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ORIGINAL ARTICLE

Randomized trial in postprandial functional dyspepsia: Reassurance and diagnostic explanation with or without traditional dietary advice

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Abstract

Background: Almost 80% of individuals with functional dyspepsia experience meal-related symptoms and are diagnosed with postprandial distress syndrome (PDS). However, studies evaluating dietary modifications in PDS are sparse. We performed a single-center randomized trial comparing reassurance and diagnostic explanation (RADE) with or without traditional dietary advice (TDA) in PDS.

Methods: Following a normal upper gastrointestinal endoscopy, individuals with PDS were randomized to a leaflet providing RADE ± TDA; the latter recommending small, regular meals and reducing the intake of caffeine/alcohol/fizzy drinks and high-fat/processed/spicy foods. Questionnaires were completed over 4 weeks, including self-reported adequate relief of dyspeptic symptoms, and the validated Leuven Postprandial Distress Scale (LPDS), Gastrointestinal Symptom Rating Scale, and Nepean Dyspepsia Index for quality of life. The primary endpoint(s) to define clinical response were (i) ≥50% adequate relief of dyspeptic symptoms and (ii) >0.5-point reduction in the PDS subscale of the LPDS (calculated as the mean scores for early satiety, postprandial fullness, and upper abdominal bloating).

Key Results: Of the 53 patients with PDS, 27 were assigned RADE-alone and 26 to additional TDA. Baseline characteristics were similar between groups, with a mean age of 39 years, 70% female, 83% white British, and coexistent irritable bowel syndrome in 66%. The primary endpoints of (i) adequate relief of dyspeptic symptoms were met by 33% ($n = 9$) assigned RADE-alone versus 39% ($n = 10$) with TDA; p-value = 0.70, while (ii) a reduction of >0.5 points in the PDS subscale was met by 37% ($n = 10$) assigned RADE-alone versus 27% ($n = 7$) with TDA; p-value = 0.43. Response rates did not differ according to irritable bowel syndrome status. There were no significant between-group changes in the gastrointestinal symptom rating scale and dyspepsia quality of life.

Conclusions & Inferences: This study of predominantly white British patients with PDS found the addition of TDA did not lead to significantly greater symptom reduction

compared with RADE alone. Alternate dietary strategies should be explored in this cohort.

KEYWORDS
diet, functional dyspepsia, postprandial distress syndrome, reassurance

1 | INTRODUCTION

Dyspepsia is common, affecting 7.2% of the global population, and is characterized by gastroduodenal symptoms of postprandial fullness, early satiety, epigastric pain, or burning.[1,2] Over 85% of individuals with dyspepsia do not have an underlying organic disease to explain the symptoms and are diagnosed as having functional dyspepsia,[3] a disorder of gut–brain interaction in which the pathophysiology is incompletely understood but includes visceral hypersensitivity, motor disturbances, impaired gastric accommodation, and central sensitization.[4] Functional dyspepsia can be further divided into the predominant meal-related subtype—termed postprandial distress syndrome (PDS)—which represents 80% of functional dyspepsia cases, or the non-meal-related epigastric pain syndrome variant.[4] While functional dyspepsia does not impact mortality, it represents a significant societal burden, being associated with increased healthcare use, mood disturbances, reduced quality of life, and impaired work productivity through presenteeism and absenteeism.[1,5]

Therapies for functional dyspepsia are limited and generally ineffective.[6] Only 15%–20% of patients appear to experience symptom improvement after a reassuringly normal upper GI endoscopy,[7–9] and with little change to psychological well-being and health-related quality of life.[9] Acid-suppressive medication such as proton pump inhibitors are frequently prescribed yet benefit 1 in 11.[10] Despite food typically triggering symptoms in PDS there is sparse data regarding dietary modifications in this patient group. Commonly reported food triggers include fatty foods, milk and dairy, alcohol, coffee, red meat, carbonated drinks, vegetables, spicy foods, carbohydrates, wheat, and citrus.[11] While reducing the intake of such foods—in the form of either traditional dietary advice (TDA) or a diet low in fermentable carbohydrates—is recommended in irritable bowel syndrome (IBS),[12] this cannot be extrapolated to PDS in which there is currently insufficient evidence due to a lack of clinical trials. An Australian study reported only 3 of 19 (16%) patients with functional dyspepsia improved with TDA[13] but was limited to being a small non-randomized trial and without differentiating functional dyspepsia subtypes. A single-center randomized trial from India found that after 4 weeks of TDA, clinical improvements were seen in 57% of participants with functional dyspepsia and 53% of those with PDS symptoms.[14] These two studies differ with regard to their design, participant numbers, and cultural settings. Hence, further studies of TDA in PDS are needed, a message corroborated by the recently published British and European Guidelines on its management.[15]

We performed a randomized trial evaluating the clinical efficacy of TDA in PDS, comparing it with a model of reassurance and diagnostic explanation (RADE) alone. We hypothesized that the addition of TDA will lead to greater symptom improvement than RADE alone.

Key points

What is established knowledge?

- Functional dyspepsia affects 7.2% of the global population.
- Approximately 80% of patients with functional dyspepsia report meal-related symptoms and are diagnosed with postprandial distress syndrome (PDS).
- There are limited data on the efficacy of dietary therapies in PDS.

What are the new findings from this study?

- The addition of traditional dietary advice (TDA) did not lead to significantly greater symptom reduction compared with reassurance and diagnostic explanation alone.
- The study was performed in a predominantly white British cohort and may not apply to other ethnicities/cultures with different cuisines.
- Alternate dietary therapies (e.g., low FODMAP diet) should be explored in PDS.

2 | METHODS

2.1 | Participants and setting

The study was carried out in accordance with the Declaration of Helsinki and approved by West Midlands Black Country Research Ethics Committee. The clinical trials.gov number is NCT05718960.

The study was conducted at Sheffield Teaching Hospitals (UK) between September and December 2022. Recruitment was through poster advertisements within the endoscopy units. The inclusion criteria were adults aged 18–60 years who fulfilled criteria for PDS, in accordance with the Rome IV diagnostic criteria, and had undergone a normal upper GI endoscopy within the last year. Additional inclusion criteria included being English literate and having internet access to complete questionnaire data.

Exclusion criteria were body mass index <20, history of eating disorders, current dietary interventions, inflammatory bowel disease, celiac disease, gastrointestinal cancer, previous abdominal surgery, scleroderma, poorly controlled diabetes, severe liver/respiratory/cardiac/psychiatric disease (with "severe" defined as repeated flares, recurrent hospital or general practitioner attendances, numerous medications, clinically appearing unwell due to that disease process), memory impairment, pregnant, current use of antibiotics/anti-inflammatory drugs/narcotics, or currently titrated antidepressants or acid-suppressive medication (i.e., not on a stable dose).

2.2 | Randomization

Patients with PDS were randomized 1:1 to a leaflet providing RADE-alone or RADE plus TDA. The randomization was computer-generated and stratified according to the presence or absence of IBS, the latter elicited during the initial screening period. This was deemed relevant as between 30%–50% of patients with functional dyspepsia have coexisting IBS,[1] which might influence response rates to assigned interventions.

The RADE-alone group was provided a leaflet explaining dyspeptic symptoms, their prevalence and burden, and reassurance that no organic disease (i.e., cancer, ulcers, and infection) was found at recent upper gastrointestinal endoscopy. Participants were informed of the diagnosis "functional dyspepsia," with the basic explanation of disturbed communication between the stomach and the brain, leading to sensitive nerves and inadequate stomach muscle function. Individuals were informed that following upper gastrointestinal endoscopy and RADE their symptoms might improve, which we plan to assess over a 4-week period.

The TDA group were given the aforementioned RADE information but also advised to adopt dietary modifications, with recommendations to eat small, regular meals and reduce the intake of caffeine/alcohol/fizzy drinks and high fat/processed/spicy foods. Both the RADE and TDA leaflets are available within supplementary materials.

2.3 | Questionnaires

Participant baseline characteristics (age, gender, race, smoking status, alcohol use, and medication) were documented and they completed the following questionnaires during the 4-week trial:

a. Leuven postprandial distress scale (LPDS)—the LPDS is a sensitive and reliable patient-reported outcome instrument to assess symptoms in functional dyspepsia/PDS.[16] It asks for eight dyspeptic symptoms (early satiety, postprandial fullness, upper abdominal bloating, epigastric pain, epigastric burning, nausea, belching, and heartburn), each scored on a 5-point scale (0 = absent to 4 = very severe). The first three dyspeptic symptoms can be combined to give an average postprandial distress syndrome (PDS) domain score. Following intervention, a reduction in the average PDS domain score of >0.5 points from baseline is a validated, meaningfully important difference that denotes clinical response.[16]
b. Adequate symptom relief of ≥50%—phrased as "Did you experience overall satisfactory relief of dyspepsia (stomach/upper

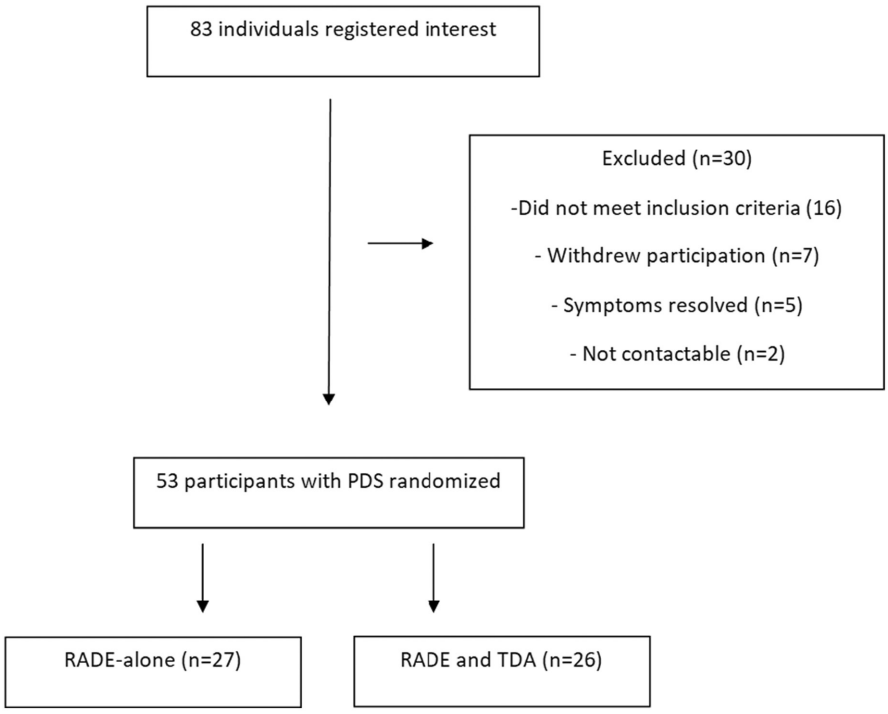

FIGURE 1 Study flow chart. RADE, reassurance and diagnostic explanation; TDA, traditional dietary advice.

abdominal) symptoms with the current treatment compared with the baseline period?" with a yes or no answer. This question has been used in randomized trials in functional dyspepsia to assess symptom response.[17,18]

c. Short form Nepean Dyspepsia Index (NDI)—this 10-item questionnaire assesses dyspepsia-related quality of life across five subscales, that is, tension/anxiety, interference with daily activities, disruption to regular eating/drinking, knowledge toward/control over disease symptoms, and interference with work/study. Each item is measured by a 5-point Likert scale ranging from 1 (not at all or not applicable) to 5 (extremely).[19]
d. Gastrointestinal symptom rating scale for IBS (GSRS-IBS)—this 13-item measures IBS-related gastrointestinal symptom severity over the last 7 days. The items belong to five symptom clusters: pain, bloating, constipation, diarrhea, and early satiety. The items are scored between 1 and 7, where 1 corresponds to "no discomfort at all" and 7 to "very severe discomfort."[20]
e. Hospital Anxiety and Depression Scale (HADS)—is a psychological screening tool to which there are in total 14 items, seven each for depression and anxiety. Each item is rated from 0 (not present) to 3 (maximum), giving a cumulative score for each subscale to range from 0 to 21. A subscale score of ≥11 is used to indicate a clinically significant level of anxiety or depression.[21]
f. The patient health questionnaire (PHQ)-12 non-GI somatic symptoms scale—this records 12 bothersome non-GI symptoms over the past month, with each item scored as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot"). A total score of >12 implies high somatic symptom reporting.[22]

The group-allocated TDA also self-reported dietary adherence as "never/rarely" (followed the dietary advice <25% of the time), "sometimes" (25%–50% of the time), "frequently" (51%–75% of the time), or "always" (76%–100% of the time).[13] Individuals following TDA >50% of the time were deemed adherent.

2.4 | Endpoints

The co-primary endpoints to define clinical response were evaluated over Weeks 3–4 as (i) ≥50% adequate relief of dyspeptic symptoms and (ii) >0.5-point reduction in the PDS subscale compared to baseline. Secondary endpoints included changes in individual LPDS items, NDI-QOL, GSRS-IBS, and the presence of anxiety, depression, and high somatic symptom reporting.

2.4.1 | Sample size and statistical analysis

Based on the assumption of up to 20% improvement following a normal upper GI endoscopy and RADE[7,8] and a 57% response rate with TDA as per a previous randomized clinical trial,[14] we aimed to randomize 25 patients per arm, with 80% power at $\alpha = 0.05$.

Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using chi-square test. Continuous data were summarized by mean and standard deviation, with comparisons between and within groups performed using (un)paired student test as appropriate. Statistical significance was set at $p < 0.05$.

3 | RESULTS

A total of 83 individuals registered interest in the study, of which 53 with PDS were randomized to RADE-alone ($n = 27$) or additional TDA ($n = 26$); see study flow chart, Figure 1. The mean age of participants was 39 years (range 21–59), 70% female, 83% white British, and co-existent IBS in 66% ($n = 35$). Baseline demographics and clinical characteristics were comparable between the groups; see Table 1.

TABLE 1 Baseline data.

	RADE ($n = 27$)	RADE + TDA ($n = 26$)	p-value
Demographics			
Mean age, years	41 (12)	39 (9)	0.50
Female	19 (70%)	18 (69%)	0.93
White race	24 (89%)	20 (77%)	0.25
Smoker	7 (27%)	5 (19%)	0.56
Alcohol	16 (59%)	12 (46%)	0.34
Acid-suppressive drugs	16 (59%)	11 (42%)	0.22
Anti-emetic drugs	2 (7%)	2 (7%)	0.97
Clinical characteristics			
Coexisting IBS	17 (63%)	18 (69%)	0.63
Anxiety	9 (33%)	11 (42%)	0.50
Depression	6 (22%)	7 (27%)	0.70
High somatic symptom reporting	6 (22%)	7 (27%)	0.70
NDI quality of life	26 (9.6)	30 (7.1)	0.10
GSRS-IBS	24 (13.3)	29 (12.3)	0.21
Total LPDS	14.4 (6.6)	15.0 (5.4)	0.74
PDS subtype	2.0 (1.0)	2.1 (0.8)	0.72
EPS subtype	1.7 (1.0)	2.1 (0.6)	0.10
Early satiety	1.5 (1.0)	1.4 (0.9)	0.71
Fullness	2.0 (1.2)	2.3 (1.0)	0.38
Upper stomach bloating	2.6 (1.1)	2.7 (0.9)	0.72
Pain	1.9 (1.1)	2.3 (0.9)	0.15
Burning	1.5 (1.1)	1.8 (0.9)	0.19
Nausea	1.4 (1.3)	1.4 (1.3)	0.95
Belching	1.7 (1.0)	1.3 (1.1)	0.12
Heartburn	1.8 (1.2)	1.8 (1.2)	0.98

Note: Values presented as mean (SD) or *n* (%). PDS subtype is the average of early satiety, fullness, and upper stomach bloating in LPDS. EPS subtype is the average of pain and burning scores in LPDS.

3.1 | Primary endpoint results

Following intervention, there was no significant difference between the groups with regard to meeting the primary endpoints (Figure 2). Adequate relief of dyspeptic symptoms was met by 33% ($n=9$) in the RADE-alone group versus 39% ($n=10$) in the TDA group; p-value=0.70, while (ii) a reduction of >0.5 points in the PDS subscale was met by 37% ($n=10$) in the RADE group versus 27% ($n=7$) in the TDA group; p-value=0.43. Adequate adherence to TDA was reported by 84%, with 65% following the diet frequently and 19% always. The RADE group reported not following any additional diet while in the trial.

3.2 | Secondary endpoint results

While significant within-group reductions in LPDS were noted for both RADE-alone and TDA, there was no between-group difference in changes for early satiety, postprandial fullness, upper abdominal bloating, epigastric pain, epigastric burning, nausea, belching, and heartburn (Table 2).

Following the 4-week intervention, there were no significant within- or between-group changes in NDI quality of life indices (tension, interference, eating and drinking, knowledge, and work) and GSRS-IBS domains (pain, bloating, constipation, diarrhea, and satiety); Table 3. At the end of the study period, there was also no difference between TDA and RADE in clinical anxiety (44% vs. 54%, $p=0.50$), depression (26% vs. 27%, $p=0.93$) or high levels of somatic symptom reporting (19% vs. 11.5%, $p=0.48$).

Finally, in the 35 individuals with coexisting IBS there was no significant difference in dyspepsia response rates—a reduction of >0.5 points in the PDS subscale—between those assigned RADE ($n=6/17$, 35%) versus TDA ($n=5/18$, 28%); $p=0.63$. In those without IBS ($n=18$), there was also no significant difference in dyspepsia response rates—a reduction of >0.5 points in the PDS subscale—between those assigned RADE ($n=4/10$, 40%) versus TDA (2/8. 25%); $p=0.50$.

4 | DISCUSSION

This UK-based study is the first randomized trial comparing the efficacy of RADE-alone versus additional TDA for the management of PDS. Almost one in three participants demonstrated an improvement in dyspeptic symptoms, which was similar between the groups, and not affected by the presence or absence of associated IBS. The assigned interventions did not lead to significant within- or between-group changes in GSRS, mood, or quality of life.

It has been demonstrated that comprehensive web-based educational tools—which include concepts aligned to RADE—are effective measures toward improving symptom severity, quality of life, and health anxiety in patients with functional dyspepsia.[23] The lack of additional benefit seen with TDA might, in part, be due to subtle dietary modifications having been made before study entry which we could not capture. For example, individuals with functional dyspepsia may eat smaller, more frequent meals with reduced fat content compared with healthy controls.[24,25] It could also be speculated that certain concepts of TDA, such as reducing the intake of spicy food, may not apply to a predominantly white British population. Notably, TDA had a minimal effect on functional dyspepsia symptoms in an Australian study.[13] In contrast, it might be of greater importance among those ethnicities and cultures where spice is commonly used within cuisines. For example, high consumption of spicy food among Iranian adults is associated with an increased severity of dyspeptic symptoms.[26] Similarly, a study from India reported almost 70% of individuals with functional dyspepsia eat hot/spicy food more than once per day, and the symptom improvement following TDA was 57%.[14] Hence, the role of TDA and its individual elements should

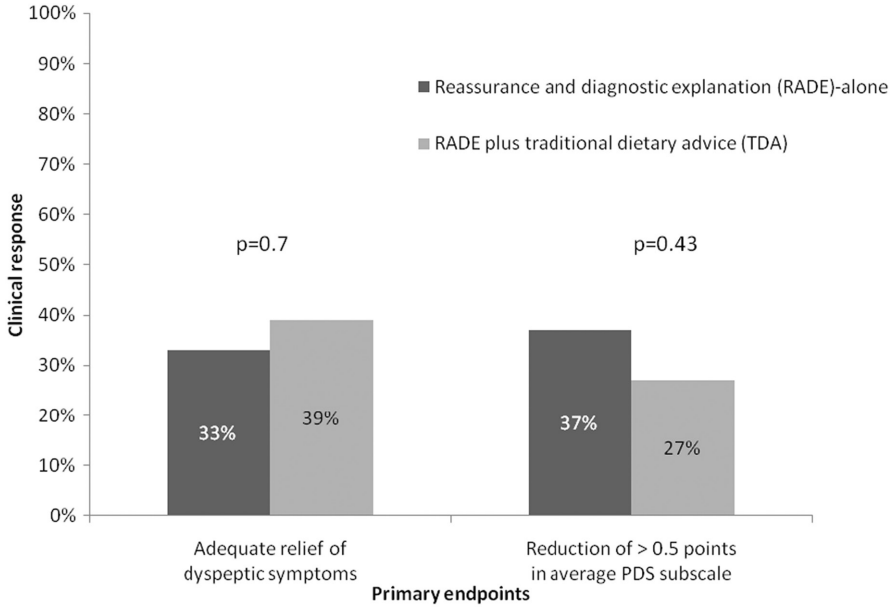

FIGURE 2 Clinical response in dyspepsia symptoms following RADE ± TDA.

TABLE 2 Within- and between-group changes in LPDS subscales following RADE ± TDA.

	Group	Mean change	*p*-value
LPDS total	RADE	−2.2	<0.001
	TDA	−1.9	0.05
	Difference	0.3	0.78
PDS total	RADE	−0.3	0.01
	TDA	−0.3	0.02
	Difference	0.0	0.98
EPS	RADE	−0.17	0.13
	TDA	−0.37	0.04
	Difference	0.20	0.33
Early satiety	RADE	−0.22	0.14
	TDA	−0.02	0.89
	Difference	0.2	0.32
Fullness	RADE	−0.20	0.13
	TDA	−0.38	0.04
	Difference	0.18	0.41
Bloating	RADE	−0.46	0.004
	TDA	−0.50	0.003
	Difference	0.04	0.86
Pain	RADE	−0.11	0.46
	TDA	−0.35	0.05
	Difference	0.24	0.30
Burning	RADE	−0.22	0.17
	TDA	−0.39	0.14
	Difference	0.17	0.59
Nausea	RADE	−0.37	0.04
	TDA	−0.04	0.87
	Difference	0.33	0.25
Belching	RADE	−0.17	0.24
	TDA	0.25	0.20
	Difference	0.42	0.08
Heartburn	RADE	−0.48	0.01
	TDA	−0.52	0.03
	Difference	0.04	0.89

be considered on an individualized basis in people with functional dyspepsia.

Moving forward, it would be useful to explore other dietary therapies in PDS, such as a diet low in fermentable oligo/di/monosaccharides and polyols (low FODMAP diet) for which there is an emerging but limited evidence base. An Australian group reported a low FODMAP diet to be superior to TDA in functional dyspepsia, with response rates of 50% versus 16%, but this was a small non-randomized observational study and did not evaluate PDS per se.[13] A single-center randomized trial from India found no difference between a low FODMAP diet and TDA in functional dyspepsia, with response rates at Week 4 being 67% versus 57%, respectively.[14]

TABLE 3 Within- and between-group changes in Nepean Dyspepsia Index (NDI) and GSRS-IBS subscales following RADE ± TDA.

	Group	Mean change	*p*-value
NDI—tension	RADE	−0.11	0.98
	TDA	0.58	0.14
	Difference	0.69	0.21
NDI—interference	RADE	0.04	0.21
	TDA	−0.08	0.89
	Difference	0.12	0.84
NDI—eating and drinking	RADE	−0.30	0.21
	TDA	−0.27	0.58
	Difference	0.03	0.96
NDI—knowledge	RADE	−0.19	0.64
	TDA	−0.81	0.06
	Difference	0.62	0.28
NDI—work	RADE	0.07	0.87
	TDA	0.35	0.35
	Difference	0.27	0.64
NDI—total	RADE	−0.48	0.69
	TDA	−0.23	0.88
	Difference	−0.25	0.90
GSRS-IBS—pain	RADE	−0.19	0.66
	TDA	−0.46	0.32
	Difference	0.27	0.65
GSRS-IBS—bloating	RADE	0.44	0.42
	TDA	−0.42	0.65
	Difference	0.87	0.41
GSRS-IBS—constipation	RADE	0.0	1.0
	TDA	0.73	0.15
	Difference	0.73	0.28
GSRS-IBS—diarrhea	RADE	0.37	0.51
	TDA	−0.65	0.43
	Difference	1.02	0.30
GSRS-IBS—satiety	RADE	0.11	0.82
	TDA	0.08	0.90
	Difference	0.03	0.97
GSRS-IBS—total	RADE	0.74	0.62
	TDA	−0.73	0.79
	Difference	1.47	0.63

However, while not powered to look at individual subtypes, it did suggest that those with PDS have a better response to a low FODMAP diet.[14] There might also be future interest in evaluating a gluten-/wheat-free diet in PDS, given that approximately a third of people with functional dyspepsia report sensitivity to wheat-based products.[27] A small open-label study comprising 22 patients with functional dyspepsia reported that 80% improved following a gluten-free diet, albeit only a quarter subsequently reacted to

gluten-containing capsules following double-blinded rechallenge.[28] There has been an attempt to identify which component of wheat may trigger symptoms in functional dyspepsia, but unfortunately was unable to meet recruitment targets.[29]

The strengths of the study include identifying a well-defined cohort of individuals with PDS based on fulfilling Rome IV symptom criteria and normal upper GI endoscopy. Furthermore, we used validated questionnaires and the primary endpoints were targeted toward capturing specific changes in dyspeptic symptoms. The online questionnaire format enabled us to build in checks to prevent missing data. Allowing individuals with coexisting IBS to be eligible for the study was important given that this is commonly representative of the functional dyspepsia patient cohort seen within clinical practice.[1] Finally, the use of leaflets as a means of providing information avoided placing an additional burden on heavily stretched dietetic and clinical services.[30] Those allocated TDA self-reported following the diet for the majority of the trial, although we did not collect nutritional intake data to corroborate this. Other study limitations include it being a single-center, 4-week trial in which long-term outcomes are not known. Recruitment was via the endoscopy units with such individuals potentially having milder symptoms and being less difficult to manage than those encountered long term in the outpatient clinic setting. As previously mentioned, the study cohort comprised mainly white British patients and our findings may not be generalizable to other ethnic races with different cuisines. We also chose not to study the effects of diet in the epigastric pain syndrome variant of functional dyspepsia, given that this accounts for 20% of cases and is non-meal related.

In conclusion, in this UK-based study of predominantly white British participants with PDS, the addition of TDA did not lead to greater symptom reduction compared with RADE alone. Alternate dietary strategies should be explored in this patient cohort.

AUTHOR CONTRIBUTIONS

IA conceived the study. RLB, LCB, and IA contributed to the study design and its conduct. RLB, LCB, and IA collected and inputted data. RCB and IA analyzed the data and wrote the initial manuscript. All authors had access to the study data, revised the manuscript, and approved the final version of the article. IA is guarantor of the article.

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CONFLICT OF INTEREST STATEMENT

No competing interests declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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