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REVIEW

Food and functional dyspepsia: a systematic review

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abdominal pain, dietary factors, food, functional dyspepsia, functional gastrointestinal disorder, wheat.

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Abstract

Background: Functional dyspepsia (FD) is a debilitating functional gastrointestinal disorder characterised by early satiety, post-prandial fullness or epigastric pain related to meals, which affects up to 20% of western populations. A high dietary fat intake has been linked to FD and duodenal eosinophilia has been noted in FD. We hypothesised that an allergen such as wheat is a risk factor for FD and that withdrawal will improve symptoms of FD. We aimed to investigate the relationship between food and functional dyspepsia.

Methods: Sixteen out of 6451 studies identified in a database search of six databases met the inclusion criteria of studies examining the effect of nutrients, foods and food components in adults with FD or FD symptoms.

Results: Wheat-containing foods were implicated in FD symptom induction in six studies, four of which were not specifically investigating gluten and two that were gluten-specific, with the implementation of a gluten-free diet demonstrating a reduction in symptoms. Dietary fat was associated with FD in all three studies that specifically measured this association. Specific foods reported as inducing symptoms were high in either natural food chemicals, high in fermentable carbohydrates or high in wheat/gluten. Caffeine was associated with FD in four studies, although any association with alcohol was uncertain.

Conclusions: Wheat and dietary fats may play key roles in the generation of FD symptoms and reduction or withdrawal eased symptoms. Randomised trials investigating the roles of gluten, FODMAPs (fermentable oligosaccharide, disaccharide, monosaccharide and polyols) and high fat ingestion and naturally occurring food chemicals in the generation of functional dyspepsia symptoms are warranted and further investigation of the mechanisms is now required.

Introduction

Functional dyspepsia (FD) is highly prevalent and debili- ties in the absence of any associated structural or metatating condition [1,2] that afflicts in 5–12% of the popula- bolic disease [5]. No objective diagnostic tools for tion in Eastern populations and 10–20% of Western functional dyspepsia are currently available, although populations [3]. The prevalence of uninvestigated dyspep- meal induction of symptoms is a consistent, reproducible sia is also significantly higher in women, smokers, those feature [1,5]. Psychological factors may influence the individuals infected with Helicobacter pylori and individu- symptoms experienced by some patients with functional als using nonsteroidal anti-inflammatory drugs [4]. dyspepsia [5] and may relate to heightened visceral hyper-

The diagnostic criteria for functional dyspepsia are sensitivity [3,5]. Few physiological disturbances have been based on expert consensus as defined by the Rome IV cri- shown to have any correlation with symptoms of functeria (updated from Rome III in 2016), with the defining tional dyspepsia, although the origin of these troublesome

symptoms is now considered to be a result of disrupted gastroduodenal neuropathophysiology, including gastric disaccommodation and duodenal eosinophilia linked to early satiety (2,5,6).

Although symptoms of burning, pressure, early satiety, nausea, belching and bloating often are reported by patients to occur following food consumption (5), very few clinical trials formally evaluate dietary interventions for the management of functional dyspepsia. These studies suggest that associations may exist between symptoms of functional dyspepsia and dietary variables such as total energy intake, total food volume, meal frequency, specific food components (i.e. nutrients or food chemicals) and also nonfood variables relating to anxiety about eating associated with previous episodes of symptoms (7,8). Specifically, dietary fats have been reported as being associated with post-prandial fullness and may be restricted in the diets of patients with functional dyspepsia (7). Wheat has been implicated in triggering symptoms of several functional gastrointestinal disorders, although whether wheat proteins or fermentable oligosaccharide, disaccharide, monosaccharide and polyols (FODMAPs) are responsible is not widely accepted (9–12). The observation of excess duodenal eosinophils in patients with functional dyspepsia, as well as in nonpatients from the community who suffer post-prandial distress, now observed globally, suggests that food antigens might play a role in the disease, perhaps through increasing duodenal permeability and stimulating immune activation (13,14). However, the nature and direction of food associations and specific 'active' components of implicated foods are generally unclear.

Current pharmacological treatment options for functional dyspepsia are suboptimal in symptom reduction (5), even though functional dyspepsia has a significant impact on quality of life, work performance and the interpersonal relationships of sufferers (15). Current dietary recommendations reported in the literature focus on eating low-fat meals, as well as more frequent, smaller meals (7,16). Dietary advice is usually provided by the gastroenterologist rather than a dietitian and is not currently substantiated by evidence from randomised controlled trials (16) or included in evidence-based practice guidelines. Such advice may not be comprehensive or sufficiently specific to result in significant improvements in symptoms, or be suitable for both post-prandial distress syndrome and epigastric pain syndrome subtypes of functional dyspepsia. Thus, there is currently no standardised approach to the dietary management of functional dyspepsia, in contrast to irritable bowel syndrome (17).

Further investigation into the reported food provocation of specific dyspeptic symptoms has been recommended (7). The aim of this systematic review is to identify and describe the influence of specific foods or food components (macronutrients, micronutrients, food chemicals, food allergens, fibre) on specific and/or overall symptoms of functional dyspepsia sufferers aged over 16 years.

Materials and methods

Search strategy

A search of the medical literature from January 1982 to February 2016 was conducted using six electronic databases: Cinahl, EMBASE, MEDLINE, Medline in Process, PsycINFO and the Cochrane central register of controlled trials. Studies examining the effect of nutrients, foods and food components in adults (over the age of 16 years) with functional dyspepsia were eligible for inclusion. Twelve search terms associated with functional dyspepsia were combined with 22 food-related terms identified as being relevant to functional dyspepsia from the existing literature (search strategy: see Supporting information, Table S1). Titles and abstracts of papers identified by the initial search were evaluated by two reviewers for alignment with the study question and inclusion/exclusion criteria. Full-text articles of all potentially relevant papers were obtained and the bibliographies of all identified relevant studies were hand-searched for additional relevant articles. Articles were assessed independently by two reviewers (KRD, TLB) in accordance with previously established eligibility criteria. Disagreement between investigators was resolved by consensus or a third reviewer (NJT).

Inclusion and exclusion criteria

Experimental, observational or epidemiological studies of people aged ≥16 years that assessed functional dyspepsia (or previous diagnostic equivalent) based on Rome I, II or III criteria or reported gastroduodenal symptoms (e.g. epigastric pain, early satiety, post-prandial fullness) and at least one dietary outcome measure, and reported on the associations between food or diet and at least one dyspeptic symptom were considered for inclusion in the review. Studies of children aged ≤16 years and a positive upper endoscopy (peptic ulcer, oesophagitis, coeliac disease or cancer) were excluded. Studies that did not involve the oral ingestion of food (e.g. infusions or dietary supplements) were excluded to ensure that

the conditions associated with symptom induction as a result of food ingestion were physiologically representative.

Assessment of methodological quality

Critical appraisal of study quality (including risk of bias) was performed independently using the ROBINS-I tool for assessing risk of bias in nonrandomised studies of interventions [18] or the RoB-2, a revised tool to assess risk of bias in randomised trials [19] (see Supporting information, Table S2). Two investigators (KRD, TLB) independently assessed the studies against the predetermined tool criteria, with disagreements resolved by consensus or by a third investigator (NJT).

Data extraction

Data were extracted independently by two reviewers into a table containing predetermined categories that had been developed by the first and second reviewers. The first reviewer (KRD) checked data extraction and disagreements about data or table contents was resolved by consensus. The following clinical data were extracted for each study: year of study, setting, country of origin, dyspepsia diagnosis information (criteria, symptoms measured, symptom severity measurement tool), nutrient, food or food consumption pattern intervention or measurement, duration of exposure (if an intervention) and food associations with dyspepsia or dyspeptic symptoms (Table 1).

Data analysis/synthesis

Data from all studies were assessed for equivalent measures for the purposes of pooling data for statistical metaanalysis. As a result of non-equivalence of measures and tools, statistical pooling was not possible, and so the findings are presented in narrative form, using tables and figures to represent the data.

The review protocol was registered on the PROSPERO register, with registration number CRD42016033296.

Results

A total of 6451 studies were identified through the search strategy (Fig. 1) with 35 full-text articles retrieved, of which 16 studies met the inclusion criteria and were included in the review (Table 1) [20–35]. The main reasons for exclusion on abstract were that studies included patients groups with overlapping co-morbidities, such as coeliac disease or irritable bowel syndrome (n = 122), were not specific to functional dyspepsia (n = 69) or did not specifically relate to oral food ingestion (n = 55) (Fig. 1).

Of the included studies, five studies were case–control studies [27–30,32], five were cohort studies [24,26,31,33,34], five were cross-sectional studies [20,21,23,25,35] and one was a randomised placebo-controlled trial [22]. The mean age of participants was 43 years (range 18–79 years). Body mass index (BMI) was reported in seven studies with a mean of 23 kg m^2.

Study quality

All 16 studies were rated moderate risk of bias based on the RoB-2 [19] or Robin-1 risk of bias tool criteria [18] (Table 1; S,T; see also see Supporting information, Table S2). Confounding bias and bias in measurement of outcomes resulted from variability between included studies in definitions of symptoms, study methods, study duration, dietary assessment methods and outcome measures (Table 1;S,T; see also see Supporting information, Table S2). Recognised Rome II criteria was used in two studies [31,35], as well as in another with a modified version used in an additional study [25], with Rome III specified in three studies [22,29,30]. In the remaining studies, diagnosis of dyspepsia or definition of dyspeptic symptoms predominantly reflected but did not specify Rome criteria [20,21,23,24,26–28,32–34]. Ten of the 11 studies specified the symptoms contributing to dyspepsia diagnosis and the number of symptoms required for diagnosis, and all studies reported that all included patients had completed an upper endoscopy showing no organic cause of symptoms.

Associations with dietary profiles

Two studies specifically investigated response to a glutenfree diet [22,31]. In one study [22], patients with a range of functional gastrointestinal conditions including functional dyspepsia reported a reduction in abdominal pain (5.9 2.8 versus 2.7 2.6; P = 0.001), bloating (6.8 2.7 versus 3.4 2.9; P = 0.001), post-prandial fullness (7.2 2.4 versus 3.9 2.5; P = 0.001), early satiety (5.7 3.3 versus 2.4 2.4; P = 0.001) and epigastric pain (6.1 2.9 versus 2.9 2.9; P = 0.001). The second study revealed that a gluten-free diet for 18 months resulted in symptom relief in 31/34 (91.9%) of patients previously shown to have no upper gastrointestinal endoscopic evidence of structural disease [31].

Compared with healthy controls, functional dyspepsia patientsreportedloweroverallenergyintakeinonestudy [28], a lower percentage energy from fat in two studies [21,28], a

higher fibre intake in one study [21] and a lower carbohydrate intake in one study [28]. Conversely, one study reported an inverse associations between symptoms and percentage carbohydrate intake [30] and one study reported functional dyspepsia patients had higher daily intakes from carbohydrates [21].

Associations with nutrients

Dietary fat was associated with onset of symptoms after a meal challenge or reported as inducing symptoms of dyspepsia in three studies [24,26,29], and specifically with

Table 1 Description and outcomes of included studies in a systematic review of food or food components and symptoms of functional dyspepsia

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Akhondi-Meybodi *et al.* (2015)	Type: Cross-sectional When: September 2008–March 2009 Where: Yazd, Iran Recruitment: Hospital GEy Dept Intervention: Nil, measured associations	Inclusion: Diagnosed FD; normal UES Exclusions: IBS; previous abdominal surgery; CAD; ulcer; erosive gastritis; cancer. Other measures: Demographics; symptom duration; endoscopy results	Subjects: 384 patients 60% female) Mean age: 39 ± 14 years (13–80 years) Location: 77% urban, 23% rural Education: 14% illiterate, 27% primary, 14% high school, 12% higher education BMI (kg m^{-2}): NR	Rome Criteria: NR Post-prandial fullness, bloating, epigastric pain, nausea or vomiting of moderate severity >3 months Upper GI endoscopy performed to rule out organic cause	Symptoms measured: FD symptoms (total); individual symptoms NR Symptom scale: Aggravate symptoms (low, medium, high, very high) Frequency of measures: Single	Dietary measurement tool: 114-item culturally specific (Iranian) FFQ questionnaire about 114 Iranian foods Validated: No Food groups: NR Nutrients: NR Food chemicals: NR Food allergens: NR Other food components: NR	Food associations with FD symptoms: (% of participants reporting): sausage/bologna (89%), pickles/vinegar (89%), soft drink (87%), grains (86%), tea (81%), salty foods (78%), pizza (77%), watermelon (75%), red pepper (72%), pasta (71%), fatty foods (57%) Severity of symptoms: NR	Moderate
Carvalho *et al.* (2010)	Type: Cross-sectional When: NR Where: Campinas, Brazil Recruitment: University Hospital GEy clinic Intervention: Nil, measured associations	Inclusion: FD symptoms, normal UES; normal AUS normal BGL Exclusion: Previous abdominal surgery; CAD; IBS clinical features. Other Measures: Meals per day; Overnight fast (h); Daytime fast (h); meal duration: time to retiring to bed after meal	Subjects: Total 71 including 41 patients (30 female) Mean age: 46 ± 12 years Control: 30 healthy volunteers Mean age: 35 ± 12 years ($P = 0.02$) SES: Low; Married (80.5% versus control 53.3%; $P = 0.02$). BMI (kg m^{-2}): Patients: 27 ± 5, Control 24 ± 4 ($P = 0.06$)	Rome criteria: NR Upper abdominal post-prandial fullness, early satiety and/or epigastric pain for at least 6 months in the preceding year; severe enough to disturb usual activities	Symptoms measured: Post-prandial fullness (78%), early satiety (76%), bloating (76%), epigastric burning (46%), epigastric pain (17%), heart-burn (34%) Symptom scale: Present or absent after meals Frequency of measures: Single	Dietary measurement tool: 60 item culturally specific (Brazilian) FFQ including eating habits plus 7-day food diary Validated: No Food groups: NR Nutrients: Total dietary fat, CHO, protein, fibre Food chemicals: NR Food allergens: NR Other food components: NR	Nutrient associations with FD: Lower % energy as fat (median 28% versus 34%; $P = 0.001$); higher % energy as CHO (median: 56% versus 50%; $P = 0.001$). FD patients consumed relatively higher fibre (median 5.5 versus 4 g day^{-1}; $P = 0.01$). No association total energy 1516 ± 425 versus 1545 ± 365 kCal ($P = 0.73$) Food associations with FD: (% of participants reporting): carbonated drinks (63%), fried foods (59%), bell pepper (56%) sausage (54%), coffee (54%), red meat (51%), banana (51%), pasta (49%) milk (44%), cucumber (44%) Food associations with epigastric burning: (>30% of participants): (Coffee, cheese, onions, pepper, milk, chocolate, pineapple) Food associations with bloating: (>30% of participants): Carbonated drinks, onions, beans, bananas Food associations with heartburn: (>30% of participants): Coffee, pepper	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Elli *et al.* (2016)	Type: RCT When: September 2014 to November 2014 Where: 15 GEy O/P Depts, Italy Intervention: GFD, cross-over gluten or placebo challenge	Inclusion: NCGS >18 years, negative IgA/IgE mediated WA; negative biopsy if high CD risk, VAS <4 for wellbeing Exclusion: CD, WA, IBD psychiatric disorders, major abdominal surgery, diabetes, systemic autoimmune diseases, anaphylactic episodes, systemic disorders, GFD previous 6 months, pregnant or breast-feeding women, on pharmacological therapy Other measures: SF36, gluten challenge, VAS health, VAS wellbeing	Subjects: 134 adults (77 IBS, 12 FD-PPD, 10 FD-EGP, 41 other FGID symptoms) following a gluten-containing diet Mean age: 39 ± 12 years Demographics: NR BMI (kg m^{-2}): 22 ± 4	Rome III criteria specified	Symptoms measured: Global wellbeing, Health satisfaction, Symptom severity (abdominal pain, bloating, post-prandial fullness, early satiety, epigastric pain and other symptoms) Symptom scale: 100 mm visual analogue Frequency of measures: Baseline, post 3-week GF diet, post gluten and placebo challenges	Dietary measurement tool: Self-report adherence GFD Validated: No Food groups: No Nutrients: No Food chemicals: No Food allergens: Gluten Other food components: NR	Food associations with FD: (>3 cm increase global wellbeing/10 cm VAS) 86% (18/21) responsive to GFD ($P = 0.80$) Food associations with FGID: (VAS symptom score/10) Abdominal pain: 5.9 ± 2.8 versus 2.7 ± 2.6 ($P = 0.001$) Bloating: 6.8 ± 2.7 3.4 ± 2.9 0.001 Post-prandial fullness: 7.2 ± 2.4 3.9 ± 2.5 ($P = 0.001$) Early Satiety: 5.7 ± 3.3 versus 2.4 ± 2.4 ($P = 0.001$) Epigastric pain: 6.1 ± 2.9 2.9 ± 2.9 ($P = 0.001$)	Moderate
Elta *et al.* (1990)	Type: Cross-sectional When: NR Where: Michigan, USA Recruitment: Hospital GEy Dept post UES; Control group: Random telephone interviews Intervention: Nil, measured associations	Inclusion: NUD; normal UES Exclusion: IBS, GERD Other measures: Ulcer (>3 mm); Aspirin; NSAIDs; tobacco; alcohol; tea; caffeinated soda drinks	Subjects: Total 110 55 NUD patients (32 female) Mean age: 40 years Control: 55 (28 female) Mean age: 41 years Demographics: NR BMI (kg m^{-2}): NR	Rome criteria: NS Epigastric pain of >4 weeks duration with no evidence of ulcer or other gastroduodenal disease	Symptoms measured: Abdominal pain, FD (total) Symptom scale: Present or absent Frequency of measures: Single	Dietary measurement tool: Coffee intake; [regular versus decaffeinated, cups per day (1–2, 3–5, 5+)], preparation, length of use, change in intake past 12 months. Tea, caffeinated carbonated beverages Validated: No Food groups: NR Nutrients: NR Food chemicals: NR Food allergens: NR Other food components: Caffeine	Food associations with FD symptoms: Coffee consumption induced dyspeptic symptoms in 53% of dyspepsia patients compared to 22% of controls, $P = 0.0036$	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Feinle *et al.* (2003)	Type: Cohort When: NR Where: Zurich, Switzerland Recruitment: University Hospital GEy Dept Intervention: Response to three yoghurt 'meals' with different nutrient composition	Inclusion: FD diagnosis Normal UES; Normal AUS Exclusion: GI surgery; medications unable to be discontinued; *Helicobater pylori*; lactose intolerance. Other measures: CCK; gastric volume; smoking; medications; reported fat content (correct or wrong)	Subjects: 15 (9 female) Age: 24–56 years Demographics: NR BMI (kg m^{-2}): 23 ± 1	Rome criteria: NS At least 3 of following symptoms for more than 6 months of at least a moderate severity: post-prandial fullness/early satiety, bloating, epigastric pain, and nausea/vomiting	Symptoms measured: Post-prandial fullness, early satiety, bloating, Epigastric pain, nausea/vomiting. Symptom scale: Severity 0–3 VAS (0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe symptoms) Frequency of measures: Single	Dietary protocol: Two × 300 g yoghurt test meals [LF yoghurt (LF) (143 kcal, 8.1% fat, 63.6% CHO, 28.3% protein. HF yoghurt (330 kcal, 66.6% fat, 23.5% CHO, 9.9% protein]. Validated: No Food groups: NR Nutrients: Total calories, fat, CHO, protein Food chemicals: NR Food allergens: NR Other food components: Reported fat content (correct or wrong)	Nutrient associations with bloating: Bloating VAS scores higher for high-fat yoghurt than low-fat yoghurt ($P = 0.042$) and when yoghurt was reported as high in fat ($P = 0.056$) Nutrient associations with nausea: Nausea VAS scores higher for high-fat yoghurt than low-fat yoghurt ($P = 0.012$) and not influenced by reported fat content Information did not affect nausea ratings within the type of yoghurt (HF-C versus HF-Wrong ($P = 0.716$); LF-C versus LF-Wrong ($P = 0.176$) Food associations with pain and discomfort: increased but no differences between study groups (HF, LF, and LF-C) Food associations with post-prandial fullness: PPF increased post HF and LF yoghurts ($P = 0.0001$); FC and perceived FC increased PPF ($P = 0.067$); PPF increased HF-C versus LF-C; $P = 0.041$; PPF increased LF-C versus LF-W; $P = 0.013$	Moderate
Filipovic *et al.* (2011)	Type: Cross-sectional When: April to October 2009 Where: Belgrade, Serbia Recruitment: Newly diagnosed FD GEy Dept. Bezanijska Kosa Hospital Intervention	Inclusion: FD diagnosis, Older than 18 years, no previous GE medications, no evidence of IBS, normal UES and AUS, Exclusion: Previous abdominal surgery, CAD or metabolic disease Other measures: unintended weight loss past 6 months, biochemical markers	Subjects: 180 newly diagnosed FD (100 females) Age: 50 ± 15 (20–79 y) Demographics: NR BMI (kg m^{-2}): 25 ± 5	Rome II criteria specified, predominant symptoms of: 1. ULD: pain centered in the upper abdomen; 2. DLD: discomfort in epigastric region ± upper abdominal fullness, early satiety, bloating, belching or nausea; 3. Nonspecific dyspepsia – dyspeptic symptom not fulfilling criteria for ULD or DLD	Symptoms measured: epigastric pain, epigastric burning, heartburn, post-prandial fullness, bloating, early satiety Symptom scale: Present or absent Frequency of measures: Single	Dietary measurement tool: 7-day alimentary diary of food eaten, drinks consumed and dyspeptic symptoms Validated: No Food groups: No Nutrients: No Food chemicals: No Food allergens: No Other food components: NR	Food associations with ULD: (symptoms >30% patients): wheat-containing foods (88%), citrus fruits (73%), carbonated drinks (65%), mayonnaise (55%), fried foods (43%), coffee (52%), pepper (55%); Food associations with DLD: (symptoms >30% patients): wheat (93%), milk and milk products (83%), horseradish (72%), bacon (55%), banana (53%), onions (47%), sweets (47%), pasta (43%), carbonated drinks (42%) Food associations nonspecific dyspepsia: (symptoms >30% patients): wheat (53%), cucumber (42%), milk products (33%)	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Halder *et al.* (2006)	Type: Cross-sectional When: NR Where: Minnesota, USA Recruitment: Primary care medical records Intervention: Nil, associations measured	Inclusion: Age and sex stratified random community sample Exclusion: Did not meet Rome II Other measures: IBS; alcohol; SSC; Education	Subjects: Total 4390 (88 FD) Age range: 20–64 years Demographics: NR for DP BMI (kg m^{-2}): NR	Modified Rome II criteria Two or more of the following criteria had to be fulfilled: frequent upper pain (>6 times year), nausea (at least weekly), vomiting (at least weekly), early satiety, and loss of appetite	Symptoms measured: FD diagnosis only; symptoms NR Symptom scale: NR Frequency of measures: Single	Dietary measure: EtOH frequency [Nil, 1–6 drinks per week, >6 drinks per week] Volume, concentration or type NR Validated: No Food groups: NR Nutrients: Alcohol Food chemicals: NR Food allergens: NR Other food components: Reported fat content (correct or wrong)	Food associations with FD symptoms: Increased alcohol consumption associated with higher odds for dyspepsia (OR 2.3; 95% CI: 1.1–5.0) independent of SSC	Moderate
Houghton *et al.* (1993)	Type: Cohort When: NR Where: Sheffield, United Kingdom Recruitment: Hospital Gey Dept, gastroscopy list and community volunteers (control) Intervention: Response to 3 soup meals with different nutrient composition	Inclusion: NUD diagnosis; normal UES Exclusion: Organic disease, ongoing medication requirements Other measures: Gastric emptying	Subjects: Total 48 including 31 NUD patients (22 female) Age range: 17–64 years Controls: 17 (8 female) Age range: 20–58 years Demographics: NR BMI (kg m^{-2}): NR	Rome criteria: NS Non-ulcer dyspeptic symptoms 3 days per week for 6 months	Symptoms measured: Epigastric pain, bloating, early satiety, nausea Symptom scale: (0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe symptoms). Average score calculated. Frequency of measures: Six (2, 10, 20, 30, 45, 60 minutes post ingestion)	Dietary protocol: 300 mL beef consommé (3 g fat, 1.2 g CHO, 4.2 g protein) or high-fat version 30 g margarine added) Validated: No Food groups: NR Nutrients: Fat, CHO, protein Food chemicals: NR Food allergens: NR Other food components: Report	Food associations with FD symptoms: Fatty soup versus bland soup: Women versus men ($P < 0.001$), Fatty soup versus women bland soup ($P < 0.025$) Food associations with epigastric pain: Bland soup (w) versus (m) $P < 0.02$; fatty soup (w) versus (m) $P < 0.02$; fatty soup (w) versus bland soup (w) $P < 0.02$ Food associations with bloating and early satiety: Fatty soup (w) versus bland soup (w) ($P < 0.02$). Food associations with nausea: Fatty soup (w) versus bland soup (w) $P < 0.02$; Fatty soup (w) versus fatty soup (m) $P < 0.02$	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Kaess *et al.* (1988)	Type: Case–control When: NR Where: Germany Recruitment: GEy Dept outpatients, community volunteer (controls) Intervention	Inclusion: NUD diagnosis, normal UES (NUD group) abnormal UES (DU group) Exclusion: Symptoms of hepatobiliary/ pancreatic/intestinal disease; foreign nationality; symptoms requiring hospitalisation Other measures: SES; employment; duodenal ulcer	Subjects: Total 150 including 50 NUD patients (36 female) Mean age: 40 years (18 –80 years) 50 DU patients (31 men) Mean age: 47 years (18–79 years) Controls: 50 (32 female) Mean age: 41 years (18–55 years) Demographics: NR BMI: NR	Rome criteria: NS NUD group: Current or recent epigastric pain or dyspeptic symptoms (HB, EGP, EGB, PPD) with no visible lesion gastroscopy DU group: Current or recent epigastric pain or dyspeptic symptoms (HB, EGP, EGB, PPD) with proven DU	Symptoms measured: Food intolerance Symptom scale: Provocation of symptoms or 'disgust' for each item for DU and NUD patients Frequency of measures: Single	Dietary measurement tool: 39-item 'nutrient' questionnaire Validated: No Food groups: NR Nutrients: Food chemicals: NR Food allergens: NR Other food components: NR	Food associations with dyspepsia: (>30% reporting intolerance, $P < 0.01$ compared to control) coffee (72%), nuts (70%): wine (68%); beer (62%); fish (66%); chocolate (62%); fumed foods (50%); soft drinks (46%); fruit juice (42%); cream (42%); baked foods (38%); tea (38%); cheese (36%); cake (36%) spices (34%); fruit (30%); milk (30%) Wheat products (46%, $P < 0.05$) Food associations with pain: Coffee (54%, $P < 0.01$); fruit juice (28%, $P < 0.05$); beer (16%, $P < 0.05$); wheat products (14%, $P < 0.05$)	Moderate
Mullan *et al.* (1994)	Type: Case–control When: October 1991 to February 1992 Where: Dublin, Ireland Recruitment: GEy Dept outpatients; Hospital outpatient and short stay Orthopaedic (controls) Intervention: 7-day food and symptom diary	Inclusion: Dyspeptic symptom score (>4); endoscopic outcome (2 groups – organic or functional) Exclusion: Other GI disease; alcohol abuse, limited communication Other measures: Age; gender; occupation; smoking	Subjects: Total 160; 40 FD patients (26 female) Mean age: 38 ± 13 years (female), 33 ± 10 (male), BMI (kg m^{-2}): 25 ± 4 (female), 27 ± 5 (male) Control: 40 controls (26 female) Mean age: 39 ± 15 (female), 34 ± 13 (male) BMI (kg m^{-2}): 24 ± 5 (female), 24 ± 5 (male) 40 OD patients (21 female) Mean age: 47 ± 20 (female), 48 ± 15 (male), BMI (kg m^{-2}): 25 ± 5 (female) 26 ± 2 (male) Control: 40 controls (26 female), Mean age: 48 ± 15 years (male), 47 ± 20 years (female) BMI (kg m^{-2}): 24 ± 5 (male), 23 ± 5 (female)	Rome criteria: NS Assessed abdominal pain, nausea/vomiting, early satiety/bloating, belching, heartburn on frequency/severity scale of 0 (less than monthly) – 3 (impacts on occupation). Entry to study: Total score >4	Symptoms measured: For inclusion into study only Symptom scale: For inclusion 0 (less than monthly) – 3 (impacts on occupation). Entry to study: Total score >4 Frequency of measures: Single	Dietary measurement tool: 7-day diary as per Irish National Nutrition Survey plus list of known exacerbating foods. Validated: Yes Food groups: Yes Nutrients: Yes Food chemicals: NR Food allergens: NR Other food components: NR	Nutrient associations with FD: FD patients (women) consumed lower energy MJ per day versus control (6.9 ± 2.0 versus 9.2 ± 2.4 MJ day^{-1}, $P < 0.001$); lower total CHO gram per day (195 ± 59 versus 89 ± 30, $P < 0.05$); lower total fat gram per day (67 ± 27 versus 9270 ± 106, $P < 0.05$); higher % protein (16.7 ± 3.4 versus 14.0 ± 3.0, $P < 0.05$) Food associations with FD: Male: Higher milk intake (g 10 MJ^{-1} day^{-1}) for dyspepsia patients than controls (437 ± 334 versus 287 ± 214, $P < 0.05$) Female: Dyspeptic patients reported higher milk intake (653 ± 462 versus 387 ± 221 g 10 MJ^{-1} day^{-1}, $P < 0.05$) and lower fresh fruit intake (g 10 MJ^{-1} day^{-1}) (42 ± 55 versus 134 ± 112 g 10 MJ^{-1} day^{-1}, $P < 0.05$) than controls	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Pilichiewicz *et al.* (2008)	Type: Case–control When: NR Where: Adelaide, AUS Recruitment: GEy Dept endoscopy list and community, volunteer pool (control) Intervention: Response to three yoghurt meals with differing nutrient composition	Inclusion: FD diagnosis, VAS total score was >3, or one symptom scored >2; normal AUS and/or UES (previous 12 months), Exclusion: Organic cause of dyspepsia, HB, IBS); *Helicobacter pylori*; positive breath or clinical tests; GI motility or appetite medication; smoker; consumed >20 g EtOH d^{-1} Other measures: Eating Restraint	Subjects: Total 16 (8 female FD patients) Age range: 23–56 years BMI: 20.0–26.7 kg m^{-2} Controls: 8 healthy females Age range: 20–50 years BMI (kg m^{-2}): 20–24	Rome III criteria: Post-prandial fullness, bloating, epigastric pain, nausea, or vomiting for >3 months of, at least a moderate severity	Symptoms measured: Nausea, bloating, abdominal discomfort and pain, fullness, hunger. Symptom scale: Visual analogue scale (0 = symptom not experienced to 3 = severe symptom) Frequency of measures: Nine [baseline, 0–60 min post meal (10 min intervals), post buffet (90 min post test meal)]	Dietary protocol: High-CHO or high-fat (500 kcal/400 g) yoghurt meals, or a low-nutrient control (180 kcal/400 g) test meals plus 7-d food diary [(g) food and energy (kJ) consumed] Validated: No Food groups: NR Nutrients: energy (kcal), weight of food (g), CHO (g), fat (g) Food chemicals: NR Food allergens: NR Other food components: NR	Food associations with nausea: High-fat (FD) versus high-fat (HS) ($P < 0.01$), High-fat (FD) versus high-CHO (FD) ($P < 0.05$), high-fat (FD) versus control meal (FD) ($P < 0.05$). Food associations with pain: High-fat meal(FD) versus high-fat (HS) ($P = 0.05$), High-fat (FD) versus high-CHO (FD) ($P < 0.05$), high-fat (FD) versus control meal (FD) ($P < 0.05$). Food associations with discomfort: High-fat (FD) versus High-fat (HS) ($P < 0.05$), High CHO (FD) versus High CHO (HS) ($P < 0.05$), control meal (FD) versus control meal (HS) ($P < 0.05$). CCK association with FD: Fasting CCK and CCK stimulation by high-FAT ($P < 0.01$) meal greater in FD ($P < 0.01$); fasting and post-prandial PYY lower ($P < 0.001$) FD versus HS; no differences fasting, or post-prandial, plasma ghrelin between FD and HS; no differences in energy intake between FD and HS	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Pilichiewicz *et al.* (2009)	Type: Case–control When: NR Where: Adelaide, AUS Recruitment: Hospital GE Dept endoscopy and O/P lists; newspaper advertisements. Control: NR Intervention: Nil, associations measured	Inclusion: FD diagnosis, normal AUS and/or UES (previous 12 months) Exclusion: Organic cause of dyspepsia, HB, IBS); *Helicobacter pylori*; positive breath or clinical tests; GI motility or appetite medication; smoker; >20 g EtOH per day Other measures: 3-FEQ; Eating Attitudes Test; Clinical Fat Intake Scale; Dyspepsia Index; HADS	Subjects: Total 41 20 FD patients (17 female, 3 male) Mean age: 45 ± 3 years (23–73 years) BMI(kg m^{-2}): 24 ± 0.9 (19–36) Controls: 21 healthy subjects (18 female, 3 male) Mean age: 40 ± 4 years (20–74 years) BMI (kg m^{-2}): 23 ± 0.5 (19–27)	Rome III criteria: Post-prandial fullness, bloating, epigastric pain, nausea, or vomiting for more than 3 months of at least a moderate severity	Symptoms measured: Abdominal pain, cramps, bloating, nausea, uncomfortable fullness after meals Symptom scale: Visual analogue from 1 to 10 [mild (1–3), modest (4–7), strong (8–10)] Frequency of measures: After each eating episode for 7 d	Dietary measurement tool: 7-day weighed/measured food and symptom diary. Validated: No Food groups: NR Nutrients: Energy (kcal), fat, protein, alcohol (g, %) Food chemicals: NR Food allergens: NR Other food components: NR	Nutrient relationship with FD: Overall FD symptoms and energy intake (z, 2.02; $P < 0.05$), inverse %CHO (z, 2.08, $P < 0.05$). No relation overall symptoms with fat, protein, alcohol or food weight consumed. Nutrient relationship with FD symptoms: Post-prandial fullness related to fat (total and %: z, 1.91; $P < 0$ .05), protein (total: z, 2.64, $P < 0.001$; %: z, 1.82, $P = 0.06$), energy intake (z, 2.12, $P < 0.05$), inversely to carbohydrate (%: z, 1.9; $P < 0.05$). Bloating related to fat ingestion (z, 1.68; $P = 0.09$)	Moderate
Santolaria *et al.* (2012)	Type: Retrospective cohort When: January to December 2007 Where: Huesca, Spain Recruitment: Hospital GEy Dept Intervention	Inclusion: DLD diagnosis; normal UES; no structural disease Exclusion: Diagnosis of coeliac disease; gastrectomy and/or severe systemic diseases Other measures: Family history GSE; GSE associated conditions, histopathology, *Helicobacter pylori*; serology; HLA	Subjects: Total 142 14 FD patients (74% female) Mean age: 46 ± 15 years BMI (kg m^{-2}): NR	Rome II criteria: Dysmotility-like dyspepsia including symptoms such as upper abdominal fullness, bloating, nausea, epigastric burning, belching, and vomiting	Symptoms measured: FD in association with gluten sensitive enteropathy Symptom severity: measured for GSE but not FD Frequency of measures: Single (FD)	Dietary measurement tool: Gluten-free diet prescribed for sub-group: assessment method and compliance rate NR Validated: No Food groups: NR Nutrients: NR Food chemicals: NR Food allergens: Gluten Other food components: NR	Gluten free diet association with FD symptoms: 34/37 (91.9%) patients who started a gluten-free diet improved their dyspeptic symptoms (78.6% Marsh type 1, 100% Marsh type 2, 100% Marsh type 3a, 100% Marsh type 3b)	Moderate

Table 1 Continued

Author (year)	Study type, date and location	Study characteristics	Subject characteristics	FD diagnostic criteria	Symptom measurement	Dietary protocol or measurement tool	Associations between food/components and FD diagnosis or symptoms	Risk of bias
Talley *et al.* (1988)	Type: Case–control When: NR Where: Sydney AUS Recruitment: GEy Dept outpatient list; electrol roll (control) Intervention: Retrospective survey of symptoms 6 months prior to diagnosis and 6 months before diagnosis (if diagnosis <5 years)	Inclusion: Essential dyspepsia; no peptic ulcer, oesophagitis, or cancer. Exclusion: Dyspepsia for <1 month; IBS; peptic ulcer; prior gastric surgery; pancreatitis; gallbladder disease; serious physical or mental disease; >85 or <16 years; inability to speak English; rural or remote Other measures: Analgesics, Non-aspirin NSAIDs, Cigarettes, demographic information	Subjects: Total 226 (113 ED patients, 113 age-matched controls) 66% female Median age: 48 years BMI (kg m^{-2}): NR	Rome criteria: NS Chronic dyspepsia: >1 month pain, discomfort or nausea referable to the upper alimentary tract, intermittent or continuous, not precipitated by exertion and not relieved within 5 min by rest, excluding patients with jaundice or dysphagia	Symptoms measured: Dyspepsia symptoms measured for classification pre study Symptom severity: >5 years duration or <5 years duration Frequency of measures: Single (ED)	Dietary measurement tool: Alcohol: g day^{-1}, $week^{-1}$ or $month^{-1}$, and type Coffee and/or tea: number of cups per day. Validated: No Food groups: NR Nutrients: Alcohol, others NR Food chemicals: caffeine Food allergens: Gluten Other food components: NR	Coffee and alcohol associations with dyspepsia: No associations reported	Moderate
Talley *et al.* (1994)	Type: Cohort When: 1990 Where: Minnesota, USA Recruitment: Random sample of primary care medical records Intervention: Nil, associations measured	Inclusion: Dyspepsia-like symptoms Exclusion: Non-Caucasian (n = 32); peptic ulcer; major psychotic episode (n = 39), those who had undergone major abdominal surgery (n = 20); current major organic medical disease or were in very poor health (n = 49). Other measures: Non-FD symptom(s) (heartburn, diarrhoea, constipation, lower abdominal pain) within 2 h of eating; or meal-unrelated; Smoking; alcohol; aspirin; paracetamol use; other psychosocial measures; SES (education level); marital status; employment	Subjects: 310 (58% female) Age range: 20–64 years BMI (kg m^{-2}): NR	Rome criteria: NS Dyspepsia: Upper abdominal pain more than 6 times in the previous year, or nausea once a month or more, or both (Categorised as ulcer-like, dysmotility-like, reflux-like dyspepsia or unspecified)	Symptoms measured: Meal-associated symptoms within 2 h of eating (bloating, nausea, upper abdominal pain, belching, epigastric pain, fullness, vomiting, discomfort); plus non-FD symptoms within 2 h and at other times Symptom scale: Diary entry ratings of 1–10: mild (1–3); modest (4–7); or strong (8–10). Included time symptoms occurred Frequency of measures: Single	Dietary measurement tool: Alcohol (<3 drinks per week, 3 or more drinks per week) Validated: No Food groups: NR Nutrients: Alcohol (drinks) Food chemicals: NR Food allergens: NR Other food components: NR	Alcohol and FD type: No associations with ulcer-like, dysmotility-like, reflux-like dyspepsia or unspecified dyspepsia found	Moderate

Table1 Continued

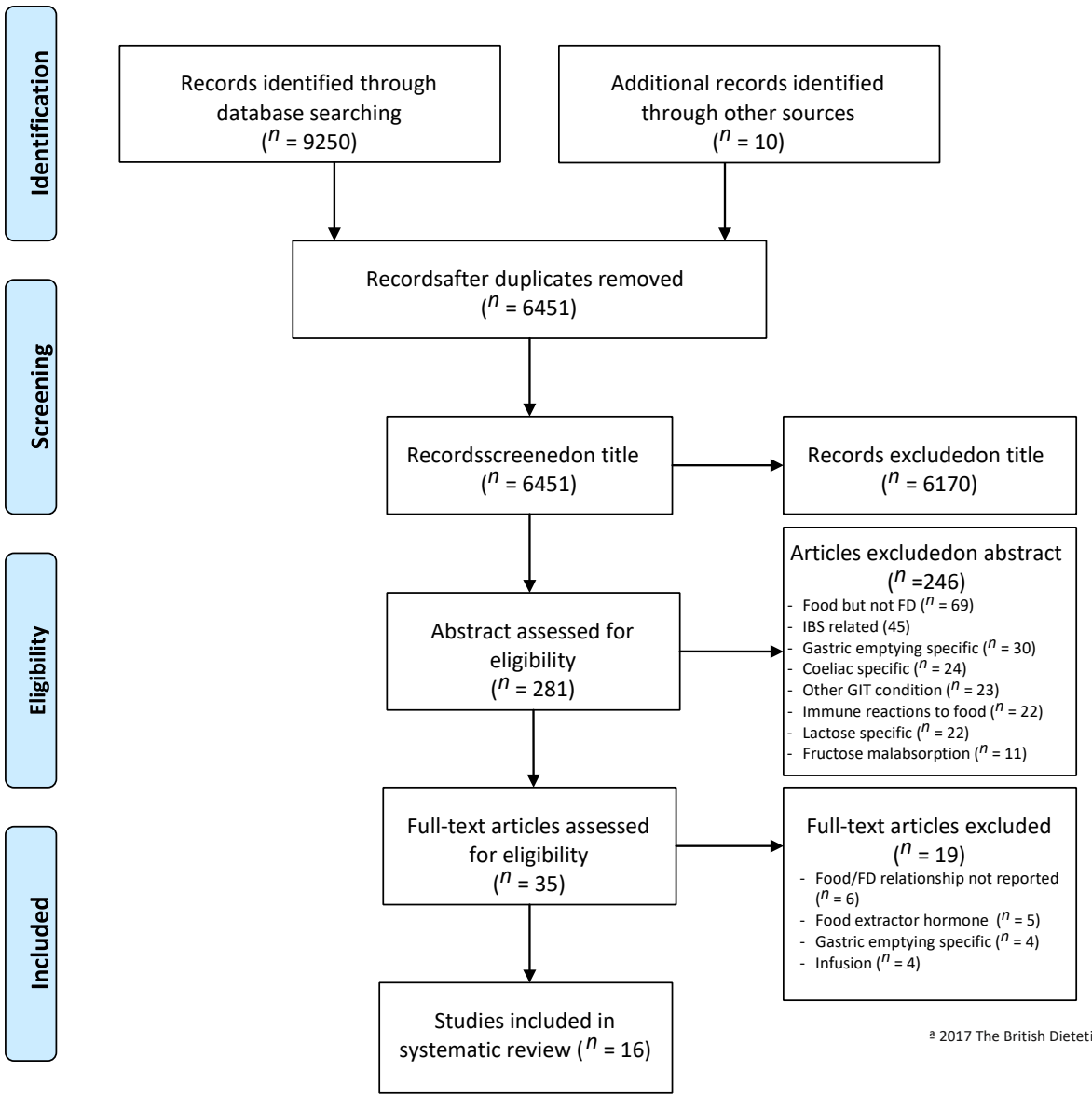
Author(year)	Studytype,dateand locationStudycharacteristicsSubjectcharacteristicsFDdiagnosticcriteriaSymptommeasurement					Dietaryprotocolor measurementtool	Associationsbetweenfood/ componentsandFDdiagnosisor symptomsRiskofbias	
WilderSmith etal. (2013)	Type:CohortWhen: January2008to May 2011 Where:Switzerland Recruitment:GEy communitybased practiceIntervention:6 weeklowfructose orlowlactosediet	Inclusion:Patients referredforevaluation ofFGIDExclusion: Evidenceoforganic diseaseOther measures:Lactose intolerance;fructose intolerance;allergies; childhoodandfamily history;centralnervous/ musculo-skeletal/cardiac symptoms;polyol-containingsweets/ chewinggum, tiredness,low concentration, headache,myalgia, arthralgia,palpitations, oralaphthoidulcers andskinrash.Meal relatedskinrashes, urticaria,rhinitis, headache,imperative defaecatoryurge, changesinstool consistency	Subjects:TotalFGID patients (FD = 606, PPD = 368, EGP = 238)73 %female Meanage: 40 (8-73 years) Symptomduration: 5.2 years BMI (kgm^{-2}):23 (13-31) 5 (1-20)	RomeIIIcriteriadivided intoFGIDsubgroups: FunctionalDyspepsia: Post-prandialfullness, bloating,epigastric pain,nausea,or vomitingfor > 3 months of,atleastamoderate severity(increases > 10 ppmofhydrogen and/or > 10 ppmof methaneabove baseline)	Symptomsmeasured:FD symptoms(bloating, flatulence,fullness, nausea,diarrhoea, abdominalcramps)plus borborygmi,GERD Symptomscale: Increaseof > 1 over baselineforatotalof 7 symptomscores, measuredforeachof6 symptoms(0 = none, 1 = mild,2 = intense) Frequencyofmeasures: baselineandhourlyfor 5 h	Dietarymeasurement tool:Briefdiet questionnairefor fructose, fructooligosaccharide, galactosaccharide, lactoseandsorbitol-containingfoodsplus openquestion avoidedandpoorly toleratedfoods) Validated:NoFood groups:NRNutrients: NRFoodchemicals: NRFoodallergens:10 commonEuropean Otherfood components: FODMAPs	FoodassociationswithFGID: %patientswithadequate symptomrelief)Fructose intolerance(84%),fructose malabsorption(86%),lactose intolerance(89%),lactosemal-absorption(90%)Adequate reliefratesinpatientswith bloatingofanylactose intolerance and/or malabsorption(96%)Average (96%) symptomreliefwasbetween6 and7onthe10-pointscalefor alltheabovesubgroups, exceptinconstipatedpatients wheretheaveragewas3	Moderate

FEQ,3FactorEatingQuestionnaire;AUS,abdominalultrasound;BGL,bloodglucoselevel;Blo,bloating;BMI,bodymassindex;C,correct;CAD,coronaryarterydisease;CCK,cholecystokinin;
CD,coeliacdisease;CHO,carbohydrate;CUD,chronicunidentifieddyspepsia;DLD,dysmotility-likedyspepsia;DU,duodenalulcer;ED,essentialdyspepsia;EGB,epigastricburning;EGP,epigastric
pain;ES,earlysatiety;EtOH,alcohol;FC,fatcontent;FD,functionaldyspepsia;FFQ,foodfrequencyquestionnaire;FGID,functionalgastrointestinaldisorder;FODMAP,fermentableoligosaccha-
ride,disaccharide,monosaccharideandpolyol;g,grams;GE,gastroenterologist;GERD,gastro-oesophagealrefluxdisease;GEy,gastroenterology;GFD,gluten-freediet;GI,gastrointestinal;GSE,
glutensensitiveenteropathy;HADS,HospitalAnxietyandDepressionscale;HB,heartburn;HF,high-fat;IBD,inflammatoryboweldisease;IBS,irritablebowelsyndrome;IBS-C,irritablebowelsyn-
drome-constipation;IBS-D,irritablebowelsyndrome-diarrhoea;LF,low-fat;M,men;Nau,nausea;NCGS,noncoeliacglutensensitivity;NR,notreported;NSAID,nonsteroidalanti-inflammatories;
NUD,non-ulcerdyspepsia;O/P,outpatient;OD,organicdyspepsia;OR,oddsratio;PPD,post-prandialdistress;PPF,post-prandialfullness;RCT,randomisedcontrolledtrial;SES,socio-economic
status;SSC,somaticsymptomscore;UES,upperendoscopy;ULD,ulcer-likedyspepsia;VAS,visualanaloguescale;Vom,vomiting;vs,versus;W,women;WA,wheatallergy.
RiskofbiasassessedusingROBINS-I:atoolforassessingriskofbiasinnonrandomisedstudiesofinterventions.
RoB2.0tool(individuallyrandomised,cross-overtrials).

dyspeptic symptoms of nausea (n = 3 studies) [24,26,29], bloating (n = 2 studies) [24,26], post-prandial fullness/discomfort (n = 2 studies) [24,29] and epigastric pain (n = 2 studies) [26,29]. Perception of fat content was reported as influencing symptoms in one study [24] and dietary fats were reported as stimulating an accentuated cholecystokinin response ($P < 0.01$) and diminished peptide-YY response ($P < 0.001$) in one study [29].

Associations with foods

Alcohol intake was found not to induce dyspepsia in two studies [32,33], whereas a Mayo Clinic study [25] reported that increased alcohol consumption was associated with increased odds for dyspepsia. More than 60% of dyspeptic patients in another study [27] reported symptom induction following wine (68%) and beer (62%) consumption. Coffee intake was associated with symptom induction in more than 50% of functional dyspepsia patients in four studies [21,23,27,35], although no association was found in one study [32] that specifically analysed coffee consumption and symptoms. Other problematic foods reported by participants to be an issue in more than one study were in descending order: grain/pasta/ wheat products (n = 6 studies) [20–22,27,31,35], soft drink/ carbonated drinks (n = 4) studies [20,21,27,35], tea (n = 2 studies) [20,27], fruit/fruit juice/watermelon (n = 3 studies) [20,27,35], milk (n = 3 studies) [21,27,35], red/bell pepper



e 1 Flow chart for retrieval and selection of articles for food and functional dyspepsia (FD) systematic review.

(n = 3 studies) [20,21,35] and takeout/processed foods (e.g. pizza/fried food) (n = 3 studies) [20,21,35].

A single study that differentiated associations between particular foods and symptoms by type of functional dyspepsia [35]. Bloating was frequent after milk consumption in the dysmotility-like group, whereas post-prandial fullness was the predominant complaint of patients after ingestion of wheat-containing foods. Foods reported to induce epigastric burning were coffee, pepper, chocolate and onions. Milk, beans, onions, banana and carbonated drinks provoked bloating [35].

Discussion

The present study aimed to determine the link between particular foods or food components and functional dyspepsia in adults. Despite the recognition of a likely dietary role in functional dyspepsia, only 16 studies met the criteria for inclusion in this review. Wheat and gluten ingestion were related to both post-prandial distress and epigastric pain symptoms of functional dyspepsia, and dietary fats had a consistent influence on post-prandial distress symptoms. Although other associations between foods or food components were not directly related to their nutrient composition, most of the foods reported as triggering symptoms either contain naturally occurring food chemicals, FODMAPs or other known triggers of food intolerances. However, because of the lack of quality dietary assessment, with few studies using recognised tools, there are limitations in the conclusions that can be drawn from these studies.

The majority of studies were carried out in western countries and data from elsewhere where diets vary are needed. Despite the study countries generally having overweight and obesity rates in excess of 50% of the adult population, most individuals in the included studies tended to be in the healthy weight range as defined by BMI. This may be the result of the reported food (and therefore energy) restriction, particularly restriction of energy dense dietary fats by patients with functional dyspepsia and early satiety or fullness or pain after eating [21,28–30]. This result is consistent with the reported link between early satiety and lower BMI [36] and the observation in a random community sample in Australia that all dyspepsia symptoms were positively associated with weight loss, with meal-related complaints such as postprandial fullness having the strongest associations [37]. It remains unclear whether functional dyspepsia results in weight loss or if functional dyspepsia occurs more often in leaner individuals compared to those who are overweight.

The prediction that dietary fats would be associated with functional dyspepsia symptoms was supported by the review findings, with dietary fat restriction and symptom induction being consistently reported in dyspeptic patient groups. The restriction of dietary fats reported by dyspeptic patients in two studies [21,28] is consistent with the reported induction of symptoms after dietary fat ingestion in four separate studies [24,26,29,35]. Dietary fat restriction as a result of symptom induction could not be established because they were reported in separate studies. The findings of this review therefore consolidate the established reported relationship between dietary fats and functional dyspepsia. Proposed mechanisms by which fats could induce dyspeptic symptoms (Fig. 2) include hypersensitivity to gastrointestinal hormones such as cholecystokinin [38,39] or slowing of gastric emptying [7], although the link between functional dyspepsia and delayed gastric emptying is tenuous [40]. Alternatively, the normal vagovagal reflex response to fat release in the upper small intestine may be altered in functional dyspepsia, explaining the link to fat inducing symptoms [41]. Further research into whether different types of fats induce different dyspeptic symptoms or whether specific symptoms relate to different action of fats on the gastrointestinal symptoms is warranted.

The variability in proportions of fat, carbohydrate and protein between functional dyspepsia patients and healthy controls is likely to be a result of reported symptoms from specific foods impacting on dietary profiles and therefore nutrient proportions. It is notable that only one study reported fibre intake specifically [21], with the patients and controls both consuming low fibre intakes of approximately 25% of recommended intake [42].

The apparently disparate collection of foods reported as inducing symptoms are each high in either fermentable carbohydrate (some soft drinks, fruit, fruit juice, watermelon, milk), wheat/gluten (grain/pasta/wheat products, takeout/processed foods) or natural food chemicals (fruit, fruit juice, red pepper, soft drink, tea). The findings in relation to lactose and fructose intolerance suggest that FODMAPs may induce symptoms via the small or large bowel [43,44]. Although the association between FODMAPs and irritable bowel syndrome is well established [17,45], the present study highlights the need for further investigation into gastrointestinal hypersensitivity to gastrointestinal distention and ingested nutrients in other conditions, including functional dyspepsia [34] (Fig. 2). Of particular interest are investigations of neural hypersensitivity to gas production and osmotic pressure within the upper digestive tract.

The role of wheat and specifically gluten in functional dyspepsia is also supported by this review. It is speculated that gluten (and other wheat related proteins) and FODMAPs are symptom triggers in irritable bowel syndrome, although this has sparked debate regarding which food

The study outcomes of gluten-free diet responsiveness amongst those with gluten-sensitive enteropathy in patients with a diagnosis of dysmotility-like dyspepsia with no previous upper gastrointestinal endoscopic evidence of structural disease [31] provides support for an allergen-induced

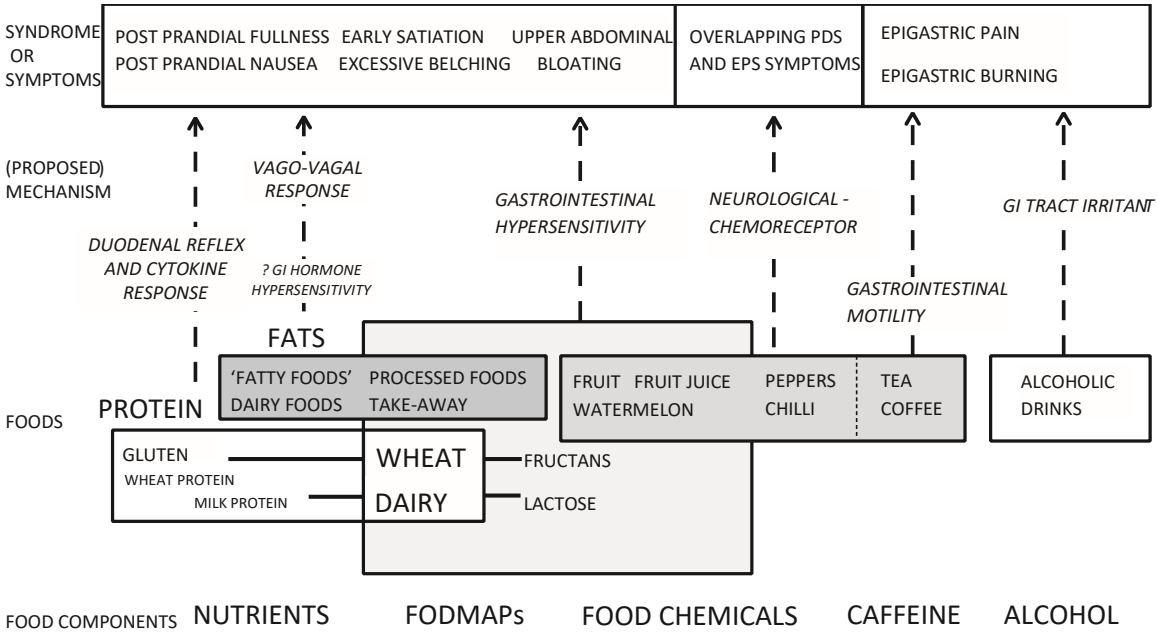


Figure 2 Food components of symptom inducing foods and associated symptoms in functional dyspepsia, with possible mechanisms of action. EPS, epigastric pain syndrome; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide and polyols; GI, gastrointestinal; PDS, postprandial distress syndrome.

component triggers which particular symptom [12]. Wheat-containing foods were implicated in functional dyspepsia symptom induction in six studies, four of which were not specifically investigating gluten [20,21,27,35] and two that were gluten-specific [22,31]. Although the implementation of a gluten-free diet in both gluten-specific studies clearly demonstrated a reduction in symptoms, the elimination of dietary wheat, barley and rye would also have substantially reduced the FODMAP content of these diets, potentially influencing the results [31].

The results of second phase of a study [22], which is not included in the results section of this review, as a result of the ingestion of gluten in capsule form, involved a double-blind gluten or placebo capsule cross-over trial. Twenty-nine percent (28/98) of patients reported the worsening of their general well-being (i.e. 3 cm or more change in general wellbeing visual analogue scale) when taking gluten capsules compared to the placebo, suggesting a sensitivity to gluten. This finding supports the hypothesis that different subgroups of the functional dyspepsia population group are sensitive to different food components.

functional dyspepsia model. This model proposes that genetically predisposed individuals are susceptible to an allergen such as gliadin leading to mucosal antigen presentation, barrier disruption and immune activation, further resulting in eosinophil recruitment [5,6,46]. The resulting inflamed duodenum may respond by inducing reflex responses and cytokine release that alter gastroduodenal function and result in meal-related symptoms [5]. Whether gliadin or nongliadin components of gluten injure and change epithelial cells by non-DQ2-restricted mechanisms has previously been questioned [9]. This review indicates the need for welldesigned clinical studies that involve randomising patients to a wheat-free or gluten-free diet and controlling for FODMAP content, aiming to investigate specific dyspeptic symptom associations with wheat food components.

Further support for the theory that different symptoms could be induced by different food components is evident [35], in that epigastric burning symptoms relate to foods tending to be high in natural food chemicals (salicylates and amines), whereas foods reported to induce bloating tended to be high in FODMAPs (milk, beans, onions). It is important that gluten and FODMAPs are differentiated in future interventions, and the possible confounding effect of ingestion of nonfood nutrients should be

considered. For example, gluten in capsule form may not be digested in the same way as when consumed in food.

The application of low food chemical diets has become more common for functional gastrointestinal conditions [43] [47], particularly in paediatric populations . However, their efficacy has been questioned [48], with a limited availability of well-designed trials to support this approach for any functional gastrointestinal conditions. The present review does suggest the need for more research into the relationship between naturally occurring food chemicals and functional dyspepsia because of the number of high chemical foods that are reported as inducing symptoms, some of which have no other likely symptom inducing active components. For example, red pepper (capsicum) contains the active component capsaicin, which has been studied specifically in patients with functional dyspepsia [49]. Oral intake of capsaicin in capsule form, and subsequent activation of chemoreceptors, induces dyspeptic symptoms in susceptible patients [49–51]. Similarly, the risk of reporting dyspepsia was associated with heavy (3 g day^{1}) dietary chilli intake in an urban multi-racial Asian population in Malaysia [52]. Although acute ingestion of natural chemicals has been shown to aggravate symptoms, there is also evidence that chronic ingestion of capsaicin as chili has the potential to reduce functional dyspepsia symptoms in small randomised, controlled studies [53]. Therefore, the future investigation of the role of chemoreceptor activation of neural pathways by natural food chemicals in FD symptom induction should exclude or account for other potential symptom-inducing components such as FODMAPs or gluten (Fig. 2).

The inconclusive results relating to the relationship between alcohol and functional dyspepsia symptoms may relate to the differing study types, as well as alcohol consumption classification and alcohol assessment. Future investigations of potential relationships between alcoholic drinks and functional dyspepsia should aim to determine whether there is a dose-dependent relationship and whether specific symptoms are triggered by specific alcoholic beverages. It is also important to determine whether alcohol itself is responsible as a gastrointestinal irritant, whether food chemicals in alcoholic drinks influence symptoms, or whether carbonation is responsible, given that three studies in this review reported carbonated drinks as inducing functional dyspepsia symptoms. Of further interest and comprising a potential area for further investigation is whether carbonated drinks induce dyspeptic symptoms (particularly gas and bloating) as a result of their carbonation or acidity or salicylate content. Similarly, the relationship between coffee and symptoms of functional dyspepsia requires clarification because variable salicylate or caffeine contents of coffee may have influenced the study outcomes in the respective included studies.

Nonvalidated diet tools and the absence of assessment of overall diet may have biased the results. Future studies should include validated dietary assessment measures that assess and report on comprehensive diet intake to allow better insight into relationships between functional dyspepsia and the diet.

Limitations

Relatively few studies were found and included in this review, limiting the conclusions that can be drawn between dietary intakes and symptoms. The lack of a standardised approach to dietary assessment methods with respect to those included studies in which primary outcome measures related to food measurement limited any comparison between studies, and this issue has been identified previously in the dietary methodology literature, even in relation to food-based randomised trials [54]. However, the present review used a standardised approach, which included a published methodology, searching a variety of online databases, assessed study quality using recognised tools and was completed in accordance with the PRISMA statement [55].

Conclusions

In conclusion, wheat and specifically gluten, and also FODMAP ingestion, high fat ingestion and naturally occurring food chemicals, may play key roles in the generation of functional dyspepsia symptoms. Randomised trials are warranted and further investigation of the responsible mechanisms is now required.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with PRISMA guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the protocol have been explained.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
No funding is declared.
KRD, NJT, MMW and TLB contributed to the study planning. KRD, NJT, MMW and TLB contributed to protocol development. KRD and TLB contributed to the literature search. KRD and TLB contributed to collecting

data. KRD, NJT, MMW and TLB contributed to interpreting data. KRD, NJT, MMW and TLB contributed to drafting the manuscript. All authors approved the final draft of the manuscript submitted for publication.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article: Table S1. Systematic review search results of dietary factors that influence functional dyspepsia. Table S2. Study quality of included studies in the food and functional dyspepsia systematic review using the ROBINS-I tool [18] or RoB 2.0 tool [19].