

Neonatal Antibiotics and Food Allergy Are Associated With FGIDs at 4–6 Years of Age

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ABSTRACT

Objectives: Antibiotics may contribute to the development of functional gastrointestinal disorders (FGIDs). This study aimed to determine whether antibiotics during the first week of life, infantile colic in the first year of life, gut-associated immune markers at 1 year of age, and allergies at 4–6 years of age in term-born children were associated with a higher prevalence of FGIDs at 4–6 years of age.

Methods: A prospective observational cohort of 436 term-born infants was followed up at the age of 4–6 years; 151 received broad-spectrum antibiotics (AB+), and 285 healthy controls (AB–). Validated Questionnaire On Pediatric Gastrointestinal Symptoms-Rome III and International Study of Asthma and Allergy in Childhood questionnaires were sent to parents of 418 available children. The independent t-test, chi-squared test or non-parametric test and logistic multivariate regression analyses were used.

Results: In total, 340 of 418 (81%) questionnaires were completed. Only the presence of functional abdominal pain was significantly higher in AB+ than AB– (4% vs 0.4%, respectively, $P = 0.045$). Children with food allergy fulfilled significantly more often the criteria for irritable bowel syndrome (IBS) and abdominal migraine (26% vs 9%, $P = 0.002$ and 7% vs 1%, $P = 0.043$, respectively) compared to non-allergic children. No differences in FGIDs existed at the age of 4–6 years between children with and without a history of infantile colic. There were significant differences in gut-associated immune markers between children with and without FGIDs.

Conclusion: Antibiotics during the first week of life resulted in a higher risk for functional abdominal pain at 4–6 years. Furthermore, food allergy was associated with IBS and abdominal migraine at 4–6 years.

Key Words: abdominal migraine, abdominal pain, atopic disorders, cohort study, irritable bowel syndrome

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What Is Known

- In adults, antibiotic treatment increases the risk of developing functional gastrointestinal disorders (FGIDs), but studies in children are less clear.
- Limited evidence suggests that allergies are associated with FGIDs.

What Is New

- This study shows that antibiotic treatment during the first week of life in term-born children is associated with a higher risk for functional abdominal pain at 4–6 years of age.
- Children with food allergy have a higher prevalence of irritable bowel syndrome and abdominal migraine at 4–6 years of age.

Functional gastrointestinal disorders (FGIDs) are common disorders in children with often a major impact on their quality of life (1). FGIDs are defined as a variable combination of chronic or recurrent gastrointestinal symptoms that, after appropriate medical evaluation, cannot be attributed to any other medical condition (2). Nowadays, they are also indicated as brain-gut disorders, emphasizing the importance of both psychosocial factors and gut factors like abnormal intestinal motility, visceral hyperalgesia, and gut inflammation in the pathophysiology of FGIDs (3).

Alterations in the gut microbiome (dysbiosis) can play a role in the pathophysiology of FGIDs as well (4–6). Antibiotics are a group of drugs that can have a profound effect on the gut micro-biome (7). In adults, antibiotic treatment increases the risk of developing FGIDs (8,9), but studies in children are less conclusive. A Swedish study showed that antibiotic treatment during the first 2 years of life increased the risk of abdominal pain in girls at 12 years of age, but not when antibiotics were administered between 9 and 12 years old (10). An Italian study demonstrated that neonatal antibiotic treatment was associated with an increased risk of FGIDs in the first year of life, although the effect was mainly found in preterm born children (11). These pediatric studies suggest that the timing of antibiotics may determine the degree of dysbiosis and hence its subsequent health effects including FGIDs (7).

The gut microbiome is developing during the first 2 years of life and disruption of the normal developmental process may have long-term consequences (12). To study the effect of antibiotic exposure during the first week of life, the INCA study (INtestinal microbiota Composition after Antibiotic treatment in early life) was setup (13). It is a prospective cohort study of infants born at term, in which associations between antibiotic exposure in the first week of life and subsequent health problems are being studied. In the INCA

study, we found that antibiotic treatment in the first week of life was associated with an increased risk of infantile colic in the first year of life (14), with a different circulating immune marker profile at one year of age (15), and with an increased risk of developing allergies at 4–6 years of age (16).

The first aim of the INCA follow-up study was to investigate if antibiotic treatment in the first week of life increases the risk of having FGIDs at the age of 4–6 years. The second aim was to examine whether findings from other studies, showing an association between atopic disorders and FGIDs, could be replicated (17,18). Since there was a relatively large group of children with infantile colic in the INCA cohort, the third aim was to determine whether infantile colic was associated with an increased prevalence of FGIDs at 4–6 years of age. Finally, we explored whether gut-associated immune markers that were significantly different at one year of age in children with and without a history of infantile colic were different for children with FGIDs at 4–6 years of age.

METHOD

Study Design

The study design of the prospective birth-cohort INCA study has been described previously (13). In short, between 2012 and 2015, 436 term-born infants were recruited from the maternity and neonatal wards of four teaching hospitals in the Netherlands. We included 285 healthy controls (AB–) and 151 infants treated with a combination of broad-spectrum antibiotics in their first week of life due to suspicion for early-onset sepsis (AB+). All hospitals used gentamycin in combination with either penicillin, amoxicillin, or amoxicillin/clavulanic acid. Blood cultures were taken before AB treatment was started. In case of a negative blood culture, combined with a low clinical suspicion of infection and low C-reactive protein, antibiotics were discontinued after 2–3 days ($n = 42$). Otherwise, antibiotics were continued for 7 days ($n = 109$).

Data Collection in the First Year of Life

At inclusion, parents filled out an online questionnaire concerning the background of the family (eg, parental atopic diseases, household education, and presence of siblings). Thereafter, a daily checklist was kept during the first year of life, reporting the presence of wheezing, crying, and other symptoms. If parents reported excessive crying > 3 days within a week, in the first three months of life, it was defined as infantile colic according to the ROME III criteria (19). Furthermore, a monthly questionnaire was filled out during the first year of life concerning nutrition, antibiotic treatment, and general practitioner visits for gastrointestinal symptoms. The symptoms were verified at 1 year of age through doctors' diagnoses via the general practitioner electronic medical database using the International Classification of Primary Care (ICPC) (20). Around 1 year of age, a blood sample was obtained if parents gave additional informed consent ($n = 149$). After centrifugation, the serum samples were aliquoted and stored at -80°C until further use. The method of analyzing the immune markers with a multiplex immunoassay has been described elsewhere (15). The fourteen gut-associated immune markers (interleukin [IL]-17F, IL-22, IL-31, IL-33, IL1R1, LIGHT, tyrosine lysine leucine-40, C-X-C Motif Chemokine Ligand 13 (CXCL13), Soluble programmed cell death receptor-1 (sPD1), tumor necrosis factor [TNF]-R2, sIL-7Ra, Gal-1, Gal-9, S100A8) that differed significantly at 1 year of age between infants with and without infantile colic were studied for differences between children with and without FGIDs.

Follow-up Study

There were 418 children (271 AB– and 147 AB+) eligible for follow-up since 18 of the 436 children dropped out of the study after the first year of life (Fig. 1). Between May 2018 and May 2019, the parents of these 418 children were approached to fill out an online questionnaire. The children were between 4 and 6 years of age at the time of follow-up, depending on the year of inclusion.

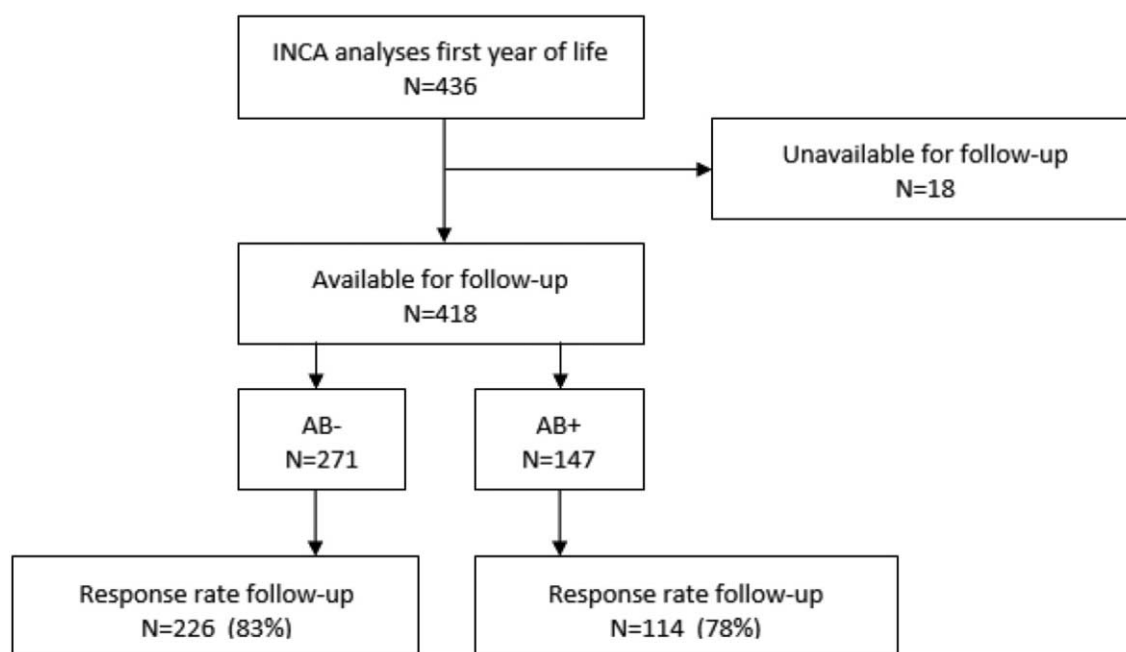


FIGURE 1. Flowchart of follow-up. AB+ = children born at term treated with antibiotics in the first week of life and AB– = healthy controls.

Data regarding the presence of FGIDs (functional dyspepsia, irritable bowel syndrome [IBS], abdominal migraine, functional abdominal pain, functional constipation, non-retentive fecal incontinence, and aerophagia) were collected using the validated ROME III questionnaire (19). Data regarding wheezing, asthma and eczema were collected through the validated ISAAC questionnaire (21). Furthermore, information about additional antibiotic use until the second year of life and the presence of both parental reported and doctor diagnosed allergies (food, drug, insect venom, inhalation, or contact allergy) was collected. Upper and lower respiratory disorders, gastrointestinal disorders, and allergies were verified through doctors' diagnoses using ICPC, if informed parental consent for requesting this information was obtained (20). Finally, with additional informed parental consent, the pharmacy was approached to collect information about antibiotic use after the neonatal period until 4–6 years of age.

Statistical Analysis

Baseline characteristics and differences between groups were analyzed using the independent *t*-test and chi-squared test or non-parametric test as appropriate. If the conditions for a chi-squared test were met, logistic regression analyses were performed and expressed as odds ratio (OR) with 95% confidence intervals (CIs), otherwise only the results of the Fisher exact test were presented. In order to prevent bias, logistic multivariate regression

analyses were only performed in case there were at least 10 events per variable (22). A *P* value < 0.05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics for Windows version 26 (Armonk, NY, USA).

Ethics

Informed consent was obtained from both parents of all participating children. The study was approved by the ethical board of the St. Antonius Hospital in Nieuwegein, the Netherlands, and was registered in the clinical trials register as NCT02536560.

RESULTS

In total, 340 of the 418 (81%) questionnaires were completed. The response rate was equally divided between AB+ and AB− (114/147 [78%] vs 226/271 [83%], *P* = 0.118). Baseline characteristics between AB+ and AB− of the follow-up cohort were similar, except for age at follow-up, delivery mode, and antibiotic-free months after the first week of life in the first year of life (Table 1). Among the 149 children with a blood sample taken, there was complete follow-up of 130 (87%) children. Pharmacy records showed no significant differences in the number of children treated with additional antibiotic courses after the first week and before the age of 2 years between the AB+ and AB− group.

TABLE 1. Baseline characteristics

	AB− N = 226	AB+ N = 114
Age (median, IQR)*	5 (4.6–5.9)	4.7 (4.4–5.0)
Sex (male n, %)	121 (54)	65 (57)
Delivery mode* (vaginal, %)	146 (65)	86 (75)
Duration (mo) any breastfeeding (median, IQR)	4 (1–8)	2.5 (1–7)
Duration (mo) exclusive breastfeeding (median, IQR)	2 (0–5)	0 (0–4)
Siblings (yes, %)	120 (53)	69 (61)
Missing	7 (3)	4 (4)
Infantile colic in the first year of life (yes, %)	34 (15)	23 (20)
Number of AB courses, after first week, in the first years of life (median, IQR)	0 (0–1)	0 (0–1)
AB free months, after first week, in the first year of life (median, IQR)	9 (7–11)	7 (2–9)
Number of courses, after first week, in the first 2 y (median, IQR)	1 (1–2)	1 (1–2)

*Significant *P* < 0.05 difference between AB+ and AB−. AB+ = children born at term treated with antibiotics in the first week of life; AB− = healthy controls, IQR = interquartile range, SD = standard deviation.

TABLE 2. Incidence of functional gastrointestinal disorders (FGIDs) between AB− and AB+, parental reported food allergic and non-food allergic children, and between children with and without colic

	AB colic N = 226 N, %	AB+ N = 114 N, %	<i>P</i> value	Non-allergic N = 298 N, %	Food allergic N = 42 N, %	<i>P</i> value	Colic − N = 283 N, %	Colic + N = 57 N, %	<i>P</i> value
Any FGID	48 (21)	32 (28)	0.161	65 (22)	15 (36)	0.047	63 (22)	15 (26)	0.587
Functional dyspepsia	3 (1)	2 (2)	1	4 (1)	1 (2)	0.485	5 (2)	0 (0)	0.594
IBS	26 (12)	13 (11)	0.978	28 (9)	11 (26)	0.002	32 (11)	7 (12)	0.833
Abdominal migraine	5 (2)	2 (2)	1	4 (1)	3 (7)	0.043	6 (2)	1 (2)	1
Functional abdominal pain	1 (0.4)	4 (4)	0.045	5 (2)	0 (0)	1	5 (2)	0 (0)	0.594
Functional constipation	13 (6)	9 (8)	0.448	19 (6)	3 (7)	0.743	17 (6)	5 (9)	0.389
Non-retentive fecal incontinence	3 (1)	2 (2)	1	4 (1)	1 (2)	0.485	4 (1)	1 (2)	1
Aerophagia	5 (2)	3 (3)	1	6 (2)	2 (5)	0.258	5 (2)	3 (5)	0.134

Significance tested with a chi-squared test or Fisher exact test. AB+ = children born at term treated with antibiotics in the first week of life; AB− = healthy controls; colic− = children without colic in the first year of life; colic+ = children with infantile colic in the first year of life. FGID = functional gastrointestinal disorder; IBS = irritable bowel syndrome. Significant *P* < 0.05 in bold.

In total, 80 of 340 (24%) children had at least one FGID, with similar prevalence in AB+ and AB- (28% vs 21%, $P = 0.161$), aOR 1.428 (95% CI 0.837–2.434, $P = 0.191$) corrected for age, delivery mode and antibiotic free months in the first year of life. IBS was the most frequently observed FGID in 39 (11%) children, followed by functional constipation in 22 (7%) children. Of all FGIDs, only the presence of functional abdominal pain was significantly higher in AB+ compared to AB- children, independent of differences at baseline (4% vs 0.4% respectively, $P = 0.045$) (Table 2).

The presence of one or more FGIDs was higher in children with parental reported food allergy compared to children without food allergy (36% vs 22%, respectively, $P = 0.047$, Table 2), although no longer significant after correction for sex and age aOR 1.955 (95% CI 0.980–3.899, $P = 0.057$). There was a significantly higher frequency of both IBS (26% and 9%, $P = 0.002$) aOR 2.821 (95% CI 1.231–6.463, $P = 0.014$) corrected for age, sex and presence of siblings, and abdominal migraine (7% and 1%, $P = 0.043$) in children with a parental reported food allergy. A doctor-diagnosed food allergy ($n = 18$) was only significantly associated with abdominal migraine (17% vs 1%, $P = 0.004$).

The percentage of children with > 1 FGID at 4–6 years was similar in children with and without infantile colic in the first year of life (26% vs 22%, respectively, OR 1.198 [95% CI 0.624–2.298, $P = 0.587$], Table 2). Moreover, this was independent from neonatal or later antibiotic exposure aOR 1.159 (95% CI 0.602–2.232, $P = 0.659$).

The gut-associated immune markers Gal-1, IL1R1, LIGHT, and sPD1 were significantly lower both in children with any FGID compared to children without a FGID as well as in children with IBS compared to children without IBS (Table 3). The marker IL-22 was significantly lower in children with any FGID compared to children without a FGID. Furthermore, the markers TNF-R2, Gal-9, CXCL13 were significantly lower in children with IBS compared to children without IBS.

DISCUSSION

In this follow-up of the INCA study, exposure to antibiotics in the first week of life was associated with functional abdominal pain at 4–6 years of age. Furthermore, IBS and abdominal migraine at 4–6 years of age were significantly more present in children with

a food allergy. No association between infantile colic and the development of an FGID at the age of 4–6 years was found. Finally, we found differences in gut-associated immune markers between children with and without FGIDs.

To date, few studies have examined the association between antibiotic exposure in early life and FGIDs later in life, as summarized in a recent review (23). The number of studies was too small to draw firm conclusions on any association between early life antibiotics and functional constipation, regurgitation, dyschezia, or functional diarrhea (23). One study showed an association between antibiotic exposure and recurrent abdominal pain in adolescent girls (10), which is in line with our finding that functional abdominal pain was significantly associated with antibiotic exposure in the first week of life; however, more prospective studies are necessary to elucidate the association between early life antibiotics and FGIDs later in life.

Our findings that children with a (parental reported) food allergy had more often an FGID is consistent with several other studies, showing an association between (food) allergies and FGIDs (24–28). There are several possible explanations for this association. First, food allergies may directly induce the development of FGIDs. In a recent study, oral ingestion of dietary antigens resulted in increased visceral pain via an immunoglobulin E (IgE)- and mast cell-dependent mechanism (29). Another possible explanation for this association may be similarities in the pathophysiological mechanism of developing allergies and FGIDs. It is known, for example, that both allergies and FGIDs like IBS have been associated with increased intestinal permeability and even inflammatory signals (30–32). Microbiota composition can substantially influence epithelial barrier function. Commensals and probiotic bacteria were demonstrated to enhance barrier integrity (33). This suggests that early-life dysbiosis, caused by antibiotics, can play a role in developing both food allergies and FGIDs (4,34). Further studies are necessary to elucidate if dysbiosis and the resulting increased permeability are essential for the development of both food allergies and FGIDs.

In contrast to our study, three studies examining infantile colic and FGIDs later in life found an association (18,35,36). Two small studies concluded that early bouts of persistent crying might be an early manifestation of abdominal pain-related FGIDs at 10 and 13 years of age (18,36). Another, larger, retrospective study

TABLE 3. Differences between gut-associated immune markers in children with functional gastrointestinal disorders and in children with irritable bowel syndrome

	No FGID N = 101 Mean (SD)* / Median (IQR)	Any FGID N = 29 Mean (SD)* / Median (IQR)	P value	IBS - N = 114 Mean (SD)* / Median (IQR)	IBS + N = 16 Mean (SD)* / Median (IQR)	p-value
IL-17F	17.9 (17.9–17.9)	17.9 (17.9–17.9)	0.052	17.9 (17.9–17.9)	17.9 (17.9–17.9)	0.247
IL-22	3.7 (2.6–7.8)	3.7 (1.5–3.7)	0.043	3.7 (2.6–7.0)	3.7 (1.2–3.7)	0.090
IL-31	24.4 (24.4–58.9)	24.4 (24.4–24.4)	0.163	24.4 (24.4–51.4)	24.4 (24.4–24.4)	0.527
IL-33	11.0 (11.0–11.0)	11.0 (11.0–11.0)	0.368	11.0 (11.0–11.0)	11.0 (11.0–11.0)	0.518
IL1R1	25.6 (9.1)*	21.7 (7.5)*	0.033	25.4 (8.8)*	20.0 (7.9)*	0.021
LIGHT	13.7 (8.1–29.9)	8.1 (5.2–14.8)	0.020	13.6 (8.1–27.9)	8.1 (5.1–10.8)	0.030
YKL-40	13647.3 (18163.0–25104.1)	19607.9 (12827.5–25616.8)	0.795	18307.1 (13668.4–25234.4)	19338.1 (12637.5–23853.7)	0.966
CXCL13	50.0 (30.2–64.7)	42.3 (25.5–53.2)	0.104	50.2 (30.6–63.4)	28.4 (23.0–48.7)	0.012
sPD1	642.0 (269.0)*	523.2 (228.0)*	0.033	635.3 (263.1)*	473.1 (232.7)*	0.021
TNF-R2	1227.1 (503.9)*	1148.1 (497.2)*	0.456	1241.8 (495.3)*	987.8 (500.5)*	0.049
sIL-7Ra	28971.5 (13478.6–46086.7)	20462.2 (4508.9–50804.1)	0.346	28761.6 (13359.6–46757.1)	19431.1 (2640.7–48051.7)	0.245
Gal-1	13143.5 (5800.9)*	10514.8 (5178.4)*	0.030	12992.6 (5757.3)*	9454.0 (4833.2)*	0.021
Gal-9	2936.0 (1408.5)*	2632.7 (1015.2)*	0.282	2969.9 (1361.0)*	2144.8 (840.5)*	0.020
S100A8	8263.5 (4964.9–13571.0)	5926.1 (4074.8–11081.8)	0.314	8132.3 (4798.1–13775.5)	6671.9 (4215.5–10453.1)	0.476

FGID = functional gastrointestinal disorder; IBS = irritable bowel syndrome; IBS- = all children without IBS; IBS+ = children with IBS; IQR = interquartile range; SD = standard deviation. Significant $P < 0.05$ in bold.

found that children with infantile colic had a higher prevalence of FGIDs at 7 years of age (35). The lack of an association found in the present study could be explained by the younger age (4–6 years) at follow-up, as many FGIDs manifest later in childhood. Longer follow-up of the INCA cohort may be necessary to draw firmer conclusions whether infantile colic is a risk factor for FGIDs at an older age. Another possible explanation may be that AB-induced infantile colic has a different pathophysiological mechanism than, for example, infantile colic in children whose parents suffer from depression (37,38).

It is remarkable that gut associated immune markers, measured at the age of 1 year, seem to be predictive for FGIDs at the age of 4–6 years, emphasizing that health problems later in life may already be triggered in early life; however, due to the explorative nature of the study, it is difficult to determine the role of changes of individual cytokines. Furthermore, there is very limited information available regarding the levels of inflammatory markers in healthy infants. Therefore, further research in larger cohorts is needed to see if these markers are indeed predictive for FGIDs later in life; however, there is no doubt that early immune signals at one year of age are at least associated with FGIDs later in life which is also true for allergies and even asthma (39).

The prospective design of this study and the high response rate (>80%) are important strengths of this study, contributing to the reliability of the results. Furthermore, we used validated questionnaires to collect the follow-up data. A limitation of any cohort study is that during follow-up, groups become smaller. As a result, only univariate analyses could be performed prohibiting correction for potential confounding, including AB type and treatment duration. Moreover, we had no data on perinatal antibiotic exposure. Furthermore, the age at follow-up of 4–6 years may have been a little early to diagnose FGIDs (40). The diagnosis of FGIDs was based on the questionnaires completed by the parents and their interpretation of the symptoms, which may have led to bias. Finally, at the time of follow-up, the ROME IV questionnaire was not yet validated in Dutch. Therefore, the ROME III questionnaire was used.

CONCLUSION

This follow-up of the INCA study showed that antibiotic treatment in the first week of life in children born at term was associated with functional abdominal pain at 4–6 years of age. Children with a food allergy significantly more often fulfilled Rome criteria for IBS and abdominal migraine at 4–6 years of age. No association was found between infantile colic in the first year of life and later FGIDs, independent from antibiotic exposure in the first week of life. Differences in gut-associated immune markers were observed between children with and without FGIDs. Future studies need to focus on pathophysiological mechanisms that may explain these associations.

REFERENCES

- Varni JW, Bendo CB, Nurko S, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. *J Pediatr* 2015;166:85–90.
- Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2016;150:1527–37.
- Jones M, Dilley J, Drossman D, et al. Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. *Neurogastroenterol Motil* 2006;18:91–103.
- Shin A, Preidis GA, Shulman R, et al. The gut microbiome in adult and pediatric functional gastrointestinal disorders. *Clin Gastroenterol Hepatol* 2019;17:256–74.
- Simren M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 2013;62:159–76.
- Pimentel M, Lembo A. Microbiome and its role in irritable bowel syndrome. *Dig Dis Sci* 2020;65:829–39.
- Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut* 2016;65:1906–15.
- Maxwell P, Rink E, Kumar D, et al. Antibiotics increase functional abdominal symptoms. *Am J Gastroenterol* 2002;97:104–8.
- Paula H, Grover M, Halder SL, et al. Non-enteric infections, antibiotic use, and risk of development of functional gastrointestinal disorders. *Neurogastroenterol Motil* 2015;27:1580–6.
- Uusijarvi A, Bergstrom A, Simren M, et al. Use of antibiotics in infancy and childhood and risk of recurrent abdominal pain—a Swedish birth cohort study. *Neurogastroenterol Motil* 2014;26:841–50.
- Salvatore S, Baldassarre ME, Di Mauro A, et al. Neonatal antibiotics and prematurity are associated with an increased risk of functional gastrointestinal disorders in the first year of life. *J Pediatr* 2019;212:44–51.
- Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med* 2016;8:343ra82.
- Rutten N, Rijkers G, Meijssen C, et al. Intestinal microbiota composition after antibiotic treatment in early life: the INCA study. *BMC Pediatr* 2015;15:204.
- Oosterloo BC, van Elburg RM, Rutten NB, et al. Wheezing and infantile colic are associated with neonatal antibiotic treatment. *Pediatr Allergy Immunol* 2018;29:151–8.
- Oosterloo BC, Van't Land B, de Jager W, et al. Neonatal antibiotic treatment is associated with an altered circulating immune marker profile at 1 year of age. *Front Immunol* 2020;10:2939.
- Kamphorst K, Vlieger AM, Oosterloo BC, et al. Higher risk of allergies at 4–6 years of age after systemic antibiotics in the first week of life. *Allergy* 2021;76:2599–602.
- Koloski N, Jones M, Walker MM, et al. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel syndrome, independent of psychological distress. *Aliment Pharmacol Ther* 2019;49:546–55.
- Savino F, Castagno E, Bretto R, et al. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatr* 2005;94:129–32.
- Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterol* 2006;130:1519–26.
- Verbeke M, Schrans D, Deroose S, et al. The International Classification of Primary Care (ICPC-2): an essential tool in the EPR of the GP. *Stud Health Technol Inform* 2006;124:809–14.
- Asher M, Keil U, Anderson H, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483–91.
- Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373–9.
- Kamphorst K, Van Daele E, Vlieger AM, et al. Early life antibiotics and childhood gastrointestinal disorders: a systematic review. *BMJ Paediatr Open* 2021;5:e001028.
- Pensabene L, Salvatore S, D'Auria E, et al. Cow's milk protein allergy in infancy: a risk factor for functional gastrointestinal disorders in children? *Nutrients* 2018;10:1716.
- Uz E, Türkay C, Aytac S, et al. Risk factors for irritable bowel syndrome in Turkish population: role of food allergy. *J Clin Gastroenterol* 2007;41:380–3.
- Zar S, Benson MJ, Kumar D. Food-specific serum IgG4 and IgE titers to common food antigens in irritable bowel syndrome. *Am J Gastroenterol* 2005;100:1550–7.
- Olen O, Neuman A, Koopmann B, et al. Allergy-related diseases and recurrent abdominal pain during childhood—a birth cohort study. *Aliment Pharmacol Ther* 2014;40:1349–58.
- Di Nardo G, Cremon C, Frediani S, et al. Allergic proctocolitis is a risk factor for functional gastrointestinal disorders in children. *J Pediatr* 2018;195:128.e1–33.e1.
- Aguilera-Lizarraga J, Florens MV, Viola MF, et al. Local immune response to food antigens drives meal-induced abdominal pain. *Nature* 2021;590:151–6.
- Samadi N, Klems M, Untersmayr E. The role of gastrointestinal permeability in food allergy. *Ann Allergy Asthma Immunol* 2018;121:168–73.
- Shulman RJ, Eakin MN, Czyzewski DI, et al. Increased gastrointestinal permeability and gut inflammation in children with functional abdominal pain and irritable bowel syndrome. *J Pediatr* 2008;153:646–50.

32. Keita AAV, Söderholm JD. Mucosal permeability and mast cells as targets for functional gastrointestinal disorders. *Curr Opin Pharmacol* 2018;43:66–71.
33. Ulluwishewa D, Anderson RC, McNabb WC, et al. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr* 2011;141:769–76.
34. Zhao W, Ho H-e, Bunyavanich S. The gut microbiome in food allergy. *Ann Allergy Asthma Immunol* 2019;122:276–82.
35. Indrio F, Di Mauro A, Riezzo G, et al. Infantile colic, regurgitation, and constipation: an early traumatic insult in the development of functional gastrointestinal disorders in children? *Eur J Pediatr* 2015;174:841–2.
36. Partty A, Kalliomaki M, Salminen S, et al. Infant distress and development of functional gastrointestinal disorders in childhood: is there a connection? *JAMA Pediatr* 2013;167:977–8.
37. Gungor S, Kiriş S, Ozkars MY, et al. Effect of maternal depression and environmental factors on infantile colic. *Erciyes Medical J* 2019;41:80–4.
38. Maxted AE, Dickstein S, Miller-Loncar C, et al. Infant colic and maternal depression. *Infant Ment Health J* 2005;26:56–68.
39. Sjolund J, Kull I, Bergström A, et al. Allergy-related diseases in childhood and risk for abdominal pain-related functional gastrointestinal disorders at 16 years—a birth cohort study. *BMC Med* 2021;19:1–11.
40. Koppen IJ, Nurko S, Saps M, et al. The pediatric Rome IV criteria: what's new? *Expert Rev Gastroenterol Hepatol* 2017;11:193–201.