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Original Article

Birth Weight and the Development of Functional Gastrointestinal Disorders in Infants

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ABSTRACT

Purpose: To assess the association between birth weight and the development of functional gastrointestinal disorders (FGIDs) in the first year of life.
Methods: This is a secondary analysis of a prospective cohort multicenter study including neonates, consecutively enrolled at birth, and followed up for one year. At birth all infants were classified by birth weight as extremely low (ELBW), very low, or low when <1,000, <1,500, and <2,500 g, respectively, and by birth weight for gestational age as appropriate (AGA, weight in the 10–90th percentile), small (SGA, weight <10th percentile), and large (LGA, weight >90th percentile) for gestational age. FGIDs were classified according to the Rome III criteria and assessed at 1, 3, 6, and 12 months of life.
Results: Among 1,152 newborns enrolled, 934 (81.1%) completed the study: 302 (32.3%) were preterm, 35 (3.7%) were ELBW, 104 (11.1%) were SGA, 782 (83.7%) were AGA, and 48 (5.1%) were LGA infants. Overall, throughout the first year of life, 718 (76.9%) reported at least one FGID. The proportion of infants presenting with at least one FGID was significantly higher in ELBW (97%) compared to LBW (74%) (p=0.01) and in LGA (85.4%) and SGA (85.6%) compared to AGA (75.2%) (p=0.0001). On multivariate analysis, SGA was significantly associated with infantile colic.
Conclusion: We observed an increased risk of FGIDs in ELBW, SGA, and LGA neonates. Our results suggest that prenatal factors determining birth weight may influence the development of FGIDs in infants. Understanding the role of all potential risk factors may provide new insights and targeted approaches for FGIDs.

Keywords: Fetal development; Birth weight; Infant, small for gestational age; Large for gestational age; Infantile colic; Infant, extremely low birth weight; Functional gastrointestinal disorders

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Conflicts of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Prenatal and perinatal events have been increasingly linked to different long-term morbidities [1]. We have recently reported that prematurity and neonatal antibiotics are independent risk factors for functional gastrointestinal disorders (FGIDs) in infancy [2]. In a Danish cohort, low birth weight was associated with more than double the risk of infantile colic, diagnosed with Wessel's criteria, compared to normal birth weight [3]. No other study focused on the effects of birth weight on colic and other functional gastrointestinal disorders. In most infants, FGIDs are a transient phenomenon that spontaneously resolve during the first year of life, but highly increase parental concerns and healthcare costs [4,5].

Furthermore, intestinal distress in infants may predispose to gastrointestinal and extra-intestinal disorders later in life [6,7].

Over the last decades, several attempts have been made to reduce the socio-economic burden of FGIDs with different preventive strategies [8-11].

One of the main limitations of these intervention trials was that an unselected general population was recruited with the possible risk of a 'diluted effect' in at-risk subjects and an 'over-treatment' effect in low-risk subjects [8].

The primary aim of this report was to investigate the association between birth weight and the development of FGIDs in infants.

MATERIALS AND METHODS

This is a secondary analysis of data collected in a multicenter prospective study enrolling both preterm and full-term neonates followed up for one year for the development of FGIDs [2].

The study was conducted between 2014 and 2016 in five Italian pediatric and neonatal units (Varese, Milano, Parma, Bari, and Catanzaro). According to the study protocol, the exclusion criteria were: a) severe acute infection or neonatal complications; b) known genetic syndromes, or congenital and malformative disorders; c) surgery; d) major neurologic, immune, metabolic, cardiac, or renal diseases; e) absence of parental consent; and f) language difficulties.

Gestational age, mode of delivery, birth weight, use of antibiotics during the first week of life, duration of hospitalization at birth, feeding pattern at 1 month of life and reported FGIDs throughout the first year of life were collected for all enrolled newborns via hospital charts, clinical visits, and parental interviews scheduled according to the study protocol at 1, 3, 6, and 12 months of age. Gestational Age was calculated from the first day of the last menstrual period and expressed in completed weeks.

Due to the multicenter design and to reduce bias concerning fetal growth, we did not collect information regarding prenatal fetal Doppler studies in the different units and all neonates were only classified according to birth weight corrected for gestational age (appropriate [AGA, weight in the 10-90th percentile], small [SGA, weight <10th percentile] and large [LGA, weight >90th percentile] for gestational age) according to Bertino et al. [12].

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Furthermore, infants were also grouped by birth weight independent of gestational age as normal (NBW, >2,500 g), low (LBW, <2,500 g), very low (VLBW, <1,500 g), and extremely low (ELBW, <1,000 g).

The information about FGIDs was collected at 1, 3, 6, and 12 months of age, by standardized questionnaires identifying and classifying the different FGIDs according to the Rome III criteria [13].

Statistical methods

The filled questionnaires and all collected data were uploaded as an Excel file and analyzed using the Stata MP15 software (Stata Corp., College Station, TX, USA).

Continuous variables are described as the mean±standard deviation and range, and categorical variables are described as proportions.

A Skewness and Kurtosis test were used to evaluate the normal distribution of continuous variables. For non-normally distributed variables, a normalization model was set. A one-way ANOVA (parametric) with Bonferroni correction were used to compare normally distributed variables between groups. A Kruskall-Wallis test and Dunn test with Bonferroni correction was used to compare non-normally distributed continuous variables between groups, as appropriate. Categorical variables were compared using a chi-squared or Fisher's exact test.

Univariate logistic regression analysis was used to evaluate the association between FGIDs and birth weight classifications, delivery mode, feeding pattern, antibiotic use during the first week of life, and the duration of hospitalization after birth (>4 days/≤4 days). The relative risk (RR) values were estimated with 95% confidence intervals (CI).

Subsequently, for each outcome, a multivariate logistic regression model was used with the same variables applied in the univariate logistic regression analysis. The adjusted RR (aRR) values were calculated with the 95% CI.

For all tests, *p*-values <0.05 were considered statistically significant.

RESULTS

Of the 1,152 newborns enrolled in the study, 934 (81.1%) completed the entire 12-month follow-up and were entered in the final analysis: 302 (32.3%) were preterm and 632 (67.7%) were full-term neonates. Of these neonates, 104/934 (11.1%), 782/934 (83.7%), and 48/934 (5.1%) were SGA, AGA, and LGA, respectively. In our population, 290 neonates (31.0%) were LBW and among them 88 were VLBW (30.3%) and 35 were ELBW (12.1%).

The demographic characteristics of participants are described in **Table 1**.

As expected, comparisons between SGA, AGA, and LGA neonates showed significant differences in gestational age, mode of delivery, birth weight, rate of breastfeeding, antibiotic use, and the duration of hospital stay (p<0.05 for all; **Table 1**). Overall, 718 neonates (76.9%) were diagnosed with at least one FGID according to the Rome III criteria.

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Table 1. Baseline demographic characteristics of the enrolled population

Variable	SGA (n=104)	AGA (n=782)	LGA (n=48)	Total (n=934)	*p*-value*	*p*-value†	*p*-value‡	*p*-value§
Pre-term	53 (51.0)	226 (28.9)	17 (35.4)	296 (31.7)	<0.001	<0.001	0.619	0.074
Full-term	36 (34.6)	459 (58.7)	26 (54.2)	521 (55.8)				
Post-term	15 (14.4)	97 (12.4)	5 (10.4)	117 (12.5)				
Gestational age (d)	252.6±28.0 (175.0–297.0)	261.5±26.8 (163.0–296.0)	254.9±31.7 (181.0–290.0)	260.1±27.3 (163.0–297.0)	0.001	0.004	0.262	0.745
Male	62 (59.6)	406 (51.9)	26 (54.2)	494 (52.9)	0.330	0.140	0.762	0.527
Female	42 (40.4)	376 (48.1)	22 (45.8)	440 (47.1)				
Cesarean section	58 (69.5)	295 (37.7)	20 (41.7)	373 (39.9)	0.002	<0.001	0.585	0.106
Vaginal birth	92 (30.5)	487 (62.3)	28 (58.3)	561 (60.1)				
Birth weight (g)	1,931.4±706.6 (560.0–3,000.0)	2,835.8±791.8 (475.0–4,130.0)	3,446.6±973.8 (990.0–4,500.0)	2,766.5±856.3 (475.0–4,500.0)	<0.001	<0.001	0.951	<0.001
Extremely low birth weight	10 (9.6)	24 (3.1)	1 (2.1)	35 (3.8)				
Very low birth weight	33 (31.7)	53 (6.8)	2 (4.2)	88 (9.4)				
Low birth weight	30 (28.9)	130 (16.6)	7 (14.6)	167 (17.9)				
Normal birth weight	31 (29.8)	575 (73.5)	38 (79.2)	644 (68.9)				
Feeding at 1 mo					0.097	0.027	0.595	0.753
Exclusively formula	40 (38.5)	220 (28.2)	16 (33.3)	276 (29.5)				
Exclusively breastfeeding	35 (33.7)	367 (46.9)	19 (39.6)	421 (45.1)				
Mixed	29 (27.8)	195 (24.9)	13 (27.1)	237 (25.4)				
Antibiotic use	58 (55.8)	236 (30.2)	26 (54.2)	320 (34.3)	<0.001	<0.001	0.001	0.853
Hospital stay (d)	19.8±21.6 (2.0–100.0)	11.4±17.8 (2.0–100.0)	14.9±22.3 (2.0–100.0)	12.5±18.7 (2.0–100.0)	<0.001	<0.001	0.038	0.116
≤4	36 (34.6)	491 (62.8)	25 (52.1)	552 (59.1)	<0.001	<0.001	0.138	0.041
>4	68 (65.4)	291 (37.2)	23 (47.9)	382 (40.9)				

Values are presented as number (%) or mean±standard deviation (range).
SGA: small for gestational age, AGA: adequate for gestational age, LGA: large for gestational age.
*Comparison between SGA, AGA, and LGA patients. †Comparison between SGA and AGA patients. ‡Comparison between AGA and LGA patients. §Comparison between SGA and LGA patients.

Of the infants with FGIDs, 284/718 (39.6%) infants reported only one FGID, 230/718 infants (32.0%) had two FGIDs, 164/718 infants (22.8%) had three FGIDs, and finally 40/718 infants (5.6%) had four different FGIDs, with no significant difference between groups (p=0.424; **Table 2**). Infant colic and regurgitation were the most commonly reported disorders, in 443/934 (47.4%) and 372/934 (40.0%) participants, respectively.

We observed a significant difference between groups in the proportion of subjects affected by infant colic and at least one FGID (**Table 2**). Both SGA and LGA neonates reported a significantly higher rate of colic compared to AGA infants (**Table 2**).

Table 2. Proportion of infants reporting FGIDs according to the type of disorder and birth weight corrected for gestational age

Variable	SGA (n=104)	AGA (n=782)	LGA (n=48)	Total (n=934)	*p*-value*	*p*-value†	*p*-value‡	*p*-value§
Regurgitation	43 (41.4)	312 (39.9)	19 (39.6)	374 (40.0)	0.959	0.777	0.966	0.837
Infant colic	64 (61.5)	350 (44.8)	29 (60.4)	443 (47.4)	0.001	0.001	0.035	0.895
Functional diarrhea	6 (5.8)	25 (3.2)	3 (6.3)	34 (3.6)	0.182	0.248	0.217	1.000
Infant dyschezia	40 (38.5)	240 (30.7)	17 (35.4)	297 (31.8)	0.239	0.109	0.492	0.719
Functional constipation	27 (26.0)	205 (26.2)	16 (33.3)	248 (26.6)	0.550	0.956	0.279	0.348
At least one FGID	89 (85.6)	588 (75.2)	41 (85.4)	718 (76.9)	0.022	0.019	0.108	0.979
Number of FGIDs diagnosis					0.424	0.471	0.350	0.304
1	29 (32.6)	239 (40.7)	16 (39.0)	284 (39.6)				
2	33 (37.1)	185 (31.5)	12 (29.3)	230 (32.0)				
3	23 (25.8)	133 (22.5)	8 (19.5)	164 (22.8)				
4	4 (4.5)	31 (5.3)	5 (12.2)	40 (5.6)				

Values are presented as number (%).
FGID: functional gastrointestinal disorder, SGA: small for gestational age, AGA: adequate for gestational age, LGA: large for gestational age.
*Comparison between SGA, AGA, and LGA patients. †Comparison between SGA and AGA patients. ‡Comparison between AGA and LGA patients. §Comparison between SGA and LGA patients.

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Furthermore, a subgroup analysis among infants whose birth weight was <2,500 g showed that ELBW infants had the highest rate of all FGIDs, with regurgitation and dyschezia affecting more than half of the infants and colic affecting two-thirds of them. ELBW group showed a significant difference for at least one FGID compared to the VLBW and LBW groups (97.1% vs. 90.9% and 79.0%, respectively, p=0.003) and for infantile dyschezia compared to the VLBW group (p=0.016). VLBW infants also had a significantly higher rate of at least one FGID compared to LBW infants (**Table 3**).

On univariate analysis, reporting at least one FGID was significantly associated with the birthing of SGA (RR=1.14, p=0.004) and LGA (RR=1.14, p=0.043) infants. In particular, infantile colic was significantly associated with the birthing of SGA (R=1.37; p<0.001) and LGA (RR=1.35; p=0.015) infants. No other significant association was found between birth weight and other FGIDs (p>0.05). The complete results of the univariate analysis according to different neonatal characteristics are reported in **Table 4**.

On multivariate analysis, SGA status was significantly associated with infantile colic (aRR=1,22; p=0.024). No other significant association was found between birth weight and other FGIDs (p>0.05). The complete results of multivariate analysis are shown in **Table 5** and **Fig. 1**.

Table 3. Proportion of infants reporting FGIDs, according to the different types of disorder and low birth weight groups

Variable	ELBW (n=35)	VLBW (n=88)	LBW (n=167)	Total (n=290)	*p*-value*	*p*-value†	*p*-value‡	*p*-value§
Regurgitation	20 (57.1)	41 (46.6)	68 (40.7)	129 (44.5)	0.184	0.291	0.368	0.075
Infant colic	23 (65.7)	55 (62.5)	91 (54.5)	169 (58.3)	0.297	0.738	0.219	0.223
Functional diarrhea	2 (5.7)	2 (2.3)	4 (2.4)	8 (2.8)	0.522	0.320	1.000	0.278
Infant dyschezia	18 (51.4)	25 (28.4)	58 (34.7)	101 (34.8)	0.054	0.016	0.306	0.064
Functional constipation	10 (28.6)	23 (26.1)	41 (24.6)	74 (25.5)	0.873	0.783	0.781	0.619
At least one FGID	34 (97.1)	80 (90.9)	132 (79.0)	246 (84.8)	0.003	0.443	0.016	0.011
Number of FGIDs diagnosis					0.167	0.042	0.533	0.143
1	6 (17.7)	34 (42.5)	47 (35.6)	87 (35.4)				
2	18 (52.9)	27 (33.8)	46 (34.9)	91 (37.0)				
3	9 (26.5)	18 (22.5)	33 (25.0)	60 (24.4)				
4	1 (2.9)	1 (1.2)	6 (4.5)	8 (3.2)				

Values are presented as number (%).
FGID: functional gastrointestinal disorders, ELBW: extremely low birth weight, VLBW: very low birth weight, LBW: low birth weight.
*Comparison between ELBW, VLBW and LBW patients. †Comparison between ELBW and VLBW patients. ‡Comparison between VLBW and LBW patients. §Comparison between ELBW and LBW patients.

Table 4. Univariate analysis of risk factors associated with FGIDs

Risk factor	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least one FGIDs	
	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value	RR (95% CI)	*p*-value
Sex (male/female)	1.09 (0.93–1.28)	0.275	1.08 (0.94–1.24)	0.255	1.63 (0.82–3.26)	0.165	0.92 (0.76–1.11)	0.391	0.98 (0.79–1.21)	0.862	1.06 (0.99–1.14)	0.114
Fetal growth												
SGA vs. AGA	1.04 (0.81–1.32)	0.775	1.37 (1.16–1.63)	<0.001	1.80 (0.76–4.30)	0.182	1.25 (0.96–1.63)	0.095	0.99 (0.70–1.40)	0.956	1.14 (1.04–1.24)	0.004
LGA vs. AGA	0.99 (0.69–1.42)	0.966	1.35 (1.06–1.72)	0.015	1.96 (0.61–6.25)	0.258	1.15 (0.78–1.72)	0.479	1.27 (0.84–1.93)	0.259	1.14 (1.00–1.29)	0.043
C-section (yes/no)	1.06 (0.91–1.25)	0.440	1.23 (1.07–1.40)	0.003	1.05 (0.54–2.05)	0.880	1.20 (1.00–1.45)	0.053	1.20 (0.97–1.48)	0.096	1.14 (1.07–1.22)	<0.001
Feeding pattern												
Exclusive formula vs. Breastmilk	1.15 (0.96–1.39)	0.129	1.25 (1.06–1.46)	0.006	2.40 (1.19–4.90)	0.014	1.00 (0.81–1.25)	0.956	1.14 (0.89–1.47)	0.310	1.11 (1.03–1.21)	0.010
Mix vs. Breastmilk	1.14 (0.94–1.38)	0.190	1.24 (1.05–1.47)	0.011	0.44 (0.13–1.56)	0.205	0.79 (0.62–1.02)	0.071	1.17 (0.90–1.52)	0.233	1.08 (0.99–1.18)	0.079
Antibiotics (yes/no)	1.24 (1.06–1.45)	0.007	1.34 (1.17–1.53)	<0.001	0.92 (0.45–1.86)	0.811	1.13 (0.93–1.37)	0.219	1.02 (0.81–1.27)	0.872	1.18 (1.10–1.26)	<0.001
Hospital stay >4 d (yes/no)	1.13 (0.96–1.32)	0.132	1.31 (1.15–1.50)	<0.001	1.01 (0.52–1.98)	0.973	1.05 (0.87–1.27)	0.613	0.93 (0.75–1.16)	0.506	1.14 (1.07–1.22)	<0.001

FGID: functional gastrointestinal disorder, RR: relative risk, CI: confidence interval, SGA: small for gestational age, AGA: adequate for gestational age, LGA: large for gestational age.

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Table 5. Multivariate analysis of risk factors associated with FGIDs

Risk factor	Regurgitation		Infant colic		Functional diarrhea		Infant dyschezia		Functional constipation		At least one FGIDs	
	aRR (95% CI)	*p*-value	aRR (95% CI)	*p*-value	aRR (95% CI)	*p*-value	aRR (95% CI)	*p*-value	aRR (95% CI)	*p*-value	aRR (95% CI)	*p*-value
Sex (male/female)	1.04 (0.89–1.23)	0.593	1.03 (0.90–1.18)	0.656	1.59 (0.80–3.17)	0.190	0.90 (0.75–1.09)	0.286	0.96 (0.77–1.19)	0.690	1.01 (0.95–1.09)	0.679
Fetal growth												
SGA vs. AGA	0.96 (0.75–1.24)	0.776	1.22 (1.03–1.45)	0.024	1.75 (0.72–4.23)	0.213	1.21 (0.92–1.59)	0.170	0.99 (0.70–1.41)	0.961	1.04 (0.95–1.13)	0.388
LGA vs. AGA	0.92 (0.64–1.32)	0.635	1.26 (1.00–1.60)	0.053	1.92 (0.60–6.14)	0.272	1.10 (0.74–1.63)	0.632	1.27 (0.83–1.93)	0.269	1.12 (0.99–1.26)	0.085
C-section (yes/no)	1.01 (0.85–1.21)	0.875	1.12 (0.97–1.29)	0.124	0.82 (0.39–1.70)	0.593	1.20 (0.98–1.47)	0.085	1.25 (0.99–1.57)	0.059	1.07 (0.99–1.16)	0.080
Feeding pattern												
Exclusive formula vs. Breastmilk	1.15 (0.94–1.40)	0.184	1.14 (0.96–1.35)	0.139	2.77 (1.26–6.09)	0.014	0.95 (0.75–1.20)	0.956	1.17 (0.89–1.54)	0.260	1.08 (0.99–1.18)	0.079
Mix vs. Breastmilk	1.09 (0.89–1.34)	0.389	1.13 (0.95–1.35)	0.168	0.49 (0.14–1.76)	0.272	0.76 (0.58–0.98)	0.037	1.21 (0.93–1.60)	0.161	1.05 (0.96–1.14)	0.312
Antibiotics (yes/no)	1.26 (1.03–1.54)	0.024	1.20 (1.02–1.41)	0.028	0.96 (0.43–2.17)	0.925	1.19 (0.93–1.51)	0.164	1.11 (0.85–1.46)	0.450	1.13 (1.04–1.23)	0.005
Hospital stay >4 d (yes/no)	0.95 (0.77–1.17)	0.626	1.05 (0.88–1.26)	<0.001	0.73 (0.31–1.74)	0.480	0.92 (0.71–1.20)	0.553	0.76 (0.57–1.02)	0.065	0.99 (0.90–1.09)	0.867

FGID: functional gastrointestinal disorder, aRR: adjusted relative risk, CI: confidence interval, SGA: small for gestational age, AGA: adequate for gestational age, LGA: large for gestational age.

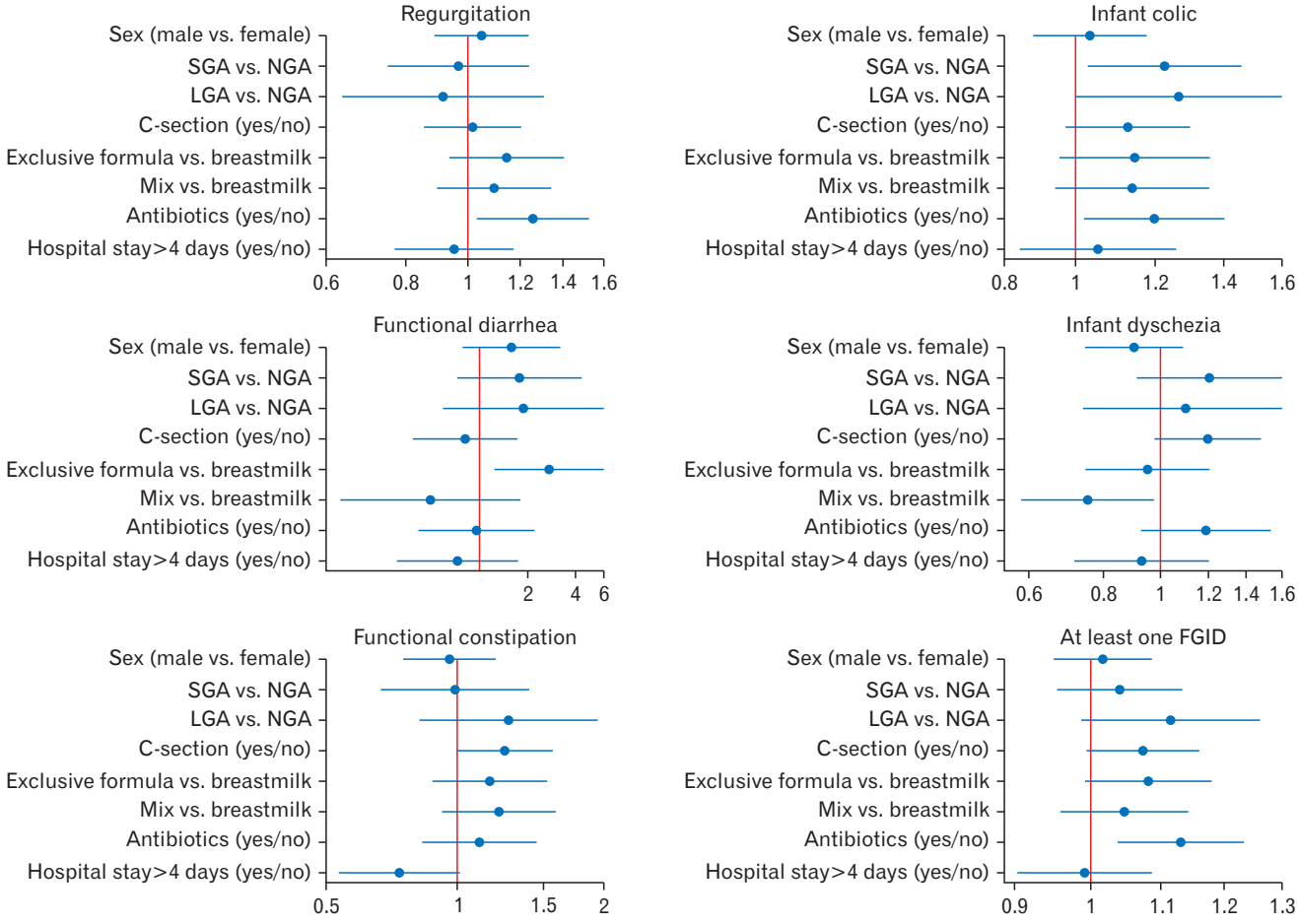

Fig. 1. Multivariate analysis of risk factors associated with FGIDs.
SGA: small for gestational age, NGA: normal for gestational age, LGA: large for gestational age, FGID: functional gastrointestinal disorder.

As previously reported [2] prematurity and neonatal use of antibiotics were significantly associated with at least one FGID (aRR=1.2; p=0.001). In particular, regurgitation and colic were associated with antibiotics, colic with prematurity, functional diarrhea with exclusive formula feeding, and infant dyschezia with exclusive breast milk.

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DISCUSSION

In this secondary analysis of a large neonatal cohort study, ELBW, SGA, and LGA newborns showed a significant increased risk for the development of at least one FGID throughout the first year of life, compared to neonates with different birth weight.

In particular, the association between infantile colic and SGA status was found to be independent of several neonatal confounders such as the mode of delivery, feeding pattern, antibiotic use, and duration of hospital stay as indirect parameters of global morbidity.

Very preterm and ELBW infants represent the leading cause of neonatal and infant death, and of severe short- and long-term morbidities including respiratory diseases, cardiovascular problems, necrotizing enterocolitis, severe infections, retinopathy, brain injury, and adverse neurodevelopmental outcomes [14]. Intrauterine inflammation, caused by infections or pro-inflammatory mediators, has been suggested as a major contributor to preterm birth [14].

Other authors demonstrated an association between fetal growth and gastrointestinal diseases, such as celiac disease [15,16] and inflammatory bowel diseases [17], speculating on a prenatal origin of disorders [18]. A previous Italian survey assessing FGIDs in 2,879 infants reported an increased prevalence of regurgitation in LBW infants and of diarrhea in preterm newborns. However, the number of preterm and LBW subjects was not specified, the follow-up was stopped at six months of life, and the Rome III criteria were not adopted [19]. In accordance with our results, an increased odds ratio (OR) of infantile colic (1.2 [95% CI, 1.1–1.3]) in SGA infants was also previously shown in the Danish National Birth Cohort [20]. In this large neonatal cohort, the authors evaluated only infantile colic, defined by Wessel's criteria, at six months of life through parental interviews, and observed the strongest association with colic among infants with a birth weight <2,000 g (OR=1.7; 95% CI, 1.3–2.2) and born before gestational week 32 (OR=1.6; 95% CI, 1.1–2.4) [20].

SGA status is a multi-factorial condition, possibly resulting from an unfavorable intrauterine environment [21]. In accordance with this theory, being SGA at birth, due to fetal adaptation to a nutrient-limited environment, may be related to 'fetal programming', a well-known cause of fetal origins of diseases later in life [22,23].

Unfortunately, as we did not collect information regarding prenatal fetal Doppler studies, we could not identify placental insufficiency or other causes of intrauterine growth restriction (IUGR) in our population and SGA status only refers to a statistical definition. Similarly, LGA status may also be associated with numerous perinatal and maternal complications [21]. Further investigations to understand the different causes of different birth weights associated with clinical gastrointestinal outcomes are warranted.

Despite FGIDs being common transient self-resolving phenomena in most infants, their etiology is not fully understood but a deregulated immune-motor response and disturbed microbiota-gut-brain axis have been suggested [24,25].

We speculate that an unfavorable intrauterine environment, due to placental insufficiency or other causes, may play a role in the developing gut, naïve immune system, and postnatal response to different stressor events.

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In accordance with this hypothesis, an increased risk of infections and aberrant immune development has been reported in both preterm [14,26] and SGA infants [27-30].

This peculiarity may alter immune response to colonizing microbiota [31,32], nutrients, or other stressors with a deep effect on intestinal homeostasis, gut sensitivity (pain perception and visceral hyperalgesia), and motor functions [33].

Strengths of our study include the presence of a large population of neonates, prospectively followed from birth to 12 months of life, the multicenter design, evaluation of all FGIDs according to the Rome III criteria, and extensive statistical analyses to limit the cumulative effect of different neonatal risk factors.

Nonetheless, we are aware of some limitations of our research. First, we based our results on parental reports with a possible overestimation of symptoms in the more vulnerable populations of ELBW and SGA related to likely increased caregiver stress. More importantly, we cannot exclude that a lack of information regarding the occurrence of viral infections [34], probiotic administration [35,36], and other potential confounders such as neonatal gastric suction or other invasive procedures [37], respiratory support or naso-gastric tube feeding, exposure to smoke [38], daycare attendance, feeding characteristics [39], cow's milk protein allergies [40], and a family history of FGIDs [41] may have influenced our risk estimates of FGIDs. Secondly, SGA and LGA statuses were poorly defined as we referred only to a statistical definition, based on an auxological cross-sectional evaluation. The exact causes of these conditions are not stated as we did not collect information regarding prenatal fetal Doppler studies.

However, our findings highlight that the simple definition for SGA or LGA, while probably misleading but easily appreciated in clinical practice, can translate to clinically relevant disorders, such as FGIDs.

Despite our exclusion of infants with known congenital anomalies and genetic syndromes, the term SGA is a heterogeneous category with a wide range of causes, including intrinsic fetal abnormalities (genetic alterations and syndromes, congenital infections and malformations [42]) and placental and maternal factors. Similarly, LGA status may derive from different known (such as maternal obesity and diabetes) and unknown causes [21,43].

We excluded major neurologic injuries such as brain malformations, seizures, hypoxic-ischemic injury, cystic periventricular leukomalacia, persistent ventriculomegaly or any brain hemorrhage with parenchymal involvement, and post-hemorrhagic hydrocephalus based on clinical criteria and routine ultrasonography findings to study infants with uncomplicated neonatal courses. However, our correlation between birth weight and FGIDs should be cautiously considered and replicated in other populations before a general conclusion can be drawn.

Our data support the role of fetal programming in the development of different disorders including FGIDs and we speculate that this may be the underlying explanation for our results although maternal and prenatal data (with serial ultrasounds) would better distinguish genetically small newborns from undernourished fetuses and from unknown causes of IUGR.

In conclusion, ELBW, SGA, and LGA newborns appear to be at an increased risk of developing FGIDSs, especially infantile colic during the first months of life.

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We speculate that abnormal birth weight determined by an aberrant intrauterine environment may predispose to FGIDs.

We need to better understand the origin and potential risk factors for FGIDs in order to improve health outcomes and management for vulnerable infants.

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