Electrogastrography Abnormalities in Pediatric Gastroduodenal Disorders: A Systematic Review and Meta-analysis

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ABSTRACT

Electrogastrography (EGG) is a non-invasive method of measuring gastric electrophysiology. Abnormal gastric electrophysiology is thought to contribute to disease pathophysiology in patients with gastroduodenal symptoms but this has not been comprehensively quantified in pediatric populations. This study aimed to quantify the abnormalities in gastric electrophysiology on EGG in neonatal and pediatric patients. Databases were systematically searched for articles utilizing EGG in neonatal and pediatric patients (≤18 years). Primary outcomes were prevalence of abnormality, percentage of time in normal rhythm, and power ratio. Secondary outcomes were correlations between patient symptoms and abnormal gastric electrophysiology on EGG. A total of 33 articles (1444 participants) were included. EGG methodologies were variable. Pooled prevalence of abnormalities on EGG ranged from 61% to 86% in patients with functional dyspepsia (FD), gastro-esophageal reflux disease (GERD), and type 1 diabetes mellitus (T1DM). FD patients averaged 20.8% ($P = 0.011$) less preprandial and 21.6% ($P = 0.031$) less postprandial time in normogastria compared with controls. Electrophysiological abnormalities were inconsistent in GERD. T1DM patients averaged 46.2% ($P = 0.0003$) less preprandial and similar ($P = 0.32$) postprandial time in normogastria compared with controls, and had a lower power ratio (SMD −2.20, 95% confidence interval [CI]: −4.25 to −0.15; $P = 0.036$). Symptom correlations with gastric electrophysiology were inconsistently reported. Abnormalities in gastric electrophysiology were identifiable across a range of pediatric patients with gastroduodenal symptoms on meta-analysis. However, techniques have been inconsistent, and standardized and more reliable EGG methods are desirable to further define these findings and their potential utility in clinical practice.

Key Words: dyspepsia, dysrhythmia, functional gastrointestinal disorders, gastric electrical activity, slow wave

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What is Known

- Abnormal gastric electrophysiology is thought to contribute to disease pathophysiology in patients with gastroduodenal symptoms.
- Electrogastrography is a non-invasive method of measuring gastric electrophysiology but these abnormalities in gastric electrophysiology in children have not been comprehensively quantified using electrogastrography.

What is New

- Abnormalities in gastric electrophysiology were identifiable across a range of pediatric disorders featuring gastroduodenal symptoms using electrogastrography, including functional dyspepsia and type 1 diabetes mellitus, in particular.
- Standardized and more reliable methods of recording gastric electrophysiology are needed to further define the clinical significance of these abnormalities.

Gastroduodenal symptoms encompassing chronic abdominal pain, abdominal distension, anorexia, and nausea and vomiting are the second leading cause of lost time from school and have significant negative impacts on quality of life, with a combined prevalence of 10% to 29% in school-aged children (1,2). These symptoms may arise from diverse underlying pathologies. The overlapping symptom presentations and a lack of pathophysiological understanding of these pathologies, however, means that therapy

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is generally empiric, targeted at patient symptoms, and often results in suboptimal patient outcomes (3,4).

Electrogastrography (EGG) is a non-invasive method of measuring gastric electrophysiology using electrodes placed on the skin (5). Abnormal gastric electrophysiology, measured using EGG, is thought to contribute to underlying disease pathophysiology in a subset of patients with gastroduodenal symptoms (6–8). The clinical correlations of EGG measurements with gastroduodenal disorders and their symptoms in the pediatric population, however, remains sparse and poorly defined, limiting the clinical utility of EGG (9).

Novel techniques capable of mapping gastric motility from the body surface at high spatiotemporal resolution are currently emerging, and are showing potential to build on the foundations of EGG with more reliable outcomes (6,8,10). The deployment of these novel techniques in pediatric patients first requires a comprehensive evaluation of known electrical abnormalities recorded by EGG to identify existing biomarkers and suitable target disorders for application of novel methods.

This systematic review and meta-analysis, therefore, aimed to quantify the abnormalities in gastric electrophysiology on EGG in neonatal and pediatric patients.

METHODS

This systematic review was compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (11,12). The protocol for this review was prospectively registered on PROSPERO (ID: CRD42020212952).

Search Strategy

The MEDLINE (OVID), EMBASE (OVID), EMBASE classic, and CENTRAL databases were systematically searched from their inception to April 2020, using a pre-defined search strategy. The keywords ''electro-gastro∗'' and ''electrogastro∗'' were combined with the Boolean operator ''OR'' (''electro-gastro∗'' OR ''electrogastro∗''). There were no limits placed on date, language, and patient age during the search. This non-restrictive search strategy was utilized in order to identify all potentially relevant articles in which EGG was used.

Article Selection

All original research articles utilizing EGG in neonatal and pediatric patients (ages $\leq$18 years) were considered for inclusion. EGG was considered as any measurement of gastric electrical activity from the body surface. All articles including patients with gastroduodenal symptoms, arising from multiple disorders including functional gastrointestinal (GI) disorders (FGIDs), structural GI disorders, multisystem disorders, immunological, and psychiatric conditions were included (13–16). Articles in which an active treatment was employed were also eligible for inclusion, provided suitable pre-treatment EGG measurements were available for analysis.

All case reports, editorials, conference proceedings, technical notes, and studies of only EGG methodology were excluded. Articles with only healthy populations, without study of one of the defined clinical disorder groups, or interventional studies without suitable pre-treatment EGG measurements, were excluded. Studies of patient populations with surgical alteration of their GI tract anatomy were excluded. Additionally, articles investigating invasive methods of EGG recording (serosal or mucosal) were excluded. Non-English articles, where an English translation was not available, were also excluded.

Two authors independently performed database searches and screened article titles and abstracts. Three authors independently conducted full text reviews for article eligibility and where discrepancies arose, they were adjudicated by a senior author.

Data Extraction

Data from each of the included articles were independently extracted by 2 authors using a pro forma spreadsheet. The data extraction points are outlined in Supplemental Digital Content 1, *http://links.lww.com/MPG/C310*.

Outcome Measures

The primary outcomes were the prevalence of any abnormality in gastric electrophysiology on EGG, percentage (%) of the EGG recording duration in which the dominant power (DP) fell within the bradygastric, normogastric, and tachygastric frequency ranges, dominant frequency (DF), DP, and power ratio (PR). Prevalence of abnormal EGG recording was defined as the proportion of patients with abnormalities in either gastric slow wave DF or DP, as defined by each article. Dysrhythmia (bradygastria or tachygastria) was defined based on each author's definition and consisted of either percentage recording time spent in abnormal (bradygastric or tachygastric) frequency ranges or time spent in the normogastric frequency range below a specified threshold (eg, $<$70%). DF was defined as the gastric slow wave frequency corresponding with the peak power on the EGG time-frequency waveform. DP was defined as the peak power value observed at the DF. PR was defined as the ratio of the postprandial DP to preprandial DP. Primary outcomes were reported according to the preprandial and postprandial phases separately wherever possible. Secondary outcomes were correlations between patient symptoms and any of the EGG outcome measures. Primary and secondary outcomes were reported separately for each disorder group. Wherever disorder groups constituted both neonatal and pediatric patients, the primary and secondary outcomes were analysed separately.

Quality Assessment

Quality assessment of all included articles is addressed in Supplemental Digital Content 2, *http://links.lww.com/MPG/C311* (17).

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) (Version 5.4.1; Cochrane Collaboration, London, United Kingdom) and via the *metacont* and *metaprop* packages in R (Version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Refer to Supplemental Digital Content 3, *http://links.lww.com/MPG/C312* for the statistical methodology (18–23).

RESULTS

Search Results

The search of databases revealed 3104 abstracts. After removal of duplicates, screening by titles and abstracts and full-text review, 33 articles were included (Supplemental Digital Content 4, *http://links.lww.com/MPG/C313*). No articles investigating high-resolution EGG techniques or body surface mapping in neonatal and pediatric patients were identified to-date.

Study Characteristics

Articles were largely prospective (n = 31 studies) rather than retrospective (n = 2) and most incorporated a control group (n = 23), with one being a randomized controlled trial (24). The articles spanned a 27-year period (1992–2019) and were most commonly conducted in the United States (n = 8) and Italy (n = 7) (Supplemental Digital Content 5, *http://links.lww.com/MPG/C314*).

In total, 1444 participants, constituting 947 patients and 497 healthy control subjects, underwent recording of gastric electrical activity with EGG across the 33 included articles. Their ages ranged from 16-day-old neonates to 18-year-old pediatric patients. There was also a slight preponderance of girls versus boys (n = 347 vs 273); sex was not reported in 11 articles (Supplemental Digital Content 5, *http://links.lww.com/MPG/C314*) (14,15,25–33).

A total of 16 clinical disorders were investigated in the retrieved articles, constituting functional dyspepsia (FD) (25,26,31,34–43), gastro-esophageal reflux disease (GERD) (28–30,32,33,39), idiopathic nausea (44,45), type 1 diabetes mellitus (T1DM) (15,24,46,47), eating disorders (including anorexia nervosa) (38), structural GI disorders (infantile hypertrophic pyloric stenosis, esophagitis, and gastritis/duodenitis) (29,48,49), muscular dystrophies (14), multisystem disorders (cystic fibrosis and Noonan syndrome) (16,50,51), infant colic (52), cow's milk protein allergy (CMPA) (32), chronic intestinal pseudo-obstruction (CIPO) (27), and malignancy (53). The diagnostic criteria for disorders and exclusion criteria of each included article are outlined in Supplemental Digital Content 6, *http://links.lww.com/MPG/C315*.

Electrogastrography apparatus, protocols, and metrics

The EGG apparatus, experimental protocols, and extracted metrics are reported in Supplemental Digital Content 7, *http://links.lww.com/MPG/C316*. As outlined in this supplementary content, significant variability in technical methods, electrode locations, methods of recording, and experimental protocols were observed.

Primary and Secondary Outcome Measures

Clinical disorders in which the primary EGG outcome measures were suitable for pooling in a meta-analysis (ie, closely comparable outcomes recorded in at least 2 articles) are presented below. Primary and secondary EGG outcome measures for the remaining disorders (ie, those with closely comparable outcomes recorded in only 1 study) are reported in Supplemental Digital Content 8, *http://links.lww.com/MPG/C317*.

Functional Dyspepsia

Thirteen articles reported on FD, and 3 of these articles including a total of 82 participants (41 patients with FD; 41 healthy subjects) were analysed (25,26,43). The pooled prevalence of any abnormality on EGG in FD patients was 74% (95% CI: 60%–91%; $I^2 = 67\%$; Fig. 1A). One article included a comparison with healthy subjects, and showed a greater proportion of abnormalities on EGG among patients with FD (59% [10/17] vs 13% [1/8]; $P = 0.042$) (37). In the preprandial period, pediatric FD patients spent 20.8% (SMD −1.32, 95% CI: −2.34 to −0.31; $P = 0.011$; $I^2 = 63\%$; Fig. 2) less time within the normogastric frequency range and 17.8% (95% CI: 10.5–25.1; $P < 0.0001$) (26) more time within the bradygastric frequency range, when compared with healthy subjects. Time spent in the tachygastric frequency range was similar (MD +2.7%, 95% CI: −2.4 to 7.9; $P = 0.29$) (26). Patients also had a similar DF (SMD −0.04; 95% CI: −0.56 to 0.48; $P = 0.88$; $I^2 = 0\%$; Fig. 2).

In the postprandial period, FD patients also spent 21.6% (SMD −1.27, 95% CI: −2.42 to −0.12; $P = 0.031$; $I^2 = 71\%$; Fig. 2) less time within the normogastric frequency range and 23.4% (95% CI: 9.7–37.2; $P = 0.0025$) (26) more time within the bradygastric frequency range, when compared with healthy subjects. Time spent within the tachygastric frequency range (MD +4.2%, 95% CI: −6.5 to 14.9; $P = 0.42$) (26) and DF (SMD +0.01, 95% CI: −0.50 to 0.53; $P = 0.97$; $I^2 = 0\%$; Fig. 2) were similar. The PR was also similar (SMD +0.28, 95% CI: −0.8 to 1.3; $P = 0.59$; $I^2 = 0\%$; Fig. 2). One article also presented the pre- and post-stimulus results arising from a ''cold pressor task'' stimulus in patients with FD (Supplemental Digital Content 8, *http://links.lww.com/MPG/C317*) (42). Correlation between patient symptoms and EGG outcome measures were performed in 7 articles reporting on FD. In those with more severe symptoms, 5 articles found either smaller changes in the PR (35,43) or greater percentage of patients with dysrhythmic change (26,35,37,40) on EGG, whereas no correlations were found in the remaining 2 articles (34,36).

Gastro-esophageal Reflux Disease

Six articles reported on GERD, and 2 of these articles including a total of 69 participants (44 patients with GERD; 25 healthy subjects) were analyzed (30,32). The pooled prevalence of any abnormality on EGG in patients with GERD was 73% (95% CI: 51%–100%; $I^2 = 67\%$; Fig. 1B). Pytrus et al (30) included a comparison with healthy subjects, and showed a greater proportion of abnormalities on EGG among patients with GERD (66% [23/35] vs 27% [4/15]; $P = 0.026$). In the preprandial period, GERD patients spent 14.1% (95% CI: 23.4– 4.9; $P = 0.0048$) less time within the bradygastric frequency range and similar amounts of time within the tachygastric (MD +7.6%, 95% CI: −0.2 to 15.4; $P = 0.054$) and normogastric (MD +0.7%, 95% CI: −8.5 to 9.9; $P = 0.87$) frequency ranges.

In the postprandial period, GERD patients spent 8.4% (95% CI: 0.8–16.0; $P = 0.032$) more time within the normogastric frequency range and similar amounts of time within the tachygastric (MD −0.6%, 95% CI: −8.8 to 7.6; $P = 0.88$) and bradygastric (MD −0.4%, 95% CI; −4.6 to 3.9; $P = 0.86$) frequency ranges. Correlation between patient symptoms and EGG outcome measures were performed in only 1 article reporting on GERD. Pytrus et al (30) found a greater percentage of patients with dysrhythmia on EGG among those experiencing severe (vs mild) GERD symptoms (80.0% vs 28.6%).

Idiopathic Nausea

A total of 27 patients with idiopathic nausea were studied in 2 articles (44,45). The pooled prevalence of any abnormality on EGG was 86% (95% CI: 62%–100%; $I^2 = 76\%$; Fig. 1C). No studies included healthy reference subjects. Correlation between patient symptoms and EGG outcome measures were performed in only 1 of the 2 articles (44), in which a greater percentage of abnormal (vs normal) EGG rhythm (77% vs 23%) was found when patients experienced nausea.

Type 1 Diabetes Mellitus

Four articles including a total of 241 participants (159 patients with T1DM; 82 healthy subjects) were analyzed

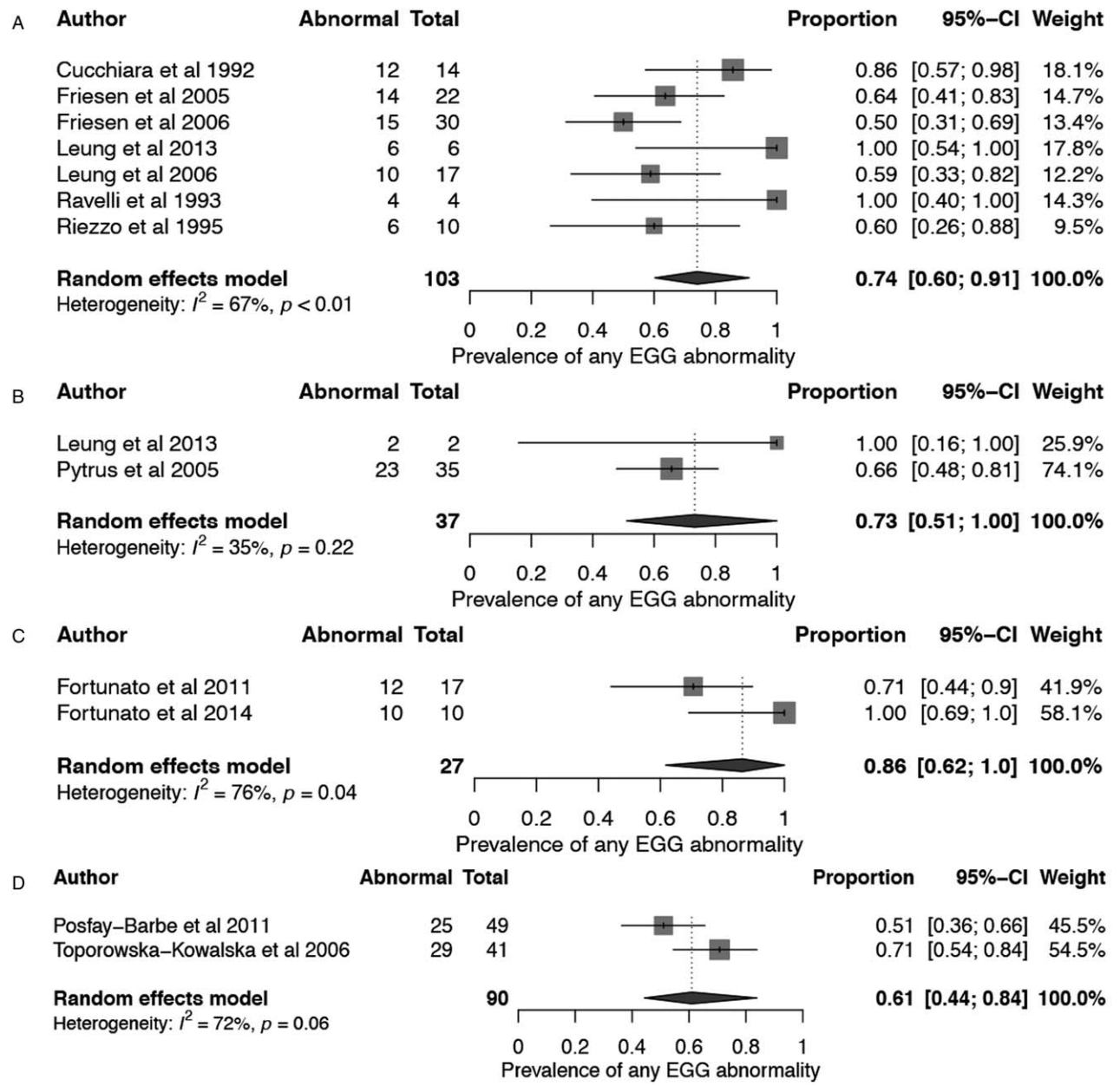

FIGURE 1. Forest plot of the pooled prevalence of any abnormality on electrogastrography in patients with (A) functional dyspepsia, (B) gastroesophageal reflux disease, (C) idiopathic nausea, and (D) type 1 diabetes mellitus.

(15,24,46,47). The pooled prevalence of any abnormality on EGG in pediatric patients with T1DM was 61% (95% CI: 44%–84%; $I^2 = 72\%$; Fig. 1D). In the preprandial period, T1DM patients spent 20.3% (SMD 0.77, 95% CI: 0.30–1.4; $P = 0.0014$; $I^2 = 55\%$; Fig. 3) more time within the bradygastric frequency range, 5.9% (SMD 1.36, 95% CI: 0.15–2.58; $P = 0.028$; $I^2 = 93\%$; Fig. 3) more time within the tachygastric frequency range and 46.2% (SMD −1.83, 95% CI: −2.83 to −0.83; $P = 0.0003$; $I^2 = 89\%$; Fig. 3) less time within the normogastric frequency range, when compared with healthy subjects. The DF was 1.8 cpm (95% CI: 2.2–1.3; $P < 0.0001$) (47) lower in patients.

In the postprandial period, the time spent within the bradygastric (SMD +0.39, 95% CI: −0.25 to 1.03; $P = 0.23$; $I^2 = 69\%$), tachygastric (SMD −0.21, 95% CI: −0.75 to 0.33; $P = 0.45$; $I^2 = 57\%$) and normogastric (SMD −0.18, 95% CI: −0.53 to 0.17; $P = 0.32$; $I^2 = 0\%$) frequency ranges and DF (MD −0.2 cpm, 95% CI: −0.5 to 0.04; $P = 0.086$) (47) were similar between T1DM patients and healthy subjects. A significantly lower PR (pooled SMD −2.20, 95% CI: −4.25 to −0.15; $P = 0.036$; $I^2 = 96\%$; Fig. 3) was observed in T1DM patients. Correlation between patient symptoms and EGG outcome measures were not assessed in patients with T1DM.

Bias and Quality

Refer to Supplemental Digital Content 2, *http://links.lww.com/MPG/C311* for the risk of bias and article quality assessment results.

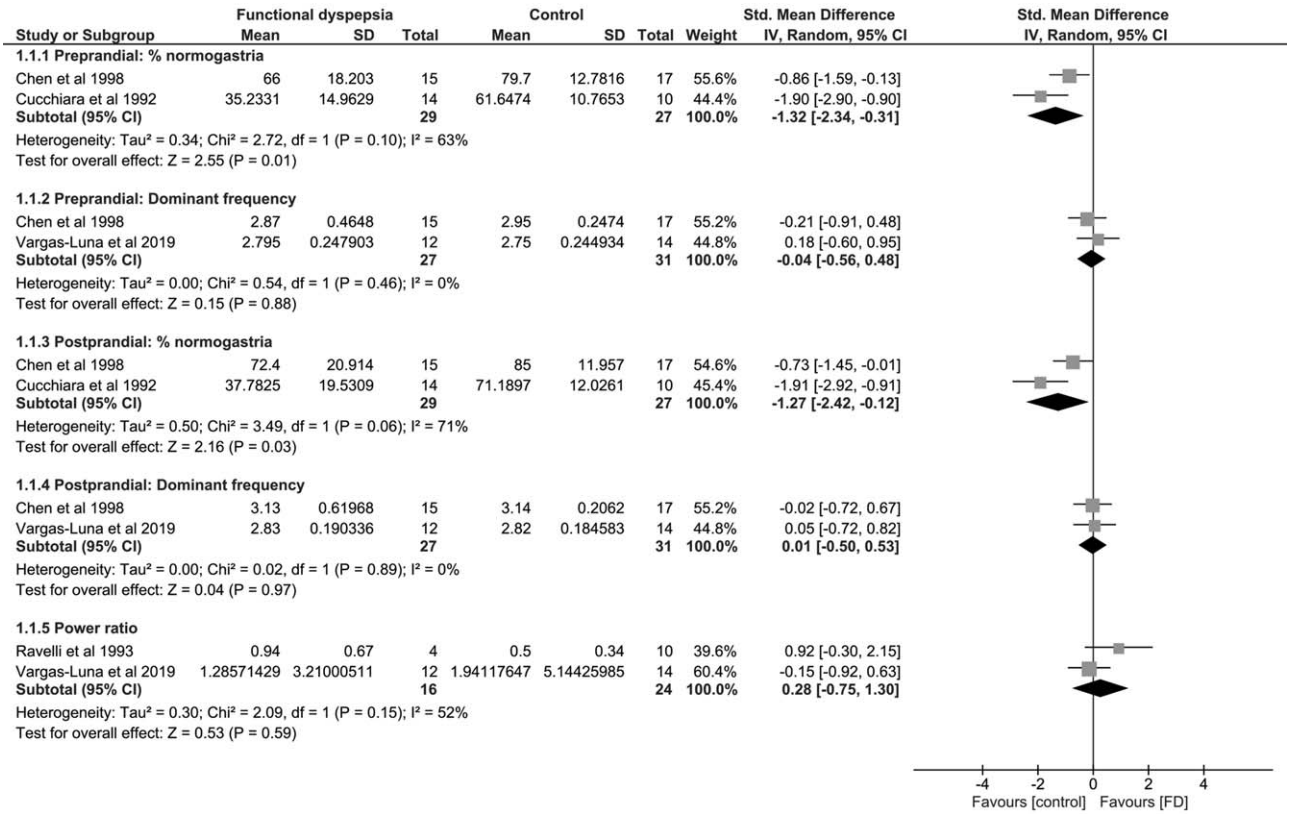

FIGURE 2. Forest plot of electrogastrography outcomes in patients with functional dyspepsia versus healthy subjects.

DISCUSSION

The present systematic review and meta-analysis sought to quantify the gastric electrophysiological abnormalities on EGG in neonatal and paediatric patients with disorders affecting gastroduodenal function. Key results were as follows: FD patients spent substantially less time in normogastric rhythms than controls (20.8% and 21.6% less pre- and postprandially, respectively). T1DM patients spent 46.2% less fasted time in normogastria and 20.3% and 5.9% more time in bradygastria and tachygastria, respectively, and had a lower PR compared with healthy controls. Abnormalities in gastric rhythm on EGG were reported in paediatric patients with GERD and idiopathic nausea; however, these findings were often inconsistent and not reported in most studies. Clinical correlations with EGG outcomes were also observed, but reported inconsistently, in patients with anorexia nervosa, infantile hypertrophic pyloric stenosis, esophagitis, muscular dystrophies, cystic fibrosis, infant colic, CMPA and CIPO. These disorders may be particularly amenable to study with emerging methodologies to further elucidate the pathogenic role of gastric electrophysiology, with a view to defining actionable diagnostic biomarkers with potential utility in clinical practice in future.

A notable finding of this study was that FD patients spent significantly less time within the normogastria frequency range, across both the fasting and postprandial recordings. Frequency abnormalities on EGG have also been identified in several studies of adult patients with FD (10,54–56), including on a recent meta-analysis of 1756 adult FD patients (57). The consistency of these findings suggests that abnormalities in gastric electrophysiology could contribute to the multifactorial pathogenesis of FD. In addition, the contributing etiologies to abnormal gastric slow wave frequency are also diverse, encompassing hormonal (58), paracrine (59), neural (autonomic and enteric nervous system) (60,61) influences as well as pacemaking abnormalities within the interstitial cells of Cajal (ICC) networks (62). Which of these factors are primarily responsible for the gastric rhythm abnormalities detected in pediatric FD patients in this study are currently unclear.

T1DM patients were also found to have abnormal gastric rhythms as compared with healthy controls, with significantly more preprandial recording time spent within the bradygastric and tachygastric frequencies, and significantly less time spent within the normogastric frequency. The etiology and pathogenesis of these gastric dysrhythmias in T1DM could be related to ICC dysfunction. Acute hyperglycemia is known to contribute to the disruption of gastric slow wave cycling, induction of gastric dysrhythmias, and hypomotility of the gastric antrum (63–66). Chronic hyperglycemia also has a deleterious effect on ICC networks, inducing cellular damage and loss, further contributing to dysrhythmogenesis (67), which could be reversible by establishing tight glycemic control. Damage to ICC activity in DM could also be consistent with our finding that T1DM patients had a lower PR than healthy controls. In a study of 57 DM patients, Kawagishi et al found the lower PR to be significantly associated with autonomic neuropathy ($P < 0.01$), which was maintained on multivariate regression analysis ($P < 0.0001$) (68). Therefore, autonomic neuropathy is likely to be an additional or alternative mechanism underpinning the reduced postprandial power among patients with T1DM, potentially related to suppression of the contractile response that contributes to the EGG power (69). Given that these studies were, however, done in pediatric populations, which would typically have relatively short disease duration, the likelihood of established autonomic neuropathy appears less likely as a primary cause.

The heterogeneous nature of the identified studies in this review brought about several limitations. In particular, only a small

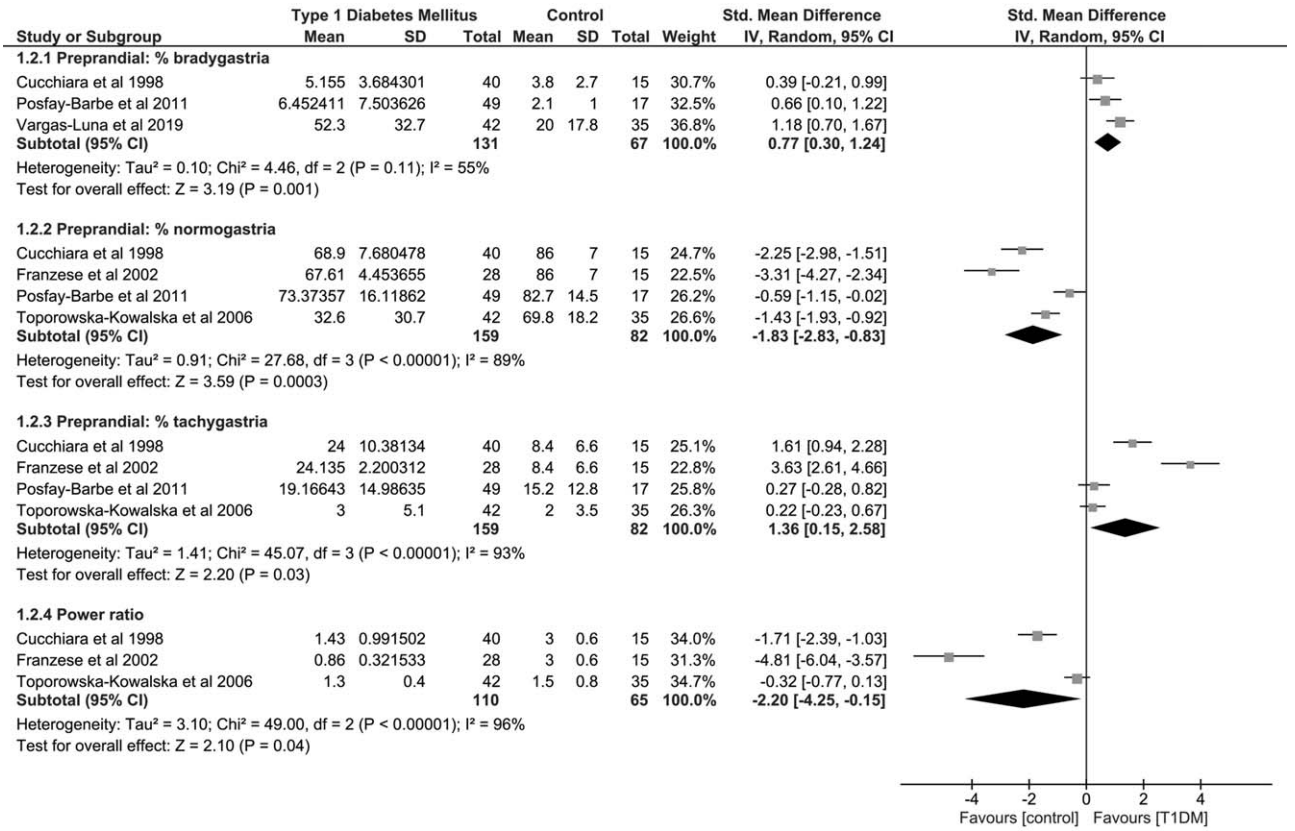

FIGURE 3. Forest plot of statistically significant electrogastrography outcomes in patients with type 1 diabetes mellitus versus healthy subjects.

number of studies ($n < 5$) reported on poolable EGG outcomes for meta-analysis. Therefore, publication bias may have further contributed to inconsistency in the pooled outcomes, which could not be statistically assessed in this review. A discussion of the observed variability in EGG methodologies is provided in Supplemental Digital Content 7, *http://links.lww.com/MPG/C316* (70). Notwithstanding, it is notable that significant abnormalities in gastric electrophysiology were observed across a wide range of disorders featuring gastroduodenal symptoms in neonatal and pediatric patients, particularly given that these are populations that are often understudied compared with adults.

The age range of pediatric patients studied also varied, and it remains unknown how gastric electrophysiology changes with anatomical development and through puberty. These developmental changes require further elucidation. The wide range of reference ranges for gastric slow wave frequency and variations in EGG outcomes also indicates the need for standardized definitions of EGG parameters and methodologies in future studies. This would facilitate further comparisons between studies, and thus more meaningful conclusions to be drawn regarding clinical correlations identified by EGG.

The low resolution of traditional EGG techniques combined with a lack of standardization among EGG methods and protocols, have limited its widespread adoption as a routine diagnostic tool for patients with gastroduodenal symptoms (71,72). Clinical uptake of EGG may be advanced by the advent of standardized techniques that have greater reliability, and therefore, a better diagnostic yield (9). Recently, high-resolution EGG techniques have been proposed, including 'body surface gastric mapping' approaches (72), which are able to non-invasively (10) map gastric electrophysiological patterns at high spatiotemporal resolutions, while revealing symptom correlations with abnormal patterns in adult patients (6,8). It would be of interest to now apply such techniques to pediatric patients to see if such results could be replicated. To this end, the results of this systematic review and meta-analysis will better inform where novel techniques could be best directed in future, while also providing a reference point for comparisons.

CONCLUSIONS

On the basis of limited heterogeneous studies, this systematic review and meta-analysis found abnormalities in gastric electrophysiology to be prevalent across a range of neonatal and pediatric disorders affecting gastroduodenal function, particularly FD and T1DM. The consistency of these findings suggests that they may have pathophysiological and diagnostic significance, warranting further evaluation. Traditional EGG has been unable to achieve widespread clinical adoption, and novel techniques that are standardized and more reliable may allow for routine clinical evaluation of gastric electrophysiology.

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