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Early life antibiotics and childhood gastrointestinal disorders: a systematic review

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ABSTRACT

Background In adults, there is increasing evidence for an association between antibiotic use and gastrointestinal (GI) disorders but in children, the evidence is scarce.

Objective Assess the association between exposure to antibiotics in the first 2 years of life in term born children and the presence of chronic GI disorders later in childhood.

Design For this systematic review the MEDLINE, Embase, WHO trial register and Web of Science were systematically searched from inception to 8 June 2020. Title and abstract screening (n=12 219), full-text screening (n=132) as well as the quality assessment with the Newcastle-Ottawa Scale were independently performed by two researchers.

Main outcome measures The association between antibiotics and inflammatory bowel disease (IBD) (n=6), eosinophilic oesophagitis (EoE) (n=5), coeliac disease (CeD) (n=6), infantile colics (n=3), functional constipation (n=2), recurrent abdominal pain, regurgitation, functional diarrhoea and infant dyschezia were examined.

Results Twenty-two studies were included, 11 cohort and 11 case–control studies. A best evidence synthesis showed strong evidence for an association between antibiotic exposure in the first 2 years of life and the presence of IBD, and CeD during childhood. Moderate evidence was found for an association with EoE and no association with functional constipation in the first year of life. There was insufficient evidence for the other studied disorders.

Conclusions The use of antibiotics in early life may increase the risk of GI disorders later in life. Further studies are necessary to unravel the underlying mechanisms and determine potential preventive measures. Meanwhile judicious use of antibiotics in early childhood is highly warranted.

PROSPERO registration number PROSPERO CRD42019132631.

What is known about the subject?

- Evidence about the association between antibiotic use and gastrointestinal (GI) disorders is increasing for adults, but in children the evidence remains scarce.
- The incidence of GI disorders in childhood is increasing.

What this study adds?

- Antibiotics in early life may increase the risk of GI disorders later in life especially inflammatory bowel disease and coeliac disease.
- Although functional GI disorders are the most frequent in childhood, very few studies examined their association with antibiotics in early life.

INTRODUCTION

The incidence of paediatric gastrointestinal disorders (GI disorders), such as paediatric inflammatory bowel disease (IBD) and coeliac disease (CeD), is rising.[1 2] The increase in paediatric GI disorders is most likely related to environmental factors and recently the focus has been on the role of the intestinal microbiome. A microbiome that has been disturbed by factors like stress, dietary change, environmental factors or drugs, can result in alterations in the immune system.[3] Several studies have shown that a disturbed microbiome can be a cause or trigger of GI disorders, probably mediated by these immunological changes.[4–7]

One of the drugs with the most profound effect on the microbiome are antibiotics.[8] The impact of antibiotics on the microbiome depends on various factors such as type of antibiotic, dosage and duration of exposure.[8] Furthermore, age at exposure is probably also important. The gut of a newborn infant is almost sterile with a low diversity and matures according to several developmental stages with increasing diversity over time.[9] The microbiome stabilises around the age of 2–3 years.[9] Since this developing gut microbiota plays an important role in the training of both innate and adaptive immune system, it is likely that antibiotics will have their biggest impact when administered in the first 2 years of life.

For the association between antibiotic use and GI disorders, that has been shown in adults,[10] there is only limited evidence in

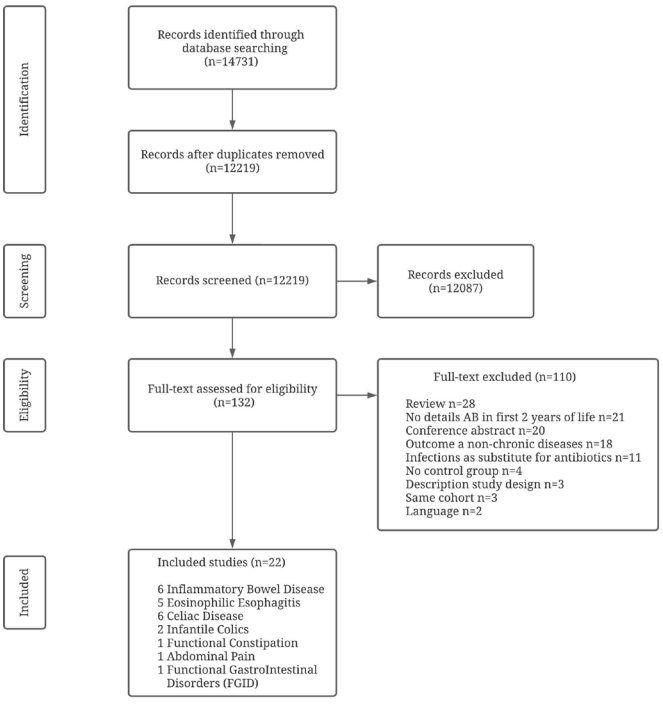

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection.

children.[11] Therefore, the aim of this systematic review was to assess the association between exposure to antibiotics in the first 2 years of life and the presence of chronic GI disorders during childhood.

METHOD

Study selection

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and registered in PROSPERO CRD42019132631.[12 13] MEDLINE, Embase, WHO trial register and Web of Science were systematically searched from inception to 8 June 2020 to identify all studies examining the association between antibiotic exposure in the first 2 years of life and the presence of common chronic (longer than 2 weeks, in order to exclude viral diarrhoea) GI disorders during the first 18 years of life. We searched for associations with IBD, eosinophilic oesophagitis (EoE), CeD, irritable bowel syndrome (IBS), (functional) abdominal pain (AP), constipation, dyspepsia, aerophagia, infantile colic, gastro-oesophageal reflux (GERD), regurgitation, dyschezia and chronic diarrhoea.

A multi stranded search approach comprised various concept combinations of children aged 0–4 years, prognosis, GI disorders and antibiotics. In order to reduce recall noise and enhance search results precision we used VOS-viewer to identify terms for NOTing out irrelevant records from databases searched.[14 15] See online supplemental file 1 for the full search strategies.

Patient and public involvement statement

As this is a systematic review of the literature, there were no patients involved in the design of the research question nor the study itself. Furthermore, for the same reason no approval for the study was required from an ethical committee.

In- and exclusion criteria

Studies were included if: (1) antibiotics were administered between full-term birth and 2 years of age; (2) study outcome was diagnosis with a chronic GI disorder during the first 18 years of life; (3) antibiotic use was before the diagnosis of the GI disorder; (4) a control group was included; (5) in case multiple studies were found examining similar outcomes in one cohort, only the study with the largest cohort was included. No restrictions were placed on the time period of publication. Searches were limited to studies conducted in humans and excluded if the full text was not available in English, Dutch, German or French.

All records found in the search were exported into Rayyan after deduplication.[16] Two researchers (KK and EVD) independently performed title and abstract screening as well as full-text screening. After consensus about the study selection, data were entered into a data extraction form, which included: author, year of publication, country, study design, cases, controls/cohort, population age, sample size exposed to antibiotics, age at exposure, details about classification by type of antibiotics, type of GI disorder, method of diagnosis, confounders for which corrected and the association between exposure and outcome.

Methodological quality

To assess the risk of bias, two researchers (KK and EVD) independently assessed the methodological quality. Discrepancies were resolved by discussion until consensus was reached. The Newcastle-Ottawa Scale (NOS) was used, which has been developed to assess the quality of observational studies.[17] The NOS includes different instruments for assessing case–control and cohort studies. Both scales contain a maximum of nine points and assess studies in three core areas: (1) selection of study participants; (2) comparability of groups; (3) detection of exposure/outcome. One point for comparability of groups was given when the study controlled for the main important confounder and a second point if controlled for a second important confounder, see online supplemental file 2. Studies were rated high quality with a score of eight or higher, moderate quality with a score between five and seven and weak quality with a score of four or less.[18]

Data analyses

To synthesise the methodological quality of the studies, a commonly used best evidence synthesis was applied per disorder in which the methodological quality was considered according to the following definitions: (1) strong evidence, provided by generally consistent findings in

Table 1A Study characteristics and association with antibiotics: inflammatory bowel disease

Author Country Design	Age at diagnosis* or cohort entry† or study endpoint‡	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Canova *et al* Italy Case–control[43]	8.8 years*	70/700	33 (47%) 0–12 months ATC code	▶ Birth order. ▶ Age mother (at birth). ▶ Apgar score at 1 min. ▶ Birth weight. ▶ Education mother. ▶ Gestational age. ▶ Multiple birth. ▶ Season of birth.	AB first 6 months of life childhood onset IBD ▶ Any course aOR=1.458, 95% CI 0.81 to 2.63. ▶ ***Dose-dependent*** – *2–3 courses aOR=2.29, 95% CI 1.01 to 5.24.* – *>4 courses aOR=6.25, 95% CI 1.70 to 23.05.* AB first 12 months of life childhood onset IBD ▶ Any course aOR=1.08, 95% CI 0.64 to 1.80. ▶ ***Dose-dependent****: >4 courses aOR=2.92, 95% CI 1.32 to 6.46.*	8/9 high
Hviid *et al* Denmark Cohort[31]	3.4 years*	117 (0.02%) (50 CD and 67 UC)/577 627	84 (72%) 0–12 months ATC code	▶ Age. ▶ Calendar period. ▶ Other times since use. ▶ Other types of antibiotics.	Increased risk of Crohn's disease after: AB use in the last 3 months: ▶ *3–11 months RR=3.32, 95% CI 1.15 to 9.56*. ▶ 1 year RR=1.53, 95% CI 0.15 to 15.46. AB use >3 months previously before diagnosis: ▶ *0–2 months RR=4.19, 95% CI 1.64 to 10.68.*	8/9 high
Kronman *et al* UK Cohort[25]	Exposed 4.2 years†	748 (0.07%)/1 072 426	436 (58%) 0–12 months Systemic AB prescriptions	▶ Age. ▶ Chronic granulomatous disease. ▶ IBD family. ▶ Primary sclerosing cholangitis. ▶ Sex. ▶ Socioeconomic deprivation.	▶ *Exposure was associated with a 5.5-fold increased IBD risk (aHR=5.51, 95% CI 1.66 to 18.28).* ▶ ***Dose-dependent****: exposure to >2 anti-anaerobic antibiotic courses was more highly associated with IBD development than exposure to one or two courses (aHR=4.77, 95% CI 2.13 to 10.68) versus (3.33, 95% CI 1.69 to 6.58).* ▶ ***Type-dependent:*** *fluoroquinolone (aHR=2.09, 95% CI 1.10 to 3.98) and metronidazole exposure (aHR=186.25, 95% CI 10.86 to 3193.65) was significantly associated with IBD.*	7/9 moderate

Continued

Table 1A Continued

Author Country Design	Age at diagnosis* or cohort entry† or study endpoint‡	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Örtqvist *et al* Sweden Cohort[27]	2 years*	95 (0.01%) 51 IBD (CD and/or UC), 20 CD and 24 UC/827 239	IBD 43 (84,3%) CD 16 (80%) UC 20 (83.3%) 0–12 months ATC code	▶ Delivery mode. ▶ Education parents. ▶ Ethnicity parents. ▶ IBD parents.	No significant associations (any and PcV antibiotics) or dose–response relationship were found.	8/9 high
Shaw *et al* Canada Case–control[38]	8.4 years*	36/360	21 (58%) 0–12 months ATC code	▶ Age. ▶ Place of residence. ▶ Sex.	▶ *One or more dispensations of antibiotics was associated with 2.9 times the odds (95% CI 1.2 to 7.0, p=0.017) of having IBD.* ▶ *Stratified by IBD type, only CD was significant (OR=5.3, 95% CI 1.6 to 17.4; p=0.006).* ▶ ***Dose-dependent**: association for 2–4 (OR=2.9, 95% CI 1.1 to 7.8; p=0.039) and 5+ (OR=5.0, 95 % CI 1.3 to 18.9; p=0.18) prescriptions.*	8/9 high
Virta *et al* Finland Case–control[40]	CD: 9.7 years‡ UC: 8.5 years‡	595 (233 CD, 362 UC)/2380	313 (52,6%) 0–12 months ATC code	▶ Age. ▶ Place of residence. ▶ Chronic diseases. ▶ Sex.	▶ Use of AB overall was not significant. ▶ ***Type-dependent:** phenoxymethylpenicillin was associated with an increased risk of CD. (aOR=2.54, 95% CI1.3 to 4.98).*	8/9 high

AB, antibiotic; aHR, adjusted HR; aOR, adjusted OR; ATC, Anatomical Therapeutic Chemical (ATC) Classification System; CD, Anatomical Therapeutic Chemical (ATC) Classification System; IBD, inflammatory bowel disease; IRR, incidence rate ratio; PcV, phenoxymethylpenicillin; UC, ulcerative colitis.

at least two high-quality studies; (2) moderate evidence, provided by generally consistent results in one high-quality study and at least one moderate-quality or low-quality study, or generally consistent results in multiple moderate-quality or low-quality studies; (3) insufficient evidence, when less than two studies were available or inconsistent findings in multiple studies.[19–21] Results were considered consistent when at least 75% of the studies showed results in the same direction.

RESULTS

Search results

Of the 14 731 retrieved records, 12 219 remained after removing duplicates. These records were screened; 132 were assessed as eligible and read in full-text of which 110 were excluded and 22 studies included in this review. Details of the selection procedure are shown in figure 1.

Study characteristics

The included studies were published between 2010 and 2020 (tables 1A–D): 11 cohort studies[22–32] and 11 case–control studies.[33–43] The studies were performed in Sweden (n=4),[27 30 35 36] the USA (n=5),[33 34 37 41 42] Italy (n=4),[22 29 32 43] Denmark (n=2),[23 31] Canada (n=2)[38 39] and one in the UK,[25] the Netherlands[26] and Finland.[40] There were two international studies, one in Denmark and Norway,[28] and another in Finland, Germany, Sweden and the USA.[24]

The associations between antibiotics and the following GI disorders were examined: IBD (n=6),[25 27 31 38 40 43] EoE (n=5),[33 34 37 39 41] CeD (n=6),[22 24 28 35 36 42] infantile colics (n=3),[23 26 32] functional constipation (n=2),[29 32] recurrent AP (n=1).[30] One study examined several functional GI disorders (FGIDs): infantile colics, functional constipation, functional diarrhoea, infant dyschezia and regurgitation.[32]

Exposure to antibiotics was studied in the first 2 years of life (n=4),[24 30 35 42] the first 18 months of life (n=1),[23] the first year of life (n=13),[22 25 27–29 31 33 34 37–40 43] the first 6 months of life (n=2)[36 41] and the first week of life (n=2)[26 32] (tables 1A–D). Since only a few studies provided details about type of antibiotics and/or number of antibiotic treatments in the first 2 years of life, the associations include mostly the overall antibiotic exposure.

Quality assessment

Ten studies were of high quality,[22 26–29 31 35 38 40 43] ten studies moderate[23–25 30 32 34 36 37 41 42] and two weak[33 39] (table 2). Frequently observed weaknesses were a high dropout rate in the cohort studies, assessment of antibiotic exposure through parental reports, and no correction for important confounders.

Inflammatory bowel disease

Exposure to early life antibiotics was associated with the development of IBD in five out of six studies[25 31 38 40 43] (NOS=7,8,8,8,8), whereas no association was found in one study examining very early onset (VEO) IBD (before 6 years of age)[27] (NOS=8). Three studies found a dose–response relation[25 38 43] and an increased risk after fluoroquinolone,[25] metronidazole[25] and phenoxymethylpenicillin[40] exposure. In two studies IBD was stratified by type and only the OR for Crohn's disease, but not for ulcerative colitis, was significant.[38 40] Forest plots of the main results are shown in figure 2A.

Eosinophilic oesophagitis

In four of the five studies early life antibiotics was associated with EoE[33 34 37 41] (NOS=4,6,7,7), whereas in one study the rates of parental reported antibiotic use were similar for cases and controls[39] (NOS=3) (figure 2B).

Coeliac disease

In four studies, of which three had a high quality, a significant association between early life antibiotics and the presence of CeD was found[22 28 35 42] (NOS=8,9,8,5), whereas in two moderate quality studies no association was found[24 36] (NOS=6,7) (figure 2C). Three studies showed a dose–response relationship between exposure to antibiotics and the risk of CeD.[22 28 42] Furthermore, use of cephalosporin[22] and multiple courses of macrolides[24] showed a positive association with the development of CeD.

Infantile colics

Two studies found a significant association between early life antibiotics and infantile colics[23 26] (NOS=6,8), while one study found no association[32] (NOS=7) (figure 2D).

Functional constipation

In both studies, no association was found between early life antibiotic use and functional constipation in the first year of life[29 32] (NOS=8,7).

Recurrent AP

The only study examining the association between antibiotic use in the first 2 years of life and the risk of recurrent AP at 12 years of age[30] (NOS=5) found that only girls, but not boys, who received antibiotics in both the first and second year of life, had an increased risk of AP at 12 years.

Regurgitation, dyschezia and functional diarrhoea

In one study no association was found between antibiotics in the first week of life and regurgitation, dyschezia and functional diarrhoea[32] (NOS=7).

Syntheses of individual results

Using the definitions for the best evidence synthesis, described in the method section, it can be concluded that there is strong evidence for an association of antibiotics in early life with IBD and CeD. There is moderate evidence for an association with EoE and no association with infantile constipation. The current evidence for an association between antibiotics in early life and the other studied GI disorders is considered insufficient.

Table 1B Study characteristics and association with antibiotics: eosinophilic oesophagitis (EoE)

Author Country Design	Age diagnosis*	Cases/controls	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Jensen *et al* North Carolina (USA) Case–control[33]	Cases 11 years*	31/52	22 (71%) 0–12 months Motherly reported	None	*Antibiotics were associated with EoE (OR=6, 95% CI 1.7 to 20.8).*	4/9 weak
Jensen *et al* North Carolina (USA) Case–control[34]	Cases 10.6 years*	127/121	91 (72%) 0–12 months Motherly reported	▶ Education mother. ▶ NICU admission.	*Antibiotics were associated with EoE (aOR=2.30, 95% CI 1.21 to 4.38).*	6/9 moderate
Radanoet *al* Massachusetts (USA) Case–control[37]	Cases 3 years*	25/74	17 (67%) 0–12 months Parental reported	▶ Age. ▶ Atopy. ▶ Atopy family. ▶ Sex.	*Antibiotics were associated with EoE (OR=3.61, 95% CI 1.11 to 11.74; p=0.03).*	7/9 moderate
Slae *et al* Canada Case–control[39]	Cases 8.6 years*	102/167	60 (59%) 0–12 months Parental reported	▶ Breast feeding. ▶ Birth order. ▶ Day care attendance (early). ▶ Exposure to farm animals. ▶ Fast food consumption.	Rates of antibiotic exposure were similar for cases and controls.	3/9 weak
Witmer *et al* USA Case–control[41]	4.2 years*	1410/2820	409 (29%) 0–6 months Pharmaceutical coding	▶ Age. ▶ Atopy (markers). ▶ Delivery mode. ▶ Erythema toxicum neonatorum. ▶ Feeding problems. ▶ Infantile colic. ▶ Medication exposure. ▶ Oral candidiasis. ▶ Prematurity. ▶ Prolonged rupture/chorioamnionitis. ▶ Reflux. ▶ Sex.	*The association with antibiotic exposure was statistically significant (aOR=1.31, 95% CI1.10 to 1.56).*	7/9 moderate

aOR, adjusted OR; NICU, Neonatale Intensive Care Unit.

Table 1C Study characteristics and association with antibiotics: coeliac disease (CeD)

Author Country Design	Age diagnosis* or study endpoint‡	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Bittker and Bell USA Case–control[42]	6.1 years*	332/241	237 (71%) 0–24 months Parental reported	▶ Age. ▶ Age mother (at birth). ▶ Education mother. ▶ Ethnicity.	▶ *Antibiotic exposure is associated with subsequent CeD (aOR=1.133, 95% CI 1.037 to 1.244; p=0.007).* ▶ ***Dose-dependent**: ORs increase with number of antibiotic courses.*	5/9 moderate
Canova *et al* Italy Cohort[22]	6.4 years*	1.227 CeD (0.6%) 866 confirmed‡ and 361 unconfirmed‡/203 557	336 (47%) 0–12 months ATC code	▶ Education mother (only in sensitivity analysis with pathological confirmed villous atrophy). ▶ Sex. ▶ Year of birth.	▶ *Increased risk of developing CeD after at least 1 AB course (IRR=1.24, 95% CI 1.07 to 1.43), (IRR=1.31, 95% CI 1.10 to 1.56) for histopathologically confirmed CeD.* ▶ ***Dose-dependent**: risk increased with more AB courses (p trend <0.01).* ▶ ***Type-dependent:** cephalosporin use was strongly associated with CeD onset (IRR=1.42, 95% CI 1.18 to 1.73), (IRR=1.51, 95% CI 1.21 to 1.89) for histopathologically confirmed CeD. For first-generation and second-generation drugs: (IRR=1.39, 95% CI 1.11 to 1.76 and third-generation and fourth-generation drugs: IRR=1.49, 95% CI 1.14 to 1.95).*	8/9 high
Kemppainen *et al* Finland, Germany, Sweden and the USA Cohort[24]	21.4 months*	783 (11.9%)/6558	Unknown 0–24 months Parental reported	▶ Breastfeeding (at 90 days of age). ▶ CeD genotype with family. ▶ Delivery mode. ▶ Maternal AB use during pregnancy. ▶ Place of residence. ▶ Probiotic use before 90 days of age. ▶ Season of birth. ▶ Sex.	▶ Exposure to AB was not associated with CeD. ▶ ***Dose-dependent**: 2 or more doses of macrolides within the first year of life (157 of 6558 (2.4%)) had elevated CeD risk (HR=1.77, 95% CI 1.18 to 2.66; p=0.006 before but not after adjustment).*	6/9 moderate
Mårild *et al* Sweden Case–control[35]	0–2 years*	132 coeliac disease/655 12 inflammation/60 17 normal mucosa/85	CeD 51 (39%) Inflammation 6 (50%) 0–24 months ATC code	▶ Age. ▶ Education mother. ▶ Number of outpatient visits before biopsy. ▶ Sex.	*Exposure to AB was associated with CeD ORs for prior AB use (CeD): cases 51/132 (38.6%) controls 189/655 (28.9%) (OR=1.58, 95% CI 1.07 to 2.34).*	8/9 high
Myléus *et al* Sweden Case–control[36]	14 months*	373/581	97 (26%) 0–6 months Parental reported	▶ Age. ▶ Place of residence. ▶ Sex.	No significantly increased risk for coeliac disease (OR=1.2, 95% CI 0.87 to 1.6; p=0.27).	7/9 moderate

Continued

Table 1C Continued

Author Country Design	Age diagnosis* or study endpoint‡	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	Significant association	Quality score
Dydensborg Sander *et al* Denmark and Norway Cohort[28]	Danish: 11.6 years‡ Norwegian: 5.4 years‡	Danish: 1427 (0.12%)/1 168 656 Norwegian: 1919 (0.36%)/537 457	Danish: 622 (43.6%) Norwegian: 390 (20.3%) 0–12 months ATC code	▲ Age mother. ▲ Associated comorbidity. ▲ Birth order. ▲ Education mother. ▲ Hospitalisation with infection. ▲ Season of birth. ▲ Sex. ▲ Type 1 diabetes child and/or mother.	▲ *Exposure to systemic AB (penicillins and extended spectrum penicillins) was positively associated with diagnosed coeliac disease in both cohorts (pooled aOR=1.26, 95% CI 1.16 to 1.36).* ▲ ***Dose-dependent**: between number of AB courses and risk of CeD (pooled aOR for each additional dispensed AB=1.08, 95% CI 1.05 to 1.11).*	9/9 high

AB, antibiotic; aOR, adjusted OR; IRR, incidence rate ratio.

DISCUSSION

This systematic review with best evidence syntheses on the association between antibiotic exposure in the first 2 years of life and chronic GI disorders during childhood showed strong evidence for this association with IBD and CeD, and moderate evidence for this association with EoE. For the other studied GI disorders, insufficient evidence was found.

The question remains to what extent the association with IBD, EoE and CeD can be attributed to antibiotic exposure itself or to other factors such as infections and parental health seeking behaviour. Infections in early life have been proposed to contribute to the development of chronic GI disorders[44 45] and it is difficult to differentiate between the role of infections and antibiotics which are prescribed for (suspected) infections. Furthermore, several GI disorders like CeD can remain undiagnosed for a long time. Higher parental health seeking behaviour can both lead to higher use of antibiotics and a higher chance of diagnosing the chronic GI disorder. Therefore, it remains unknown whether antibiotics are the true causative agent in the observed associations or whether they are intermediates in different mechanistic pathways through microbiome perturbations or changes in immune development after (suspected) infections.

Most studies found a clear association between antibiotics in early life and IBD. The study that focused on VEO-IBD, found no association between antibiotics and VEO-IBD. VEO-IBD is considered a different entity from later-onset IBD,[44] since genetics play a far more important aetiological role than microbial dysbiosis.[45] This may explain the lack of an association with early life antibiotics.

The primary goal of antibiotic administration is to prevent detrimental effects of serious and sometimes even life-threatening infections. However, especially in early life, antibiotics are overused, since they are often prescribed for viral upper respiratory tract infections.[46 47] Given its association with the occurrence of IBD, CeD and EoE, it is highly important to prevent antibiotic overuse by strict adherence to guidelines. If antibiotics are necessary, treatment would be adjusted to minimise dysbiosis. Another possible solution is to shorten the time of antibiotic administration. Oosterloo *et al* found more health issues in the first year of life after 7 days compared with 2 days of antibiotics in the first week of life.[26] Furthermore, whenever possible, narrow-spectrum antibiotics rather than broad-spectrum should be used, because these specifically reduce the capacity of pathogens to cause disease while leaving commensals unharmed.[48] If adjustment of antibiotic treatment is not possible, interventions that restore or prevent dysbiosis should be considered, such as administration of prebiotics or probiotics or faecal transplants.[49–52]

Some limitations of this review need to be considered. As no randomised controlled trials were available, only associations but not causality can be examined. Additionally, the studied results were not evaluated for their

Table 1D Study characteristics and association with antibiotics: FGIDs: infantile colics, functional constipation (FC), recurrent abdominal pain (AP) and regurgitation, functional diarrhoea and infant dyschezia

Author Country Design	Age diagnosis*	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Infantile colics						
Hestbaek *et al* Denmark Cohort[23]	0–6 months*	2183 (8.1%)/26 983	Excessive 895 (41%) extreme excessive 355 (50%) 0–6 months Motherly reported	None	*At 6 months old, statistically significant associations between excessive crying and the use of antibiotics due to ear infections (OR=1.47, 95% CI 1.18 to 1.82) were found.*	6/9 moderate
Oosterloo *et al* The Netherlands Cohort[26]	0–1 year*	74 (20%)/362	33 (45%) 0–7 days Broad-spectrum AB intravenous for 2–3 days (AB2) or 7 days (AB7)	▶ Atopy family. ▶ Birth order. ▶ Breastfeeding. ▶ Day care attendance. ▶ Delivery mode. ▶ Education parents. ▶ Tobacco exposure.	▶ *Antibiotic treatment was an independent risk factor for infantile colic (aOR=1.66, 95% CI1.00 to 2.77, p=0.05).* ▶ *Doctors-diagnosed infantile colic was higher in AB+ than in AB− (4.0% vs 0.4%; p=0.014).* ▶ ***Duration-dependent**: parent-reported infantile colic was higher in AB7 compared with no antibiotics (AB−) and AB2 (24.8%, 14.4% and 14.3%, p=0.048 and p=0.015).*	8/9 high
Salvatore *et al* Italy Cohort[32]	0–1 year*	265 (41.9%)/632	141 (22.3%) 0–7 days Hospital chart and parental report	▶ Birth weight. ▶ Breast feeding (at 1 month of life). ▶ Delivery mode. ▶ Duration of hospitalisation at birth. ▶ Gestational age. ▶ Neonatal complications.	No association was found (OR=1.16; 95% CI 0.79 to 1.70, p=0.439).	7/9 moderate
Functional constipation (FC)						
Salvatore *et al* Italy Cohort[32]	0–1 year*	128 (26.6%)/632	141 (22.3%) 0–7 days Hospital charts and parental reported	▶ Birth weight. ▶ Breast feeding (at 1 month of life). ▶ Delivery mode. ▶ Duration of hospitalisation at birth. ▶ Gestational age. ▶ Neonatal complications.	No association was found (OR=0.77; 95% CI 0.49 to 1.20, p=0.242)	7/9 moderate

Continued

Table 1D Continued

Author Country Design	Age diagnosis*	Cases/controls or cohort	Cases exposed Time exposure Recording details	Confounders for which corrected	*Significant* association	Quality score
Turco *et al* Italy Cohort[29]	0–1 year*	43 (10.7%)/465	15 (34.8%) 0–12 months Parental reported	▶ Anti-inflammatory drugs or corticosteroids. ▶ Atopy and in family. ▶ Birth order. ▶ Breast feeding and weaning. ▶ Education parents. ▶ Fever episodes before onset. ▶ FGIDs family. ▶ Nursery school age. ▶ Place of residence (>3000 citizens). ▶ Sex. ▶ Vitamin and food supplements.	No statistically significant association was found (26% vs 19%).	8/9 high
Recurrent abdominal pain (AP)						
Uusijärvi *et al* Sweden Cohort[30]	12 years*	Monthly: 231 (8.7%) Weekly: 111 (4.2%)/2654	Monthly 1900 (71.5%) Weekly 81 (72,9%) 0–24 months Parental reported	▶ Asthma at 12 years of age. ▶ Asthma at 1 year. ▶ Sex.	*Stratified analyses showed that girls, who received antibiotics during both the first and the second year of life, had an increased risk of AP at 12 years (OR=1.65, 95% CI 1.09 to 2.49).*	5/9 moderate
Regurgitation, functional diarrhoea and infant dyschezia						
Salvatore *et al* Italy Cohort[32]	0–1 year*	Regurgitation: 236 (37.3%) Functional diarrhoea: 24 (3.8%) Infant dyschezia: 199 (31.5%)/632	141 (22.3%) 0–7 days Hospital charts and parental reported	▶ Birth weight. ▶ Breast feeding (at 1 month of life). ▶ Delivery mode. ▶ Duration of hospitalisation at birth. ▶ Gestational age. ▶ Neonatal complications.	No association was found for regurgitation (OR=1.29, 95% CI 0.88 to 1.90, p=0.190), functional diarrhoea (OR=0.90, 95% CI 0.33 to 2.45, p=0.835), or infant dyschezia (OR=1.29, 95% CI 0.87 to 1.93, p=0.205).	7/9 moderate

AB, antibiotic; FGIDs, functional gastrointestinal disorders.

Table 2 Quality assessment

	Selection				Comparability		Outcome/exposure			
	1	2	3	4	5	6	7	8	9	
Cohort studies*	**Representativeness**	**Selection**	**Exposure**	**Outcome**	**Most important**	**Second important**	**Assessment**	**Duration of follow-up**	**Adequacy follow-up**	**Score**
Canova *et al*[22]	*	*	*	*		*	*	*	*	8/9
Hestbaek *et al*[23]	*	*	*	*				*	*	6/9
Hviid *et al*[31]	*	*	*	*		*	*	*	*	8/9
Kemppainen *et al*[24]		*		*	*	*	*	*		6/9
Kronman *et al*[25]		*	*	*	*	*	*	*		7/9
Oosterloo *et al*[26]	*	*	*	*	*	*	*	*		8/9
Örtqvist *et al*[27]	*	*	*	*	*	*	*		*	8/9
Salvatore *et al*[32]	*	*	*	*		*	*	*		7/9
Dydensborg Sander *et al*[28]	*	*	*	*	*	*	*	*	*	9/9
Turco *et al*[29]	*	*	*	*	*	*		*	*	8/9
Uusijärvi *et al*[30]	*	*		*				*	*	5/9
Case–control studies†	**Case definition**	**Cases**	**Controls**	**Definition controls**	**Most important**	**Second important**	**Exposure**	**Ascertainment**	**Non-response rate**	**Score**
Bittker and Bell[42]			*	*	*			*	*	5/9
Canova *et al*[43]	*	*	*	*		*	*	*	*	8/9
Jensen *et al*[33]	*	*		*				*		4/9
Jensen *et al*[34]	*	*	*	*				*	*	6/9
Mårild *et al*[35]	*	*	*	*		*	*	*	*	8/9
Myléus *et al*[36]	*	*	*	*		*		*	*	7/9
Radano *et al*[37]	*	*		*	*	*		*	*	7/9
Shaw *et al*[38]	*	*	*	*		*	*	*	*	8/9
Slae *et al*[39]	*			*				*		3/9
Virta *et al*[40]	*	*	*	*		*	*	*	*	8/9
Witmer *et al*[41]		*	*	*	*	*		*	*	7/9

Comparability: most important confounder: IBD and CeD: presence of IBD/ CeD in 1st degree family member, EoE: sex, colics: atopy child and/or family, functional constipation: maternal education/ social economic status, abdominal pain: lactose intolerance/cow's milk allergy. Comparability: second important confounder: IBD: ethnicity and/or age, EoE: presence of other atopic diseases and/ or ethnicity, CeD: sex and/or season of birth and/or the presence of other autoimmune diseases, colics: presence of GERD and/or type of feeding and/or being a first child, functional constipation: sex and/or age, abdominal pain: anxiety/depression/stress in the child and/or the parents.

*Cohort studies: 1. representativeness of the exposed cohort, 2. selection of the non-exposed cohort, 3. ascertainment of exposure, 4. demonstration that the outcome of interest was not present at start of the study, 5. comparability of cohorts on the basis of the design or analysis most important factor, 6. comparability of cohorts on the basis of the design or analysis second important factor, 7. assessment of outcome 8. was follow-up long enough for outcomes to occur and 9. adequacy of follow-up of cohort.

†Case–control studies: 1. is the case definition adequate? 2. representativeness of the cases, 3. selection of controls, 4. definition of controls, 5. comparability of cases and controls on the basis of the design or analysis most important factor, 6. comparability of cases and controls on the basis of the design or analysis second important factor, 7. ascertainment of exposure, 8. same method of ascertainment for cases and controls and 9. non-response rate.

CeD, coeliac disease; EoE, eosinophilic oesophagitis; GERD, gastro-oesophageal reflux ; IBD, inflammatory bowel disease.

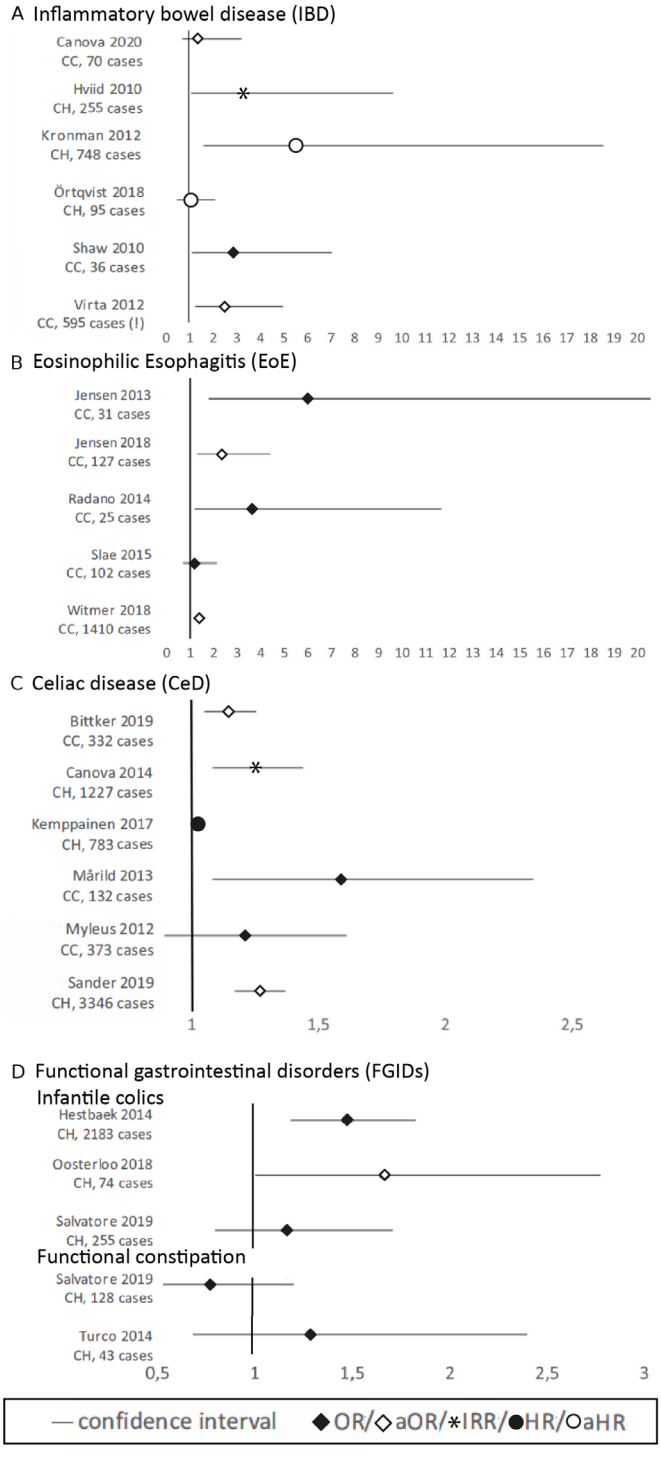

Figure 2 Forest plots per gastrointestinal disorder. (A) IBD; (B) EoE; (C) CeD; (D) FGID (infantile colics and functional constipation). CC, case control study, CH, cohort study, (!) Virta 2012 only shows the results of the phenoxymethylpenicillin analyses, overall use of antibiotics was not significant.

precision and associations with wide CIs can indicate uncertainty about the magnitude of the association. Hence, the results must be interpreted with caution. Furthermore, both age at exposure as well as age at diagnosis varied substantially between the studies. In addition, study outcomes were also very heterogeneous, excluding a meta-analysis. Therefore, a best evidence synthesis was applied, taking the quality of the studies into account. Furthermore, the recording of antibiotic exposure was in half of the studies parental reported, which may have led to recall bias. The antibiotics were mostly analysed as overall use, without distinguishing between types of antibiotics and therefore, it was not possible to determine associations between certain type of antibiotics and GI disorders. Finally, for several functional GI disorders, like IBS or GERD, only few or even no studies were found which prohibits any conclusions on these GI disorders.

One of the strengths of this review is that the search string was built and performed by an information scientist. Besides the published articles, also conference abstracts were checked for relevant studies. Furthermore, this review studies the association between antibiotics in early life and all chronic GI disorders in childhood, which provides insights in the available evidence but also shows the gap of knowledge for these associations.

For future research, it is recommended to study the association between early life antibiotics and the presence of those GI disorders that currently lack sufficient studies. Furthermore, it is necessary to gain insights in the specific effect of different types of antibiotics on the microbiome in order to optimise therapies that can prevent or counteract the detrimental effects of antibiotics in early life.

CONCLUSION

This systematic review shows strong evidence for an association between antibiotic exposure in the first 2 years of life and the presence of IBD and CeD later in childhood. For the other included GI disorders, only moderate or insufficient evidence was found. In order to decrease the incidence of IBD and CeD, antibiotic administration in early life should be critically considered. Moreover, interventions need to be developed to restore the microbiome after unavoidable antibiotic exposure in order to prevent detrimental health consequences later in life.

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