Education Register contains information on the highest level of completed education and ongoing education.[3] We used information on maternal educational levels from the year of each child's birth. We classified the educational levels as: Compulsory education: 10 years of education. Medium length: Additional four years of vocational education or 3 years of general education leading to a university admission certification possibly followed by 1-2 years of further education. Higher education: Education beyond medium length.
From the Norwegian Medical Birth Register[4] we included variables for sex, month and year of birth, birthweight, gestational age, and maternal type 1 diabetes.
Maternal educational level was derived from Statistics Norway. We classified the educational levels as: Compulsory education: 10 years of education. Medium length: Additional 4 years of vocational education or 3 years of general education leading to a university admission certification. Higher education: Education beyond medium length.
Season of birth was categorized as winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), or autumn (September, October, and November). Birthweight was categorized as <2,500 grams, 2,500-4,500 grams or ≥4,500 grams. Gestational age was categorized as <32 weeks, 32-37 weeks, 37-42 weeks, or ≥42 weeks. Weight for gestational age was calculated as children below or at the 10th percentile, children between the 10th and the 90th percentiles, or children at or above the 90th percentile for gestational age and sex. Maternal age at birth was categorized as <20 years, 20-25 years, 25-35 years, 35-40 years, or ≥40 years. Maternal smoking during pregnancy was registered as a dichotomous yes or no.

1.2 Statistics

To test the effect of adjusting for the potential confounders, we compared the children with non-missing information on the potential confounder(s) of interest in a logistic regression model including year of birth and sex with a model including year of birth, sex, and the potential confounder(s) (complete case analysis). Continuous variables were examined both as continuous variables when appropriate and categorized as indicated above.
First we examined the effect of gestational age, weight for gestational age, season of birth, maternal parity, maternal educational level, and maternal age. Information on maternal smoking during pregnancy was missing for a large proportion of the mothers and therefore we analyzed the effect of smoking separately.
Furthermore, we examined the effect of adjusting for potential confounders available only in the Danish cohort: maternal country of birth, maternal autoimmune disease diagnosed before the birth of the child, and maternal pre-pregnancy BMI (only available 2004–2010).
To address the issue of missing data, we analyzed the model including gestational age and weight for gestational age, season of birth, maternal parity, maternal education, and maternal age with multiple imputation of missing data. Missing data in a variable used in the analysis was seen in 4.8% of the Danish children and 4.7% of the Norwegian children. Imputation was conducted using multiple imputations by chained equations. For the sake of simplicity, variables with <2% missing data (gestational age, weight for gestational age, maternal parity, and maternal age) were single imputed with the mode of the variable, leaving education (Denmark: 3.2% missing. Norway: 4.0%). We performed 20 imputations following White.[5] The imputation model included information on year of birth, sex, season

of birth, gestational age, birthweight for gestational age, maternal age, maternal educational level, maternal parity, mode of delivery, maternal type 1 diabetes as well as antibiotic exposure in the first year of life and diagnosed celiac disease. Multiple imputations of missing data did not change the conclusions (data not shown).

2. Registrations of antibiotic exposure

2.1 The Danish National Prescription Register

Before 1996, prescriptions were issued under the parents' CPR numbers (most often the mother's) with indication of the child's age. After 1996, all children had their own health insurance card and prescriptions were issued to the child. This practice was fully implemented by 2000. Prescriptions for the child issued to the mother's CPR number were included in this study. To assess potential bias resulting from this, we restricted the analyses to children born in 1996–2012 and children born in 2000-2012. The stratification did not change the conclusions (data not shown).

2.2 The Norwegian National Prescription Register

Approximately 30% of the prescriptions from the first year of life in the Norwegian National Prescription Register lack ID numbers (range 17%-56% per year; see Table S.1) precluding the individual-level linkage. Prescriptions with missing ID numbers were not included in the study and thus the exposure to antibiotics was underestimated and the children exposed to antibiotics were misclassified as unexposed. We have no reason to assume that this is dependent on celiac disease diagnosis. To examine potential bias due to missing ID numbers, we stratified the analyses according to the proportion of missing ID numbers: 2004–2007 (42% missing), 2008–2009 (26% missing), and 2010–2013 (20% missing). The association was strongest in the group with the least missing data, indicating that the misclassification of the exposed children as unexposed likely biased the results toward no association. Supporting this is the comparison of information from the Norwegian National Patient Register with maternally reported use of antibiotics in the MoBa showing comparable associations (see Table S.7 and Table S.8).

2.3 Antibiotic exposure in the MoBa

The questionnaires at 6 and 18 months of age asked the mothers of children participating in the MoBa about any medications administered to the children including antibiotics (Table S.4). As previously described, a proportion of the prescriptions in the Norwegian National Prescription Register lacked the ID numbers. Therefore, maternally reported information on the use of antibiotics in the children was added so that the analysis in the MoBa included prescriptions registered in the Norwegian National Prescription Register and maternally reported use of antibiotics in the questionnaires. For each of the age periods 0–6 months, 6–12 months, and 12–18 months, we categorized children in the MoBa cohort as exposed to antibiotics if the child had a registration of a dispensed antibiotic in the Norwegian National Prescription Register or if the mother indicated use of antibiotics in the MoBa questionnaire. For the Number of dispensed antibiotics we used the highest number of prescriptions in the Norwegian National Prescription Register or antibiotic courses indicated in the MoBa questionnaire, and added the number of prescriptions/antibiotic courses for each age period. The number of exposed children identified in the prescription register and the MoBa respectively is shown in Table S.7. We speculate that the low proportion of children with an indication of antibiotic use in the MoBa in the age period 6-12 months was attributable to maternal lack of recall bearing in mind that the questionnaires were completed when the children were 6 and 18 months of age.

To examine the effect of combining the information, all the analyses were performed with prescriptions registered in the Norwegian National Patient Register, antibiotic courses indicated in the MoBa questionnaires, and the combined variables. These calculations are shown in Table S.8.

3. Definition of outcome

To investigate the effect of outcome definition, we analyzed data with different definitions of celiac disease. In the Danish cohort we used one or more registration of celiac disease, two or more registrations of celiac disease, confirmed diagnoses as used in the main analyses (biopsy compatible with celiac disease (Marsh 2–3), anti-tissue transglutaminase IgA at ten or more the upper limit of normal or positive EMA test).
In the Norwegian cohort we used one or more registrations of celiac disease and two or more registrations of celiac disease. Table S.9 shows that the definition of outcome does not change the conclusions.

4. References

1. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39:22-5.
2. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45:320-3.
3. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health 2011;39:91-4.
4. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand 2000;79:435-9.
5. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377-99.

5. Supplementary tables

Table S.1. Registrations lacking ID numbers in the Norwegian Prescription Register.

Year of dispense	Lacking ID-number *(%)*	Analyses stratified for year of dispense *OR (95% CI)*[a]
2004	35	1.19 (1.02–1.40)
2005	31	
2006	56	
2007	46	
2008	27	1.17 (0.93–1.46)
2009	26	
2010	19	1.54 (1.21–1.96)
2011	21	
2012	23	
2013	17	

[a] Odds ratio with 95% confidence interval for celiac disease when comparing children with ≥1 dispensed antibiotics to children with no dispensed antibiotics adjusted for year of birth and sex.

Table S.2. ICD-10 codes used for the generation of study variables from the Danish National Patient Register.

Variable	Included ICD 10 codes	Description
Hospital admissions in the neonatal period with infections likely to require antibiotic treatment	A39	Meningococcal infection
	A40	Streptococcal sepsis
	A41	Other sepsis
	H65	Nonsuppurative otitis media
	H66.0	Acute suppurative otitis media
	H66.4	Suppurative otitis media, unspecified
	H66.9	Otitis media, unspecified
	J13	Pneumonia due to *Streptococcus pneumoniae*
	J14	Pneumonia due to *Haemophilus influenzae*
	J15	Bacterial pneumonia, not elsewhere classified
	L00	Staphylococcal scalded skin syndrome
	M00	Pyogenic arthritis
	N10	Acute tubulointestinal nephritis
	N12	Tubulointestinal nephritis, not specified
	N30.0	Acute cystitis
	N39.0	Urinary tract infection, site not specified
	P36	Bacterial sepsis of newborn
	P38	Omphalitis of newborn
	P39.0	Neonatal infective mastitis
	P39.3	Neonatal urinary tract infection
Hospital admission with an infectious disease in the first year of life	A00-B99	Certain infectious and parasitic diseases
	G0	Inflammatory diseases of the central nervous system
	H10	Conjunctivitis
	H65	Nonsuppurative otitis media
	H66	Suppurative and unspecified otitis media
	H67	Otitis media in disease classified elsewhere
	I00-I02	Acute rheumatic fever
	J00-J06	Acute upper respiratory infections
	J09-J18	Influenza and pneumonia
	J20-J22	Other acute lower respiratory tract infections
	J32	Chronic sinusitis
	J36	Peritonsillar abscess
	L00-L08	Infections of the skin and subcutaneous tissue
	N10	Acute tubulointestinal nephritis
	N11	Chronic tubulointestinal nephritis
	N12	Tubulointestinal nephritis, not specified as acute or chronic
	N30	Cystitis
	N34.0	Urethral abscess
	N39.0	Urinary tract infection, site not specified
	M00	Pyogenic arthritis
	M01	Direct infections of joint in infectious and parasitic diseases classified elsewhere
	R50.9	Fever, unspecified
	R56.0	Febrile convulsions
	P23	Congenital pneumonia
	P36	Bacterial sepsis of newborn
	P39	Other infections specific to the neonatal period
Comorbidity associated with celiac disease	E10, E14	Type 1 diabetes
	E03.9, E05, E06.3	Autoimmune thyroid disease
	K73.2 K75.4,	Autoimmune hepatitis
	M08.0	Juvenile rheumatoid arthritis
	Q90	Down's syndrome
	Q96	Turner's syndrome
Maternal autoimmune disease	E05.0, E06.0, O09.92B, O99.2C	Autoimmune thyroid disease
	M05, M06	Rheumatoid arthritis
	E10, O24.0	Type 1 diabetes
	K90.0	Celiac disease

Table S.3. ATC codes used for sub-classification of systemic antibiotics.

Subtype of antibiotics	ATC code	Antibiotics dispensed in the first year of life	
		Denmark *Number per 1,000 (%)*	Norway *Number per 1,000 (%)*
Beta-lactamase sensitive penicillins	J01CE	245 (34)	91 (39)
Penicillins with extended spectrum	J01CA	399 (54)	56 (24)
Macrolides, lincosamides, and steptogramins[a]	J01F	61 (8)	55 (24)
Sulphonamides and trimethoprim	J01E	4.2 (0.6)	20 (9)
Systemic antibiotics not included in other subgroups[b]	J01* not included in other categories	7.6 (1)	9.2 (4)

[a] This group includes macrolides (J01FA): Denmark: 100% of the subgroup, Norway 93% of the subgroup, and lincosamides (J01FF): Norway: 7% of the subgroup.

[b] This group includes tetracyclines (J01AA), beta-lactamase-resistant penicillins (J01CF): Denmark 26% of the subgroup, Norway 12% the subgroup, combinations of penicillins including beta-lactamase inhibitors (J01CR): Denmark 64% of the subgroup, Norway 4% of the subgroup, cephalosporins (J01DB-D): Denmark (4%) of the subgroup, Norway 50% of the subgroup, aminoglycosides antibacterials (J01G), quinolone antibacterials (J01M), glycopeptide antibacterials (J01XA), polymyxins (J01XB), steroid antibacterials (J01XC01): Denmark 3% of the subgroup, imidazole derivates (J01XD), nitrofuratoin (J01XE): Denmark 1% of the subgroup, Norway 32% of the subgroup, and other antibacterials (J01XX).

Table S.4. Included questions from DNBC and MoBa questionnaires at 6 and 18 months of age.

Cohort	Subject	Questionnaire 6 months of age	Questionnaire 18 months of age
DNBC	Infections	Common cold[a] Loose stools/diarrhea[a] Acute otitis media[b] Bronchitis (dry or loose cough)[b] Pneumonia[b]	Common cold[a] Diarrhea[a] Acute otitis media[b] Bronchitis[b] Pseudocroup[b] Tonsillitis[a] Fever≥38.5[a] Pneumonia[b] Scarlatina[b]
	Fungal infections	Oral thrush[a] Other fungal infections[a]	Oral thrush or other fungal infections[a]
	Breastfeeding	Do you breastfeed your boy/girl now? *Yes* *No (→ next question)* *No, but the child gets mother's milk from own mother* *No, but the child gets mother's milk from another woman* *The child was never breastfed* *Do not know* *Do not wish to answer* *Undefined* *Not applicable*	Did you breast feed your child after it turned 6 months old? *Yes* *No (→ next question)* *Do not know* *Do not want to answer*
		How old were your child when you stopped breastfeeding her/him every day? *End of daily breastfeeding: __months__weeks__days* *Never breastfeeding* *Do not know* *Do not wish to answer* *Undefined* *Not applicable*	When did you stop breastfeeding? *Stop breast feeding: ___ months ___ weeks* *Still breast feed* *Do not know* *Do not want to answer*
MoBa	Infections	Common cold[b] Throat infection[b] Ear infection[b] Bronchitis/RS virus/pneumonia[b] Gastric flu/diarrhea[b] Urinary tract infection[b] Pseudocroup[b]	Common cold[b] Throat infection[b] (confirmed streptococcal infection/other type of sore throat) Ear infection[b] Bronchitis/RS virus/pneumonia[b] Gastric flu/diarrhea[b] Urinary tract infection[b] Pseudocroup[b]
	Breastfeeding	What did you give your child to drink during the first week of life? *Breast milk* *Water* *Sugar water* *Formula* *Other, specify: _____* *Do not know/do not remember* What has your child been given to drink during the first 6 months of his/her life? (Enter a cross for each month you gave your child the relevant drink.) *Breast milk* *Standard Collett formula* *Collett formula with Omega 3* *Standard NAN formula* *Nan HA1 formula* *Other milk, specify:_____* *Water* *Squash/Juice*	What type of milk has your baby been given since he/she was 6 months old? (You can enter more than one cross.) *Breast milk* *Formula* *Formula in case of milk intolerance* *Whole milk (sweet)* *Low-fat milk normal (sweet)* *Extra low-fat milk (sweet)* *Skimmed milk (sweet)* *Yogurt with active* Lactobacillus*, all types* *Other yogurt* *Other types of sour milk*

	Antibiotics	Have your child ever been given any medication? *No* *Yes* If yes, give the name of the medicines and when they were given (include all types of medication, as well as natural medicines, taken both on a regular and occasional basis) *Name of medicine*_____ How old was your child when he/she took this medication?	Have your child received any medication since the age of 6 months? (This means any type of medication, including natural medicines and herbal remedies) *No* *Yes* If yes, give the name of the medication and what age your child was when he took it.(Include all types of medication, as well as natural medicines) *Name of medicine*_____ How old was your child when he/she took this medication?

[a] Number of episodes ≥3 days.
[b] Number of episodes.

Table S.5. Distribution of selected characteristics and potential confounders by dispensed systemic antibiotic in the first year of life.

Characteristic	Denmark		Norway	
	No dispensed antibiotics in the first year of life (n=716,838) *Number (%[a])*	**≥1 Dispensed antibiotics in the first year of life** (n=451,818) *Number (%[a])*	**No dispensed antibiotics in the first year of life** (n=438,529) *Number (%[a])*	**≥1 Dispensed antibiotics in the first year of life** (n=98,928) *Number (%[a])*
Celiac disease				
Yes	805 (0.11)	622 (0.14)	1,529 (0.35)	390 (0.39)
No	716,033 (99.9)	451,196 (99.9)	437,000 (99.7)	98,538 (99.6)
Sex				
Male	347,391 (48)	252,278 (56)	219,677 (50)	56,199 (57)
Female	369,447 (52)	199,540 (44)	218,852 (50)	42,729 (43)
Season of birth				
Winter (December-February)	170,195 (24)	104,680 (23)	102,075 (23)	23,551 (24)
Spring (March-May)	165,286 (23)	129,008 (29)	110,441 (25)	27,891 (28)
Summer (June-August)	189,336 (26)	120,502 (27)	118,382 (27)	25,231 (26)
Autumn (September-November)	192,021 (27)	97,628 (22)	107,631 (25)	22,255 (22)
Birthweight				
<2,500 grams	39,155 (5)	20,769 (5)	17,460 (4)	8,632 (9)
2,500-4,500 grams	645,309 (90)	410,126 (91)	406,407 (93)	86,319 (87)
≥4,500 grams	23,741 (3)	17,018 (4)	14,423 (3)	3,910 (4)
Missing	*8,633 (1.2)*	*3,905 (0.9)*	*239 (-)*	*67 (-)*
Gestational age				
Preterm birth (<37 weeks)	47,454 (7)	27,901 (6)	24,332 (6)	11,064 (11)
Term birth (≥37 weeks)	662,809 (92)	421,055 (93)	411,113 (94)	87,148 (88)
Missing	*6,575 (0.9)*	*2,862 (0.6)*	*3,084 (0.7)*	*716 (0.7)*
Parity				
First child	338,728 (47)	174,306 (39)	190,588 (43)	35,876 (36)
Second or more child	371,701 (52)	273,897 (61)	247,941 (57)	63,052 (64)
Missing	*6,409 (0.9)*	*3,615 (0.8)*	*0*	*0*
Maternal educational level[c]				
Compulsory education	134,713 (19)	98,812 (22)	70,334 (16)	17,544 (18)
Medium length	324,113 (45)	214,981 (48)	124,131 (28)	29,823 (30)
Higher education	232,095 (32)	126,330 (28)	226,263 (52)	47,747 (48)
Missing	*25,917 (3.6)*	*11,695 (2.6)*	*17,801 (4.1)*	*3,814 (3.9)*
Maternal age				
<25 years old	96,338 (13)	66,174 (15)	72,274 (16)	16,462 (17)
25-35 years old	494,567 (69)	316,435 (70)	282,095 (64)	64,787 (65)
≥35 years	125,923 (18)	69,200 (15)	84,160 (19)	17,679 (18)
Missing	*10 (-)*	*9 (-)*	*0*	*0*
Smoking[c]				
Yes	111,403 (17)	81,974 (20)	49,035 (11)	11,418 (12)
No	501,358 (78)	310,140 (76)	314,994 (72)	71,210 (72)
Missing	*28,189 (4)*	*17,964 (4)*	*74,500 (17)*	*16,300 (16)*
Associated co-morbidity[d]				
Yes	4,171 (0.58)	2,980 (0.66)	*N/A*	*N/A*
No	712,667 (99.4)	448,838 (99.3)	*N/A*	*N/A*
Type 1 diabetes in the child				
Yes	1,726 (0.24)	1,115 (0.25)	690 (0.16)	151 (0.15)
No	715,112 (99.8)	450,703 (99.8)	437,839 (99.8)	98,777 (99.8)
Type 1 diabetes in the mother				
Yes	3,469 (0.48)	2,567 (0.57)	1,966 (0.45)	609 (0.62)
No	713,369 (99.5)	449,351 (99.5)	436,563 (99.6)	98,319 (99.4)
Hospitalization with infection				
Yes	73,396 (10)	100,192 (22)	*N/A*	*N/A*
No	643,442 (90)	351,626 (78)	*N/A*	*N/A*
Maternal BMI[e]				
<18.5	11,141 (4)	6,661 (4)	*N/A*	*N/A*
18.5-25	163,100 (60)	100,650 (56)	*N/A*	*N/A*
≥25	78,172 (29)	59,540 (33)	*N/A*	*N/A*
Missing	*19,116 (7)*	*13,422 (7)*	*N/A*	*N/A*
Maternal country of birth				
Denmark	619,067 (86)	390,156 (86)	*N/A*	*N/A*
Other Western countries	25,706 (4)	10,984 (2)	*N/A*	*N/A*

Non-Western countries	71,623 (10)	50,493 (11)	*N/A*	*N/A*
Missing	*442 (-)*	*185 (-)*	*N/A*	*N/A*
Children participating in MoBa/DNBC	**No dispensed antibiotics in the first 18 months of life** (n=21,151) *Number (%[a])*	**≥1 Dispensed antibiotics in the first 18 months of life** (n=33,931) *Number (%[a])*	**No dispensed antibiotics in the first 18 months of life** (n=32,185) *Number (%[a])*	**≥1 Dispensed antibiotics in the first 18 months of life** (n=21,072) *Number (%[a])*
Maternally reported infections				
0-3 episodes	5,782 (27)	2,932 (9)	6,113 (19)	1,844 (9)
4-6 episodes	7,864 (37)	8,771 (26)	10,653 (33)	4,830 (23)
7-9 episodes	3,686 (17)	7,239 (21)	8,215 (26)	5,673 (27)
≥10 episodes	3,819 (18)	14,989 (44)	7,204 (22)	8,725 (41)
Duration of breastfeeding				
0-3 months	2,449 (12)	5,385 (16)	2,581 (8)	2,165 (10)
3-6 months	3,150 (15)	6,191 (18)	2,596 (8)	1,934 (9)
6-9 months	6,137 (29)	9,607 (28)	5,603 (17)	3,917 (19)
9-12 months	4,472 (21)	6,485 (19)	8,372 (26)	5,282 (25)
≥12 months	4,943 (23)	6,263 (18)	13,033 (40)	7,774 (37)
Maternally reported fungal infections				
0 episodes	13,978 (66)	21,216 (63)	N/A	N/A
1-2 episodes	6,282 (30)	10,806 (32)	N/A	N/A
≥ 3 episodes	891 (4)	1,909 (6)	N/A	N/A

[a] The denominator is the total number of children without or with a registration of a dispensed antibiotic in each country. The percentages may not add up to 100 because of rounding.

[b] The classification of maternal educational levels in Denmark and Norway is not straightforwardly comparable due to differences in the classification of educational levels:
Denmark: Compulsory education: 10 years. Medium length: Additional four years of vocational education or 3 years of general education leading to a university admission certification possibly followed by 1-2 years of further education. Higher education: Education beyond medium length.
Norway: Compulsory education: 10 years. Medium length: Additional 4 years of vocational education or 3 years of general education leading to a university admission certification. Higher education: Education beyond medium length.

[c] Maternal smoking during pregnancy is only available in the period 1995–2010 in the Danish cohort.

[d] Co-morbidity includes: Down's syndrome, Turner's syndrome, type 1 diabetes mellitus, autoimmune thyroid disease, juvenile rheumatoid arthritis, autoimmune hepatitis.

[e] Only available in the period 2004–2010.

Abbreviations: DNBC: The Danish National Birth Cohort; MoBa: The Norwegian Mother and Child Cohort Study

Table S.6. Effect of adjusting for potential confounders.

Potential confounders included in addition to year of birth and sex	**Included in analyses**	**Adjusted for year of birth**	**Adjusted for year of birth and sex**	**Adjusted for year of birth, sex and additional potential confounder(s)**
	Number (cases)	*OR (95% CI)*[a]	*OR (95% CI)*[a]	*OR (95% CI)*[a]
Norway				
Gestational age, weight for gestational age, maternal age, educational level, and parity	512,212 (1,890)	1.21 (1.08–1.35)	1.21 (1.08–1.35)	1.25 (1.11–1.40)
Smoking	446,657 (1,582)	1.19 (1.05–1.35)	1.20 (1.06–1.36)	1.20 (1.06–1.36)
Denmark				
Gestational age, weight for gestational age, maternal age, educational level, and parity	1,112,319 (1,396)	1.24 (1.11–1.38)	1.30 (1.17–1.45)	1.32 (1.18–1.47)
Smoking	1,004,868 (1,327)	1.23 (1.11–1.38)	1.30 (1.16–1.45)	1.31 (1.18–1.47)
Hospital contact with infection	1,168,649 (1,420)	1.25 (1.12–1.39)	1.31 (1.18–1.46)	1.32 (1.18–1.47)
Maternal autoimmune disease	1,168,649 (1,420)	1.25 (1.12–1.39)	1.31 (1.18–1.46)	1.31 (1.18–1.46)
Maternal country of birth	1,168,022 (1,419)	1.25 (1.13–1.39)	1.32 (1.18–1.46)	1.32 (1.19–1.47)
Maternal BMI	419,263 (479)	1.05 (0.87–1.26)	1.10 (0.92–1.33)	1.10 (0.91–1.32)

[a] Odds ratio (OR) for celiac disease with 95% confidence interval (CI) when comparing children with ≥1 dispensed antibiotics to children with no dispensed antibiotics in the first year of life.

Table S.7. Children categorized as exposed to antibiotics in the first 18 months of life in the MoBa cohort.

Age period	≥1 dispensed antibiotic in the Norwegian National Prescription Register	Indication of antibiotic use in the MoBa questionnaires	≥1 dispensed antibiotic in the Norwegian National Prescription Register and indication of antibiotic use in the MoBa questionnaires
	%[a]	%[b]	%[c]
0–6 months	32	94	27
6–12 months	73	58	32
12–18 months	72	78	53

We categorized children in the MoBa as exposed to antibiotics if the child had a registration of a dispensed antibiotic in the Norwegian National Prescription Register or if the mother indicated use of antibiotics in the MoBa questionnaire. This was done for each of the age periods 0–6 months, 6–12 months, and 12–18 months. The table shows how many of the children categorized as exposed who had a registration in the Norwegian National Prescription Register, indication of antibiotic use in the MoBa questionnaire, or both.

[a] Percentage of children categorized as exposed to antibiotics registered in the Norwegian National Prescription Register

[b] Percentage of children categorized as exposed to antibiotics registered in MoBa

[c] Percentage of children categorized as exposed to antibiotics registered in the Norwegian National Prescription Register and in MoBa

Table S.8. Effect of exposure definition (Table S.7)

	Norwegian National Prescription Register *OR (95% CI)*[a]	**MoBa** *OR (95% CI)*[a]	**Combined (Norwegian National Prescription Register or MoBa)** *OR (95% CI)*[a]
Any antibiotics (0–18 months)	1.22 (1.00–1.48)	1.19 (0.98–1.44)	1.21 (1.00–1.45)
Number of dispensed antibiotics	1.08 (1.01–1.16)	1.15 (1.05–1.27)	1.09 (1.03–1.16)
+Adjustment for infections			
Any antibiotics (0–18 months)	1.18 (0.97–1.44)	1.15 (0.95–1.40)	1.17 (0.97–1.41)
Number of dispensed antibiotics	1.07 (0.99–1.15)	1.13 (1.03–1.24)	1.08 (1.01–1.14)
+Adjustment for breastfeeding			
Any antibiotics (0–18 months)	1.23 (1.01–1.49)	1.20 (0.99–1.45)	1.22 (1.01–1.46)
Number of dispensed antibiotics	1.09 (1.01–1.16)	1.15 (1.05–1.27)	1.09 (1.03–1.16)

[a] Odds ratio (OR) with 95% confidence interval (CI) for celiac disease when comparing children exposed to antibiotics in the first 18 months of life to children not exposed to antibiotics in the first 18 months of life as a reference. Adjusted for year of birth and sex.

Table S.9. Effect of outcome definition.

Exposure	Denmark			Norway	
	≥1 registration (cases)	***≥2 registrations (cases)***	**Confirmed cases**	***≥1 registration***	***≥2 registrations***
	n=1168,656 (2,174 cases)	n=1,168,656 (1,781 cases)	n= 1,168,656 (1,427 cases)	n=537,457 (2,515 cases)	n=537,457 (1,919 cases)
	OR (95% CI)	*OR (95% CI)* [b]		*OR (95% CI)* [b]	*OR (95% CI)* [b]
Number of cases					
Any antibiotics[b]	1.37 (1.25–1.49)	1.36 (1.24–1.50)	1.31 (1.18–1.46)	1.26 (1.14–1.38)	1.21 (1.09–1.36)
Number of dispensed antibiotics[b]	1.11 (1.08–1.13)	1.11 (1.08–1.14)	1.08 (1.05–1.12)	1.10 (1.05–1.15)	1.09 (1.03–1.15)

[a] Odds ratio (OR) for celiac disease (defined as indicated) with 95% confidence interval (CI) when comparing ≥1 dispensed antibiotics or number of antibiotics courses to no dispensed antibiotics in the first year of life. Adjusted for year of birth and sex.