Upper GI: cosa c'è di nuovo

Dispepsia

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A complex of symptoms referable to the gastroduodenal region of the gastrointestinal tract including epigastric pain or burning, postprandial fullness, or early satiety

Ford AC et al. Lancet 2020

Uninvestigated dyspepsia

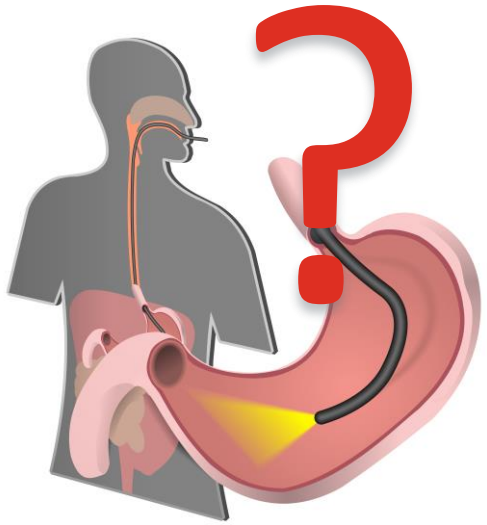
Table 1. Prevalence (95% confidence interval) of uninvestigated dyspepsia in European countries, according to Rome I–IV criteria

Nation	Rome I criteria	Rome II criteria	Rome III criteria	Rome IV criteria
Belgium				5.0 (4.1–6.0)
Croatia			16.6 (13.8–19.6)	
Finland		7.9 (7.0–8.8)		
France			4.0 (3.8–4.2)	8.5 (7.3–9.8)
Germany				6.9 (5.8–8.1)
Iceland	17.8 (15.8–20.0)			
Italy		15.1 (13.0–17.4)	21.4 (19.1–23.9)	9.1 (7.9–10.4)
The Netherlands				4.0 (3.3–5.0)
Norway			6.9 (5.4–8.6)	
Poland				8.3 (7.2–9.6)
Portugal			40.4 (32.8–48.2)	
Romania			7.6 (4.2–12.4)	7.4 (6.3–8.6)
Russia	37.5 (34.5–40.5)			10.3 (9.0–11.7)
Spain		2.0 (0.9–3.8)		7.4 (6.3–8.6)
Sweden	17.5 (10.8–25.5)	22.5 (4.2–49.8)	20.2 (17.7–22.8)	8.2 (7.0–9.5)
Turkey		9.5 (7.4–11.9)		2.8 (0.2–8.1)
UK			5.9 (4.9–7.0)	7.1 (6.2–8.1)

Higher prevalence in:

- Women
- Smokers
- NSAIDs users
- HP +ve

Barberio B et al, Aliment Pharmacol Ther 2020
Fracasso P, Dig Dis 2021
Zagari RM et al Gastroenterology 2010
Ford AC et al, Gut 2015



Functional dyspepsia

(up to 80%)

Ford AC et al. Lancet 2020

Clinical history

THE RATIONAL CLINICAL EXAMINATION

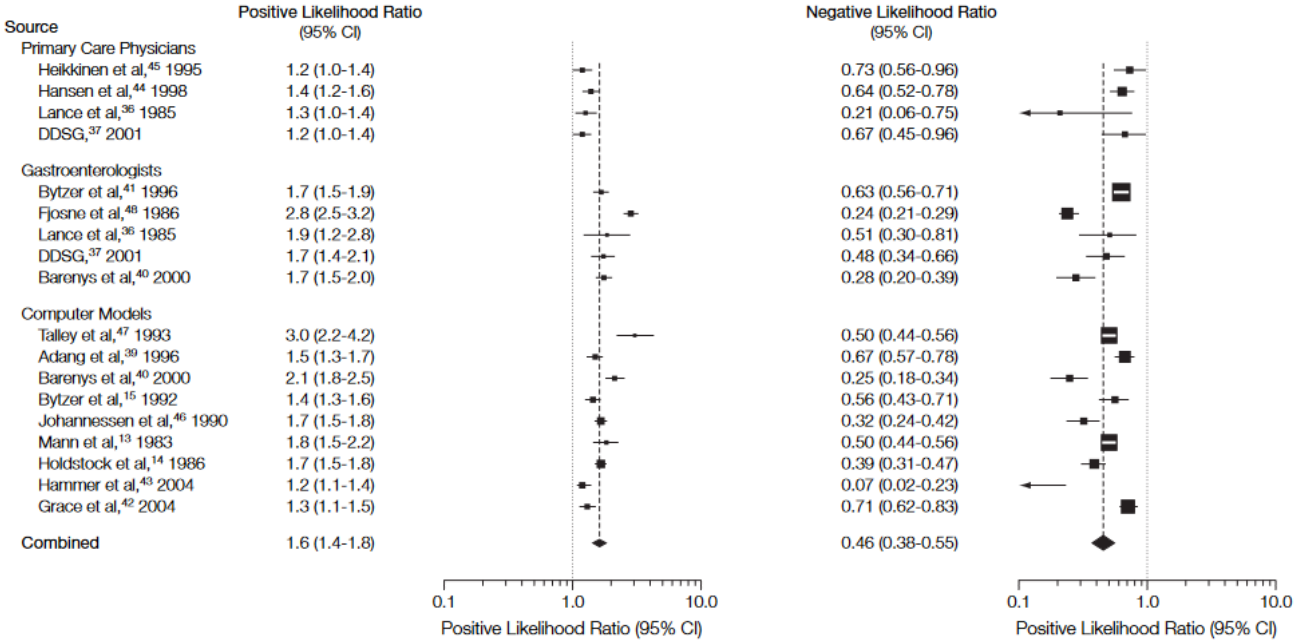
CLINICIAN'S CORNER

Can the Clinical History Distinguish Between Organic and Functional Dyspepsia?

15 studies, >11000 pts – 42% organic dyspepsia

Neither clinical impression nor computer models (incorporating patient demographics, risk factors, history items, and symptoms) adequately distinguished between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia

Figure 2. Positive and Negative Likelihood Ratios of Different Approaches to Diagnosing an Organic Cause of Dyspepsia



CI indicates confidence interval; DDSG, Danish Dyspepsia Study Group. Each square represents an individual study. The size of the square is a measure of the size of the study and the horizontal line through the square indicates a graphical representation of the 95% CI of that study. For the combined analysis, the diamond and vertical dashed line indicate the pooled positive or negative likelihood ratio, with the left and right ends of the diamond indicating the pooled 95% CI.

Moayyedi P et al, JAMA 2006

Laboratory testing

	UGIM ($n=160$)	No UGIM ($n=2164$)	p
Median duration of symptoms (months)	4 (1–120)	24 (1–600)	<0.001
Recent onset of symptoms	120 (75%)	403 (18.6%)	<0.001
Alarm feature	127 (79.4%)	695 (32.1%)	<0.001
Sex (male)	119 (74.4%)	1428 (66%)	0.03
Age	52.99 ± 11.8	41.04 ± 12.48	<0.001
Age > 40 years	130 (81.3%)	1063 (49.1%)	<0.001
Serum albumin level (g/dl)	3.85 ± 0.75	4.57 ± 0.44	<0.001
Serum albumin ≤ 3.5 g/dl	43 (26.9%)	70 (3.2%)	<0.001
Hemoglobin level	10.8 ± 2.5	13.03 ± 1.9	<0.001
Hemoglobin level ≤ 11 g%	83 (51.9%)	288 (13.3%)	<0.001
Smoking (yes)	24 (15%)	237 (11%)	0.12

Table 2 Risk factors for upper gastrointestinal malignancy in patients with dyspepsia on multivariate analysis using logistic regression

Risk factors	Odds ratio	95% CI		p
		Lower	Upper	
Age (> 40 years)	3.32	2.09	5.209	<0.001
Albumin (≤ 3.5 g/dl)	3.42	1.97	5.932	<0.001
Hb (≤ 11 g/dl)	3.37	2.23	5.082	<0.001
Recent onset of symptoms	8.71	5.81	13.07	<0.001
Alarm symptom	4.98	3.24	7.668	<0.001

Western countries?

Dutta AK et al, Dig Ds Sci 2018

Limited Value of Alarm Features in the Diagnosis of Upper Gastrointestinal Malignancy: Systematic Review and Meta-analysis

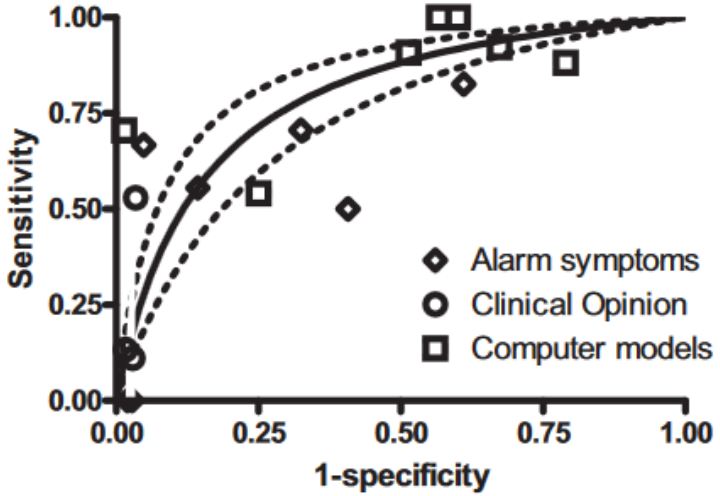
Table 2. Alarm Symptoms of an Underlying Upper Gastrointestinal Cancer.
Age >55 yr with new-onset dyspepsia*
Evidence of overt gastrointestinal bleeding including melena or hematemesis
Dysphagia, especially if progressive, or odynophagia
Persistent vomiting
Unintentional weight loss
Family history of gastric or esophageal cancer
Palpable abdominal or epigastric mass or abnormal adenopathy
Evidence of iron-deficiency anemia after blood testing

* In regions with a high background prevalence rate of gastric cancer, such as Southeast Asia, a lower age threshold should be considered.

Weight loss

Dysphagia

Anemia



15 studies: 57,363 patients - 458 (.8%) cancers

Table 3. Summary of Results of Studies Included in the Systematic Review on Individual Alarm Feature in Diagnosing Upper GI Malignancy

Reference No.	Feature	PPV (95% CI)	NPV (95% CI)	LR+	LR−
12	Weight loss	1.5% (.3%–4.3%)	99.6% (99%–99.9%)	2.8 (1.02–5.3)	.72 (.35–.997)
13	Weight loss	6.7% (3.7%–11.0%)	98.9% (98%–99.6%)	2.9 (1.9–3.7)	.43 (.22–.71)
14	Weight loss	15.8% (3.4%–39.6%)	99.2% (98.8%–99.5%)	21.2 (6.8–60)	.87 (.68–.96)
21	Weight loss	2.7% (1.9%–3.7%)	99.9% (99.8%–99.9%)	11.2 (8.6–14)	.60 (.49–.70)
22	Weight loss	6.8% (4.8%–9.2%)	97.6% (96.7%–98.4%)	1.9 (1.5–2.3)	.64 (.48–.80)
23	Weight loss	8.3% (5.9%–11.4%)	98.7% (97.9%–99.3%)	2.7 (2.2–3.2)	.38 (.24–.57)
24	Weight loss	11.7% (7.0%–18.1%)	98.0% (97.4%–98.5%)	5.3 (3.3–8.0)	.79 (.68–.88)
25	Weight loss	2.8% (1.1%–5.7%)	99.7% (98.9%–100%)	2.9 (1.7–3.7)	.3 (.09–.75)
12	Dysphagia	1.5% (.3%–4.3%)	99.6% (99.1%–99.9%)	2.8 (1.02–5.3)	.72 (.35–.996)
13	Dysphagia	7.1% (3.9%–11.9%)	98.8% (97.6%–99.5%)	3.0 (1.9–4.0)	.48 (.26–.75)
14	Dysphagia	3.4% (.09%–17.8%)	99.2% (98.7%–99.5%)	4.0 (.7–20.4)	.97 (.80–1.00)
22	Dysphagia	6.5% (4.7%–8.7%)	97.6% (96.6%–98.4%)	1.8 (1.4–2.1)	.62 (.46–.80)
24	Dysphagia	5.2% (2.4%–9.6%)	99.8% (99.5%–99.9%)	10.4 (6.1–14.5)	.42 (.21–.68)
12	Anemia	0% (0%–9.7%)	99.5% (98.9%–99.8%)	0 (0–13.8)	1.0 (.63–1.0)
14	Anemia	1.25% (.03%–6.8%)	99.1% (98.7%–99.5%)	1.4 (.25–7.0)	.99 (.81–1.02)
21	Anemia	1.0% (.5%–1.7%)	99.8% (99.7%–99.8%)	4.1 (2.4–6.7)	.89 (.81–.95)
22	Anemia	4.9% (2.3%–9.1%)	96.3% (95.3%–97.2%)	1.3 (.7–2.4)	.97 (.86–1.03)

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; DOR, diagnostic odds ratio.

- Clinical opinion: low sensitivity and high specificity
- Symptom scores - computer models: high sensitivity and modest specificity.
- Alarm symptoms: intermediate sensitivity and specificity

Vakil N et al, Gastroenterology 2006

Clinical trial: a randomized trial of early endoscopy, *Helicobacter pylori* testing and empirical therapy for the management of dyspepsia in primary care

Table 3. Numbers endoscoped and findings by strategy

	Strategy						
	Early endoscopy (n = 187)	Test and refer positive (n = 52)	Test and refer negative (n = 145)	Test and treat positive (n = 46)	Test and treat negative (n = 152)	Empiric therapy (n = 178)	Total
No referred according to protocol	187	52	–	–	–	–	
Refused endoscopy	17 (9)	3 (6)	4*	1*	0	1*	26
Total number of patients having endoscopy	172† (92)	49 (94)	44 (30)	14 (30)	35 (23)	70 (39)	385
Endoscopic findings at first endoscopy‡							
Normal	70 (41)	15 (31)	22 (50)	5 (36)	17 (47)	33 (47)	162 (42)
Hiatus hernia only	11 (6)	5 (10)	3 (7)	1 (7)	2 (6)	1 (1)	23 (6)
Oesophagitis§	64 (37)	15 (31)	23 (52)	8 (57)	19 (53)	37 (53)	169 (44)
Gastro-oesophageal cancer	0	1 (2)	1 (2)	1 (7)	1 (3)	0	4 (1)
Duodenal ulcer/erosive duodenitis	34 (20)	12 (24)	2 (5)	3 (17)	2 (6)	4 (6)	57 (15)
Gastric ulcer	5 (3)	6 (12)	1 (2)	1 (7)	1 (3)	1 (1)	15 (4)

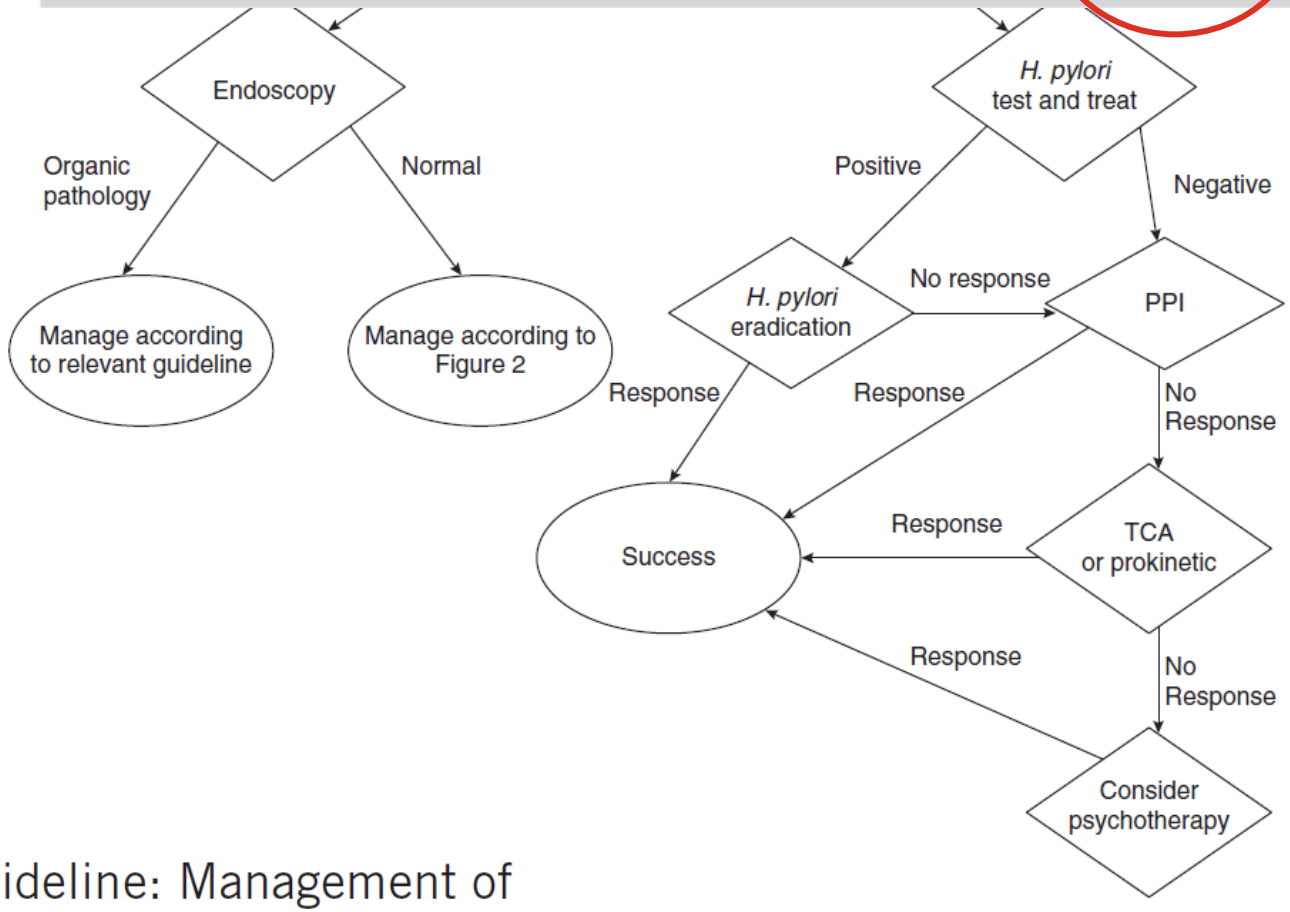
Percentage values are given in parentheses.
* Patients subsequently referred but failed to attend.
† Includes 2 endoscoped later.
‡ Some patients had multiple findings.
§ Including Barretts.

	2 months No or minimal symptoms	**1 year** No or minimal symptoms	Subsequent consultations
Early endoscopy	74%	No differences	40%
Empirical therapy	55% *		60%

Duggan AT et al, Aliment Pharmacol Ther 2008

Undiagnosed dyspepsia

Informal Question	PICO Question			
	Population	Intervention(s)	Comparator	Outcome
What is the most appropriate initial evaluation for patients ≥60 years of age with dyspepsia?	Adult uninvestigated dyspepsia patients stratified by age	Endoscopy	Symptomatic management	1. Upper GI cancers detected 2. Early upper GI cancers detected 3. Rates of upper GI malignancy by age 4. Adverse events



CME

ACG and CAG Clinical Guideline: Management of Dyspepsia

Moayyedi PM et al, Am J Gastroenterol 2017

United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia

Statement	Endorsement	Grade of Evidence	References
5.1. Upper GI endoscopy is mandatory for establishing a diagnosis of FD.	Yes	A	1,10,149–151
5.2. In primary care, uninvestigated dyspepsia can be managed without endoscopy if there are no alarm of risk factors.	Yes	A	149–151
5.3. Upper GI endoscopy is mandatory if there are alarm symptoms or risk factors.	Yes	A	1,10,149–151
5.4. Screening blood test are useful when considering a diagnosis of FD.	No	B	152
5.5. Every patient with dyspeptic symptoms should be tested for *H. pylori* (non-invasively or at gastroscopy).	Yes	A	1,10,81,149,150,153,154
5.9. Upper abdominal ultrasound is useful when considering a diagnosis of FD.	No	B	1,150,165,166
5.10. A gastric emptying test is useful when considering a diagnosis of FD.	No	B	1,91,150,167,168
5.11. Esophageal pH monitoring is useful in FD to rule out GERD.	No	B	13,169–171

Wauters L et al, Neurogastroenterol Motil 2021

H pylori

Chronic gastritis

- Gastrin and ghrelin
  ↑Acid output
  Somatostatin
  ↑Acid output
- Hypersensitivity
  Duodenal acidification
- Motility
  Accomodation
  Gastric emptying
  nNOS
  ICC

Efficacy of *Helicobacter pylori* eradication therapy for functional dyspepsia: updated systematic review and meta-analysis

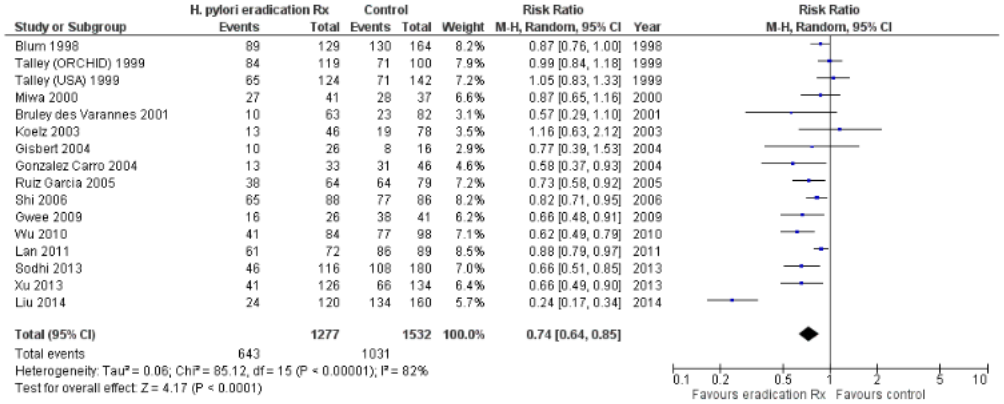


Figure 4 Forest plot of RCTs of *H. pylori* eradication therapy: effect on symptom cure or improvement in FD in those with successful *H. pylori* eradication therapy versus control therapy. FD, functional dyspepsia; *H. pylori*, *Helicobacter pylori*; RCTs, randomised controlled trials.

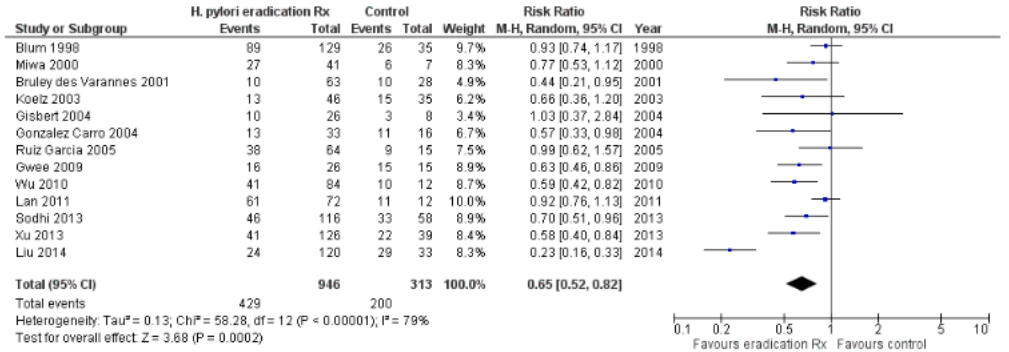


Figure 5 Forest plot of RCTs of *H. pylori* eradication therapy: effect on symptom cure or improvement in FD in those with successful *H. pylori* eradication therapy versus unsuccessful *H. pylori* eradication therapy. FD, functional dyspepsia; *H. pylori*, *Helicobacter pylori*; RCTs, randomised controlled trials.

Ford AC et al. Gut 2022
Suzuki H et al, Nat Rev Gastroenterol Hepatol 2013

Functional Dyspepsia

Functional dyspepsia

One or more of the following:
- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning

AND

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Postprandial Distress Syndrome (PDS)

One or both of the following at least 3 days a week:

Bothersome postprandial fullness (i.e., severe enough to impact on usual activities)
Bothersome early satiation (i.e., severe enough to prevent finishing a regular size meal)

Epigastric Pain Syndrome (EPS)

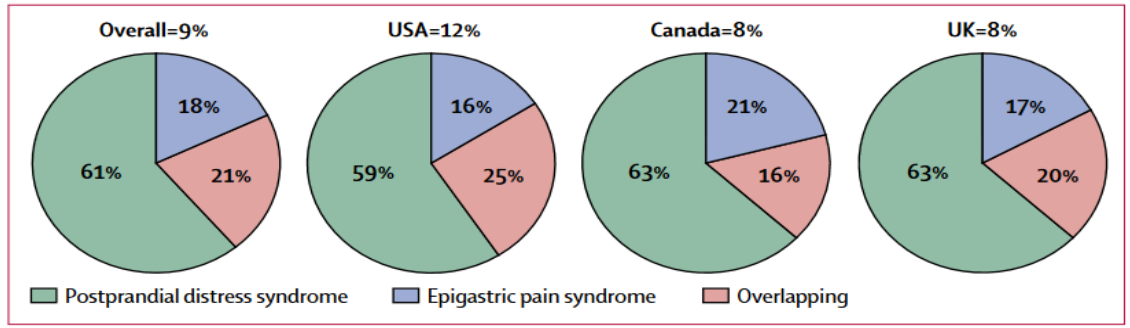
One or both of the following symptoms at least 1 day a week:

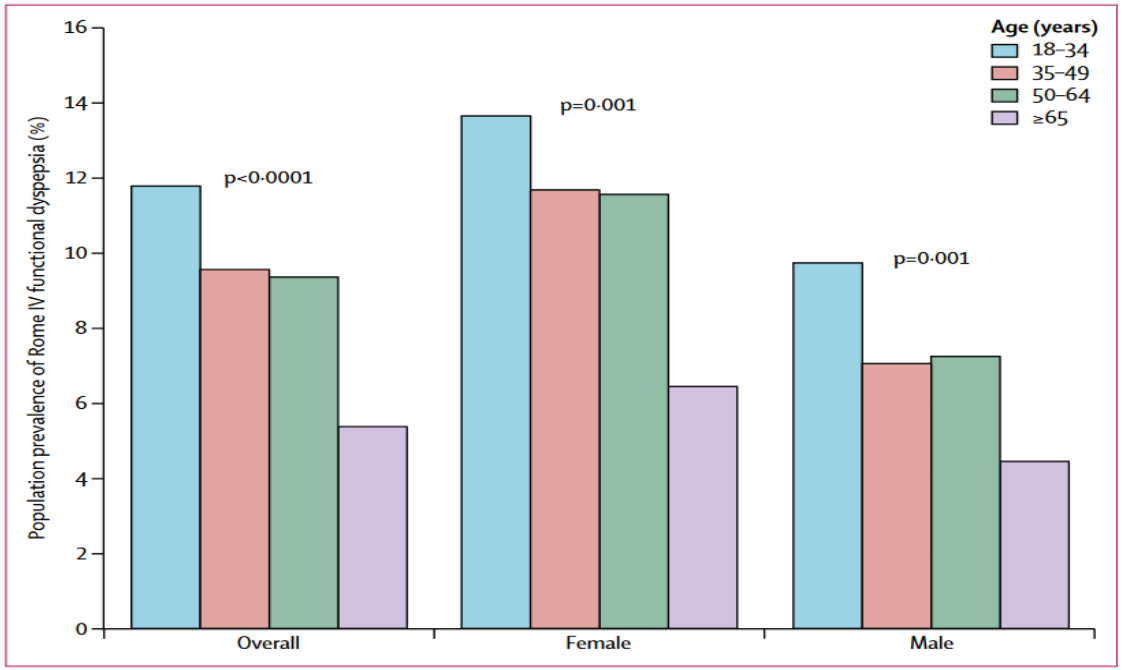
Bothersome epigastric pain (i.e., severe enough to impact on usual activities)
Bothersome epigastric burning (i.e., severe enough to impact on usual activities)

Stanghellini V et al, Gastroenterology 2016

Characteristics

6300 general population adults, Internet questionnaire





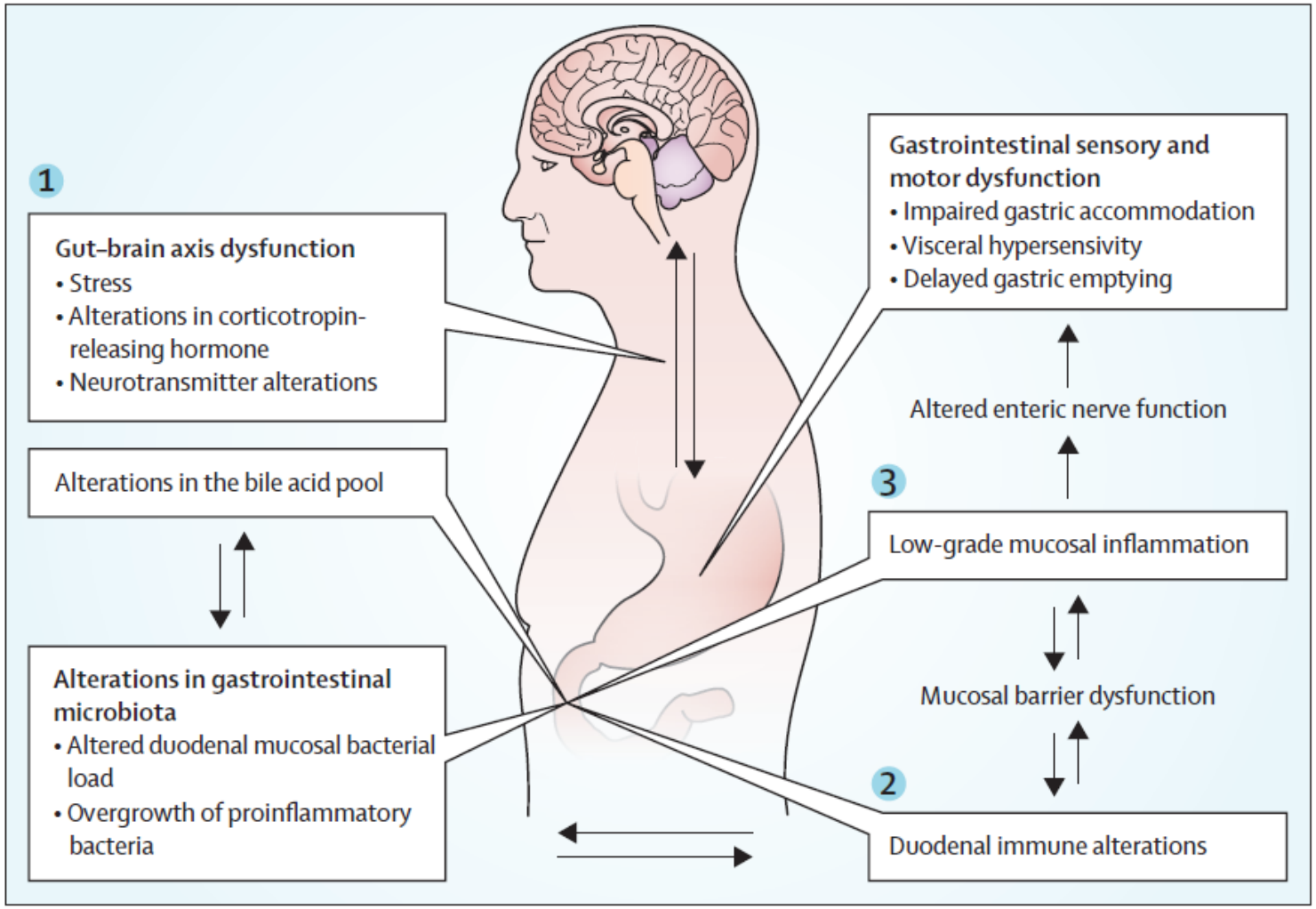
	PDS (n=339)	EPS (n=97)	Overlapping PDS and EPS (n=115)	p value
Demographics				
Age (years)	45 (16·8)	42·5 (15·6)	41·2 (14·4)	0·068
Female	211 (62%)	52 (54%)	68 (59%)	0·302
White	242 (71%)	70 (72%)	77 (67%)	0·622
Relationship status				
Single	91 (27%)	36 (37%)	34 (30%)	0·146
Married or cohabiting	198 (58%)	47 (49%)	60 (52%)	0·164
Divorced	35 (10%)	11 (11%)	15 (13%)	0·721
Widowed	15 (4%)	3 (3%)	6 (5%)	0·748
Symptom scores				
PHQ-12 somatisation score	8·0 (4·0)	8·5 (4·3)	11·3 (4·7)	<0·0001*†
Number of somatic symptoms	5·8 (2·5)	6·1 (2·6)	7·5 (2·5)	<0·0001*†
SF8-PCS	43·8 (11·2)	40·9 (11·2)	37 (10·1)	<0·0001*†
SF8-MCS	41·5 (12·8)	40·0 (13·3)	37·6 (11·3)	0·016*
Overlapping FGIDs				
IBS	50 (15%)	41 (42%)	83 (72%)	<0·0001*†‡
Functional heartburn	21 (6%)	11 (11%)	35 (30%)	<0·0001*†
Health-care usage				
Seen doctor for gastrointestinal health problems	118 (35%)	53 (55%)	69 (60%)	<0·0001*‡
More than once yearly health-care visits	241 (71%)	70 (72%)	93 (81%)	0·118*
Medication taken at least once a week				
Antiemetic	39 (12%)	13 (13%)	32 (28%)	<0·0001*†
Acid-suppressing drug	122 (36%)	54 (56%)	74 (64%)	<0·0001*‡
Analgesic	156 (46%)	58 (60%)	73 (64%)	0·0001*‡
Antidepressant	71 (21%)	26 (27%)	43 (37%)	0·002*
Any of the above medication	218 (64%)	80 (83%)	97 (84%)	<0·0001*‡

Data are mean (SD) or n (%). PDS=postprandial distress syndrome. EPS=epigastric pain syndrome. PHQ-12=Patient Health Questionnaire-12 somatic symptom scale. SF8-PCS=short form-8 quality-of-life form-physical component score. SF8-MCS=SF8-mental component score. FGIDs=functional gastrointestinal disorders. *Indicates the overlap group is significantly different compared with the PDS group. †Indicates the overlap group is significantly different compared with the EPS group. ‡Indicates EPS group is significantly different compared with the PDS group. Presented p values are across the groups.

Table 2: **Comparison between Rome IV functional dyspepsia subtypes**

Aziz I et al, Lancet Gastroenterol Hepatol 2018
Barberio B et al, Clin Gastoenterol Hepatl 2021

Pathophysiology

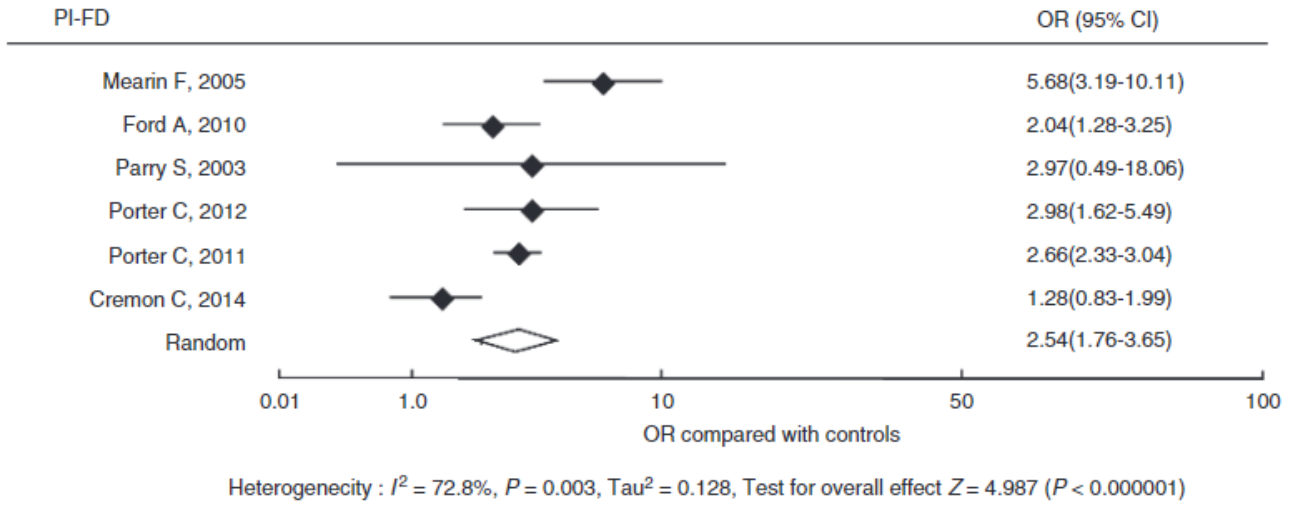


Ford AC et al. Lancet 2020

Postinfectious FD

- Salmonella spp
- Escherichia coli O157
- Campylobacter jejuni
- Giardia lamblia
- Yersinia enterocolitica
- Norovirus

PI-FD



PI-IBS

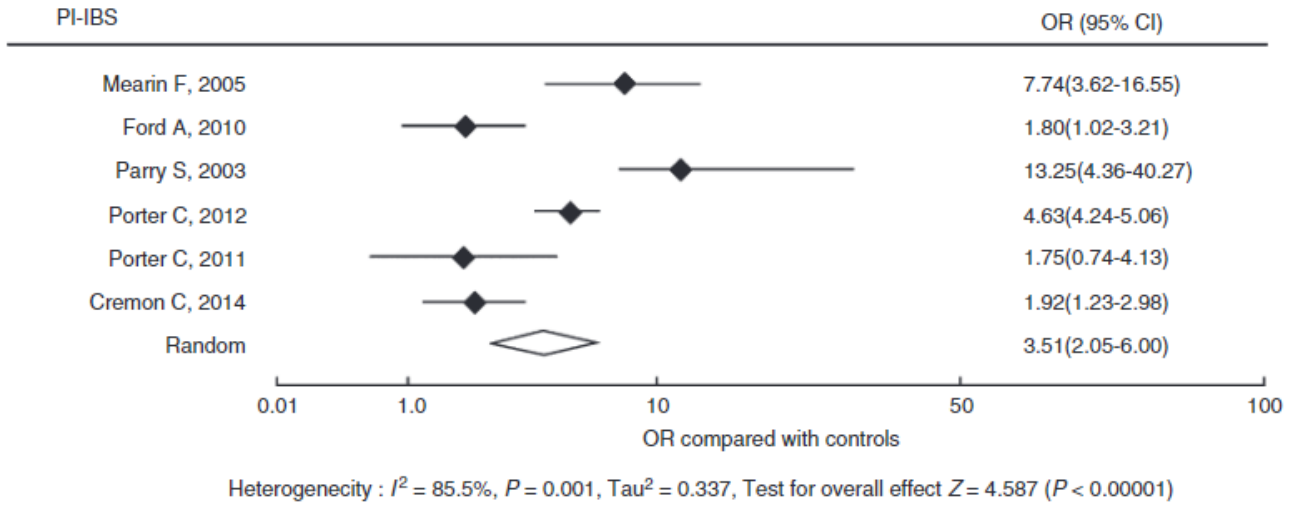
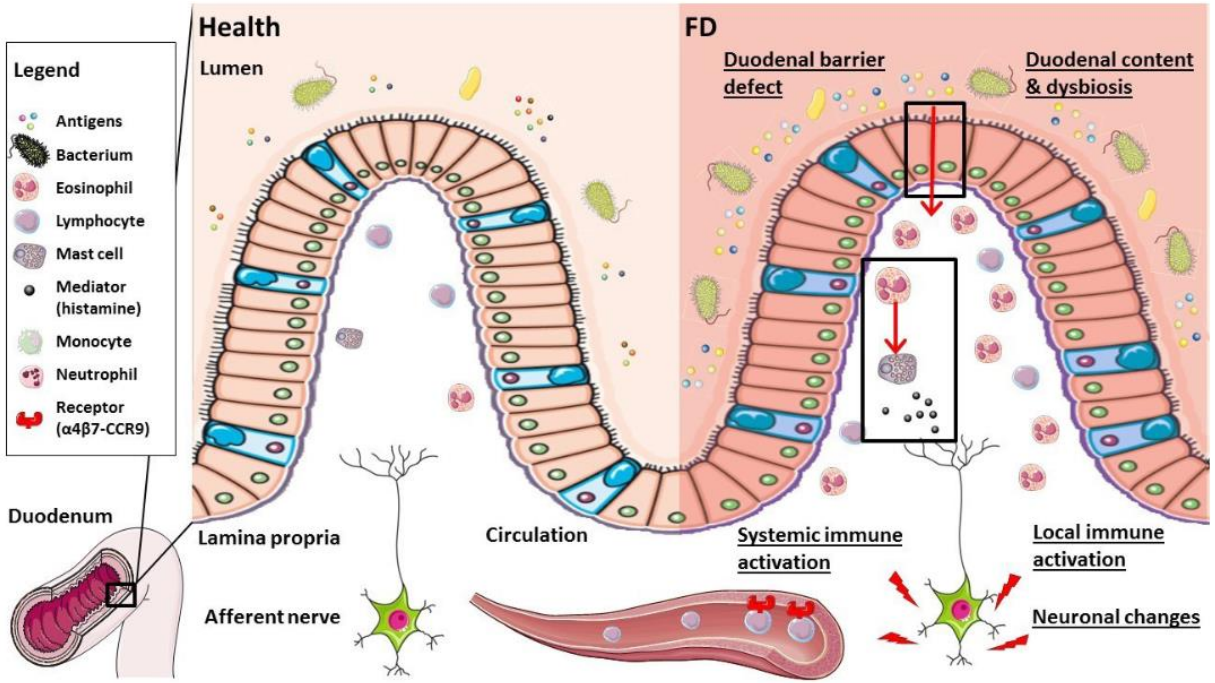
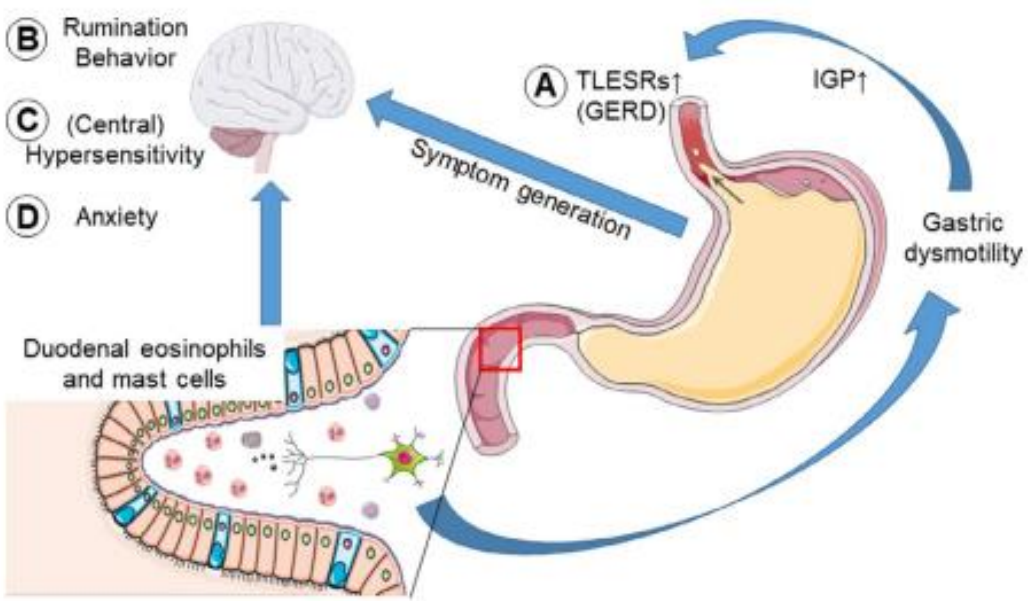


Figure 2 | Meta-analysis of six studies that demonstrated relative risk for post-infectious FD and post-infectious IBS. The relative risk and its confidence intervals (95% CI) for each study are plotted on a logarithmic sacle. The diamond-shaped box represents the pooled relative risk and the 95% CI.

Futagami S et al, Aliment Parmachol Ther 2020

Duodenal barrier dysfunction and low-grade inflammation

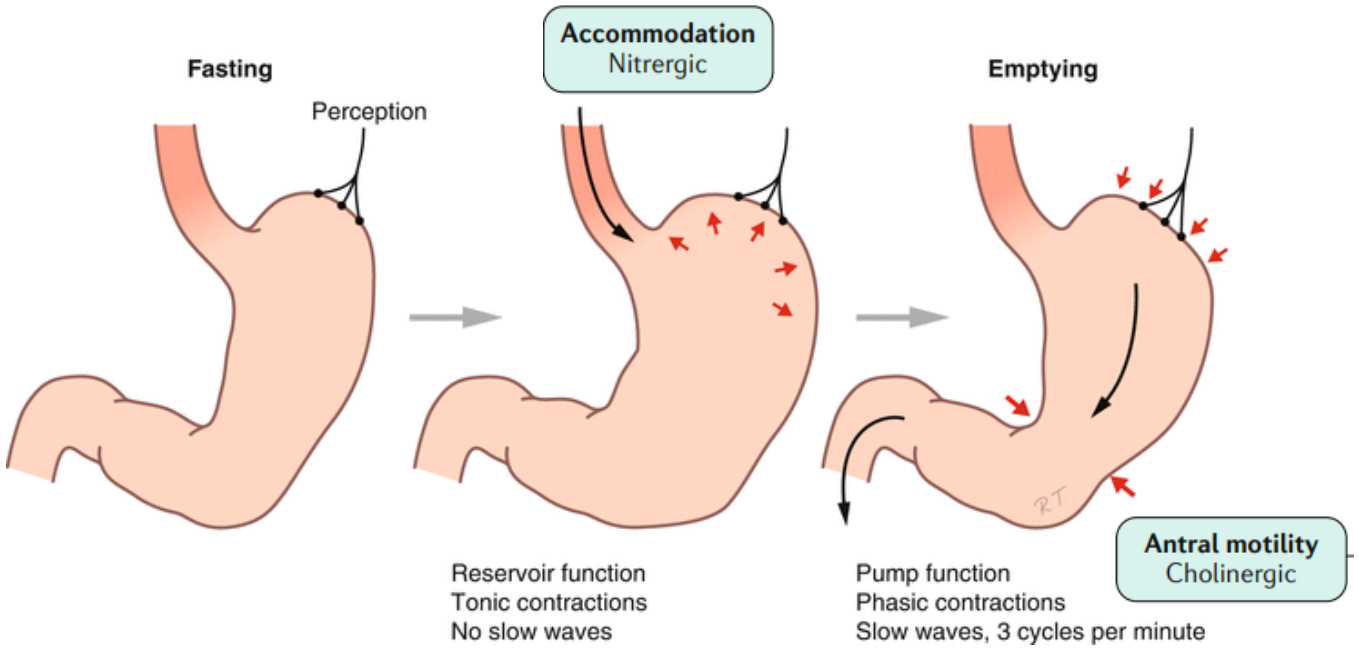




Wauters L et al, Gut 2020

Wauters L et al, Neurogastroenterol Motil 2021

Altered gastric motility



Camilleri M, et al Nat Rev Dis 2018

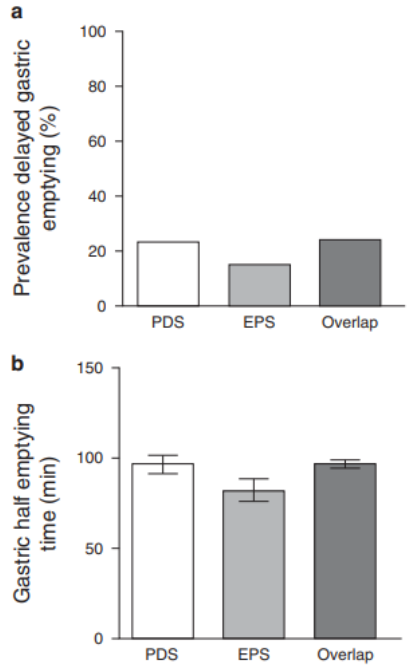


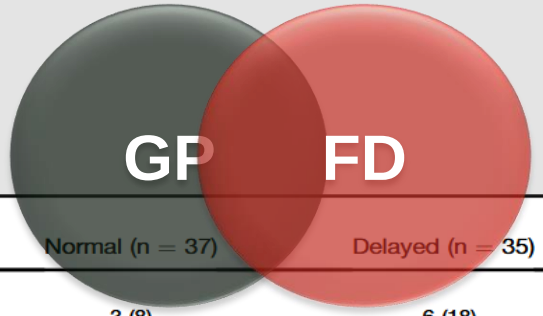
Figure 5. Gastric emptying. (**a**) Prevalence of delayed gastric emptying i the PDS, EPS, and overlap groups. (**b**) The gastric half emptying time in the subgroups. Data are presented as median (interquartile range (IQR)) EPS, epigastric pain syndrome; PDS, postprandial distress syndrome.

Vanheel H et al, Am J Gastroenterol 2017
Karamanolis G et al, Gastroenterology 2006

Gastroparesis??

“Gastric dysmotility” symptoms

- Nausea
- Vomiting
- Pain
- Postprandial fullness
- Early satiety
- Weight loss
- Belching
- Bloating



Characteristic	Normal (n = 37)	Delayed (n = 35)	*P* value[a] for association with group status
GI symptoms (Rome Criteria)[b]			
Functional dyspepsia	3 (8)	6 (18)	.29
Functional bowel symptoms	10 (28)	13 (37)	.32
GI symptom severity: PAGI scale[c]			
Heartburn/regurgitation	0.25 (0.08)	0.30 (0.07)	.60
Nausea, vomiting	0.06 (0.02)	0.18 (0.08)	.15
Satiety	0.65 (0.13)	0.67 (0.15)	.92
Abdominal bloating	0.89 (0.21)	0.70 (0.17)	.50
Upper-abdominal pain	0.28 (0.11)	0.49 (0.16)	.39
Lower-abdominal pain	0.35 (0.13)	0.42 (0.14)	.63
Total PAGI symptom score	0.41 (0.09)	0.46 (0.10)	.73
Quality of life: PAGI scale[c]			
Daily activities	0.018 (0.005)	0.03 (0.01)	NA
Diet	0.05 (0.017)	0.07 (0.02)	NA
Psychological	0.04 (0.01)	0.04 (0.01)	NA
Clothing	0.15 (0.04)	0.17 (0.09)	NA
Relationship	0.01 (0.006)	0.05 (0.03)	NA
Total	0.05 (0.02)	0.08 (0.03)	.49

NA, not assessed.
[a]Fisher exact test or Wilcoxon rank-sum test.
[b]Values are presented as N (%).
[c]Symptoms and QOL are ranked on a scale of 0 (none) to 5 (very severe), where 1 represents very mild symptoms.

Bharucha AL et al, Gastroenterology 2015
Rey E et al, J Neurogastroenterol Motil 2012

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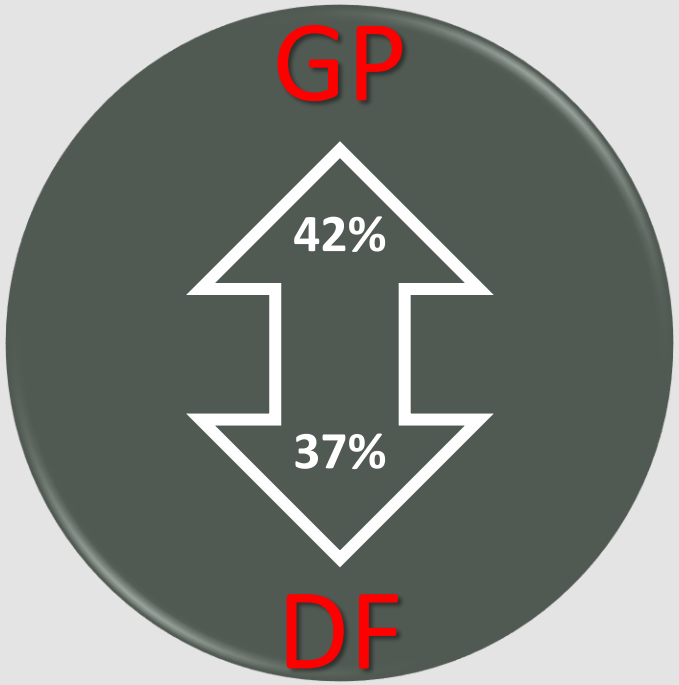
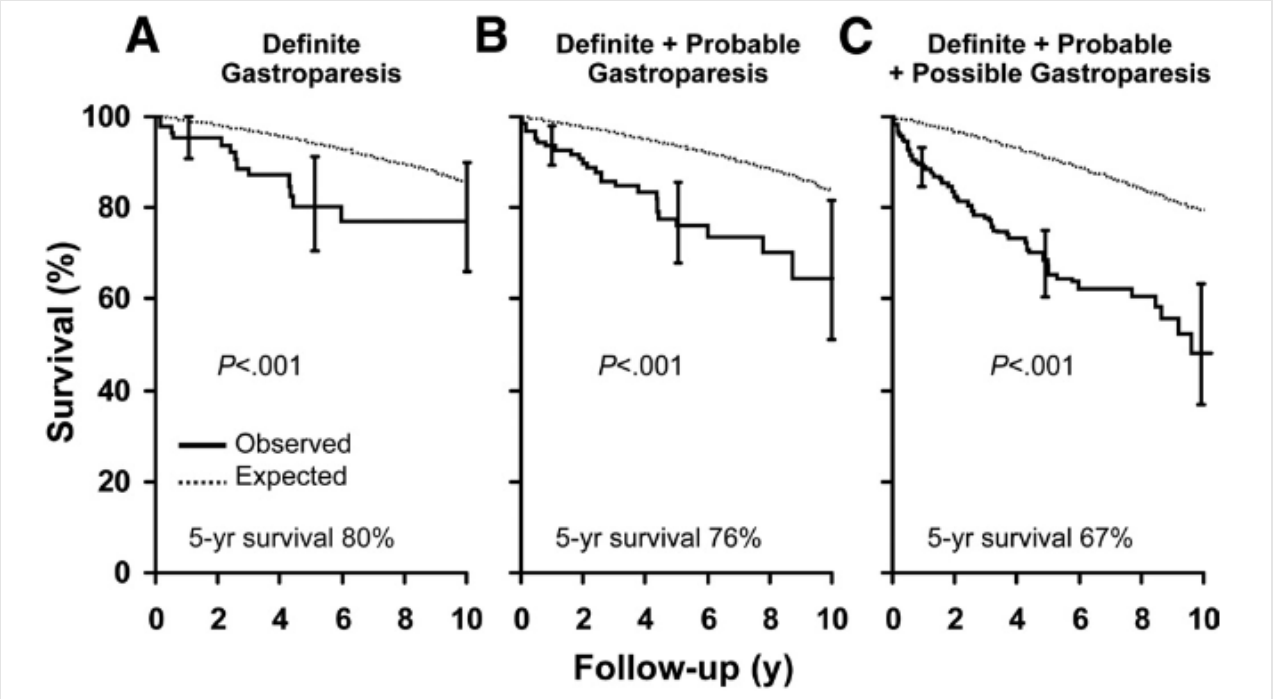
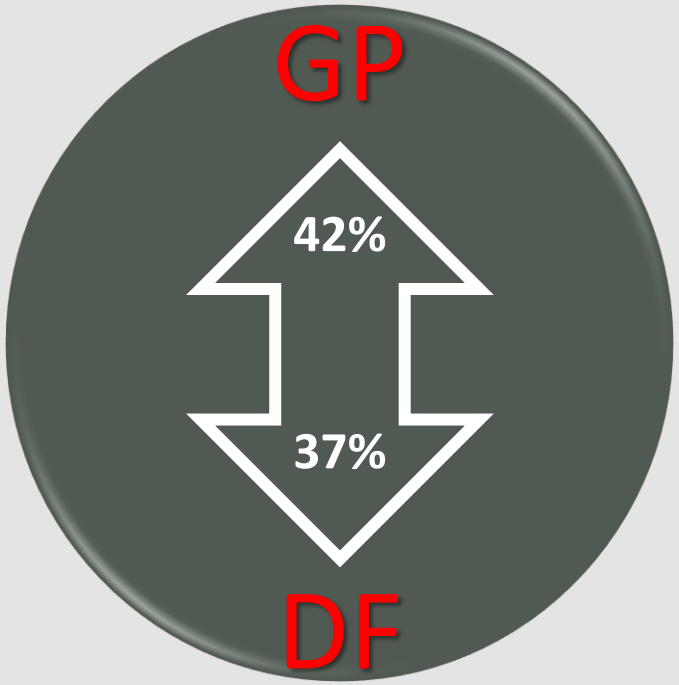
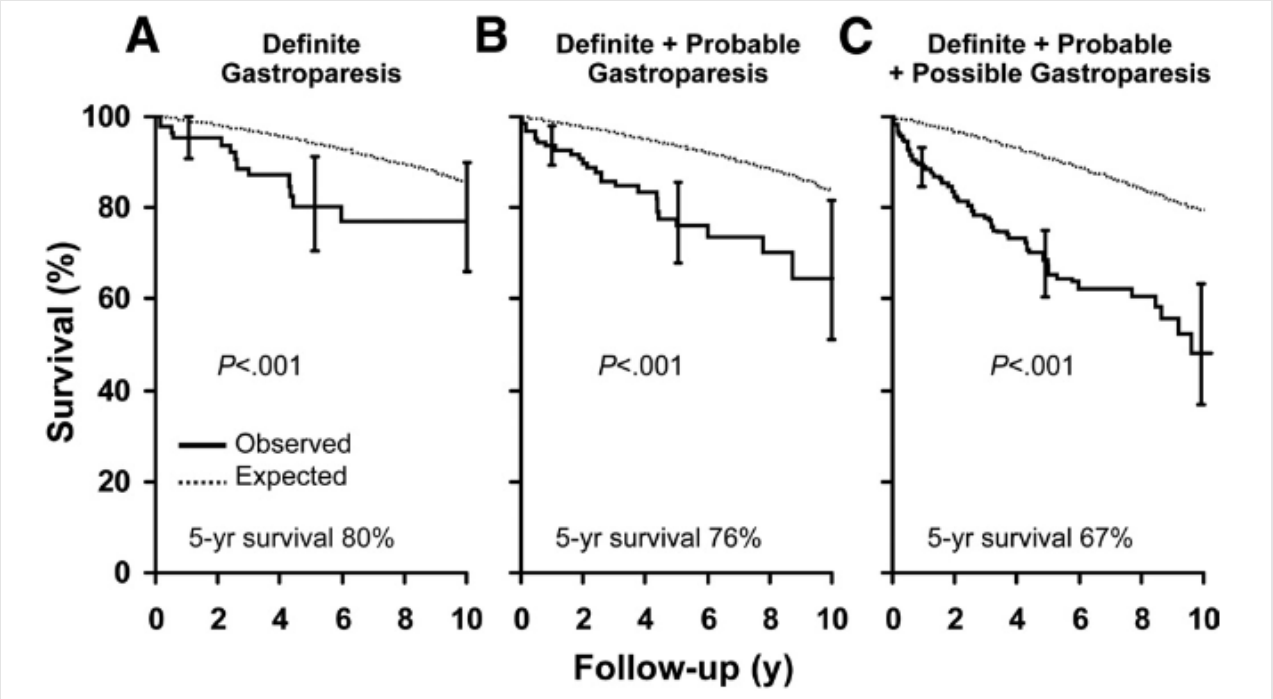




Pasricha PJ et al, Gastroenterology 2021

Jung H et al , Gastroenterology 2009



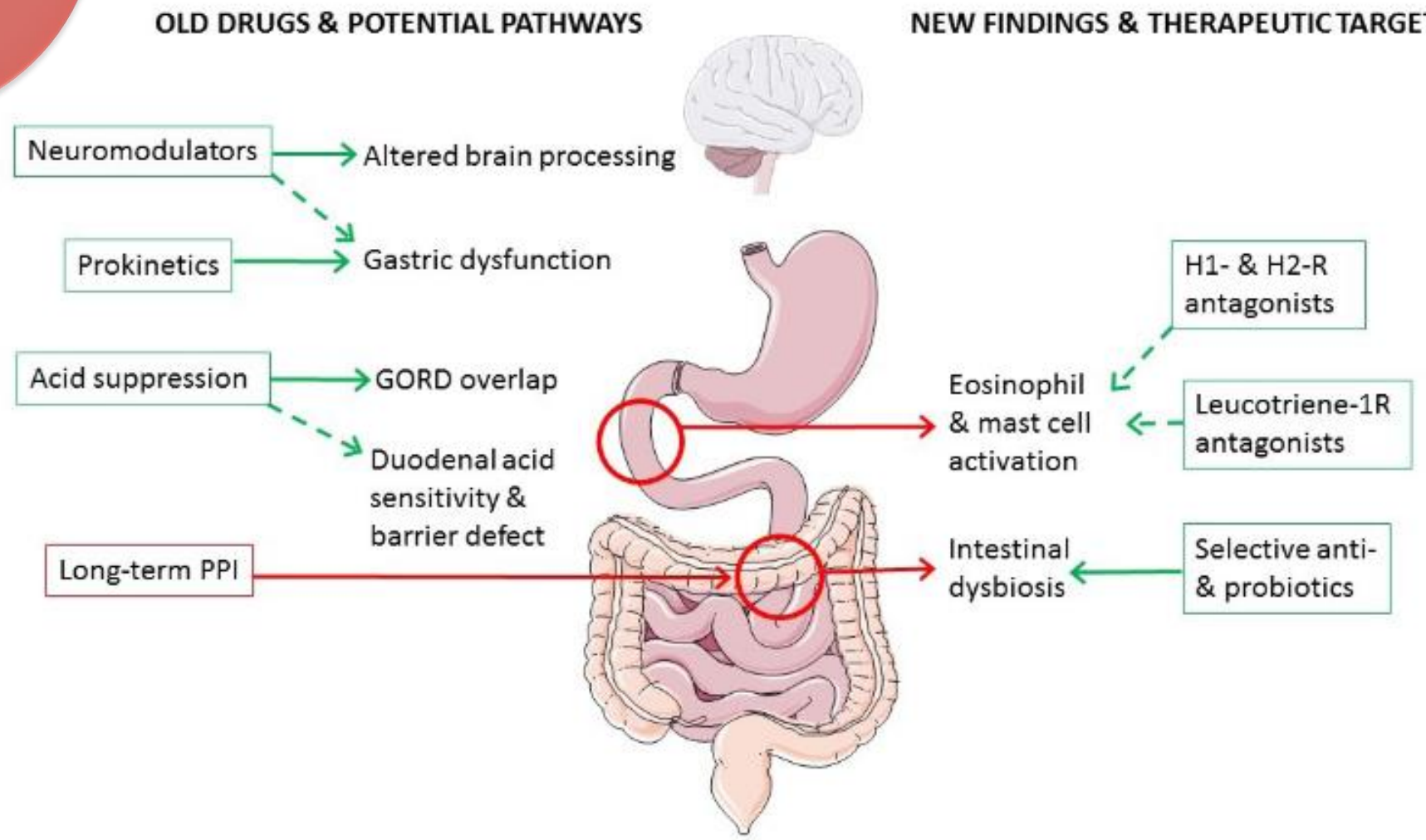


Pasricha PJ et al, Gastroenterology 2021

Jung H et al , Gastroenterology 2009

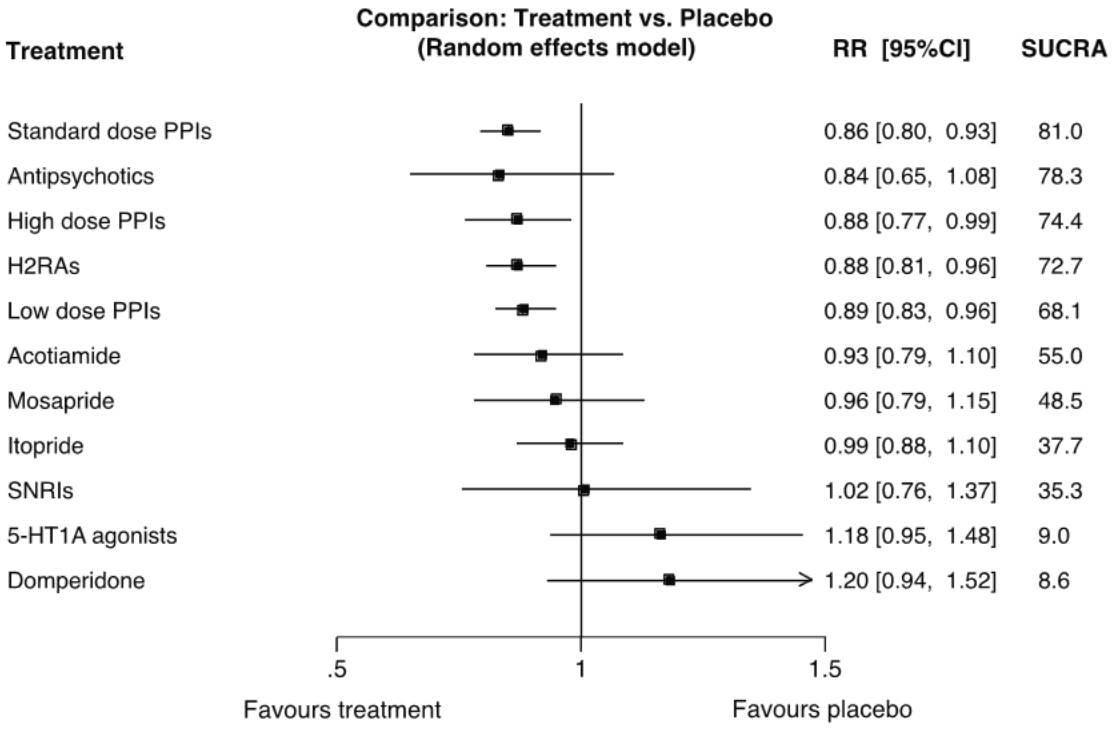
Therapy

Functional dyspepsia



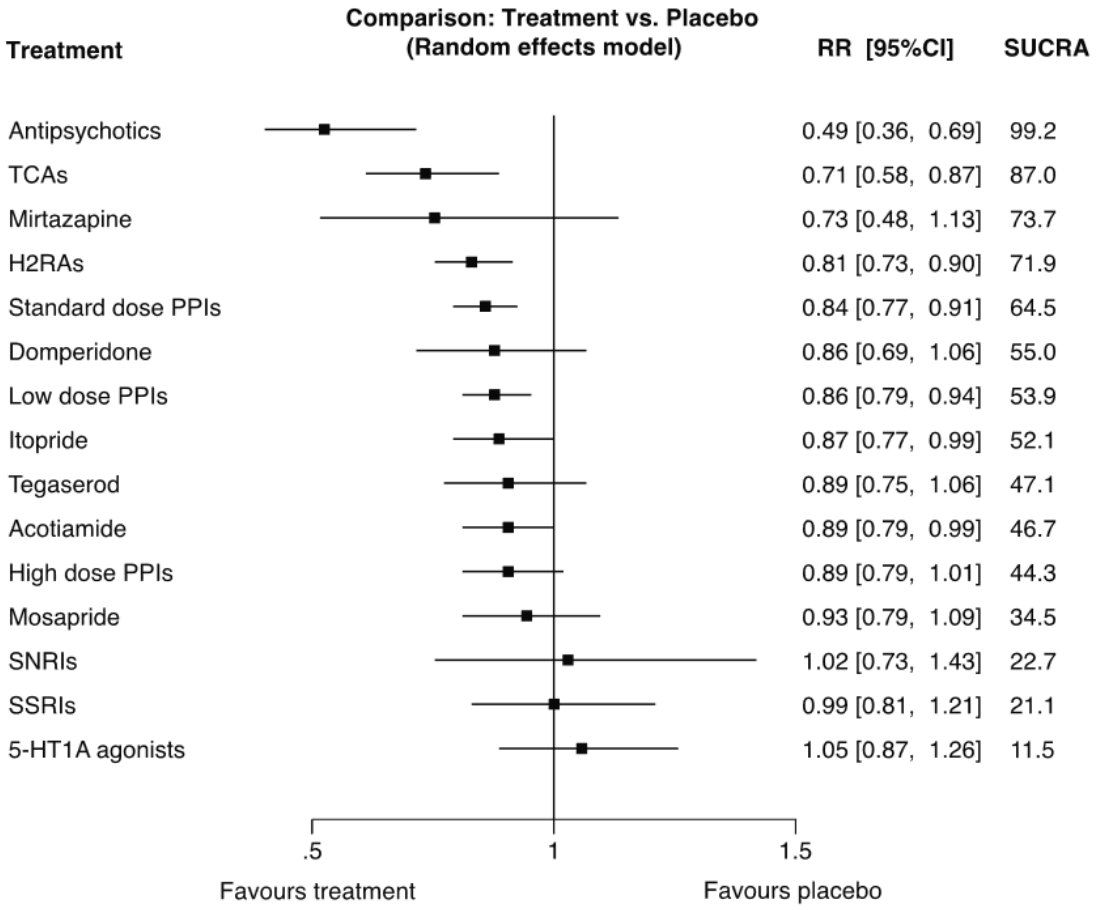
Resolution

Figure 4. Forest Plot for Failure to Achieve Resolution of FD Symptoms.



Improvement

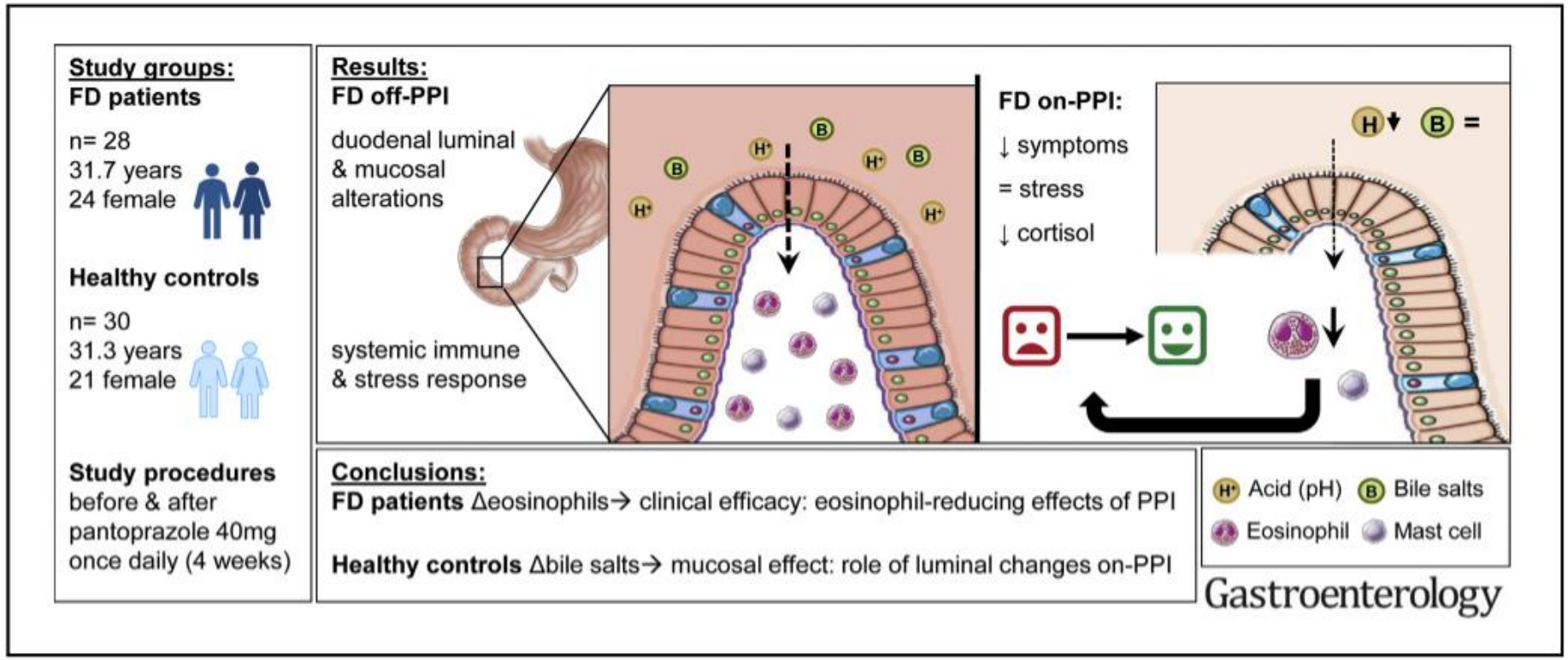
Figure 2. Forest Plot for Failure to Achieve an Improvement in FD Symptoms.



Ford AC et al, APT 2020

Proton Pump Inhibitors Reduce Duodenal Eosinophilia, Mast Cells, and Permeability in Patients With Functional Dyspepsia

Lucas Wauters,[1,2] Matthias Ceulemans,[2] Dennis Frings,[2] Maarten Lambaerts,[2] Alison Accarie,[2] Joran Toth,[2] Raf Mols,[3] Patrick Augustijns,[3] Gert De Hertogh,[4] Lukas Van Oudenhove,[2] Jan Tack,[1,2] and Tim Vanuytsel[1,2]



Wauters L et al, Gastroenterology 2021

Diet in FD and gastroparesis

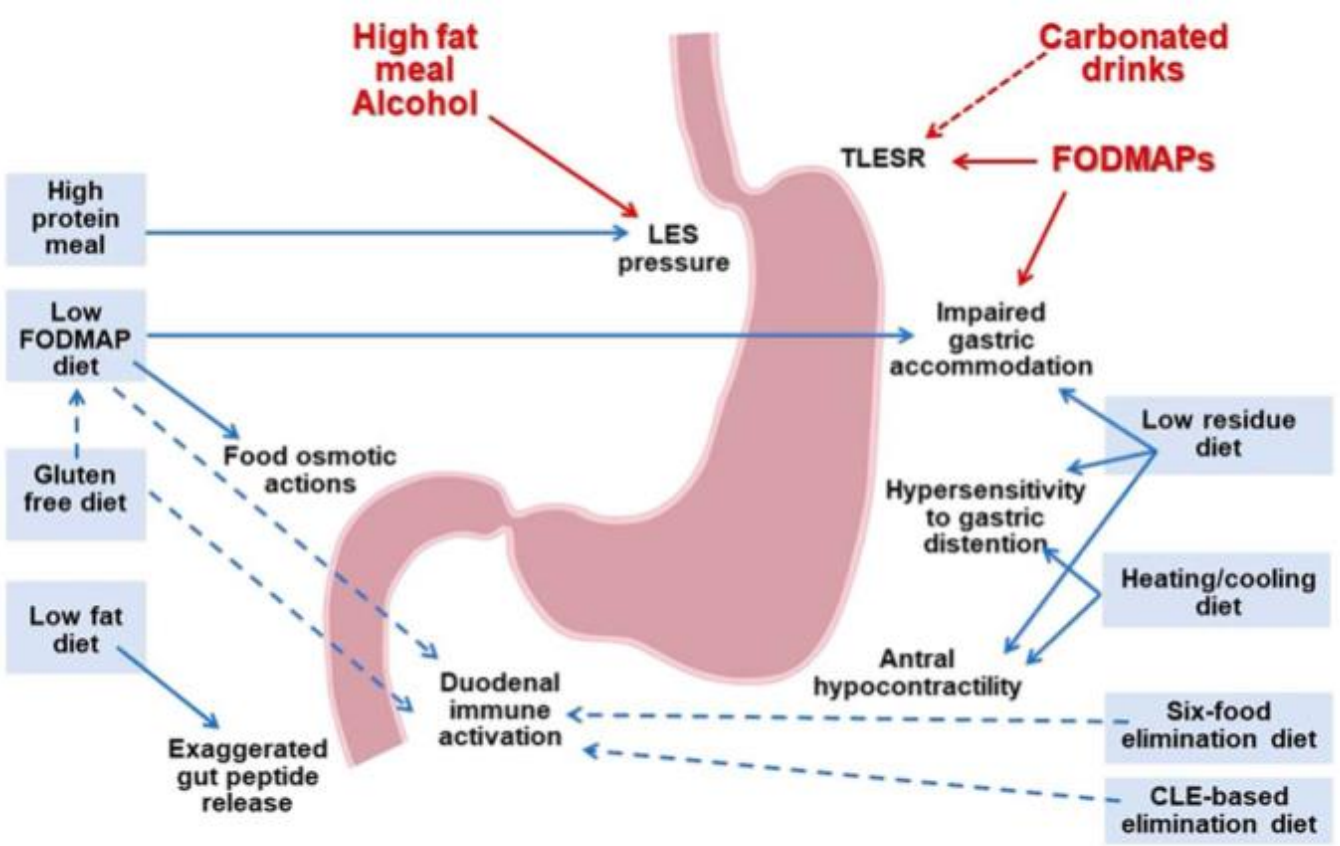
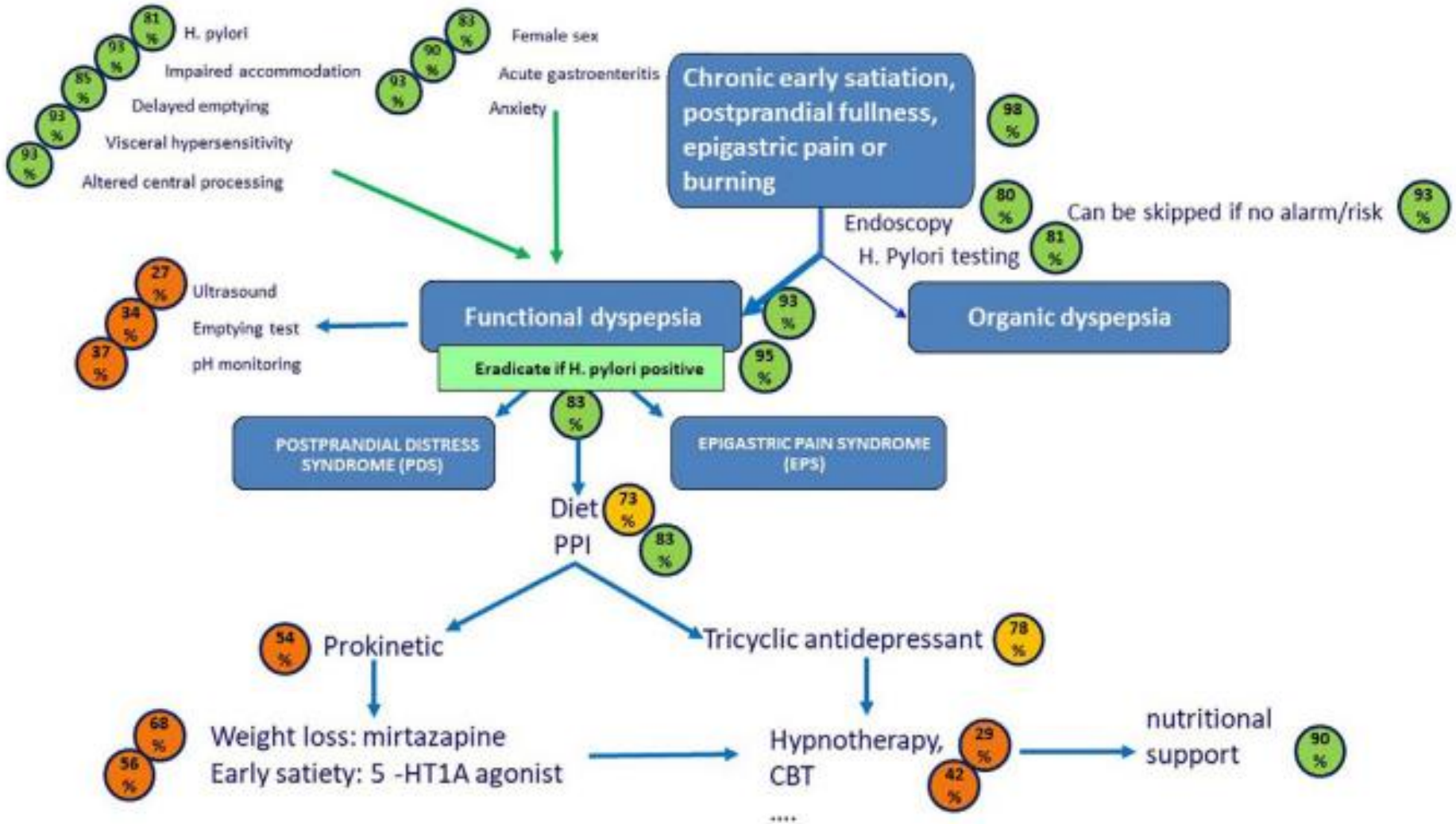


Table 1. Overview of therapeutic diets studied in functional dyspepsia and gastroparesis

Diet	Compared with	Treatment period (wk)	No. of patients	Patient population	Treatment response (%)	Results	Reference
Low FODMAP	Standard dietary advice	Not reported	59	FD/IBS	50	FODMAP showed more benefit than the standard diet	(67)
Low FODMAP	Traditional dietary advice	4	105	FD	67	Benefit with both diets	(68)
Low FODMAP gluten free	Baseline	4	9	FD	Not reported	Tendency to symptom improvement	(69)
Low FODMAP	Baseline	6	25	FD	62	FODMAP significantly improved symptoms	(58)
A 6-food elimination diet	Baseline	6	11	FD	71	Tendency to symptom improvement	(59)
Gluten-free diet	Baseline	Retrospective	142	Dysmotility-like FD, but large subgroup with overlapping celiac disease	92	Symptom improvement and improvement of histology and celiac serology	(86)
Gluten-free diet	Baseline	6	77	Refractory FD, negative for coeliac disease	35	Symptom improvement and improvement of histology and celiac serology	(87)
Gluten free diet	Baseline	3	22	134 patients with DGBI, of whom only 22 experienced FD	Not reported	Only 14% worsened on rechallenge.	(88)
Low-residue diet	Large particle size diet	One meal	7	Diabetic gastroparesis	Not reported	Size increases the gastric emptying rate and reduces the postprandial blood glucose dip	(89)

DGBI, disorder of gut–brain interaction; FD, functional dyspepsia; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome.

Tack J et al, Am J Gastroenterol 2022



Wauters L et al, Neurogastroenterol Motil 2020