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Review Article

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Functional Gastrointestinal Disorders in Neonates and Toddlers According to the Rome IV Criteria: A Systematic Review and Meta-Analysis

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

ABSTRACT

Functional gastrointestinal disorders (FGIDs) are classified as a combination of persistent gastrointestinal symptoms. The Rome IV criteria can elucidate several factors in the pathogenesis of FGIDs. The frequency of FGIDs can differ between clinical and nonclinical settings and between geographic regions. To determine the global prevalence of FGIDs in neonates and toddlers according to the Rome IV criteria. We included cohort and descriptive observational studies reporting the prevalence of FGIDs according to the Rome IV criteria in children aged 0–48 months. We searched the Medline, Embase, Lilacs, and CENTRAL databases from May 2016 to the present day. Furthermore, unpublished literature was searched to supplement this information. The Strengthening the Reporting of Observational Studies in Epidemiology statement was used to evaluate the risk of bias. A meta-analysis of the proportions was performed using MetaProp in R. The results are reported in forest plots. We identified and analyzed 15 studies comprising 48,325 participants. Six studies were conducted in Europe, three in Latin America, two in North America, and four in Asia. Most participants were 12–48 months old (61.0%) and were recruited from the community. The global prevalence of FGIDs was 22.0% (95% confidence interval, 15–31%). The most common disorder was functional constipation (9.0%), followed by infant regurgitation syndrome (8.0%). Its prevalence was higher in the Americas (28.0%). FGIDs, as defined by the Rome IV criteria, are present in 22% of children, and the most common primary disorder is functional constipation. A higher prevalence of FGIDs has been reported in America.

Keywords: Gastrointestinal diseases; Infant; Preschool

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are defined as a combination of gastrointestinal symptoms that present in a persistent fashion, which cannot be better explained by other medical conditions [1]. Although the underlying physiopathology remains elusive, some authors state that FGIDs are caused by disturbances of the gut-brain interaction related to motility disturbance, visceral hypersensitivity, altered mucosal and immune

function, altered gut microbiota, and altered central nervous system processing [2]. The fourth version of the Rome criteria, published in 2016, reinforced clinical examination as the main diagnostic tool, introduced new syndromes, updated the definitions of previously existing disorders, and explored new perceptions in the neurobiology of pain, the brain-gut axis, and the intestinal microbiome, leading to a better understanding of the underlying physiopathology [3]. Currently, no unique laboratory marker can be used to confirm the presence of FGIDs; therefore, clinical examination remains the basis for diagnosis [3].

The relevance of the Rome IV criteria for the pediatric population lies in the more profound understanding of the role of internal and external factors in the pathogenesis of FGIDs in acknowledging these disorders, developing prevention strategies, and encouraging early identification and treatment to improve personal and family quality of life [4]. Even though FGIDs are common in the pediatric population, their frequency can differ between clinical and nonclinical settings, as well as across the world; for instance, in 2016, Ferreira-Maia et al. [5] reported a prevalence of FGIDs in neonates and toddlers between 27.1% and 38.0% according to the Rome II and III criteria.

Multiple studies and systematic reviews have addressed the identification of FGIDs using the Rome II and Rome III criteria in the pediatric population [5]. However, a meta-analysis of FGIDs in the pediatric population according to the Rome IV criteria has not been published.

This study aimed to determine the global prevalence of FGIDs in neonates and toddlers aged 0–48 months, according to the Rome IV criteria.

MATERIALS AND METHODS

This review was performed according to the Cochrane Collaboration recommendations [6], and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

Eligibility criteria

1. Study designs

We included cohort and descriptive observational studies.

2. Participants

All studies must involve 1) both male and female children aged 0–48 months; 2) the identification of FGIDs according to only the Pediatric Rome IV criteria, based on the Questionnaire on Pediatric Gastrointestinal Symptoms ROME IV version (QPGS-RIV, parental and/or self-report form), medical records, or clinical evaluation in a clinical or nonclinical setting; and 3) reports of epidemiological data (prevalence) concerning FGIDs.

3. Primary outcome

Prevalence of FGIDs in children aged 0–48 months according to the Rome IV criteria.

4. Exclusion criteria

Studies with no specific data for age groups, including patients with organic diseases (cow milk protein allergy, bronchopulmonary dysplasia, organic constipation, lactose intolerance, laryngomalacia, and gastroesophageal reflux disease).

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Information sources

We searched the Medline (OVID), Embase, Lilacs, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from May 2016 to the present. To ensure literature saturation, references from relevant articles identified through the search, conferences, thesis databases, Open Grey, and Google Scholar were scanned. We contacted the authors by e-mail in the case of missing information. No language restrictions were applied.

Data collection

Two researchers reviewed each reference by title, abstract, and full-text. They then applied pre-specified inclusion and exclusion criteria. Disagreements were resolved by consensus, and disagreements that could not be resolved were resolved by a third reviewer.

Two trained reviewers used a standardized form to extract the following information from each article: study design, geographic location, authors' names, title, objectives, inclusion and exclusion criteria, number of patients included, timing, definitions of outcomes, outcomes, association measures, and funding sources.

Data analysis/synthesis of results

Statistical analyses were performed using R software (R Core Team 2020, Vienna, Austria). We performed a meta-analysis of proportions using the command MetaProp and the inverse method (logit-transformed proportions). Information was pooled using a random-effects meta-analysis according to the expected heterogeneity. Additionally, the estimated effects of the included studies were reported in forest plots with 95% confidence intervals (95% CIs). Heterogeneity was evaluated using the I^2 test. For interpretation, we determined that values of <50% and >50% for the I^2 test corresponded to low and high levels of heterogeneity, respectively.

Publication bias

An evaluation was conducted to identify reporting or publication biases using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [8].

Sensitivity analysis

We performed a sensitivity analysis, extracted weighted studies, and ran an estimated effect to identify differences.

Subgroup analysis

We performed a subgroup analysis based on continent (America, Asia, Europe, Africa, and Oceania) and each FGID according to the Rome IV criteria.

RESULTS

Study selection

We identified 8,140 studies using database searches (**Fig. 1**). After exclusion, a total of 15 studies, including children aged 0–48 months, fulfilled the inclusion criteria [9-23].

Characteristics of included studies

The total sample size ranged from 65 [11] to 20,932 [23] participants. The studies by Chanis and Velasco-Benitez [11], Beser et al. [14], Campeotto et al. [16], Ozdemir and Beser [18], and

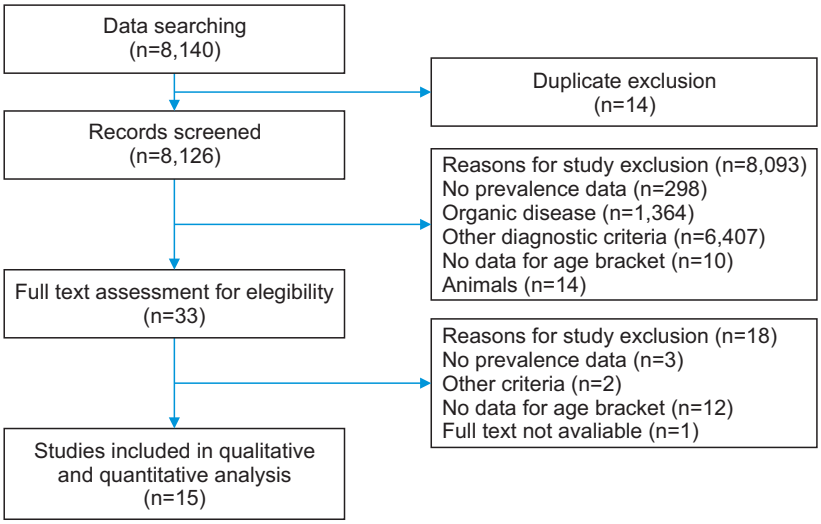

Fig. 1. Flow chart showing the study selection.

Chew et al. [21] only included children younger than 12 months; while that of Russo et al. [17] included children aged 0–17 years. For this analysis, we included only children aged 0–4 years.

Six studies were conducted in Europe (Russia, Croatia, Romania, France, Italy, Belgium, and the Netherlands), three in Latin America (Colombia, El Salvador, and Panama), two in North America (the United States), and four in Asia (Turkey, Malaysia, and China). The majority of patient data were obtained from Asian studies, especially from China. Almost all studies were conducted in a single country, with the exception of the study by Steutel et al. [20], who performed a multicenter study in Italy, Belgium, and the Netherlands.

Five studies [11,12,16,20,21] focused on primary care, while four used a community-based setting, four used third-level hospitals, and two used online community panels. Assessments of FGIDs were mainly based on parental reports using the QPGS-IV (n=12), whereas Beser et al. [14] and Campeotto et al. [16] assessed FGIDs using clinical evaluation, and Milošić et al. [13] used medical records for diagnosis.

Based on the reported data, most participants were female (n=2,021); however, only Velasco-Benítez et al. [9], Robin et al. [19], Chew et al. [21], and Zwiener et al. [22] provided an accurate depiction of the races and ethnicities of their participants, with the white race being the most common (n=1,155), followed by mixed-race children (n=775) (**Table 1**).

Risk of bias assessment

The study by Robin et al. [19] achieved twenty-six points, whereas that by Steutel et al. [20] achieved only 12 points; the median score for all the included studies was 16 points. All studies provided information on the background, study design, methodology for the setting, follow-up time, assessment of variables, designated outcomes, number of participants, outcome events, and a good summary of their findings. However, only Russo et al. [17], Robin et al. [19], and Chew et al. [21] addressed potential biases. No study reported sensitivity analyses, boundaries for continuous variables, or absolute risks in their results (**Table 2**).

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Table 1. Characteristics of patients in the included studies

Author, year	Study design	Country	Setting	Age bracket	FGID assessment	n	≥1 FGIDs	FGID subgroups		Infant colic	Infant dyschezia	Cyclic vomiting syndrome	Rumination	Functional constipation	Functional diarrhea
								Infant regurgitation							
Velasco-Benitez et al., 2019 [9]	Cross-sectional	Colombia	Community-based	0–4 yr	Parental report QPGS-IV	1,298	417	61		6	7	16	17	304	6
Zablah and Velasco-Benítez, 2019 [10]	Cross-sectional	Salvador	Community-based	0–4 yr	Parental report QPGS-IV	202	54	25		9	18	4	0	27	3
Chanis and Velasco-Benitez, 2019 [11]	Cross-sectional	Panamá	Primary care	0–12 mo	Parental report QPGS-IV	65	26	14		16	2	0	0	5	0
Chikunov and Ilenkova, 2019 [12]	Cross-sectional	Russia	Primary care	0–4 yr	Parental report QPGS-IV	300	124	11		38	11	5	3	45	12
Milošić et al., 2019 [13]	Cross-sectional	Croatia	Tertiary hospital	0–18 yr	Clinical records	1,729	57	NR		NR	NR	NR	NR	41	NR
Beser et al., 2014 [14]	Cross-sectional	Turkey	Tertiary hospital	1–12 mo	Clinical evaluation	15,940	834	319		58	234	NR	NR	NR	NR
Vlad et al., 2019 [15]	Cross-sectional	Romania	Tertiary hospital	0–3 yr	Parental report QPGS-IV	308	66	27		9	12	3	10	23	NR
Campeotto et al., 2019 [16]	Cross-sectional	France	Primary care	0–12 mo	Clinical evaluation	1,722	1,220	706		310	NR	NR	NR	155	52
Russo et al., 2019 [17]	Prospective longitudinal	Italy	Community-based	0–17 yr	Parental and self-report QPGS-IV	220	11	NR		NR	NR	NR	NR	11	NR
Ozdemir and Beser, 2018 [18]	Case control	Turkey	Tertiary hospital	0–12 mo	Parental report QPGS-IV	481	28	20		11	3	NR	NR	NR	NR
Robin and Beser, 2018 [19]	Cross-sectional	United States	Online panel community	0–18 yr	Parental report QPGS-IV	1,515	73	14		3	0	6	6	51	0
Steutel et al., 2018 [20]	Cross-sectional	Belgium, Italy, Netherlands	Primary care	0–4 yr	Parental report QPGS-IV	2,751	376	50		107	56	27	46	112	14
Chew et al., 2018 [21]	Cross-sectional	Malaysia	Primary care	0–12 mo	Parental report QPGS-IV	566	82	56		3	50	0	11	6	1
Zwiener et al., 2017 [22]	Cross-sectional	United States	Online panel community	1–47 mo	Parental report QPGS-IV	296	73	14		3	0	6	6	51	0
Ji et al., 2018 [23]	Cross-sectional	China	Community-based	0–3 yr	Parental report QPGS-IV	20,932	4,041	1,960		326	NR	NR	NR	1,755	NR

FGIDS: functional gastrointestinal disorder, QPGS: Questionnaire on Pediatric Gastrointestinal Symptoms, NR: no report.

Prevalence of functional gastrointestinal disorders

The overall prevalence of FGIDs was 22% (95% CI, 15-31%, I^2=99%) (**Fig. 2**). The analysis for each FGID showed a higher prevalence of functional constipation (9%; 95% CI, 6–13%), followed by infant regurgitation syndrome (8%; 95% CI, 5–13%), and infant colic (3%; 95% CI, 1–6%) (**Fig. 2**).

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Table 2. Risk of bias assessment

Author, year	Statements																														
	Title		Intro-duction		Methods													Results											Discussion				Other
	Specifies study design	Adequate summary	Provides background	Details objectives	Details key elements of study design	Describes setting and follow-up	Eligibility criteria and methods	Describes outcomes	Details assessment for variable	Addresses possible bias	Details Study size measurement	Details handling of quantitative variables	Describes statistical methods	Details analysis for subgroups	Details analysis for missing data	Describes sampling strategy	Performs sensitivity analysis	Details number of individuals	Details reasons for exclusion	Shows flow diagram	Provides participants characteristics	Indicates missing data	Describes follow-up time	Reports number of outcome events	Gives unadjusted/confounder-adjusted estimates	Reports category boundaries (for continuous variables)	Translates relative risk to absolute risk	Reports other subgroup analysis	Summarizes key results according to objective	Discusses limitations	Provides interpretation of results	Discusses generalizability of results	Discloses sources of funding
	1a	1b	2	3	4	5	6	7	8	9	10	11	12a	12b	12c	12d	12e	13a	13b	13c	14a	14b	14c	15	16a	16b	16c	17	18	19	20	21	22
Velasco-Benitez et al., 2019 [9]	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	?	?	1	0	0	1	0	?	1	0	?	?	1	1	0	1	0	0
Zablah and Velasco-Benítez, 2019 [10]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Chanis and Velasco-Benitez, 2019 [11]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Chikunov and Ilenkova, 2019 [12]	0	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Milošić et al., 2019 [13]	0	1	1	1	1	1	1	1	1	0	0	1	1	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Beser et al., 2014 [14]	0	1	1	1	1	1	1	1	1	0	1	1	0	0	0	?	?	1	1	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Vlad et al., 2019 [15]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Campeotto et al., 2019 [16]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	1	1	0	1	0	0
Russo et al., 2019 [17]	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	?	?	1	1	0	1	0	?	1	0	?	?	1	1	1	1	0	1
Ozdemir and Beser, 2018 [18]	0	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	1	0	0	?	1	0	?	?	0	1	0	1	0	0
Robin and Beser, 2018 [19]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?	1	1	1	1	1	?	1	0	?	?	1	1	1	1	1	0
Steutel et al., 2018 [20]	0	1	1	0	1	1	1	1	1	0	0	1	1	0	0	?	?	1	0	0	0	0	?	1	0	?	?	0	1	0	1	0	0
Chew et al., 2018 [21]	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0
Zwiener et al., 2017 [22]	0	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	1	0	?	1	0	?	?	0	1	0	1	0	0

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Table 2. (Continued) Risk of bias assessment

Author, year	Statements																																						
	Title		Intro-duction		Methods															Results															Discussion				Other	
	Specifies study design	Adequate summary	Provides background	Details objectives	Details key elements of study design	Describes setting and follow-up	Eligibility criteria and methods	Describes outcomes	Details assessment for variable	Addresses possible bias	Details Study size measurement	Details handling of quantitative variables	Describes statistical methods	Details analysis for subgroups	Details analysis for missing data	Describes sampling strategy	Performs sensitivity analysis	Details number of individuals	Details reasons for exclusion	Shows flow diagram	Provides participants characteristics	Indicates missing data	Describes follow-up time	Reports number of outcome events	Gives unadjusted/confounder-adjusted estimates	Reports category boundaries (for continuous variables)	Translates relative risk to absolute risk	Reports other subgroup analysis	Summarizes key results according to objective	Discusses limitations	Provides interpretation of results	Discusses generalizability of results	Discloses sources of funding
Ji et al., 2018 [23]	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	?	?	1	0	0	0	0	?	1	0	?	?	0	1	0	1	0	0

1: Meets criteria, 0: Does not meet criteria. ?: No information, 1a: Indicates the study's design with a commonly used term in the title or the abstract, 1b: Provides in the abstract an informative and balanced summary of what was done and what was found, 2: Explains the scientific background and rationale for the investigation being reported, 3: States specific objectives, including any prespecified hypotheses, 4: Presents key elements of the study design early in the paper, 5: Describes the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, 6: Gives the eligibility criteria, and the sources and methods of selection of participants, 7: Clearly defines all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable, 8: For each variable of interest, gives sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group, 9: Describes any efforts to address potential sources of bias, 10: Explains how the study size was determined, 11: Explains how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why, 12a: Describes all statistical methods, including those used to control for confounding, 12b: Describes any methods used to examine subgroups and interactions, 12c: Explains how missing data were addressed, 12d: If applicable, describes analytical methods taking account of sampling strategy,12e: Describes any sensitivity analyses,13a: Reports numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed, 13b: Gives reasons for non-participation at each stage, 13c: Considers use of a flow diagram, 14a: Gives characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders, 14b: Indicates number of participants with missing data for each variable of interest, 14c: Indicates follow-up time, 15: Reports numbers of outcome events or summary measures,16a: Gives unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included, 16b: Reports category boundaries when continuous variables were categorized, 16c: If relevant, considers translating estimates of relative risk into absolute risk for a meaningful time period, 17: Reports other analyses performed—e.g., analyses of subgroups and interactions, and sensitivity analyses, 18: Summarizes key results with reference to study objectives, 19: Discusses limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias, 20: Gives a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence, 21: Discusses the generalizability (external validity) of the study results, 22: Gives the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

Global distribution of functional gastrointestinal disorders

We found a higher prevalence of FGIDs among American countries (28.70%; 95% CI, 24.38–33.44%; I^2=73.1%), followed by European (21.39%; 95% CI, 6.38–52.07%, I^2=99.7%), and Asian (16.72%; 95% CI, 10.10–26.40%, I^2=99.2%) countries.

DISCUSSION

FGIDs are a common cause of gastrointestinal complaints among infants and toddlers [9,19]. Based on data from 15 countries worldwide, we found a global prevalence of FGIDs of 22% in children younger than four years according to the Rome IV criteria; this frequency is lower than that reported by Ferreira-Maia et al. [5], using the previous Rome criteria (27.1–38.0%). We also found that functional constipation and infant regurgitation were the most common forms of FGIDs. For the remaining FGIDs, we found a prevalence between 1% and 3%. This result differed from those of Ferreira-Maia et al. [5], which may be due to the diagnostic update of the Rome IV criteria. For colic, its description was determined by both the clinician

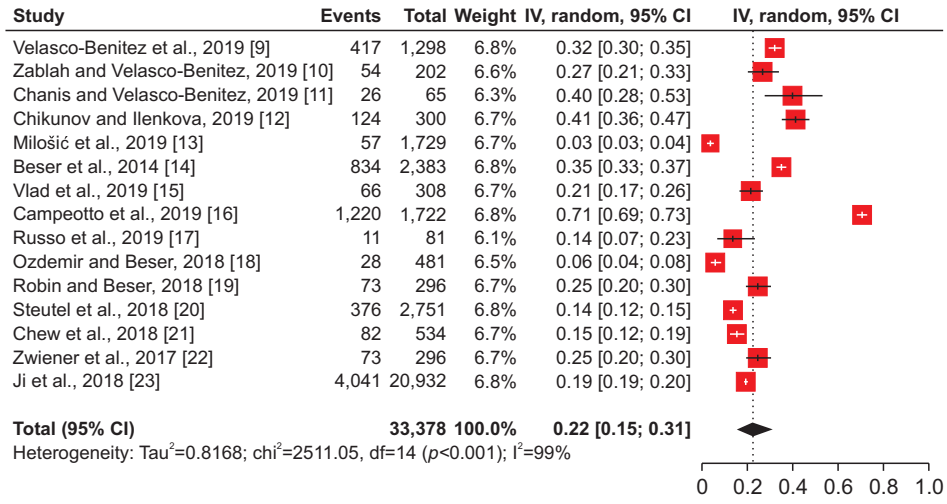

Fig. 2. Random effect meta-analysis for the global prevalence of FGIDs in neonates and toddlers.
CI: confidence interval, FGID: functional gastrointestinal disorders.

and the researcher; in rumination, the accepted evolution of symptoms was for at least two months, cyclical vomiting was present for at least six months, and functional diarrhea was accepted as occurring up to four times per day. Additionally, dyschezia, which occurs in children up to nine months, and functional constipation differs between children with and without toilet training [1].

High statistical heterogeneity was observed in this analysis (I^2=99%), possibly reflecting the variety of population characteristics, sample sizes, FGID assessments, and sampling methods among the studies. However, in clinical practice and previous studies using the Rome III criteria, a significant variation in prevalence was reported by van Tilburg et al. [24] (27%) and Chogle et al. [25] (40.5%), and therefore could be expected.

Despite the existence of a standardized definition of FGIDs, multiple assessment methods are currently available, as shown in this research.

The prevalence of FGIDs in the Americas was the highest among all continents. On this continent, migration and colonization have resulted in racially heterogeneous populations with similar cultural backgrounds in the same region. This result can also explain the high heterogeneity observed among studies in this region. Moreover, social, psychological, and biological aspects are known to influence the perception and interpretation of symptoms such as pain [26]. For instance, lower pain tolerance has been reported in African American adults [27].

In contrast, the Hispanic population exhibited a lower prevalence of chronic pain; however, this population reported a higher severity of symptoms with more sensitivity and less tolerance to a painful stimulus [28] than those reported by non-Hispanic white adults. The cultural interpretation of illness in some Hispanic populations as divine punishment or proving faith led to individuals seeking religion or traditional medicine [29] as a coping mechanism, and possibly delayed the search for Western medical care.

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Language can also influence specific medical terms, especially FGIDs, where the symptoms are vague and susceptible to subjective interpretation. Additionally, the use of colloquial expressions increases the number of terms that describe a symptom, and these terms can differ in meaning or cannot be understood at all, even in the same region [30]. Translations can also limit the assessment of symptoms, especially in questionnaires in other languages; for example, the term 'fussy baby' does not translate literally in Spanish and requires a strict interpretation from a translator to capture the essence of the phrase.

Strengths and limitations

This meta-analysis provides new insights into FGIDs in neonates and toddlers, using the most recent criteria developed for this purpose. The findings remain consistent with previous studies, reassuring that the Rome IV criteria are consistent across settings and populations. The use of PRISMA, Cochrane Collaboration, and STROBE strategies following a standardized method ensures proper search and qualitative analysis.

Although all studies had a similar weight in the analysis, the high heterogeneity among the studies raises the question of whether other variables or confounders played a role. The variation in prevalence rates reflects sampling methods and population characteristics. Cross-sectional studies, such as those included in this research, are not ideal for prevalence assessment; however, they can be easier to set up and still help to determine the prevalence in a specific population and time, allowing data extraction and extrapolation, although at the cost of being less valid for examining cause-effect relationships, and having methodological deficiencies such as sample size, setting, and possible bias. However, the recruitment of patients in primary care and third-level hospitals could lead to an increased prevalence of

GI symptoms, constituting a selection bias. Other biases related to a delay in publication (file drawer bias) and language differences must be accounted for; however, an active search for gray literature and nonpublished data was performed to ensure an exhaustive literature search, including various languages and settings.

Conclusions

FGIDs, as defined by the Rome IV criteria, are present in 22% of children, and the most common primary disorder is functional constipation. A higher prevalence of FGIDs was reported in America. It is necessary to conduct more studies with high methodological quality to ensure proper bias assessment and external validity. We suggest that multicenter research with standardized conditions, including children from all continents, should be conducted to properly characterize FGIDs worldwide.

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