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ORIGINAL ARTICLE

Functional gastrointestinal disorders, quality of life, and behaviour in adolescents with history of infant colic

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Abstract

Aim: To assess the prevalence of functional gastrointestinal disorders (FGIDs), health-related quality of life (HRQOL), and behavioural problems in a cohort of adolescents with a history of infant colic (IC), as defined by Wessel's criteria.

Methods: 388 adolescents, aged 15–18 years, who participated in a randomised controlled trial for infants with colic, were invited for our observational follow-up study. Prevalence of FGIDs was assessed with the Rome IV Questionnaire on Paediatric Gastrointestinal Disorders (RIV-QPGD), HRQOL through self-report of the Paediatric Quality of Life Inventory (PedsQL), and behavioural problems through parent-report of the child behaviour checklist (CBCL). Multivariable models were used to compare prevalence rates of FGIDs and HRQOL scores.

Results: 190 (49%) adolescents with a history of IC (cases) and 381 controls were included (median age 17.0 [IQR 16.0–17.0] and 16.0 [15.0–17.0] years, respectively). Cases had a significantly higher risk for postprandial distress syndrome compared to controls (aOR 2.49 (95%CI 1.18–5.25), $p = 0.002$). After multivariable regression, total, physical and school HRQOL scores were significantly lower in cases compared to controls ($p = 0.003$, 0.001, and 0.009).

Conclusion: Adolescents with a history of IC demonstrate higher prevalence rates of postprandial distress syndrome compared to controls. However, conclusions should be made with caution due to attrition and information bias.

KEYWORDS
adolescence, functional gastrointestinal disorders, infant colic, long-term outcomes

Abbreviations: CBCL, Child Behaviour Checklist; FAPD, Functional abdominal pain disorder; FGID, Functional gastrointestinal disorder; GI, Gastrointestinal; HRQOL, Health-related quality of life; IC, Infant colic; OR, Odds ratio; PDS, Postprandial distress syndrome; RCT, Randomised controlled trial; RIV-QPGD, Rome IV Questionnaire on Paediatric Gastrointestinal Disorders.

1 | INTRODUCTION

Infant colic (IC), also known as excessive crying, is a common reported behavioural clinical entity of early infancy involving crying that is persistent, inconsolable, excessive and unexplained of character.[1] Wessel's criteria, also known as the 'rule of threes' (crying for ≥3 h per day, on ≥3 days per week, in the last 3 weeks)[2] are most widely used to diagnose infant colic, followed by the Rome IV criteria.[1,3] A recent meta-analysis found a pooled prevalence of 17%–25% of IC according to Wessel's criteria.[4] The aetiology of IC remains incompletely understood. Several pathophysiological mechanisms are suggested to contribute, such as an imbalanced central nervous system, parental psychological mechanisms, mode of feeding, cow's milk protein intolerance and altered microbiota.[5] Moreover, it is suggested that the gastrointestinal (GI) tract might be etiologically involved.[5] For this reason, parents of children with infant colic often consult a paediatric gastroenterologist, and therefore, the Rome IV criteria for neonates and toddlers (aged 0–4 years) consider IC as a functional gastrointestinal disorder (FGID).[1,6] Finally, in only 5% of infants, an organic cause for the crying is found.[7] It is suggested that there might be an association between the neonatal FGID infant colic and the development of paediatric FGIDs.[8] Paediatric FGIDs diagnosed according to the Rome IV criteria for children and adolescents (aged 4–18 years), are characterised by chronic GI symptoms, which cannot be attributed to another medical condition after appropriate evaluation, and are categorised in one of the three FGID subgroups: functional nausea and vomiting disorders (FNVD), functional abdominal pain disorders (FAPDs) or functional defecation disorders (FDD).[9] Paediatric FGID patients have a lower health-related quality of life (HRQOL), increased risk for anxiety and depression disorders, and higher school absenteeism rates compared to healthy controls.[10–12] Rome IV prevalence rates for paediatric FGIDs range from 21% to 25%.[13,14] Due to overlapping pathophysiological mechanisms between IC and paediatric FGIDs, these two entities have been linked to each other.[15] For example, it has been suggested that a decrease in microbial bacterial diversity early in life, as found in IC, is associated with an increased risk for FGIDs later in life.[16] In addition, it is hypothesised that early life events, such as IC, may alter psychosocial development in terms of coping skills, susceptibility to stressful events, and psychological state.[17] These factors may influence gut sensitivity and motility through the concept of the gut-brain axis, leading to the development of FGIDs.[17,18] Prospective studies on the association between IC and the risk of developing FGIDs according to the Rome IV criteria later in life are lacking. The aim of this study was to compare the prevalence of FGIDs in adolescents with a history of IC to the prevalence rates of FGIDs in a control group. In addition, health-related quality of life (HRQOL) scores of adolescents with a history of IC were compared with the control group. Finally, behavioural problems in adolescents with a history of IC were compared to norm data.

Key notes

- Prospective studies on the association between infant colic and the development of functional gastrointestinal disorders (FGIDs) later in life are lacking.
- Adolescents with a history of infant colic might have a significantly higher risk of developing postprandial distress syndrome.
- Although results should be interpreted with caution, they do suggest the need for psychological and behavioural management strategies in infants with colic to preclude the development of FGIDs later in life.

2 | METHODS

2.1 | Study design and participants

This follow-up study included adolescents who participated in a randomised controlled trial (RCT) between February 2001 and March 2003, conducted at the Wilhelmina Children's Hospital in Utrecht, The Netherlands.[19] During the original RCT, the effect of a 3-month standardised intervention of regularity and stimulus reduction compared to the same approach supplemented with swaddling in excessively crying infants up to 12 weeks of age was examined.[19] Inclusion criteria were a healthy infant with a maximum age of 12 weeks and 6 days born after a minimal gestational age of 32 weeks, who cried excessively according to their parents or healthcare professionals. The modified Wessel's criteria (i.e., crying for more than 3 h/24 h for at least 3 days in the previous 3 weeks) were used to define excessive crying.[2] The design and results of this RCT have been described in detail elsewhere.[19]

This follow-up study was exempt from the Medical Research Involving Human Subject Act according to the institutional review board of the University Medical Center Utrecht. All families of infants who started the intervention during the original RCT and who gave informed consent for follow-up ($n = 388$), were invited for participation in this follow-up study between August 2018 and March 2019. Adolescents and their parents were approached by telephone (a maximum of five times) or by e-mail. After they gave their verbal consent to participate, adolescents were asked to complete two online questionnaires regarding gastrointestinal symptoms and quality of life. Parents were asked to complete three online questionnaires regarding gastrointestinal symptoms of their child, behavioural problems of their child, and parental psychological distress. For secure and valid data storage and collection, the Web-based database Castor Electronic Data Capture (EDC) (Ciwit BV, Amsterdam, The Netherlands) was used. A maximum of three reminders were sent for completion of the questionnaires.

2.2 | Questionnaires

Information on the Rome IV Questionnaire on Paediatric Gastrointestinal Disorders (RIV-QPGD),[20] the Paediatric Quality of Life Inventory 4.0 (PedsQL 4.0),[21] and the Child Behaviour Checklist (CBCL),[22,23] is demonstrated in Appendix S1.

2.3 | Control group

To compare findings on the RIV-QPGD and PedsQL questionnaires, a control group of adolescents aged 15–18 years was recruited at one high school in the Netherlands. Over 75 high schools were contacted and invited to participate; however, only 1 schoolboard agreed to participate. This school was situated in an urban area. All available classes that included adolescents aged 15–18 years, were asked to participate in this study. The aspired sample size was the same number of participants compared to the group of adolescents with a history of IC. Furthermore, a drop-out rate of approximately 20% was taken into account. Adolescents of this school completed the self-report form of the RIV-QPGD and the self-report form of the PedsQL generic scale 4.0.

2.4 | Statistical analysis

First, baseline characteristics of the participants versus non-participants of the intervention group were compared using independent t-tests and Chi-square tests. Next, baseline characteristics of the adolescents with a history of infant colic (further referred to as the "cases") were compared with the control group using Mann–Whitney *U*-tests and Chi-square tests. The main outcome variable was the prevalence of FGIDs. Differences in prevalence rates of FGIDs were compared between cases and controls using an univariable logistic regression model. In a multivariable logistic regression model, the association between the prevalence rates of FGIDs in the cases and control group was adjusted for gender, maternal education, and parental ethnicity. Age was not taken into consideration as a confounder, as differences in prevalence rates of FGIDs in the ages 15–18 years were not considered clinically relevant. Odds ratios (ORs), adjusted ORs (aORs), and their corresponding 99% confidence intervals (CIs) were calculated. Secondary analysis focused on the agreement between parent- and self-reported FGIDs using Cohen's kappa as a measure of concordance (poor ($\kappa < 0.001$), slight ($\kappa = 0.0–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), or almost perfect ($\kappa = 0.81–1.00$)).[24] PedsQL scores were reported as means (SD) or in case of skewed data, as medians (IQR). A 10log-transformation of the median scores on the skewed PedsQL scales was conducted before univariate analysis of variance was used to test the relationship between HRQOL scores in the cases and control group. A multiple linear regression model was used to control for the confounders' gender, maternal education, and parental ethnicity. In addition, the association was adjusted for the presence of any FGID, and the interaction term between the presence of any FGID in either the cases or control group. Beta coefficients (Bs), adjusted Bs, and their corresponding 99% CI were given. Clinically relevant behavioural problems were evaluated as the percentage of cases scoring in the borderline or clinical range of the CBCL scales. Percentages with corresponding 99% CIs were reported and compared to published population norms by use of these 99% CIs.

All analyses were performed using IBM SPSS Statistics 26 for Windows (SPSS Inc., Chicago, IL, USA). To correct for multiple testing, the level of statistical significance was set at $p < 0.01$.[25]

3 | RESULTS

A total of 388 children were eligible to participate in our follow-up study, of whom 94 children were unreachable due to invalid contact information and 73 parents/children did not respond. Finally, 221 (57.0%) children were reached, of which 31 were excluded due to incomplete RIV-QPGD data ($n = 21$), refusal to participate ($n = 5$) and withdrawal of participation ($n = 5$). A total of 190 (48.9%) adolescents with a history of IC were included, with a mean (SD) follow-up of 16.9 (0.4) years after treatment. Table S1, shows the baseline characteristics of the participants ($n = 190$) compared to the non-participants ($n = 198$). Participants had a Dutch ethnicity significantly more often compared to non-participants ($p = 0.007$). No other significant differences were found.

With regard to the controls, 450 adolescents were eligible to participate, of which 13 declined participation. Therefore, 437 questionnaires were distributed to the adolescents who consented to participate in this study. Of them, 56 were excluded due to incomplete RIV-QPGD data. In total, 381 (84.7%) adolescents were included in our study.

3.1 | Demographics

Demographic characteristics of the cases and controls are demonstrated in Table 1. Cases were older than controls (17.0 (IQR 16.0–17.0) vs. 16.0 (IQR 15.0–17.0) years, $p < 0.001$). Furthermore, mothers of cases were less educated than mothers of controls ($p < 0.001$) and more parents of the cases had a Dutch ethnicity compared to controls ($p < 0.001$).

3.2 | Prevalence of FGIDs

Table 2 demonstrates the prevalence of the different FGIDs. A total of 29.5% (95% CI 19.9%–39.2%) of the adolescents with a history of IC fulfilled symptom-based criteria for at least one Rome IV FGID. This was not significantly different from controls, of whom 24.4% (95% CI 19.7%–31.1%) met the criteria for at least one FGID ($p = 0.177$). Postprandial distress syndrome (PDS) was significantly

TABLE 1 Baseline characteristics of the cases versus controls.

	Cases ($n=190$)	Controls ($n=381$)	p
Age (years, median, IQR)	17.0 (16.0–17.0)	16.0 (15.0–17.0)	<0.001[a]
Age categories (n, %)			
15 year	1 (0.5)	131 (34.4)	<0.001
16 year	79 (41.6)	129 (33.9)	
17 year	109 (57.4)	85 (22.3)	
18 year	1 (0.5)	36 (9.4)	
Gender (n, %)			
Boy	98 (51.6)	176 (46.2)	0.225[b]
Girl	92 (48.4)	205 (53.7)	
Education mother (n, %)			
Low	4 (2.1)	11 (2.9)	<0.001[b]
Middle	104 (54.7)	90 (23.6)	
High	82 (43.2)	275 (72.2)	
Missing	0 (0)	5 (1.3)	
Ethnicity parents (n, %)			
Dutch[c]	164 (86.3)	257 (67.5)	<0.001[b]
Non-Dutch	26 (13.7)	123 (32.2)	
Missing	0 (0)	1 (0.3)	
RIV-QPGD filled out by (%)			
Child	12 (6.3)	381 (100)	N.A.
Parent	29 (15.3)	N.A.	
Child and parent	149 (78.4)	N.A.	

Note: Low = no education/primary school; Middle = pre-vocational secondary education/secondary vocational education/senior general secondary education/pre-university secondary education; High = higher professional education/university.

Abbreviations: IQR, interquartile range; N.A., Not Applicable.

[a]Mann Whitney *U*-test.

[b]Chi-square.

[c]Defined as both parents are born in the Netherlands.

more prevalent in the cases compared to the controls, (18.0% vs. 10.0%, respectively, $p=0.009$). The risk for cases developing this FGID remained significant after adjustment for gender, maternal education, and parental ethnicity (aOR 2.49, 95% CI 1.18–5.25, $p=0.002$). Functional dyspepsia (FD) (20.1% and 12.9%, respectively, in the cases and controls, p = 0.030), was the most prevalent FGID, followed by functional constipation (FC) (9.0% and 9.2%, respectively, in the cases and controls, $p=0.970$).

3.3 | Agreement between self- and parent-report on the RIV-QPGD

In 149 of the 190 completed RIV-QPGDs of the adolescents with a history of IC, there was a self-report form *and* a parent-report form available. In 29 cases, the RIV-QPGD was completed only by the parents and 12 were completed solely by the child. Therefore, a total of 161 adolescents (85%) with a history of IC completed a self-report form of the RIV-QPGD. Agreement between parent- and self-report for meeting criteria for any FGID, for a FNVD or a FAPD was fair to moderate (Cohen's kappa coefficients: 0.38, 0.38 and 0.55, respectively) (Table S2). For FDDs, there was slight interrater agreement (Cohen's kappa coefficients: 0.199).

3.4 | HRQOL

In total, 156 cases and 375 controls completed the self-report form of the PedsQL generic scale 4.0. As shown in Table 3, cases had significantly lower mean and median scores on all PedsQL generic scales compared to the controls ($p \leq 0.006$). After controlling for gender, maternal education, parental ethnicity, the presence of any FGID and the interaction for the presence of any FGID in either the case or control group in the multivariable analysis, the cases remained to have significantly lower total HRQOL (adjusted B (95% CI) = −5.20 (−8.66 to −1.75), $p=0.003$), physical HRQOL (adjusted B (95%CI) = −1.08 (−1.14 to −1.04), $p=0.001$) and school HRQOL (adjusted B (95%CI) = −6.91 (−12.10 to −1.72), $p=0.009$) compared to controls.

3.5 | Behavioural problems

A total of 172 parents of adolescents with a history of IC completed the CBCL. Table 4 shows the proportion of cases scoring in the deviant range of the CBCL scales compared to the norm group. Based on the 95% confidence intervals of the proportions of the case group, a significantly larger proportion of cases compared to the norm group scored in the deviant range of the somatic complaints scale (26.2% vs. 16.6%, respectively) and the thought problems scale (20.3% vs. 12.2%, respectively).

4 | DISCUSSION

This follow-up study found that in almost 30% of adolescents with a history of infant colic (IC) at least one functional gastrointestinal disorder (FGID) according to the Rome IV criteria was present. This was however not significantly different compared to an age-matched control group. In contrast with the control group, adolescents with a history of IC did have a significantly higher risk of fulfilling symptom-based Rome IV criteria for postprandial distress syndrome (PDS). In addition, HRQOL scores of adolescents with a history of IC were significantly lower compared to controls, irrespective of the presence of any FGID.

In contrast to earlier studies, we did not find a difference in the development of any FGID when comparing adolescents with a history of IC and controls.[8,26,27] Due to the differences in design, definitions, age of the participants and sample sizes between our

TABLE 2 Prevalence of FGIDs in cases and controls, and corresponding odds ratios.

	Cases ($N = 190$) N (%, 95% CI)	Controls ($N = 381$) N (%, 95% CI)	OR (99% CI)	p	aOR[a] (95% CI)	p
Any FGID	56 (29.5, 19.9–39.2)	93 (24.4, 19.7–31.1)	1.31 (0.78–2.19)	0.177	1.35 (0.77–2.38)	0.170
Multiple FGID	17 (8.9, 3.8–14.8)	22 (5.8, 3.1–9.3)	1.58 (0.67–3.76)	0.173	1.81 (0.70–4.68)	0.106
Functional nausea and vomiting disorder (FNVD)	12 (6.3, 2.4–11.5)	18 (4.8, 1.9–7.9)	1.33 (0.50–3.57)	0.458	1.45 (0.49–4.29)	0.380
Cyclic vomiting syndrome	2 (1.1, 0.0–3.6)	0 (0, 0–0)	N.A.	N.A.	N.A.	N.A.
Functional nausea	8 (4.2, 1.1–9.2)	12 (3.2, 1.0–5.6)	1.34 (0.40–4.34)	0.533	1.31 (0.36–4.83)	0.589
Functional vomiting	0 (0, 0–0)	2 (0.5, 0.0–1.6)	N.A.	N.A.	N.A.	N.A.
Adolescent rumination syndrome	0 (0, 0–0)	1 (0.3, 0.0–1.3)	N.A.	N.A.	N.A.	N.A.
Aerophagia	2 (1.1, 0–3.6)	3 (0.8, 0.0–2.3)	1.33 (0.13–14.08)	0.758	3.02 (0.20–45.74)	0.295
Functional abdominal pain disorder (FAPD)	44 (23.3, 16.3–32.5)	61 (16.3, 11.4–21.9)	1.57 (0.88–2.78)	0.043	1.74 (0.91–3.31)	0.027
Functional dyspepsia (either PDS or EPS)	38 (20.1, 13.0–28.6)	49 (12.9, 8.8–17.8)	1.67 (0.91–3.09)	0.030	1.93 (0.97–3.82)	0.014
Postprandial distress syndrome (PDS)	34 (18.0, 11.3–26.4)	38 (10.0, 6.3–14.0)	1.95 (1.01–3.75)	0.009	2.49 (1.18–5.25)	0.002
Epigastric pain syndrome (EPS)	11 (5.8, 1.7–10.7)	20 (5.3, 2.5–8.4)	1.09 (0.40–2.95)	0.822	1.08 (0.36–3.22)	0.863
Irritable bowel syndrome	7 (3.7, 0.5–7.4)	11 (2.9, 0.8–5.5)	1.26 (0.35–4.46)	0.644	1.24 (0.31–4.95)	0.693
Abdominal migraine	4 (2.1, 0–5.1)	9 (2.4, 0.6–4.6)	0.98 (0.20–4.81)	0.968	1.12 (0.20–6.17)	0.879
Functional abdominal pain – not otherwise specified	2 (1.1, 0–3.5)	1 (0.3, 0.0–1.1)	3.94 (0.17–93.07)	0.265	3.85 (0.14–106.15)	0.295
Functional defecation disorder (FDD)	17 (9.0, 4.5–14.9)	35 (9.2, 5.5–12.9)	0.99 (0.44–2.21)	0.970	0.97 (0.41–2.31)	0.938
Functional constipation	17 (9.0, 4.5–14.9)	35 (9.2, 5.5–12.9)	0.99 (0.44–2.21)	0.970	0.97 (0.41–2.31)	0.938
Nonretentive faecal incontinence	0 (0, 0–0)	0 (0, 0–0)	N.A.	N.A.	N.A.	N.A.

[a]Adjusted for gender, education of the mother and ethnicity of the parents.

TABLE 3 PedsQL self-reported health related quality of life scores.

4.0 Generic Core Scales	Cases ($N=156$)	Controls ($N=375$)	B[a] (95% CI)	*p*	Adjusted B[a,b] (95% CI)	*p*
Total score (mean, SD)	80.5 (11.7)	85.0 (10.1)	−4.48 (−6.46 to −2.50)	<0.001	−5.20 (−8.66 to −1.75)	0.003
Physical functioning (median, IQR)	90.6 (84.4–93.8)	93.8 (87.5–100)	−0.019 (−0.030 to −0.008)	0.001	−0.035 (−0.055 to −0.015)	0.001
Psychosocial health (mean, SD)	76.7 (13.3)	81.7 (11.9)	−5.00 (−7.31 to −2.69)	<0.001	−4.94 (−9.04 to −0.85)	0.018
Emotional functioning (median, IQR)	75.0 (60.0–85.0)	80.0 (65.0–95.0)	−0.044 (−0.068 to −0.020)	<0.001	−0.038 (−0.080 to 0.004)	0.078
Social functioning (median, IQR)	90.0 (80.0–100.0)	95.0 (85.0–100.0)	−0.020 (−0.035 to −0.005)	0.009	−0.006 (−0.034 to 0.021)	0.646
School functioning (mean, SD)	70.8 (16.8)	74.9 (14.7)	−4.16 (−7.04 to −1.29)	0.005	−6.91 (−12.10 to −1.72)	0.009

Abbreviation: SD, standard deviation.

[a]The scores on the physical functioning, emotional functioning and social functioning scales were log transformed to normalise the data. The beta coefficients of these scales therefore display a 10log score, which corresponds to a 1.08, 1.09 and 1.01 decrease, respectively, of the median scores of these three scales for the cases compared to the controls.

[b]Multivariate ANOVA. Adjusted for: gender, maternal education, parental ethnicity, presence of any FGID, interaction term between FGID and case or control group.

TABLE 4 Proportion of cases scoring in the deviant range of the child behaviour checklist (CBCL), with corresponding norm data.

CBCL scales	Cases ($n=172$) % (99% CI)	Norm data, %
Total Problems Scale	27.9 (18.9–36.9)	22.0
Internalising problems	33.1 (24.7–42.0)	26.8
Anxious/depressed	16.9 (9.9–25.0)	14.4
Withdrawn/depressed	14.5 (8.5–22.0)	12.8
Somatic complaints	**26.2 (18.5–34.5)**	**16.6**
Externalising problems	18.0 (10.9–27.7)	20.9
Rule-breaking behaviour	9.3 (4.5–15.4)	14.1
Aggressive behaviour	9.9 (4.0–16.8)	9.2
Other Syndrome Scales		
Social problems	12.8 (6.8–20.6)	9.5
Thought problems	**20.3 (12.4–28.0)**	**12.2**
Attention problems	18.0 (10.7–26.1)	10.9

Note: Bold values indicate a significant difference, based on the 95% confidence intervals of the proportions of the case group.

Abbreviation: CBCL, child behaviour checklist.

study and the aforementioned studies, comparability of our results is limited and conclusions should therefore be made with caution. However, it should be noted that our study is one of the first to prospectively assess the relation between IC and FGIDs, diagnosed according to the symptom-based Rome IV criteria,[9] in a relatively large number of participants.

The significantly higher prevalence of PDS in adolescents with a history of IC compared to controls is more in line with the aforementioned prospective study by Savino et al., which followed colicky and non-colicky infants until the age of 10 years for assessment of GI disorders.[27] Despite the fact that this prospective study used the Rome II criteria for adults to define paediatric recurrent abdominal pain in their study, they found a relationship between a history of IC and the development of a FAPD.[27] Their study design, population and operationalisation of variables are comparable to the current study. This might suggest that infant colic is an early manifestation of one of the FAPDs later in life. However, conclusions should be interpreted with caution, as information on important confounders that might be related to PDS, including diet, body mass index, alcohol intake and drug treatment, was missing in our study.

Moreover, it is hypothesised that a decreased diversity of the gut microbiome in early life might contribute to the development of FAPDs at a later age.[16] In children and adolescents with FAPDs, alterations in the gut microbiota composition have been described compared to healthy controls.[28–30] It is suggested that mediators of these altered gut microbiota influence intestinal permeability,

activity of enteroendocrine cells, and the immune system, thereby leading to symptom generation in childhood FAPDs.[31,32] These altered gut microbiota in children might be associated with an imbalanced microbiome in younger years. In infants with colic, the gut microbiome has been demonstrated to have lower abundances of *Bifidobacterium* and *Lactobacillus* compared to controls.[33] It has been suggested that the presence of these species is inversely associated with crying time in infants in the first 3 months of life.[34] The negative association might be explained by the fact that specific *Bifidobacterium* spp. and *Lactobacillus* spp. exert beneficial effects on epithelial function, gastrointestinal motility and functioning of the intestinal immune system,[35–38] and have the potential to antagonise against gas-producing bacteria.[39] Evidence for a possible association between dysbiosis of the gut microbiome and infant colic is supported by promising results of a meta-analysis of RCTs demonstrating the effect of the probiotic *L. reuteri* in reducing colic symptoms in breastfed infants with colic.[40] However, long-term follow-up studies of these infants are warranted to examine if these infants will be prevented from developing FGIDs later in life. Taken together, it might be speculated that dysbiosis of the gut microbiota in early life, associated with IC, may manifest later on in life resulting in functional abdominal pain.

It could also be hypothesised that mothers of infants with colic demonstrate more psychopathology, which could continue to reflect on their children when they reach adolescence. In turn, this might result in altered psychopathology in these adolescents, including anxiety, somatisation, stress, or altered personality traits. These factors are suggested to contribute to the development of FAPDs. This especially might hold true for PDS, a syndrome that is reflected by "the feeling of being full", or early satiation. Moreover, the adolescents in our study demonstrated to have more thought problems according to the CBCL, which might also be linked to altered psychopathology.

We found that the total HRQOL, physical HRQOL, and school HRQOL were significantly lower in adolescents with a history of IC compared to healthy controls. Remarkably, this association was irrespective of the presence of any FGID, or other confounders, such as gender, parental ethnicity, and maternal education. Compared to the HRQOL scores of the Dutch norm population,[41] the healthy controls in our study demonstrated higher scores on the total, physical functioning and school functioning scales of the PedsQL. The high HRQOL scores in our control group might partly explain the differences in HRQOL scores in our study between adolescents with a history of IC and controls. Another explanation might lie in the fact that the mothers of the cases were significantly lower educated than the mothers of controls. It has been demonstrated that high QoL scores are associated with high parental education.[42,43] Moreover, it might be hypothesised that excessive crying during infancy might influence the parent–child relationship, which might result in diminished QoL later on in life.

One of the strengths of our study is the prospective nature of the follow-up. The diagnosis of IC was made at the time of the original RCT of Van Sleuwen et al.,[19] which eliminated recall bias. Another strength is the use of the clinical diagnostic Rome IV questionnaire to diagnose FGIDs based on symptom patterns.[44] The relatively large number of included participants might be seen as a strength as well. Despite this large number, however, the response rate was fairly low (around 50%). This is a limitation of our study. The long mean follow-up duration of 16.9 years resulted in invalid contact information for approximately 25% of the families, who were eligible to participate in our follow-up study in the beginning, but had to be excluded afterwards. The low response rate increased the risk of attrition bias and hampered generalisability of our results. In addition, selection bias might have been introduced since participants were aware of the content of the distributed questionnaires, which may have made families of children with GI symptoms more willing to participate. Also, the use of the modified Wessel's criteria as inclusion criteria for infant colic at the time of the original RCT, might have introduced selection bias as well. The use of the modified Wessel's criteria has been debated, as they were found to be arbitrary, culturally dependent, impractical to use, with too little focus on the unsoothable character of crying, and with the invalid use of the word "paroxysmal."[1] In comparison to the Rome IV criteria for infant colic, the modified Wessel's criteria might be harder to fulfil, which may have led to limited external validity of our study results. Another limitation is the lack of a longitudinally followed control group. The control group in our study was cross-sectionally recruited during school lessons at different high schools. Focus was set on the inclusion of adolescents since self-reports of the RIV-QPGD and PedsQL were considered most important. Due to stricter legislation, school boards did not allow us to contact the parents. Therefore, information on the control group on their early life years and a history of IC was lacking, which might have limited our conclusions. Furthermore, several baseline characteristics of the control group were significantly different from the cases. We therefore adjusted for these baseline characteristics in our multivariable regression models. Nevertheless, these differences impede strong conclusions based on our observations.

In conclusion, we found that adolescents with a history of IC demonstrated a significantly higher prevalence of postprandial distress syndrome compared to controls. Furthermore, HRQOL was significantly lower in adolescents with a history of IC compared to controls, even when controlled for the presence of any FGID. Although our results should be interpreted with caution due to selection and attrition bias, they do suggest the need for psychological and behavioural management strategies in infants with colic to preclude the development of FGIDs later in life. These management strategies might include psychoeducation and support throughout childhood to recognise psychological factors that might contribute to the development of FAPDs, including depression, anxiety, stress and somatisation, and to teach appropriate coping mechanisms.[45] The family system, including parental behaviours, should be part of this management strategy as well.

AUTHOR CONTRIBUTIONS

Judith Zeevenhooven: Writing – review and editing; writing – original draft; investigation; methodology; validation; formal analysis;

project administration; data curation; supervision; resources; conceptualization. **Lucas Zeevenhooven:** Investigation; writing – review and editing; formal analysis; resources; data curation; project administration. **Angela Biesbroek:** Investigation; writing – review and editing; formal analysis; project administration; data curation; resources. **Renske Schappin:** Writing – review and editing. **Arine M. Vlieger:** Writing – review and editing; supervision. **Bregje E. Van Sleuwen:** Conceptualization; supervision; methodology; writing – review and editing. **Monique P. L'Hoir:** Conceptualization; writing – review and editing; supervision; methodology. **Marc Benninga:** Conceptualization; writing – review and editing; supervision; methodology; project administration; validation; investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

The institutional review board of the Medical Ethical Committee of the Amsterdam UMC, location AMC, deemed this study exempt from review according to the Medical Research Involving Human Subject Act. Adolescents were asked for their verbal consent.

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REFERENCES

1. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443-1455.e2.
2. Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. Pediatrics. 1954;14:421-35.
3. Steutel NF, Benninga MA, Langendam MW, de Kruijff I, Tabbers MM. Reporting outcome measures in trials of infant colic. J Pediatr Gastroenterol Nutr. 2014;59:341-6.
4. Wolke D, Bilgin A, Samara M. Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in infants. J Pediatr. 2017;185:55-61.e4.
5. Zeevenhooven J, Browne PD, L'Hoir MP, de Weerth C, Benninga MA. Infant colic: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2018;15:479-96.
6. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2006;130:1519-26.
7. Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. Pediatrics. 2009;123:841-8.
8. Partty A, Kalliomaki M, Salminen S, Isolauri E. Infant distress and development of functional gastrointestinal disorders in childhood. JAMA Pediatr. 2013;167:977-8.
9. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150:1456-1468.e2.
10. 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.e2.
11. Gulewitsch MD, Enck P, Schwille-Kiuntke J, Weimer K, Schlarb AA. Rome III criteria in parents' hands: pain-related functional gastrointestinal disorders in community children and associations with somatic complaints and mental health. Eur J Gastroenterol Hepatol. 2013;25:1223-9.
12. Assa A, Ish-Tov A, Rinawi F, Shamir R. School attendance in children with functional abdominal pain and inflammatory bowel diseases. J Pediatr Gastroenterol Nutr. 2015;61:553-7.
13. Robin SG, Keller C, Zwiener R, et al. Prevalence of pediatric functional gastrointestinal disorders utilizing the Rome IV criteria. J Pediatr. 2018;195:134-9.
14. Saps M, Velasco-Benitez CA, Langshaw AH, Ramírez-Hernández CR. Prevalence of functional gastrointestinal disorders in children and adolescents: comparison between Rome III and Rome IV criteria. J Pediatr. 2018;199:212-6.
15. Indrio F, Dargenio VN, Francavilla R, Szajewska H, Vandenplas Y. Infantile colic and long-term outcomes in childhood: a narrative synthesis of the evidence. Nutrients. 2023;15:15.
16. Milani C, Duranti S, Bottacini F, et al. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. Microbiol Mol Biol Rev. 2017;81:1-67.
17. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150:1262-1279.e2.
18. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2015;12:159-71.
19. van Sleuwen BE, L'hoir MP, Engelberts AC, et al. Comparison of behavior modification with and without swaddling as interventions for excessive crying. J Pediatr. 2006;149:512-7.
20. Palsson OS, Whitehead WE, van Tilburg MAL, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology. 2016;150:1481-91.
21. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39:800-12.
22. Verhulst FC, Van der Ende J, Koot HM. Handleiding voor de CBCL/4–18 [Dutch Manual for the CBCL/4–18]. Academic Medical Center Rotterdam/Erasmus University, Sophia Children's Hospital, Department of Child and Adolescent Psychiatry; 1996.
23. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. ASEBA; 2001.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-74.
25. Jafari M, Ansari-Pour N. Why, when and how to adjust your P values? Cell J. 2019;20:604-7.
26. Indrio F, Di Mauro A, Riezzo G, Cavallo L, Francavilla R. 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.
27. Savino F, Castagno E, Bretto R, Brondello C, Palumeri E, Oggero R. A prospective 10-year study on children who had severe infantile colic. Acta Paediatr Suppl. 2005;94:129-32.
28. Saulnier DM, Riehle K, Mistretta T-A, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology. 2011;141:1782-91.
29. Rigsbee L, Agans R, Shankar V, et al. Quantitative profiling of gut microbiota of children with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol. 2012;107:1740-51.

30. Shankar V, Homer D, Rigsbee L, et al. The networks of human gut microbe-metabolite associations are different between health and irritable bowel syndrome. ISME J. 2015;9:1899-903.
31. Simrén M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013;62:159-76.
32. Öhman L, Törnblom H, Simrén M. Crosstalk at the mucosal border: importance of the gut microenvironment in IBS. Nat Rev Gastroenterol Hepatol. 2015;12:36-49.
33. de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics. 2013;131:e550-e558.
34. Pärtty A, Kalliomäki M, Endo A, et al. Compositional development of *Bifidobacterium* and *Lactobacillus* microbiota is linked with crying and fussing in early infancy. PLoS One. 2012;7:e32495.
35. Ewaschuk JB, Diaz H, Meddings L, et al. Secreted bioactive factors from Bifidobacterium infantis enhance epithelial cell barrier function. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2008;295:G1025-G1034.
36. Chichlowski M, De Lartigue G, German JB, Raybould HE, Mills DA. Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. J Pediatr Gastroenterol Nutr. 2012;55:321-7.
37. Liu Y, Fatheree NY, Mangalat N, Rhoads JM. Human-derived probiotic *Lactobacillus reuteri* strains differentially reduce intestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1087-G1096.
38. Smits HH, Engering A, van der Kleij D, et al. Selective probiotic bacteria induce IL-10–producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin. J Allergy Clin Immunol. 2005;115:1260-7.
39. Savino F, Cordisco L, Tarasco V, et al. Antagonistic effect of *Lactobacillus* strains against gas-producing coliforms isolated from colicky infants. BMC Microbiol. 2011;11:157.
40. Sung V, D'Amico F, Cabana MD, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. Pediatrics. 2018;141:e20171811.
41. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in The Netherlands. BMC Pediatr. 2009;9:68.
42. Kulkarni AV, Cochrane DD, McNeely PD, Shams I. Medical, social, and economic factors associated with health-related quality of life in Canadian children with hydrocephalus. J Pediatr. 2008;153:689-95.
43. Sherman EMS, Griffiths SY, Akdag S, Connolly MB, Slick DJ, Wiebe S. Sociodemographic correlates of health-related quality of life in pediatric epilepsy. Epilepsy Behav. 2008;12:96-101.
44. Palsson OS, Whitehead WE, van Tilburg MAL, et al. Development and validation of the Rome IV diagnostic questionnaire for adults. Gastroenterology. 2016;150:1481-91.
45. Salvatore S, Abkari A, Cai W, et al. Review shows that parental reassurance and nutritional advice help to optimise the management of functional gastrointestinal disorders in infants. Acta Paediatr. 2018;107:1512-20.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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