



Review article

A systematic review of psychological, clinical and psychosocial correlates of perceived food intolerance

Alessandra De Petrillo^{a,*}, Lyndsay D. Hughes^b, Serena McGuinness^b, Danniella Roberts^b, Emma Godfrey^b^a King's College London, Department of Psychology, Institute of Psychiatry Psychology & Neuroscience, De Crespigny Park, London SE5 8AF, United Kingdom^b Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 5th floor Bermondsey Wing, Guy's Hospital Campus London Bridge, London SE1 9RT, United Kingdom

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ABSTRACT

Objective: Perceived food intolerance (PFI) is a distressing condition reported by 3% - 35% of individuals, whereas prevalence of food allergy is 0.9%–3%. The present paper aims to systematically review the evidence for psychological, clinical and psychosocial factors associated with PFI in order to advance the current understanding.**Methods:** Articles published from 1970 until October 2020 were identified. Case-control, prospective cohort, cross-sectional and retrospective studies published in English that a) included a subject population of adults over 18 with PFI and b) examined psychological, clinical and/or psychosocial factors of PFI were reviewed against inclusion criteria. Methodological quality was assessed, data extracted, and a narrative synthesis conducted.**Results:** Of 2864 abstracts identified, thirty-six articles met inclusion criteria. Evidence consistently found PFI is associated with female sex, and individuals with PFI often report physical health complaints including gastrointestinal and extraintestinal symptoms, and gastrointestinal and atopic conditions. Evidence for an association between psychological factors and PFI was inconsistent, although some suggested increased levels of common mental disorders and distress. Findings regarding psychosocial factors were mixed and sociodemographic data were infrequently collected.**Conclusions:** PFI is associated with female sex and gastrointestinal and extraintestinal complaints. Limited high-quality evidence supports the role of psychological factors associated with PFI. High-quality research using prospective and longitudinal designs with multivariate analyses is needed. Future research should explore modifiable psychological factors as potential targets for intervention and identify clinical and psychosocial risk factors of PFI to aid in formulating a biopsychosocial model of PFI.

1. Introduction

Food hypersensitivity (FH) represents an area of interest in the public domain yet remains a challenge for healthcare professionals and patients alike. Symptoms can be unpredictable and distressing, ranging from gastrointestinal (GI) upset to life-threatening immunological response, which can lead to frequent contact with healthcare professionals, food avoidance, psychological distress, and reduced quality of life (QoL) [1–5]. Further, repeat healthcare visits pose an economic burden, with significantly higher costs for providing services for those

with FH [6].

The terms 'sensitivity', 'hypersensitivity', 'intolerance', 'allergy' and 'adverse reactions' have historically been used interchangeably, contributing to confusion. A European Academy of Allergy and Clinical Immunology position statement [7] recommended the umbrella term 'hypersensitivity' to be used for both allergenic (immune mediated) and nonallergenic (non-immune mediated) food reactions that "cause objectively reproducible symptoms and signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" (p.816). However, the US National Institute of Allergy and Infectious Diseases [8]

Abbreviations: FH, Food Hypersensitivity; QoL, Quality of life.; PFI, Perceived Food Intolerance.; FA, Food Allergy.; GI, Gastrointestinal.; CMD, Common Mental Disorder.; IBS, Irritable Bowel Syndrome.; GSA, Gastrointestinal Symptom Anxiety.; FGID, Functional Gastrointestinal Disorder..

* Corresponding author.

E-mail addresses: alessandra.de_petrillo@kcl.ac.uk (A. De Petrillo), emma.l.godfrey@kcl.ac.uk (E. Godfrey).

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have proposed terminology of 'food allergy' and 'food intolerance' to refer to allergenic and nonallergenic reactions respectively. In the current systematic review, 'food allergy (FA)' will describe allergic and clinically confirmed FH reactions, and 'perceived food intolerance (PFI)' will refer to self-reported FH reactions that are not necessarily clinically confirmed. PFI has been used in the literature to refer to "symptoms related to intake of food with or without objective findings" [9] (p.667), and 'intolerance' is argued to be a widely recognised and used term by lay persons and the media [10,11]. FH will be used as an umbrella term where appropriate.

FA reactions are predominantly cell- or antibody-mediated, with typical allergenic symptoms including swelling, itching or burning in the mouth and throat, or in severe reactions, anaphylaxis [12–14]. PFI reactions are mediated through enzymatic, pharmacological and additional undefined mechanisms, often not evidenced through diagnostic investigations [13–15]. Associated symptoms are typically delayed and include GI symptoms of bloating, pain and abnormal bowel movements, extraintestinal symptoms including fatigue, headaches and joint pain, or any of these in combination [13,14,16].

Evidence from a meta-analysis suggests that FH is reported by 3%–35% of adults [12], yet only 1%–3% have a verified FA [12,17–20], suggesting many adults report PFI when there is no evidence of a FA. Some evidence indicates that prevalence of FH is increasing [14,20–23], but this is not consistently found, as research has additionally demonstrated incidence is not increasing [20,24]. True prevalence estimates are limited by diagnostic challenges [25] and it is difficult to know whether the reported rise in prevalence is due to an actual increase, or increased awareness and reporting. There is a significant discrepancy in prevalence between PFI and FA, and it is important to explore factors which may be associated with reporting PFI, as it can have a considerable impact on QoL [3].

Research investigating correlates of PFI is limited, but suggests it is more often reported in women [26,27] and in those who meet criteria for Irritable Bowel Syndrome (IBS) [9,28–33]. Further, Lillestøl et al. [27] found 57% of individuals with PFI met criteria for any psychiatric disorder, which is above the reported population prevalence of common mental disorders (CMD) in England, of around one in six [34]. Evidence additionally suggests elevated anxiety, depressive and somatic symptoms in people with PFI compared to controls, though study designs and analyses preclude determining the direction of these relationships [26,27,30].

PFI can affect psychological, psychosocial and health-related well-being. A qualitative study exploring the lived experience of PFI by Nettleton et al. [35] described the emotional impact of not having an authentic 'illness identity' and related experiences of anxiety, uncertainty and negative perceptions from others, including medical professionals, as there is no 'explanation' for PFI. Additional research suggests general practitioners hold a strong association between PFI and psychological distress [4]. Illness-related beliefs can directly influence an individuals' cognitive and emotional response to illness-related information and related coping strategies [36,37]. Further, specific beliefs can increase attention towards information in line with the belief [38], and it is possible that symptom- and food-related beliefs can increase attention towards information in line with these beliefs, potentially contributing to symptoms or a likelihood of reporting PFI, though this is not known.

The current understanding of PFI is limited by a paucity of data specifically exploring factors associated with PFI. To the authors' knowledge, there has been no previous systematic review exploring correlates of PFI. It is important to rigorously consider the evidence for psychological, clinical and psychosocial factors that are associated with an increased likelihood of reporting PFI, which can contribute to a greater understanding of PFI and help to advance future interventions.

This review has systematically identified and evaluated the existing literature for evidence of (a) modifiable psychological correlates, as primary objectives and (b) clinical or psychosocial correlates, as

secondary objectives, that are associated with PFI. For the purpose of this review, psychological variables were defined as those related to emotions, beliefs and thoughts which could potentially be modified in treatment, trait characteristics such as personality, and psychosomatic variables. Clinical factors were defined as comorbid physical health conditions. Psychosocial factors were defined as demographic and socioeconomic factors.

2. Methods

2.1. Search strategy

The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42019122826), and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [39] (see Appendix A). Electronic databases (Web of Science, Scopus, PsycINFO, MEDLINE, EMBASE and Global Health) were systematically searched from 1970 to October 13, 2020 by the first author (A.D.) and two independent reviewers (S.M.) and (D.R.). Search terms involved combining key word searches and terms were selected to identify studies on PFI and reduce capturing those on FA. Reference lists of articles meeting inclusion criteria were hand-searched for additional relevant studies. See Supplementary materials & Appendix B for further search strategy details.

2.2. Study screening and selection

Articles identified were screened in two stages using PICOS criteria and an a priori screening table (see Table 1) by A.D., S.M and D.R. See Supplementary materials for all inclusion and exclusion criteria. When necessary, disagreements were resolved through a discussion with a fourth independent reviewer (E.G. or L.H.). At the first stage, identified papers were examined for duplicates and initially screened by title and abstract. At the second stage, full text articles were reviewed for relevance and inclusion (see Table 1). Where the full text was not available, attempts to contact study authors were made.

Table 1

A priori PICOS screening table used to screen the full text of each paper against inclusion and exclusion criteria.

Inclusion Criteria PICOS inclusion criteria	Exclusion Criteria PICOS exclusion criteria
(i) Subject population included adults >18 who self-reported PFI.	(i) Caregivers; or children and adolescents under 18 where data was not separated
(ii) Any comparators to be included	(ii) Medically diagnosed nut allergy and anaphylactic allergy
(iii) Descriptive study designs (except those excluded) including case control, prospective, cohort, retrospective, and cross-sectional studies with $n \geq 5$ participants.	(iii) Individuals with a diagnosis of celiac disease or inflammatory bowel disease
(iv) Examined psychological, clinical and/or psychosocial factors associated with perceived food intolerance	(iv) Focus on food additives such as sulphite, food colouring, or alcohol intolerance, as this was not the aim of the current review
To guide the selection of appropriate studies, factors that were deemed relevant included;	(v) Only included prevalence information (with no additional psychological, clinical or psychosocial information), or an outcome of PFO (including food/nutrient intake, dietary patterns or changes, diet adherence, pathophysiological changes, and impact on QoL)
(i) Psychological factors including affect, CMD and/or distress, information relating to beliefs or cognitive patterns; personality traits; symptoms and symptom severity	(vi) Any of the following study designs: intervention study, outcome study, randomised controlled trial, replication study, study abstract, single-N case study, letter, consensus statement, incomplete report, book chapter, theses and reviews.
(ii) Clinical factors including self-reported and confirmed diagnoses	
(iii) Psychosocial factors including demographic and socioeconomic information	

2.3. Data extraction and synthesis

A.D., S.M. and D.R. extracted and tabulated relevant data into a predesigned spreadsheet. The heterogeneity of data from included studies and multifaceted nature of the research question precluded meta-analysis and the reporting of summary measures. A narrative synthesis was conducted, and psychological, clinical, and psychosocial factors were grouped into related constructs and variables following discussions between A.D., E.G. & L.H. Cohen's *d* was calculated by hand where data were available. See Supplementary materials for further details.

2.4. Quality assessment

Methodological quality of each study was assessed by A.D., S.M. and D.R. using adapted criteria from the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [40] for an overall global rating of strong, moderate or poor. Any discrepancies were resolved through discussion with a E.G. or L.H. (see Supplementary materials for further details, and Appendix C for the adapted EPHPP used in the current review).

3. Results

3.1. Results of the search and study overview

The initial search of electronic databases retrieved 2864 articles. The hand-search yielded 3 additional articles, which were excluded. 729 duplicates were removed, and 2135 papers were screened. 147 papers were eligible for full-text review, of which 111 did not meet eligibility criteria. 36 articles were included in the final review. Fig. 1 presents the PRISMA flow diagram for the selection and inclusion process.

3.2. Study characteristics

The characteristics of included studies and their samples are presented in Table 2. See Supplementary materials for further information.

3.2.1. Overview of studies

Thirty-six articles, including a total of 169,237 participants were eligible for inclusion. Sample sizes ranged from 43 [41] to 64,316 participants [42]; the median sample size was 606 (IQR = 138–2182). Participants were recruited from 24 countries (Table 2). Studies were cross-sectional ($n = 30$), case-control ($n = 5$) and longitudinal ($n = 1$)

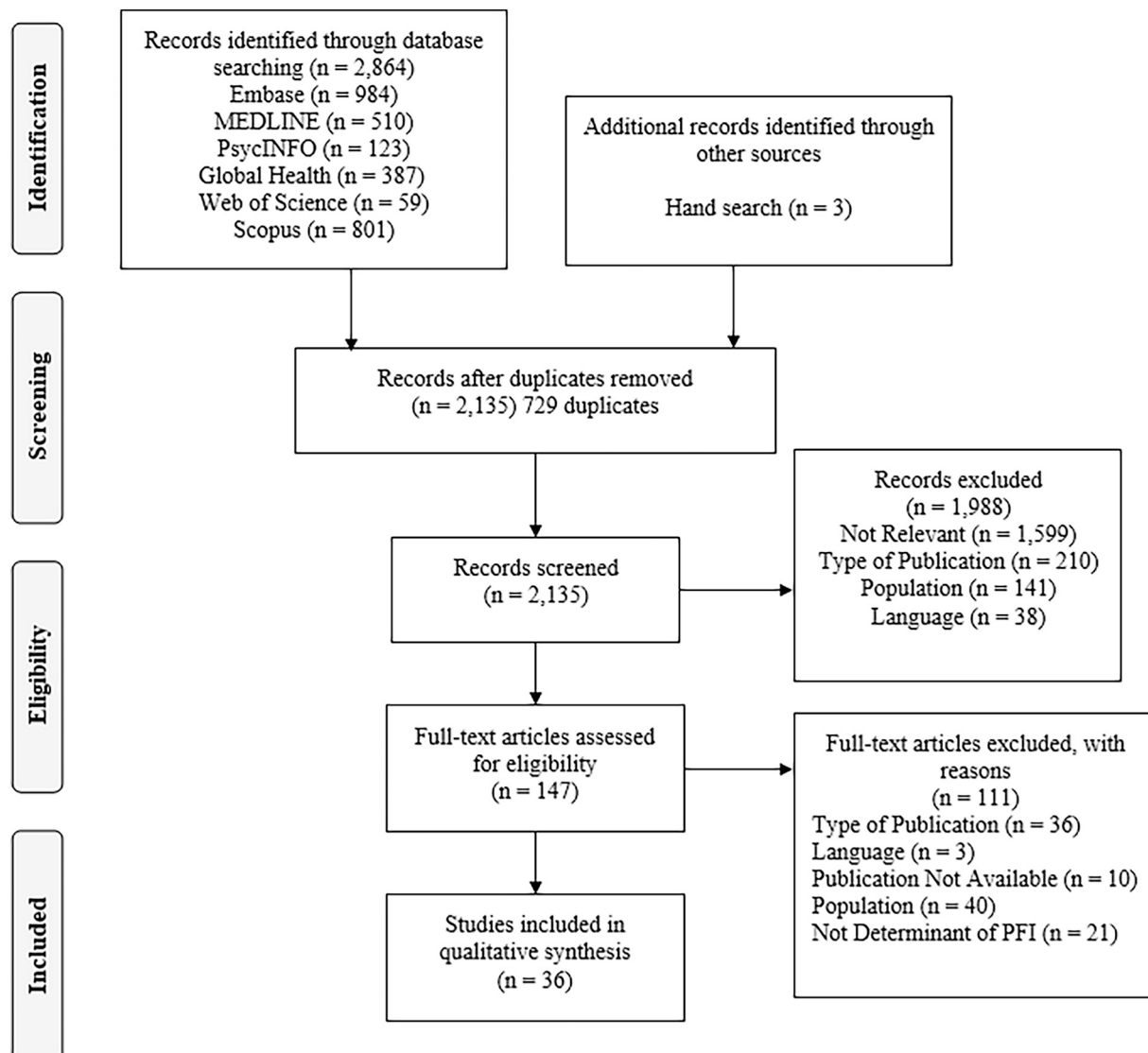


Fig. 1. PRISMA flow diagram (Moher et al., 2010).

Table 2
Study characteristics.

Author (year)	Country	N	Diagnostic Status /No Status	Age (M ± SD/Range)	Female (%)	Setting Study Design	PFI & Prev. %	Quality	Measures Used
1. Barr, S. I. (2013)	Canada	2251	N/S	NR	48.5%	Population-based	PFI-L 16.3%	Weak	MHBS
2. Berstad, A., et al. (2012)	Norway	84	PFI	37 (Range:18–77)	68%	Dept. of Medicine	PFI 100%	Moderate	FFS, IBS-SSS
3. Bohn, L., et al. (2013)	Sweden	197	IBS	35.3 (±11.9)	72%	GI Dept. patients	PFI 84%	Moderate	HADS, VSI, PHQ-15, IBS-SSS
4. Cabrera-Chavez, F., et al. (2017)	Argentina	1209	N/S	30 (Range:18–84)	52.4%	Community sample	PFI-G 7.61%	Weak	
5. Chen, J. et al. (2020)	USA	1574	N/S	21.9 (±0.62)	70.39%	Cohort Community	PFI 14.4%	Poor	SCL-90
6. Dainese, R., et al. (2014)	France	51	IBS	45 (±16)	80.4%	GI Dept. patients	PFI-L 41%	Moderate	HADS, BDI
7. Elieson, L. M., et al. (2017)	Hungary	335	N/S	35.1 (±13.8)	75.8%	Online community sample	PFI 51.2%	Weak	SHAI, SSAS, MHW, HCAMQ
8. Gelincik, A., et al. (2008)	Turkey	11,816	N/S	NR	72.9%	Population-based	PFI 9.5%	Moderate	
9. Golley, S., et al. (2015)	Australia	1184	N/S	51.6 (±16.8)	52.9%	Population-based	PFI-G 7.3%	Weak	Medical History, WI
10. Hidese, S., et al. (2019)	Japan	11,876	Total Depression	41.4 (±12.3)	49.9%	Online community sample	PFI 14.5%	Weak	NEO-N K6
11. Jakobsen, M. D., et al. (2016)	Norway	10,876 64,316	Control N/S	56.1 (Range:41–76)	100%	Cross-Sectional Norwegian Women Cancer sample	PFI 6.8%	Moderate	Medical History
12. Jansen, J. J. N., et al. (1994)	Netherlands	1483	N/S	NR	65%	Cross-Sectional Housing register	PFI 13.35%	Weak	
13. Knibb, R. C., et al. (1999)	UK	535	N/S	48 (Range:18–90)	55%	Cross-Sectional Community sample	PFI 24%	Weak	GHQ-28, EPQ
14. Lee, H. J., et al. (2019)	Korea	393 101 167 125	Total IBS GI No-IBS Control	NR	NR	Cross-Sectional GI clinic outpatients	PFI 44.8%–79.2%	Weak	IBS-SSS
15. Liden, M., et al. (2010)	Sweden	241	Rheumatoid Arthritis	NR	83%	Dept. of Rheumatology	PFI 27%	Weak	
16. Lillestol, K., et al. (2010)	Norway	205 130 75	Total PFI Matched controls	39.5 (Range: 18–80)	82.3%	Clinical Allergy Case-Control	PFI 100%	Strong	MINI, HADS, MADRS, GHQ-30, EPQ-N
17. Lind, R., et al. (2005)	Norway	166 56 50 70	Total PFI Healthcare workers Matched controls	39 (Range: 19–80)	89%	Allergy clinic Case-Control	PFI 100%	Strong	SHC, MHW
18. Lind, R., et al. (2008)	Norway	116 46 70	Total PFI Matched Control	40.6 (Range: 19–80)	89%	Allergy clinic Case-Control	PFI 100%	Moderate	
19. Lind, R., Lied, G et al. (2010)	Norway	70	PFI	39.2 (Range: 18–75)	74%	Allergy & GI clinic Cross-Sectional	PFI 100%	Moderate	HADS, VSI, SHC, IBS-SQ
20. Lind, R., Lillestol, K. et al. (2010)	Norway	129 64 65	Total PFI Matched control	37.9 (±11.7)	83%	Allergy & GI clinic Case-Control	PFI 100%	Moderate	SHC, CJSQ, UCL
21. Manu, P., et al. (1993)	USA	200 27 27	CFS PFI + CFS Matched control CFS	40.0 (±6.5)	64%	Medical clinic Case-Control	PFI 13.5%	Strong	NIMH-DIS
22. Monsbakken, K. W., et al. (2006)	Norway	84	IBS	48.5 (±15)	69%	National Health Survey; Population-based	PFI 70% with IBS	Moderate	HSCL-10, Musculoskeletal Quest.
23. Nybacka, S., et al. (2018)	Sweden	270 223 47	Total IBS Control	31 (Range:18–72)	74%	GI clinic Cross-Sectional	PFI 19%	Weak	HADS, PHQ-15
24. Parker, S. L., et al. (1990)	Canada	45 23 22	Total PFI FA	41.5 (± 9.6)	91.3%	Allergy clinic Cross-Sectional	PFI 100%	Moderate	
25. Patelis, A., et al. (2014)	Iceland & Sweden	2307	ECRHS I & ECRHS II	33.6 (±7.3) 42.4 (±7.2)	53%	ECRHS sample Longitudinal	PFI 20.6%	Strong	

(continued on next page)

Table 2 (continued)

Author (year)	Country	N	Diagnostic Status /No Status	Age (M ± SD/Range)	Female (%)	Setting Study Design	PFI & Prev. %	Quality	Measures Used
26. Patten, S. B. and J. V. Williams (2007)	Canada	36,984	N/S	NR	NR	Canadian Community Health Study; Population-based Cross-Sectional	PFI 8.2%	Moderate	WMH-CIDI
27. Puente-Fernandez, C., et al. (2016)	Mexico	1253	N/S	19 (Range:18–25)	58.2%	University students Cross-Sectional	PFI 30.1%	Weak	
28. Rentzos, G., et al. (2015)	Sweden	1527	WSAS	NR	NR	West Sweden Asthma Study; Population-based Cross-Sectional	PFI 53.1% with asthma	Weak	
29. Rix, K. J., et al. (1984)	UK	43	Total PFI	40.8 (Range: 21–67)	65%	Allergy & Psychiatry Outpatients Cross-Sectional	PFI 100%	Moderate	CIS, SRT
30. Saberi-Firooz, M., et al. (2007)	Iran	1978	N/S	49.9 (±11.14)	70.7%	Population-based Cross-Sectional	PFI-L 28.4%	Weak	
31. Soost, S., et al. (2009)	Germany	3227	N/S	NR	55.6%	Population-based Cross-Sectional	PFI	Weak	
32. Tomba, C., et al. (2012)	Italy	114	Total GI	42 (±15)	72%	GI unit outpatients Cross-Sectional	PFI-L 29%	Moderate	SCL-90R
33. van Gils, T., et al. (2016)	Netherlands	785	N/S	47 (±18)	60%	Community sample Cross-Sectional	PFI-G 6.2%	Weak	Medical History
34. Vesa, T. H., et al. (1998)	Finland	427	N/S	52 (R: 36–74)	52%	Community Cross-Sectional	PFI-L 31%	Moderate	
35. Vierk, K. A., et al. (2007)	USA	4482	N/S	NR	61.2%	Population-based Cross-Sectional	PFI 9.1%	Weak	
36. Woods, R. K., et al. (2001)	Australia 15 countries	17,280	ECRHS	33.2 (±7.2)	52%	ECRHS sample; Community Cross-Sectional	PFI 12.2%–19.9%	Moderate	

BDI = Beck Depression Inventory; CIS = Clinical Interview Schedule; CJSQ = Cooper's Job Stress Questionnaire; EPQ = Eysenck Personality Questionnaire; FFS = FibroFatigue Scale; HADS = Hospital Anxiety Depression Scale; HCAMQ = Holistic Complementary and Alternative Medicine Questionnaire; HSCL-10 = Hopkin Symptom Check List 10; IBS-SQ = IBS Symptom Questionnaire; IBS-SSS = IBS Severity Scoring System; K6 = Kessler 6-item Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; GHQ = General Health Questionnaire (28 and 30); MHBS = Milk Health Beliefs Scale; MHW = Modern Health Worries; MINI = Mini International Neuropsychiatric Interview; NEO = NEO Personality Inventory; NIMH-DIS = National Institute of Mental Health Diagnostic Interview Schedule; PHQ-15 = Patient Health Questionnaire; SCL-90 = Symptom Checklist 90; SHAI = Short Health Anxiety Inventory; SHC = Subjective Health Complaints Inventory; SRT = Symptom Rating Test; SSAS = Somatosensory Amplification Scale; UCL = Utrecht Coping List; VSI = Visceral Sensitivity Index; WI = Whitely Index; WMH-CIDI = World Mental Health Composite International Diagnostic Interview; N/S = no diagnostic status; NR = not reported; PFI = Perceived Food Intolerance; IBS = Irritable Bowel Syndrome; GI = gastrointestinal; CFS = Chronic Fatigue Syndrome

designs. Included studies were conducted within clinical ($n = 15$), community ($n = 13$), and population-based ($n = 8$) settings. Three studies investigated wheat and/or gluten intolerance (PFI-G) and five studies investigated lactose intolerance (PFI-L).

3.2.2. Sample characteristics

The age of participants ranged from 18 to 90 (see Table 2), with a

median age of 40.3 (IQR = 35–47). Nine studies did not report sample age, of which three did not report sample characteristics [43–51]. There was a high proportion of female participants, with a median percentage of 69% (IQR = 55–79).

3.2.3. PFI characteristics

Prevalence ranged from 7.3% (PFI-G) [52] to 9.5% [44] in

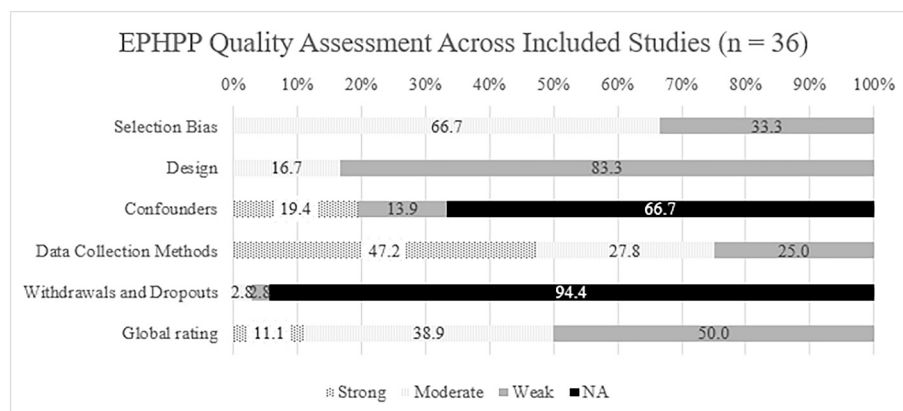


Fig. 2. Adapted EPHPP quality assessment rating across studies.

population-based studies, 6.2% (PFI-G) [53] to 51.2% [54] in community studies, and in clinical samples (excluding PFI outpatient samples), PFI was reported by 19% [55] to 84% [56] of IBS outpatients, 13.5% of patients with Chronic Fatigue [57] and 27% of those with Rheumatoid Arthritis [47].

3.3. Methodological quality assessment

Results from the quality assessment are presented in Fig. 2 and Table 3. Fig. 2 demonstrates percentage proportions of component ratings and global rating across all articles. Table 3 depicts individual quality ratings for each included article. Overall, 11.1% of articles received a global rating of 'Strong', 38.9% of 'Moderate', and 50% of 'Weak'. Study design was a primary area of bias in 30 studies due to employing a cross-sectional design. Six articles received a rating of 'moderate' on study design; five with a case-control design [27,30,33,57,58], and one employed a longitudinal design [59]. See Supplementary materials for further information, and Appendices E, G and I for a summary chart of methodological quality ratings across studies.

3.4. Identified correlates: psychological, clinical and psychosocial

Variables were identified and categorised into related groups (see Fig. 3). Findings are discussed below, and are summarised in detail in Appendix D, F and H. See Table 5 for a plot summary of statistical results at the bivariate and multivariate level.

3.5. Psychological correlates

Fifteen variables were identified in 23 studies, and categorised into five groups (see Fig. 3). Psychological correlates were measured using self-report measures and diagnostic assessments, described in Table 2. Where possible, effect sizes were calculated and are reported in Table 4 and Appendix E.

3.5.1. Common Mental Disorders (CMD) and distress

Anxiety was reported in twelve studies. Seven reported significant findings, including an increased prevalence of anxiety [48,53] and elevated self-reported anxiety in individuals with PFI compared to those without [26,27,55,60,61], of which two established elevated anxiety in women with PFI [26,27]. Effect sizes could only be calculated for three studies [26,27,61], reporting small effect sizes at a sample level (see Table 4), however, moderate effect sizes were established for Knibb et al.'s [26] findings suggesting elevated anxiety in a female-PFI subgroup compared to women without PFI ($d = 0.59$) and to men with PFI ($d = 0.57$). Five studies did not report significant findings [32,41,56,57,62], and Dainese et al.'s [60] findings did not retain significance at a multivariate level. Overall, only one methodologically strong study established elevated anxiety in PFI [27].

Health anxiety, a conceptual fear of disease that can contribute to hypervigilance and the misinterpretation of symptoms [63], was measured in two studies. A community study found health anxiety was associated with PFI ($d = 0.62$) (see Table 4), though the methodological quality was poor; sample characteristics, the level of confounders controlled in analysis or set criterion variables were not adequately described [54]. A population study found no association [52].

Symptom anxiety was reported in three studies. GI symptom-specific

Table 3
Adapted EPHPP quality assessment ratings for each included study.

Author (year)	Selection Bias	Design	Confounders	Data Collection	Withdrawals	Global Score
Barr, S. I. (2013)	—	—	X	+	X	—
Berstad, A., et al. (2012)	+	—	X	+	X	+
Bohn, L., et al. (2013)	+	—	X	++	X	+
Cabrera-Chavez, F., et al. (2017)	—	—	X	+	X	—
Chen, J., et al. (2020)	+	—	++	++	—	—
Dainese, R., et al. (2014)	+	—	X	++	X	+
Elieson, L. M., et al. (2017)	—	—	—	—	X	—
Gelincik, A., et al. (2008)	+	—	X	+	X	+
Golley, S., et al. (2015)	—	—	X	—	X	—
Hidese, S., et al. (2019)	—	—	—	++	X	—
Jakobsen, M. D., et al. (2016)	+	—	X	+	X	+
Jansen, J. J. N., et al. (1994)	+	—	X	—	X	—
Knibb, R. C., et al. (1999)	—	—	X	++	X	—
Lee, H. J., et al. (2019)	+	—	—	++	X	—
Liden, M., et al. (2010)	—	—	—	—	X	—
Lillestol, K., et al. (2010)	+	+	++	++	X	++
Lind, R., et al. (2005)	+	+	++	+	X	++
Lind, R., et al. (2008)	+	+	++	—	X	+
Lind, R., Lied, G., et al. (2010)	+	—	X	++	X	+
Lind, R., Lillestol, K. et al. (2010)	+	+	++	—	X	+
Manu, P., et al. (1993)	+	+	++	++	X	++
Monsbakken, K. W., et al. (2006)	+	—	X	++	X	+
Nybacka, S., et al. (2018)	+	—	—	++	X	—
Parker, S. L., et al. (1990)	+	—	X	—	X	—
Patelis, A., et al. (2014)	+	+	X	+	+	++
Patten, S. and Williams, J. (2007)	+	—	X	++	X	+
Puente-Fernandez, C., et al. (2016)	—	—	X	++	X	—
Rentzos, G., et al. (2015)	+	—	X	—	X	—
Rix, K. J., et al. (1984)	+	—	X	++	X	+
Saberi-Firooz, M., et al. (2007)	—	—	X	—	X	—
Soost, S., et al. (2009)	—	—	X	+	X	—
Tomba, C., et al. (2012)	+	—	++	++	X	+
van Gils, T., et al. (2016)	—	—	X	+	X	—
Vesa, T. H., et al. (1998)	+	—	X	++	X	+
Vierk, K. A., et al. (2007)	—	—	X	++	X	—
Woods, R. K., et al. (2001)	+	—	X	+	X	+

Legend — Poor + Moderate ++ Strong X N/A

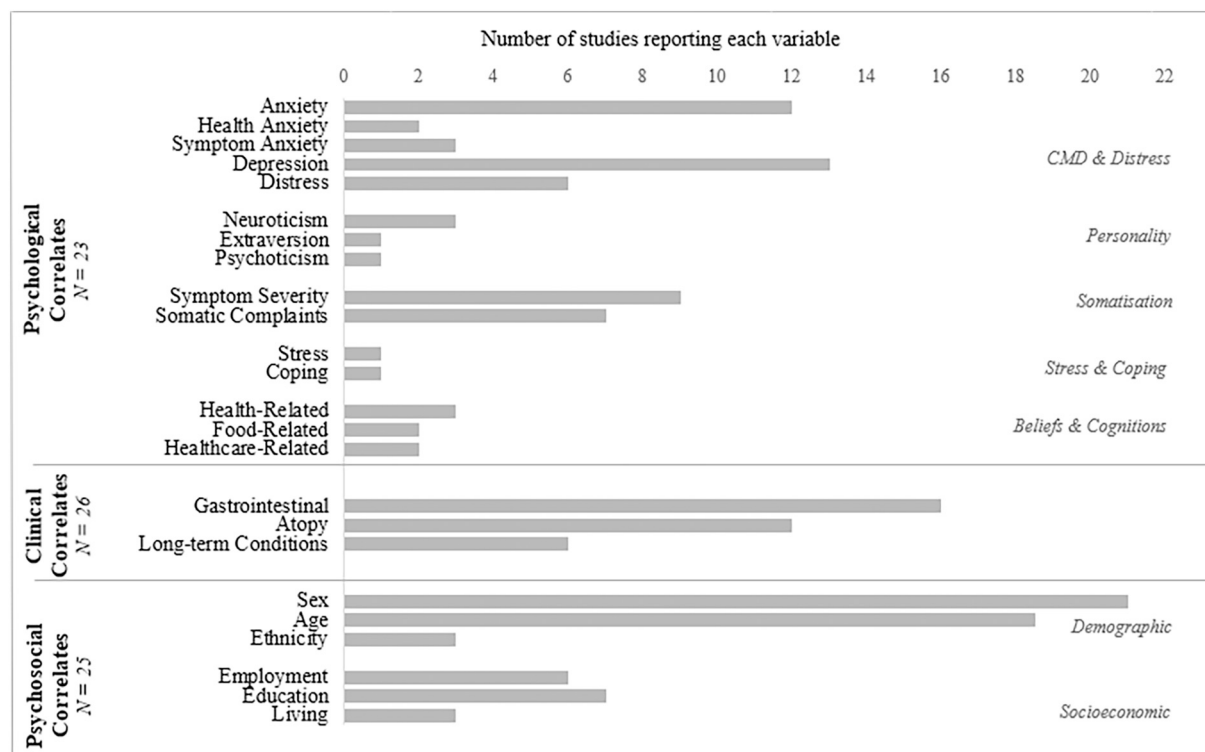


Fig. 3. Graphic representation of all identified correlates and variables along with the name of the variable grouping along the righthand side, and the number of studies reporting each variable.

anxiety (GSA) is thought to contribute to distress in IBS [64], a patient group that frequently reports PFI, and is measured using the Visceral Sensitivity Index (VSI) [65]. A related construct of somatosensory amplification refers to the tendency to be hypervigilant to somatic sensations and appraise them as aversive [66]. A methodologically weak study [54] concluded somatosensory amplification was significantly associated with PFI ($d = 0.36$) (see Table 4). In two moderate quality studies, Lind et al. [32] found higher VSI scores reported by those with PFI and case-level anxiety ($r = 0.48$), however, Böhn et al. [56] found no correlation between GSA and PFI ($r = 0.04$).

Depression was reported in thirteen studies. Eight described significant findings including an increased incidence of depression in PFI [48,52], increased odds of reporting PFI amongst individuals with self-reported depression [42,67], and elevated self-reported depressive symptoms in individuals with PFI compared to those without [26,55,60,61]. Knibb et al. [26] further reported elevated depressive symptoms in their female-PFI subgroup compared to women without PFI ($d = 0.51$) and men with PFI ($d = 0.36$). Effect sizes could only be calculated for two studies [26,61], reporting small effect sizes at a sample level (see Table 4). Significant findings were not reported in five studies [27,32,56,57,62], and neither of two strong studies [27,57] supported a role of depression in PFI.

Distress was included as a variable for six studies where measures were used that provided an overall measure of psychological distress without separating anxiety or depression, however, this was assessed using different measures across studies. Increased distress was reported by individuals with PFI compared to those with FA [41] and without PFI [67], and elevated distress in women with PFI was reported by two studies [26,27], though effect sizes were small (see Table 4). Two studies did not report significant findings [9,62]. Overall, only one study of strong quality supports elevated distress in PFI, which was significant in women only [27].

3.5.2. Personality traits

Personality traits were reported in three studies. Three studies

investigated neuroticism; two reported that neuroticism was significantly higher in PFI as compared to controls, with small ($d = 0.32$ – 0.42) [26] and large ($d = 0.50$) [27] effect sizes, respectively (see Table 4). However, at a multivariate level, an association was not established [52]. One study measured extraversion and psychoticism [26], determining extroversion was higher in women with PFI and increased levels of psychoticism in men with PFI compared to women with PFI [26]. With the current evidence, it is not possible to conclude personality traits influence PFI.

3.5.3. Somatisation

Symptom severity (including GI and extraintestinal symptoms) was reported in nine studies comprised of IBS (5/9) and PFI (4/9) samples. In IBS samples, one study reported an association between GI symptom severity and PFI-L [60], three studies determined increased GI [46,55,56] and extraintestinal [56] symptom severity reported by those with increasing severity of PFI, and one study did not report significant findings [9]. In PFI outpatient samples, increased severity of GI and extraintestinal symptoms were reported in PFI compared to controls [30,33]. Further, Lind et al. [32] concluded women had increased extraintestinal symptom severity versus men, which was supported by a moderate effect size ($d = 0.57$). Effect sizes could not be calculated for any other study reporting symptom severity (see Table 4). One study did not provide a test statistic, though reported 55% of their sample had severe GI symptoms [68]. Overall, evidence supports increased symptom severity in PFI, including the one study of strong methodological quality reporting significant findings [30]. Five studies were comprised of IBS samples, and PFI outpatients often met criteria for IBS [30,33,68]. Given that IBS is characterised by GI symptoms, it is difficult to determine if it is PFI or IBS that contributes to symptom severity.

Somatic complaints, measured by frequency of complaints, total number of symptoms reported, or scores on measures of somatisation, were reported in seven studies. Individuals with PFI reported significantly more somatic complaints as compared to individuals with chronic fatigue [57] and controls [26,30,33], with Lind et al.'s [33] finding

Table 4

Effect sizes calculated (where possible) for data reported under Psychological Correlates.

Author REF #	Quality	CMD & Distress					Personality Traits			Somatisation		Stress and Coping		Beliefs and Cognitions		
		Anxiety	Health Anxiety	Symptom Anxiety	Depression	Distress	Neuroticism	Extraversion	Psychoticism	Symptom Severity	Somatic Complaints	Stress	Coping	Food-Related	Health-Related	Healthcare Related
Barr, S. I. (2013) REF#: 43	Weak													X		
Berstad, A., et al. (2012) REF#: 68	Moderate									X						
Böhn, L., et al. (2013) REF#: 56	Moderate	X		X	X					X						
Chen, J. et al. (2020) REF#: 61	Poor	d = 0.38**			d = 0.35**											
Dainese, R., et al. (2014) REF#: 60	Moderate	X			X					X						
Elieson, L.M., et al. (2017) REF#: 54	Weak		d = 0.62***	d = 0.36**										d = 0.39**	d = 0.22**	X
Golley, S., et al. (2015) REF#: 52	Weak		X		X		X									X
Hidese, S., et al. (2019) REF#: 67	Weak				X	X										
Jakobsen, M. D., et al. (2016) REF#: 42	Moderate				X										X	
Knibb, R. C., et al. (1999) REF#: 26	Weak	d = 0.27** 0.59*** 0.57***			d = 0.37** 0.51*** 0.36**	d = 0.41**	d = 0.37**	d = 0.25**	d = 0.55***		d = 0.27** 0.38** 0.43**					
Lee, H. J., et al. (2019) REF#: 46	Weak									X						
Lillestøl, K., et al. (2010) REF#: 27	Strong	d = 0.37**			NS	d = 0.36**	d = 0.50***									
Lind, R., et al. (2005) REF#: 30	Strong									X	X			X	X	
Lind, R., et al. (2008) REF#: 58	Moderate										X					
Lind, R., Lied, G et al. (2010) REF#: 32	Moderate	X		X	X					d = 0.57***	d = 0.57***					
Lind, R., Lillestøl, K. et al. (2010) REF#: 33	Moderate										d = 1.21****		X	X		
	Strong	X			X						X					

(continued on next page)

Table 4 (continued)

Author REF #	Quality	CMD & Distress					Personality Traits			Somatisation		Stress and Coping		Beliefs and Cognitions		
		Anxiety	Health Anxiety	Symptom Anxiety	Depression	Distress	Neuroticism	Extraversion	Psychoticism	Symptom Severity	Somatic Complaints	Stress	Coping	Food-Related	Health-Related	Healthcare Related
Manu, P., et al. (1993) REF#: 57	Moderate															
Monsbakken, K. W., et al. (2006) REF#: 9						NS				X						
Nybacka, S., et al. (2018) REF#: 55	Weak	X			X					X						
Patten, S.B. & Williams (2007) REF#: 48	Moderate				X											
Rix, K. J., et al. (1984) REF#: 41	Moderate					X										
Tomba, C., et al. (2012) REF#: 62	Moderate				X	X					X					
van Gils, T., et al. (2016) REF#: 53	Weak	X														

Classification of Cohen's d effect sizes: trivial* ($d \leq 0.2$); small** ($d > 0.2$); moderate*** ($d > 0.5$); large*** ($d > 0.8$); very large**** ($d > 1.3$).

X: Impossible to calculate effect size based on reported results, NS: data was provided to calculate Cohen's d, but it was non-significant data.

supported by a very large effect size ($d = 1.21$). A case-control study indicated that women report more GI symptoms than men but did not provide a test statistic [58]. However, further evidence found women with PFI reported more somatic complaints compared to men with PFI [26,32] and women without PFI [26], supported by large effect sizes (see Table 4). Finally, one study demonstrated an association between increased somatisation scores and PFI [62]. In summary, moderate and strong quality evidence suggests individuals with PFI report more somatic complaints and report them more frequently than those without PFI.

3.5.4. Stress and coping

Stress impacts GI motility and function and has been reported as a contributing factor in functional gastrointestinal disorders (FGID) [69–71]. Job stress and coping were investigated in one case-control study with PFI outpatients [33]. The authors found individuals with PFI reported significantly lower job stress than controls and concluded no significant differences in coping strategies used. Limited evidence precludes drawing conclusions regarding the contributing effects of perceived stress and coping strategies in PFI.

3.5.5. Beliefs and cognitions

Health, food and healthcare related beliefs were investigated in five studies. Health-related beliefs were reported in three studies. Lind et al. [30] found no group differences in health-related worries, though conversely, Elieson, Domotor and Koreles [54] reported elevated health-related worries in individuals with PFI ($d = 0.22$), though this did not retain significance at a multivariate level [54]. One study with a female-only sample reported an association between PFI and poor perceived health, though this was not collected on a standardised assessment [42]. Food-related beliefs were reported in three studies. Lind et al. [30] determined PFI outpatients were significantly more worried about food additives and genetically modified food than controls, and Barr [43] determined fewer of those with PFI-L had positive beliefs about milk products. One study did not report significant findings [54].

Healthcare-related beliefs were reported in two studies that determined PFI and PFI-G were associated with positive beliefs about complementary and alternative medicine [52,54], and less receptiveness towards conventional medicine [52]. Overall, research into the role of beliefs in PFI is limited, and the only methodologically strong study [30] did not report significant findings.

3.6. Clinical correlates

Twenty-six articles described clinical correlates of reported health conditions, represented by three variables (see Fig. 3).

3.6.1. Gastrointestinal

GI correlates were reported in sixteen studies. In five studies with PFI-only samples, 71% - 99% met criteria for IBS [27,30,32,33,68]. Five studies recruited individuals with IBS [9,46,55,56,60]; PFI was reported in each study and two of these additionally reported significantly higher prevalence of PFI in adults with IBS than controls [46,55]. In non-clinical samples, four studies found that PFI increased the odds of reporting IBS [53,72–74]. Two studies reported that IBS was significantly more prevalent in PFI-G [52,75].

3.6.2. Atopy

Atopy was described in twelve studies, including previously-studied samples of respiratory health [59,76], and asthma [49], and a pre-determined sample with rheumatoid arthritis [47]. Four studies reported significant multivariate associations between PFI and atopy [44,50,72], including a study spanning 15 countries [76]. Five studies reported significant bivariate findings; two reported a higher prevalence of PFI in IBS + atopy [55] and asthma [49], and three found atopy was more often reported in PFI [45,47,59]. Two studies with PFI outpatients

Table 5

Plot summary of statistical results at the bivariate and multivariate level.

			Number of studies reporting significant findings (refer to Table 2 for reference numbers)									
			Cross-Sectional				Case-Control				Longitudinal	
			Descriptive/Bivariate		Multivariate		Descriptive/Bivariate		Multivariate		Descriptive/Bivariate	
			<i>p</i> < 0.05	NS/*	<i>p</i> < 0.05	NS/*	<i>p</i> < 0.05	NS/*	<i>p</i> < 0.05	NS/*	<i>p</i> < 0.05	NS/*
Psychological	CMD and Distress	Anxiety	5 ^{26,33,5,6,13,23}	4 ^{3,19,29,32}		1 ⁶	1 ¹⁶	1 ²¹				
		Health Anxiety Symptom		1 ³	1 ⁷ 2 ^{7,19}	1 ⁹						
		Anxiety Depression	5 ^{9,26,5,6,13,23}	3 ^{3,19,32}	2 ^{10,11}	1 ⁶		2 ^{16,21}				
		Distress	2 ^{13,29}	2 ^{22,32}	1 ¹⁰		1 ¹⁶					
	Personality	Neuroticism	1 ¹³	1 ⁹			1 ¹⁶					
		Extraversion	1 ¹³									
		Psychoticism	1 ¹³									
	Somatisation	Somatic Complaints	2 ^{13,19}		2 ^{11,32}		3 ^{17,20,21}	1 ¹⁸				
		Symptom Severity	5 ^{19,6,3,14,23}	2 ^{2*,22}			2 ^{17,20}					
		Stress						1 ²⁰				
	Stress and Coping Beliefs and Cognitions	Coping						1 ²⁰				
		Health & Illness			1 ¹¹	1 ⁷	1 ¹⁷					
		Food Related	1 ¹			1 ⁷	1 ¹⁷					
		Healthcare			2 ^{6,8}							
Clinical	Gastrointestinal		9 ^{4,9,14,23,3,6,22,2,19}		4 ^{27,30,33,34}		3 ^{16,17,20}					
		Atopic	5 ^{23,28,12,15,27}	3 ^{6,2*,24*}	4 ^{36,27,8,31}						1 ²⁵	
		Long-term conditions	2 ^{11,33}	1 ^{2*,15**,22**}	1 ¹¹			1 ^{22*}				
	Demographic	Sex	9 ^{1,3,4,9,10,12,27,35}	6 ^{6,8,14,22,29,32}	7 ^{9,27,30,31,33,34,36}						1 ²⁵	
Psychosocial	Age		5 ^{1,10,33,24,7}	12 ^{3,4,6,11,14,22}	2 ^{8,11}							
				29,30,34,35,36 ^{31*}								
		Ethnicity	1 ^{1,5}	1 ³⁵								
	Socioeconomic	Employment	1 ²⁹	3 ^{12,14,24}	1 ¹¹		1 ²⁰					
		Education	1 ³⁵	4 ^{12,14,24,33+}	2 ^{11,31}							
		Living Circumstances			1 ^{11,33,36}							

Legend: *p* < 0.05 = significant at the 0.05 level, NS = not significant, * = no test statistic used so cannot determine significance.

Note: Anxiety and Depression; Ref. [6] had significant findings at bivariate level and no significant findings at multivariate level.

** Long-term conditions; Refs. [15]** & [22]** 100% of samples had Rheumatoid Arthritis and Chronic Fatigue respectively.

+ Education Level; Ref [33]+ approached statistical significance.

did not report a test statistic; 38% reported at least one atopic disease [68], and 30% reported a family history of atopy [77]. One study did not report significant findings [60].

3.6.3. Long-term conditions

Long-term conditions such chronic fatigue, rheumatoid arthritis, fibromyalgia, and other conditions were described in six studies; four reported comorbidities described by individuals with PFI, and two investigated PFI in pre-determined clinical samples of rheumatoid arthritis [47] and chronic fatigue [57], with 27% and 13.5% reporting PFI, respectively.

In a female-only sample, Jakobsen et al. [42] determined the odds of PFI increased with increasing comorbidities reported, and concluded self-reported chronic fatigue, hypothyroidism and fibromyalgia were associated with PFI. Conversely, van Gils et al. [53] found no association between these conditions and PFI-G. One study reported chronic fatigue and fibromyalgia were reported by 85% and 71% of PFI outpatients, respectively, though no test statistic was provided [68]. One study did not report significant findings [9].

3.7. Psychosocial correlates

Six variables were identified in 25 studies, and categorised into two groups (see Fig. 3).

3.7.1. Demographic factors

Sex differences were reported in 21 studies, though across included studies, a large proportion of the samples were female (see Table 2). Fifteen studies reported significant findings, including establishing female sex as a predictor of PFI [50,52,53,72–74,76], reporting a higher prevalence of PFI in females [43,45,51,52,59,67,72,75] and one study found women reported more symptomatic foods than men [56]. One study indicated significant findings but did not describe these [54]. Six studies did not report significant findings [9,41,44,46,60,62].

Age was described in nineteen studies, of which eight determined age was a significant correlate of PFI. Six studies, two multivariate [42,44] and four bivariate [43,50,53,67] reported younger age in PFI, however, Soost et al. [50] did not report significance levels. Conversely, Parker et al. [77] reported PFI was associated with older age. One study reported significant findings but did not describe these further [54]. Eleven studies did not report significant findings

[9,41,45,46,51,56,60,73–76].

Ethnicity was included in three studies. Barr [43] and Chen [61] found a higher proportion of non-Caucasians reported PFI, and Vierk et al. [51] reported no findings.

3.7.2. Socioeconomic factors

Employment status was reported in six studies, and three reported significant findings. Not being in full-time employment was associated with PFI in a female-only sample [42], and Lind et al. [33] determined part-time employed PFI outpatients reported more somatic complaints than those employed full-time. Rix, Pearson and Bentley [41] concluded PFI outpatients were more likely employed in 'professional' careers compared to psychiatric outpatients. Three studies reported no significant findings [45,46,77].

Education was included in seven studies. Three studies with large sample sizes reported a higher level of education was associated with PFI [42,50,51], and this approached significance in another study [53]. Three studies did not report findings [45,46,77].

Living circumstances were described in three studies. Jakobsen et al. [42] determined poor childhood economic living conditions and living in an urban region predicted PFI, and van Gils et al. [53] additionally determined living in an urban region predicted PFI-G. Woods et al. [76] reported that living in Germany, Iceland, Sweden and Norway were predictors of PFI.

4. Discussion

This is the first systematic review in PFI to the authors' knowledge, which provides an overview of psychological, clinical and psychosocial correlates of PFI. Thirty-six studies met inclusion criteria and were reviewed, of which 11% were strong, 39% were moderate and 50% were poor quality, as assessed with a modified EPHPP.

4.1. Summary of findings

Prevalence of PFI was reported at 7.3%–9.5% in population studies, 6.2%–51.2% in community studies, and 19%–84% in clinical samples largely comprised of PFI and IBS samples. An accumulation of evidence suggested that PFI was associated with being female, reporting IBS, reporting frequent and severe GI and extraintestinal symptoms, and reporting atopy.

Research reporting psychological correlates provided some evidence for elevated anxiety, depression and distress in PFI, although further research is needed to establish whether causal relationships exist. Findings relating to personality, stress, coping and beliefs and cognitions were limited, as these variables were only explored in a small number of studies of poor and moderate quality. Stress is an established correlate of FGID [69–71,78,79] however, only one study in the current review measured stress. Further, research has not yet explored PFI-specific beliefs or illness perceptions, which have been shown to contribute to distress in allergy [80] and IBS [81–83], and this may be an important area to explore. Overall, the results were generally inconsistent, of poor methodological quality, and do not allow causal inferences to be drawn. Furthermore, only seven studies provided data whereby effect sizes could be calculated, and it was not possible to conduct a meta-analysis due to heterogeneous outcomes across studies. High-quality research using common, validated measures and conducted across multiple timepoints is needed. Individuals with PFI report reduced QoL [3] and it is possible that modifiable correlates including psychological distress, stress and illness perceptions influence outcome in PFI. These correlates contribute to a biopsychosocial understanding of IBS [81,82,84] and given similarities between these two conditions, may also be important in improving the current understanding PFI.

Evidence from studies reporting clinical correlates do not support a better understanding of the relationship between PFI and IBS and atopy, and whether this is related to stress, immune functioning,

neuroendocrine pathways, or other additional mechanisms. High-quality evidence is required to understand if specific comorbidities contribute to reporting PFI, or vice versa, and if so, the mechanism of this relationship, which can help identify groups that are more likely to report PFI. Further, it is possible that clinical comorbidities contribute to reduced QoL [3] and increased cost of providing healthcare due to increased service use [6], but this is not known.

Limited evidence from studies reporting psychosocial correlates suggested associations between PFI and younger age, higher education and living in an urban region, and one study demonstrated a relationship between poor childhood conditions and PFI [42]. Early adverse experiences are an established correlate of IBS [85] and it is possible that this might be significant in PFI, though this cannot currently be concluded. Overall, psychosocial factors were infrequently reported, and high-quality research is needed to elucidate psychosocial correlates that may increase the risk of reporting PFI.

4.2. Implications for future research and clinical practice

In order to better understand factors involved in predictive risk and maintenance of PFI, prodromal, prospective and longitudinal research in individuals both with and without PFI at baseline is needed. An association between IBS and PFI was suggested, and it is possible that this represents shared mechanisms; that individuals with IBS may be more likely to attribute symptoms to PFI; or that GI symptom overlap means that many individuals with PFI meet criteria for IBS, although this is not known. It will be important to disentangle IBS and PFI, as attributing PFI to IBS or vice versa could limit our understanding of possible important differences in these conditions. Evidence-informed therapies have been demonstrated to improve outcome for people with IBS [82,86–88], though it is currently not possible to conclude that these would be successful for individuals with PFI. To inform a biopsychosocial understanding of PFI and any future intervention to improve outcome, high quality research exploring correlates including life stressors, psychological distress and illness perceptions [79,81–86] is required. Further, increased awareness of the various correlates of PFI may help inform a physician's understanding of PFI, as individuals with PFI have previously reported negative perceptions from medical professionals [35]. Communication and the doctor-patient relationship have implications for health-related behaviours and outcome [89,90], and so this may influence outcome for people with PFI. Research in IBS populations has highlighted the need for improved communication [91] while reporting that a positive doctor-patient relationship improves symptom management and QoL [92].

4.3. Strengths and limitations

Significant effort was made to insure reliability of this review. The author, in addition to a second and third reviewer, screened the titles and abstracts of all studies and assessed relevant full texts against a priori defined inclusion and exclusion criteria. Data extraction and quality assessment of all included studies was conducted independently by the author and the two reviewers to reduce bias, enhance rigor and capture methodological issues described.

The results are limited by the quality of the literature currently available. Few studies were methodologically strong. Most were cross-sectional, limiting an understanding of cause and effect. Many were subject to selection bias, including self-selection and purposive sampling methods, limiting how representative the samples are. Across studies reporting psychological variables, lack of appropriate data analyses was an evident weakness, with only a third conducting multivariate analyses. Furthermore, only seven studies provided data to calculate effect sizes, which precluded understanding the magnitude of the findings across studies. Future research must be rigorous, employing commonly used validated outcome measures and longitudinal designs to further facilitate conclusions of causal effects through meta-analysis.

The review was further limited as only a small number of psychological variables have been investigated and did not explore those significant in similar conditions such as IBS, including illness perceptions [81–83]. Berstad et al. [94] hypothesised that individuals with PFI will develop a cognitive and attentional bias towards information in line with PFI-specific beliefs, influencing the appraisal of information and related behaviours. It is necessary to further explore this hypothesis and investigate the role of illness-specific beliefs and how these relate to outcomes in people with PFI. Finally, contributing factors evidenced in IBS including gut infection [95, 96] have not been fully explored, although they may contribute to the experience of GI symptoms in PFI.

5. Conclusions

The findings of this review suggest PFI is associated with female sex, GI and extraintestinal symptoms, and IBS. PFI prevalence rates varied across settings and between studies but appeared common in community and clinical samples. There is some evidence that CMD and distress are elevated in PFI, though much research has been poorly conducted using heterogeneous methodologies, so it is difficult to draw any robust conclusions. There are similarities between PFI and IBS that should be explored to elucidate whether they are similar or overlapping conditions, as this has implications for understanding and managing PFI. Overall, the findings highlight the need for high-quality research to improve the current understanding of PFI. Specifically, to consider the role of illness perceptions, stress, psychological distress and somatic symptoms, which may be crucial to improving outcome, QoL and self-management of PFI.

Ethical standards

This research did not involve human or animal experimentation. This study is a systematic review and did not require submission to the King's College London research ethics board for approval and clearance. All authors have read and approved the final version of this paper for submission to the Journal of Psychosomatic Research.

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Declaration of Competing Interest

The authors have no competing interests to report.

Appendix A. Supplementary data

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SUPPLEMENTARY MATERIALS & APPENDICES: A systematic review of psychological, clinical and psychosocial correlates of perceived food intolerance.

SUPPLEMENTARY MATERIAL: A systematic review of psychological, clinical and psychosocial correlates of perceived food intolerance.

Overview

This document contains supplementary content to provide further details on systematic review methodology and results, including:

Methods

Search Strategy

The systematic review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42019122826¹) and was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Appendix A). Search terms involved combining key word searches for perceived food intolerance using various synonyms, combinations, operators, truncations, wild cards and limiters and terms were selected to identify studies on PFI and reduce capturing those on FA. For example, food intolerance was searched for by the key words (“food intolerance” or “food hypersensitiv*” or “food sensitiv*”) and perceived was searched for using the key words (“perceived” or “self-report*” or “self report*” or “subjective”). As this is an understudied area, the decision was made to only use these terms, and manually screen out studies that did not meet criteria. See Appendix B for the full search strategy and search terms.

Screening and Selection

Inter-rater agreement was assessed using Cohen’s Kappa. At the abstract screening stage, Cohen’s Kappa was 0.78 between A.D. and S.M., and 0.82 between A.D. and D.R. At the full-text stage, Cohen’s Kappa was 0.80 between A.D. and S.M. and 0.76 between A.D. and D.R.

Inclusion Criteria

Studies were included if they had (i) a subject population of adults >18 who self-reported PFI, (ii) descriptive study designs including case control, prospective, cohort, retrospective, and cross-sectional studies with N = > 5 participants, (iii) any comparators, and (iv) examined psychological, clinical and/or psychosocial factors associated with PFI. To guide the selection of appropriate studies, factors that were deemed relevant included; (i) Psychological factors including affect, CMD and/or distress, information relating to beliefs or

¹ https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019122826

cognitive patterns; personality traits; symptoms and symptom severity (ii) Clinical factors including self-reported and confirmed diagnoses (iii) Psychosocial factors including demographic and socioeconomic information.

Exclusion Criteria

Studies were excluded if they had (i) a subject population including caregivers, children and/or adolescents <18 where data were not reported separately, individuals with medically diagnosed nut or anaphylactic allergy, Coeliac Disease or Inflammatory Bowel Disease, and/or a food additive or alcohol intolerance, (ii) study designs including intervention, outcome, replication, single-N case studies, randomised controlled trials, study abstracts, letters, consensus statements, incomplete reports, book chapters, theses and reviews; (iii) only included prevalence information (with no additional psychological, clinical or psychosocial information), or an outcome of PFO (including food/nutrient intake, dietary patterns or changes, diet adherence, pathophysiological changes, and impact on quality of life).

Data Extraction and Synthesis

Information deemed relevant to the review question was extracted and tabulated by three reviewers (A.D., S.M. and D.R). Extracted data included publication data, country of origin, study design, recruitment method, sample characteristics, data analysis methodology, data collection methodology (including any outcome measures used), and main findings related to psychological variables, clinical variables, and psychosocial variables.

Quality Assessment

Methodological quality of each study included was assessed using adapted criteria from the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [40] by A.D., S.M. & D.R. This instrument was developed in order to support the quality of systematic reviews and assesses the methodological quality of an article across eight areas of potential bias, including A) selection bias; B) study design; C) confounders; D) blinding; E) data collection method, F) withdrawals and dropouts G) intervention integrity and H) analysis. The EPHPP then rates the article as 'strong', 'moderate' or 'weak' on components A-F, which are used to determine the global rating. The current review did not include criteria concerning blinding (D) or intervention integrity (G), as we did not include controlled trials or intervention studies. Each article included was rated on five areas of potential bias: selection bias; study design; confounders; data collection method, and withdrawals and dropouts (see Appendix C for the adapted EPHPP used in the current review). Scores from each section translate into an overall methodological quality score of

'Strong' (no ratings of 'weak'), 'Moderate' (one rating of 'weak') or 'Poor' (two or more ratings of 'weak'). There was an agreement rating of 80% between A.D. and S.M, and 78% between A.D. and D.R. regarding the global ratings of methodological quality. All discrepancies were resolved through discussion with a fourth independent reviewer (E.G./L.H.).

Results

Overview of Studies

Participants were recruited from 24 countries including Korea, Hungary, Sweden, Argentina, Netherlands, Norway, Mexico, Canada, Iceland, France, Australia, Italy, Turkey, Iran, Germany, United Kingdom, Finland, Japan, USA, Belgium, Switzerland, Ireland, Spain, and New Zealand. Statistical analyses were predominantly descriptive, inferential and bivariate, and few studies used multivariate analyses including correlation, regression, and mediation analyses. See Appendix D for a plot summary of statistical results at the bivariate and multivariate level.

Sample Characteristics

Eight studies were national/population based. Thirteen studies were community-based, of which four were comprised of populations from previously defined cohort studies (42, 52, 53, 61). Fifteen studies were comprised of outpatients recruited from GI, allergy, and medical outpatient departments, including patients with GI conditions (n = 5), PFI (n = 8), Rheumatoid Arthritis (n = 1), and Chronic Fatigue (n = 1).

PFI Characteristics

Commonly reported offending foods were wheat, gluten, dairy (including milk and cheese), fruits, vegetables (including legumes and cruciferous vegetables), and eggs. Individuals with PFI often reported symptoms in response to more than one food (9, 30, 46, 54, 55, 56, 58, 61) and one study (56) indicated that women reported more food items than men. The most commonly reported GI symptoms were bloating, flatulence, abdominal discomfort, abdominal pain, nausea, altered bowel habits (constipation and/or diarrhoea). The most commonly reported extraintestinal symptoms were tiredness, headache, joint/muscle pain, and mood changes.

Methodological Quality Assessment

According to EPHPP criteria, most studies were subject to selection bias, largely due to consecutive and convenience sampling methods by means of self-selection or clinic referrals, and thus might not be representative of the general population. Eight studies used

probability sampling methods including random digit dialing and postal (9, 43, 44, 48, 50, 51, 52, 73) however this resulted in lower response rates, contributing to 'moderate' and 'weak' ratings. Study design was a primary area of bias in 29 studies, who received ratings of 'weak' due to their cross-sectional design, which does not allow for variables of interest to be measured over time, and many did not account for confounding or extraneous variables that may have influenced psychological or clinical correlates. Six articles received a rating of 'moderate' on study design; five employed a case-control design with age- and sex-matched controls (27, 30, 33, 57, 58) which can reduce the chance that findings were due to uncontrolled variables, and one employed a longitudinal design (59). Seventeen studies used known reliable and valid measures, though most validated measures used were self-report, which may be prone to biases in reporting due to their subjective nature. As most studies were one-time survey studies, EPHP criteria indicates that the withdrawal and dropout component is not applicable for these studies and was only relevant in one longitudinal study

Appendix A: PRISMA Checklist

Section/topic	#	Checklist item	Reported page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Paper, page 3. Supplementary materials, Page 1.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3, 6 + Supplementary materials
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3, 6

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 + Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results section, Table 5, Appendix D, F, H,
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Results + discussion, Pgs 12 - 23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Results + Limitations in discussion, Pgs 12-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions in discussion, Pg 23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Pg 24

Appendix B: Search Strategy

MEDLINE

1. food intolerance.mp. or exp Food Hypersensitivity/ or exp Food Intolerance/
2. (food hypersensitivit* or food sensitivit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. (perceived or self-report* or self report* or subjective).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 3 and 4

PsycINFO

1. (food intolerance or food hypersensitivit* or food sensitivit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

EMBASE

1. (food intolerance or food hypersensitivit* or food sensitivit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2. nutritional intolerance.mp. or exp nutritional intolerance/
3. 1 or 2
4. (perceived or self-report* or self report* or subjective).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. 3 and 4

Global Health

1. (food intolerance or food hypersensitivit* or food sensitivit*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
2. (perceived or self-report* or self report* or subjective).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
3. 1 and 2

Web of Science

TI=(food intolerance* OR food sensitivit* OR food hypersensitivit*) AND TI=(perceived OR subjective OR self-report*)

Scopus

(TITLE-ABS-KEY (food AND intolerance OR food AND hypersensitivit* OR food AND sensitivit*) AND TITLE-ABS-KEY (perceived OR self-report* OR self AND report* OR subjective)

Appendix C: Adapted EPHPP

Adapted EPHPP, modified for suitability for cross-sectional and case-control studies with no intervention.

A) Selection Bias

Q1- Are the individuals selected to participate in the study likely to be representative of the target population?

1. Very likely
2. Somewhat likely
3. Not likely
4. Can't tell

Q2 – What percentage of selected individuals agreed to participate?

1. 80 – 100% agreement
2. 60 – 79% agreement
3. Less than 60% agreement
4. Not applicable
5. Can't tell

Rate this section	Strong	Moderate	Weak
<i>See dictionary</i>	1	2	3

B) Study Design

1. Randomised controlled trial
2. Controlled clinical trial
3. Cohort analytic (two group pre +post)
4. Case-control
5. Cohort (one group pre + post)
6. Interrupted time series
7. Other (specify)
8. Can't tell

Rate this section	Strong	Moderate	Weak
<i>See dictionary</i>	1	2	3

C) Confounders

Q1 – Were there important differences between groups?

1. Yes
2. No
3. Can't tell

The following are examples of confounders; race, sex, marital status/family, age, SES (income or class), education, health status

Q2 – If yes, indicate the percentage of relevant confounders that were controlled either in the design or analysis

1. 80-90%
2. 60-79%
3. Less than 60%

4. Can't tell

Rate this section	Strong	Moderate	Weak
<i>See dictionary</i>	1	2	3

D) Data Collection Method

Q1 – Were data collection tools shown to be valid?

1. Yes
2. No
3. Can't tell

Q2- Were data collection tools shown to be reliable?

1. Yes
2. No
3. Can't tell

Rate this section	Strong	Moderate	Weak
<i>See dictionary</i>	1	2	3

E) Withdrawals and Drop Outs

Q1 - For longitudinal studies, were withdrawals and drop-outs in terms of numbers and/or reasons?

1. Yes
2. No
3. Can't tell
4. Not applicable (one-time survey)

Q2 – Indicate the percentage of participants completing the study

1. 80-90%
2. 60-79%
3. Less than 60%
4. Can't tell
4. Not applicable

Rate this section	Strong	Moderate	Weak
<i>See dictionary</i>	1	2	3

Global Rating

1 Strong (no weak ratings)

2 Moderate (one weak rating)

3 Weak (two or more weak ratings)

Appendix D: Psychological correlates summary of findings

Author (year)	Variable (Measure)	CMD and Distress Findings	Cohen's d *
Bohn, L., et al. (2013)	Anxiety (HADS) Depression (HADS) Symptom anxiety (VSI)	Anxiety: PFI (as defined as food-related GI symptoms) not significantly correlated with anxiety ($r = -0.11$; $p = 0.13$) Depression: PFI (as defined as food-related GI symptoms) not significantly correlated with depression ($r = -0.05$; $p = 0.50$) Symptom Anxiety: No significant correlations between food-related GI symptoms and symptom specific anxiety ($r = 0.04$; $p = 0.55$)	X X X
Chen, J., et al. (2020)	Anxiety (SCL-90) Depression (SCL-90)	Anxiety: Mean anxiety symptom scores were higher in PFI compared to those without PFI ($M = 8.28$, $SD = 3.70$) vs. $M = 6.93$, $SD = 3.4$). Those reporting any PFI had significantly higher mean anxiety scores ($\beta: 1.19$; 95% CI: 0.71–1.67) vs those reporting specific PFI to wheat, milk, egg, tree nut, avocado and banana. Those with multiple PFI's reported significantly higher anxiety scores than those with a single PFI ($\beta: 1.44$; 95% CI: 0.30–2.59). Depression: Mean depressive symptom scores were higher in PFI compared to those without PFI ($M = 11$, $SD = 4.17$) vs. $M = 9.55$, $SD = 4.02$). Those reporting any PFI had significantly higher mean depressive scores ($\beta: 1.26$; 95% CI: 0.70–1.83) vs those reporting specific PFI to milk, egg, avocado and banana. Those with multiple PFI's reported significantly higher depressive scores than those with a single PFI ($\beta: 1.54$; 95% CI: 0.21–2.86).	d = 0.38 d = 0.35
Dainese, R., et al. (2014)	Anxiety (HADS) Depression (BDI)	Anxiety: PFI-L had higher median HADS-A scores ($Mdn = 13$ [IQR = 8–14] vs. $Mdn = 8$ [IQR = 5–12], $p < 0.01$). No significant association found ($OR = 1.270$, $p = 0.29$). Depression: PFI-L (vs. non) had higher median BDI scores ($Mdn = 8$ [IQR = 5–10] vs. $Mdn = 3$ [IQR = 2–7], $p < 0.01$). No association found ($OR = 1.138$, $p = 0.32$).	X X
Elieson, L.M., et al. (2017)	Health anxiety (SHAI) Symptom anxiety (SSAS)	Health Anxiety: PFI associated with health anxiety ($OR = 1.103$, $p < 0.001$), and health anxiety is a significant mediator of PFI ($b = 1.002$, $p < 0.001$). PFI (vs non-PFI) had higher SHAI scores ($M = 33.98$ ($SD = 5.521$) vs. $M = 29.79$ ($SD = 7.812$)), no p value. Symptom Anxiety: PFI associated with somatosensory amplification ($OR = 1.041$, $p = 0.028$). Following mediation analysis, mediated by health anxiety ($b = -0.0040 \pm 0.214$, NS). PFI ($M = 28.05$, $SD = 6.768$) had higher mean SSAS scores than non-PFI ($M = 25.71$, $SD = 6.307$), no p value.	d = 0.62 d = 0.36
Golley, S., et al. (2015)	Health Anxiety (WI) Depression (Medical History)	Health Anxiety: No significant associations ($OR = 1.18$; 95% CI [0.88–1.58], $p = 0.26$). Depression: PFI-G (vs. non-PFI-G) more likely to report history of depression (32.9% vs. 19.5%, $\chi^2 (1) = 8.47$, $p < 0.004$).	X X
Hidese, S., et al. (2019)	Depression (Self report) Distress (K6)	Depression: PFI significant and positive predictor for a self-reported lifetime history of clinical depression ($OR = 1.46$, 95% CI [1.13–1.88], $p = 0.0037$). Individuals with 2 ($OR = 1.75$), 3 ($OR = 2.02$), and 4 ($OR = 2.27$) allergens were significantly more common in the depression group ($p < 0.001$). Distress: PFI (vs non-PFI) associated with severe psychological distress ($K6 \geq 13$) ($OR = 1.32$, $p < 0.001$).	X X

Jakobsen, M.D., et al. (2016)	Depression (Medical History)	Depression: PFI associated with self-reporting depression (OR = 1.30, $p < 0.001$)	X
Knibb, R. C., et al. (1999)	Anxiety Depression Distress (all GHQ-28)	Anxiety: Higher scores in PFI sample $t(533)=3.1$, $p < 0.002$, PFI women vs. non-PFI women, ($t(116)=3.2$, $p < 0.002$), and PFI women vs. PFI men ($t(134)=3.3$, $p < 0.001$). Depression: Higher scores in all PFI ($t(187)= 2.53$, $p < 0.01$), PFI women vs. non-PFI women, ($t(106)=2.6$, $p < 0.02$), and PFI women vs. PFI men ($t(136)=2.1$, $p < 0.04$). Distress: PFI associated with “at-risk for diagnosis of minor psychiatric disorder”, $\chi^2(3)=8.7$, $p < 0.03$. PFI women (vs. PFI men) scored significantly higher for psychiatric caseness, $t(136)=2.40$, $p < 0.02$.	$d = 0.27$, $d = 0.59$, $d = 0.57$ $d = 0.37$, $d = 0.51$, $d = 0.36$ $d = 0.41$
Lillestol, K., et al. (2010)	Anxiety (MINI, HADS) Depression (MINI, HADS, MADRS) Distress (GHQ-30, MINI)	Anxiety: 34.2% PFI met anxiety disorder criteria on MINI (most frequently, GAD and panic disorder). PFI women scored significantly higher than controls on HADS-A ($M = 5.3$, $SD = 3.7$ vs. $M = 4.0$, $SD = 3.3$ $p = 0.013$) and HAD-Total ($p = 0.021$). Case-level HADS-A (≥ 8) found in 23.5% of PFI vs. 12.5% controls ($p > 0.05$; NS). Depression: 15.8% PFI met depressive disorder criteria on MINI; lower prevalence in MADRS findings (8%). No significant difference in HADS-D scores ($M = 2.6$, $SD = 2.3$ vs. $M = 2.1$, $SD = 3.0$, $p = 0.168$). Case-level HADS-D in 2.5% PFI vs. 8.3% (NS). Distress: 56.6% PFI met psychiatric disorder criteria on MINI. PFI associated with higher GHQ-30 scores ($M = 28.5$, $SD = 8.2$ vs. $M = 25.6$, $SD = 8.1$, $p = 0.022$) in women only.	$d = 0.37$ NS $d = 0.36$
Lind, R., Lied, G., et al. (2010)	Anxiety (HADS) Depression (HADS) Symptom anxiety (VSI)	Anxiety: Mean HADS-A score ($M = 4.9$, $SD = 3.5$). Case-level HADS-A (≥ 8) found in 24%. Gender or symptom severity (SHC & IBS-SQ) not associated. Depression: Mean HADS-D score ($M = 4.6$, $SD = 2.4$). Case-level HADS-D (≥ 8) found in 14%. Gender or symptom severity (SHC & IBS-SQ) not associated. Symptom Anxiety: No significant differences in VSI scores between women vs men ($M = 32.2$, $SD = 17.6$ vs. $M = 25.6$, $SD = 13.1$, $p = 0.14$). Symptom anxiety and HAD-A significantly correlated ($r = 0.48$, $p < 0.0001$). Higher VSI scores found in individuals with HADS-A score ≥ 8 ($p = 0.0004$), and IBS-SQ score ≥ 25 ($p = 0.001$). Symptom anxiety was a significant predictor of GI symptom severity (IBS-SQ) ($\beta = 0.186$; $p = 0.02$).	X X NS
Manu, P., et al. (1993)	Anxiety Depression (both NIMH-DIS)	Anxiety: Anxiety disorder prevalence similar between groups (11.1% vs. 14.8%). Depression: Prevalence of depressive disorders similar between groups (66.6% vs. 62.9%). No significant differences in depressive complaints between groups (NS).	X X
Monsbakken, K. W., et al. (2006)	Distress (HSCL-10)	Distress: No significant differences in HSCL-10 scores between PFI ($M = 1.61$, $SD = 0.55$) and non-PFI ($M = 1.52$, $SD = 0.30$), $p = 0.35$. No significant correlation between PFI and distress ($r_s = 0.04$, $p = 0.73$).	NS
Nybacka, S., et al. (2018)	Anxiety Depression (both HADS)	Anxiety: PFI scored significantly higher than non-PFI ($M = 9.2$ vs 7.5 $p = 0.029$). <i>SD not reported for PFI (page 6 in paper)</i> Depression: PFI scored significantly higher than non-PFI ($M = 5.6$ vs 4.5 $p = 0.049$). <i>SD not reported for PFI</i>	X X

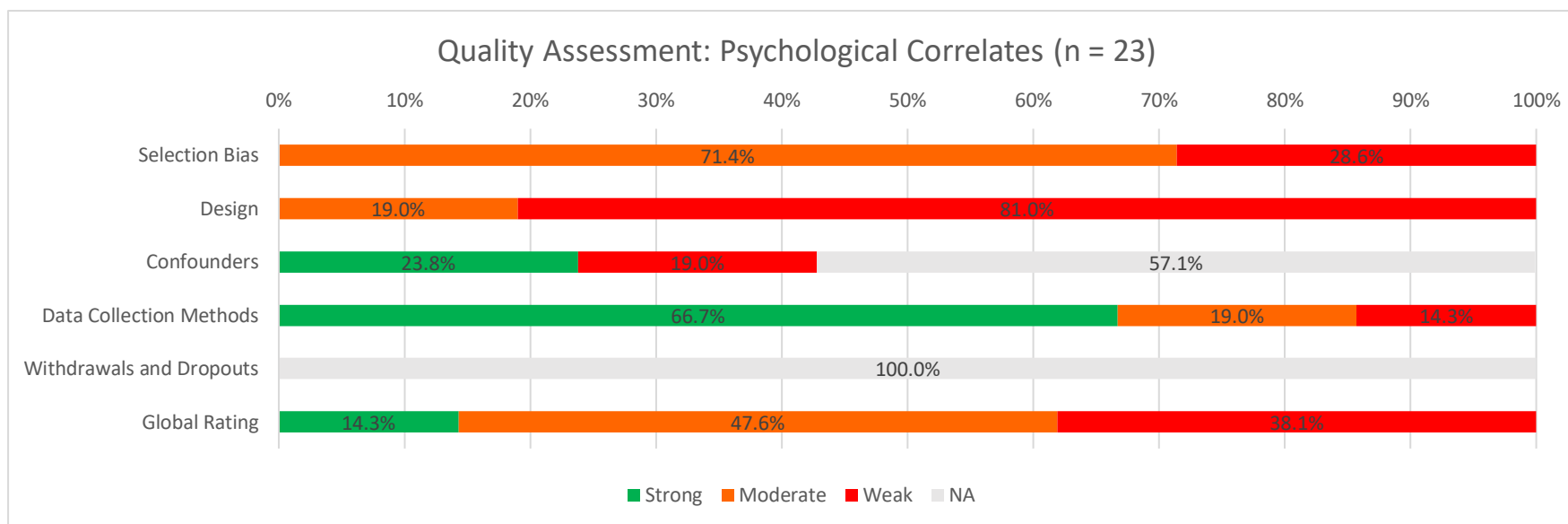
Patten, S. & Williams, J. (2007)	Anxiety (WMH-CIDI)	Anxiety: Significant differences in social phobia prevalence [95% CI] in adults >45 with PFI (3.5% [2.3-4.7]) vs. non-PFI (1.8% [1.5-2.2]), $p < 0.05$. Of entire social phobia group (all ages) 14.5% [9.7-19.4] were PFI adults >45, $p < 0.05$. Panic disorder NS.	X
	Depression (WMH-CIDI)	Depression: Significant differences in MDD prevalence [95% CI] in adults >45 with PFI (5.7% [4.2-7.2]) vs. non-PFI (3.0% [2.6-3.4]), $p < 0.05$. Of entire MDD group (all ages), 14.5% [10.8-18.2] were adults >45 with PFI, $p < 0.05$.	X
Rix, K.J., et al. (1984)	Anxiety (CIS)	Anxiety: Psychiatry outpatients had higher mean scores on CIS anxiety ($M = 2.05$ vs. $M = 1.89$, no SD) and anxious manifest abnormalities ($M = 0.17$ vs. $M = 0.9$, no SD) than PFI outpatients ($p < 0.05$)	X
	Distress (CIS, SRT)	Distress: Mean CIS scores for PFI ($M = 20.5$, Range:10-36) significantly higher than dFA ($M = 5$, Range: 2-8), $p < 0.01$, but not significantly different than psychiatry outpatients ($M = 21.4$, no SD), $p > 0.05$. No significant findings on SRT; psychological changes were not induced by food in PFI outpatients. No significant differences on psychiatric diagnosis, personal/family history of psychiatric disorder, or number who had seen a psychiatrist.	X
Tomba, C., et al. (2012)	Anxiety	Anxiety: PFI-L did not have significantly higher anxiety t scores, ($p > 0.05$; NS).	X
	Depression	Depression: PFI-L did not have significantly higher depression t scores, ($p > 0.05$; NS).	X
	Distress (all SCL-90R)	Distress: PFI-L did not have significantly higher global severity index (distress) t scores, ($p > 0.05$; NS). <i>Note no $M(SD)$ reported for any of the above.</i>	X
van Gils, T., et al. (2016)	Anxiety (Medical History)	Anxiety: 16.3% of PFI-G reported anxiety vs 3.1% non-PFI-G (OR = 6.0, 95% CI [2.5-14.3], $p < 0.001$)	X
Author (year)	Variable (Measure)	Personality Findings	
Golley, S., et al. (2015)	Neuroticism (NEO-N)	PFI-G not associated with neuroticism (OR = 0.82; 95% CI [0.55-1.21], $p = 0.31$).	X
Knibb, R. C., et al. (1999)	Neuroticism Extroversion Psychoticism (all EPQ)	Neuroticism: Higher scores in all PFI ($t(516) = 4.25$, $p < 0.0001$), PFI women vs non-PFI women, ($t(283) = 3.5$, $p < 0.001$), and PFI men vs non-PFI men, $t(231) = 2.44$, $p < 0.02$), indicating more neurotic.	$d = 0.37$, $d = 0.42$, $d = 0.32$
		Extroversion: Higher scores in PFI women vs. non-PFI women, ($t(283) = 2.1$, $p < 0.04$), and vs. PFI men, ($t(129) = 2.67$, $p < 0.008$), indicating more extroverted.	$d = 0.25$, $d = 0.47$
		Psychoticism: Higher scores in PFI men vs. PFI women, ($t(101) = 2.74$, $p < 0.007$), indicating less socially compliant. Scores increased with an increase in social deprivation ($r = 0.18$, $p < 0.04$) in PFI.	$d = 0.55$
Lillestol, K., et al. (2010)	Neuroticism (EPQ-N)	PFI ($M = 9.2$, SD = 5.2) had significantly higher scores than controls ($M = 6.5$, SD = 5.5) $p < 0.001$. This was found in male as well as in female subgroups (scores not reported).	$d = 0.50$

Author (year)	Variable (Measure)	Somatisation Findings	
Berstad, A., et al. (2012)	Symptom severity (IBS-SSS)	Severe IBS symptoms (55%).	X
Bohn, L., et al. (2013)	Symptom severity (Non-GI: PHQ-15 GI: IBS-SSS)	Degree of PFI associated with increasing IBS symptom severity ($p = 0.004$) and increasing extraintestinal symptom severity ($p = 0.030$), such that IBS patients who reported a higher number of food items causing GI symptoms had increased symptom severity.	X
Dainese, R., et al. (2014)	Symptom severity (IBS-SSS)	IBS patients with PFI-L had higher symptom severity scores [305 (192–326) vs. 233 (129–304) $p = 0.05$]. PFI-L was significantly associated with IBS symptom severity (OR = 1.019, 95% CI [1.002–1.037], $p = 0.02$)	X
Knibb, R. C., et al. (1999)	Somatic complaints (GHQ-28)	PFI (vs. non-PFI) reported significantly more somatic symptoms, ($t(533) = 3.1$, $p < 0.002$). PFI-women reported significantly more somatic symptoms vs non-PFI women ($t(293) = 3.24$, $p < 0.001$) PFI-women reported significantly more somatic symptoms vs. PFI men ($t(136) = 2.5$, $p < 0.01$).	d = 0.27 d = 0.38 d = 0.43
Lee, H.J., et al. (2019)	Symptom severity (GI: IBS-SSS)	Patients who reported a higher number of food items causing GI symptoms had increased IBS symptom severity ($p = 0.020$)	X
Lind, R., et al. (2005)	Somatic complaints (SHC) Symptom severity (SHC)	Somatic Complaints: PFI reported more complaints ($Mdn = 22.5$, IQR = 15.5 – 32) vs. healthy controls ($Mdn = 5$ IQR = 2 –9) & general population ($Mdn = 9.5$, IQR = 4 – 15.5), $p < 0.0001$. Five most common complaints were tiredness, bloating, headache, diarrhoea, & back pain. 39% of PFI reported ≥ 15 complaints in last 30 days. Symptom Severity: PFI had higher SHC severity scores, $p < 0.001$ (for all five domains: GI, Musculoskeletal, pseudoneurology, allergy, flu). 65% of PFI (vs. 14% general population) scored above normal (≥ 20).	X X
Lind, R., et al. (2008)	Somatic complaints (no measure)	Somatic Complaints: Concluded that results demonstrate that more women than men report GI symptoms. No test statistic or additional data provided.	X
Lind, R., Lied. G, et al. (2010)	Somatic complaints (SHC) Symptom severity (Non-GI: SHC GI: IBS-SQ)	Somatic Complaints: Total complaints last month ($M = 13.8$, SD = 6). Women, had more complaints each month ($M = 14.7$, SD = 5.5) vs men ($M = 11.2$, SD = 6.8) ($p = 0.03$). Five most common complaints were tiredness, gas discomfort, stomach pain, headache, and diarrhoea. 47% reported ≥ 15 complaints in last 30 days. Symptom Severity: Women ($M = 14.7$, SD = 5.5) had higher SHC severity scores than men ($M = 11.2$, SD = 6.8), $p = 0.03$. IBS symptom severity similar in men and women. Symptom anxiety significant predictor for GI symptom severity ($\beta = 0.186$, $p = 0.02$).	d = 0.57 d = 0.57

Lind, Liljestol, K., et al. (2010)	Somatic complaints (SHC) Symptom severity (SHC)	Somatic Complaints: PFI ($M = 23.5$, $SD = 9.7$) reported significantly more total subjective health complaints than controls ($M = 11.7$, $SD = 9.8$), $p = 0.0001$. The five most common complaints were gas discomfort, diarrhoea, stomach discomfort, tiredness and headache. 36% of PFI reported ≥ 15 complaints in last 30 days. Symptom Severity: PFI had higher SHC severity scores on GI, $p < 0.001$; allergy ($p < 0.001$), pseudoneurology ($p < 0.05$) and musculoskeletal complaints ($p = 0.002$). 67% of PFI (vs 17% controls) scored above normal (≥ 20).	d = 1.21
Manu, P., et al. (1993)	Somatic complaints (NIMH-DIS)	PFI (vs. non-PFI) had more lifetime functional extraintestinal symptoms ($p < 0.05$), including irregular menstrual periods ($\chi^2 = 6.1$, $df = 1$, $p < 0.02$), dizziness/light headedness ($\chi^2 = 4.1$, $df = 1$, $p < 0.05$), and diarrhoea ($\chi^2 = 4$, $df = 1$, $p < 0.05$). PFI had significantly higher (33% vs. 7%) prevalence of somatisation disorder ($p < 0.025$).	X
Monsbakken, K. W., et al. (2006)	Symptom Severity (Musculoskeletal Questionnaire)	Musculoskeletal pain score not significantly different between PFI and non-PFI ($p = 0.13$, NS). However, there were significant correlations between musculoskeletal pain score and psychological distress (HSCL-10) ($r_s = 0.43$, $p < 0.001$).	X
Nybacka, S., et al. (2018)	Symptom severity (Non-GI: PHQ-15, GI: IBS-SSS)	IBS with PFI patients ($M = 12.9$, no SD) reported more extraintestinal symptoms than non-PFI ($M = 10.8$, no SD) $p = 0.023$. No differences in IBS symptom severity found.	X
Tomba, C., et al. (2012)	Somatic complaints (SCL-90R)	High somatisation t scores associated with PFI-L (OR = 4.184; 95% CI [1.704–10.309], $p = 0.0009$).	X
Author (year)	Variable (Measure)	Stress & Coping Findings	
Lind, Liljestol, K., et al. (2010)	Stress (CJSQ) Coping (UCL)	Stress: PFI (vs. controls) reported lower job stress ($M = 27.7$, 95% CI (23.5-32.0) vs. $M = 35.3$, 95% CI (31.1-39.6), $p = 0.01$) and perceived less stress in 'communication' ($M = 8.5$, 95% CI (6.8-10.3) vs. $M = 11.2$, 95% CI (6.9-13), $p = 0.02$), 'leadership' ($M = 4.9$, 95% CI (3.8-5.1) vs. $M = 6.5$, 95% CI (5.3-7.7), $p = 0.04$), and 'relocation' ($M = 3.8$, 95% CI (3.0-4.7) vs. $M = 5.3$, 95% CI (4.4-6.2), $p = 0.01$). No 'workload' group differences ($p = 0.07$). Coping: PFI and controls used similar coping strategies with no significant differences in total scores ($M = 42.7$, 95% CI (41.2–44.) vs. $M = 42.9$, 95% CI (41.6-44.2). PFI generally used an active coping pattern, scoring high on instrumental mastery-oriented coping and low on avoidance coping.	X X
Author (year)	Variable (Measure)	Beliefs & Cognitions Findings	
Barr, S.I., (2013)	Food Related (MHBS)	PFI-L (vs. non-PFI-L) had lower MHBS scores ($M = 25.1(\pm SE) 0.3$ vs. $29.3(\pm 0.1)$, $F=158$, $p < 0.001$), indicating fewer of those with PFI-L responded in a manner indicating positive beliefs about milk products.	X

Elieson, L. M., et al. (2017)	Food-Related (MHW) Health-Related (MHW) Healthcare-Related (HCAMQ)	Food-Related: PFI ($M = 17.31$ SD = 5.941) had higher Tainted Food subscale scores than non-PFI ($M = 15.13$, SD = 5.213). No significant association between PFI and food worries (OR = 1.035, $p = 0.123$) Health-Related: PFI ($M = 71.05$, SD = 24.807) higher MHW mean scores than non-PFI ($M = 66.10$, SD = 18.993), no p value reported. No significant association for health worries (OR = 1.001, $p = 0.817$) Healthcare-Related: PFI associated with positive complementary and alternative medicine attitudes (OR = 0.932, $p < 0.001$).	$d = 0.39$ $d = 0.22$ X
Golley, S., et al. (2015)	Healthcare-Related (History)	Healthcare-Related: PFI-G significantly associated with positive receptiveness to complementary medicine (OR = 1.68, 95% CI [1.32-2.14], $p < 0.001$), and less receptiveness to conventional medicine (OR = -0.50; 95% CI [0.49-0.76], $p < 0.001$).	X
Jakobsen, M.D., et al. (2016)	Health-Related (Medical History)	PFI is associated with poor perceived health (OR = 2.56, $p < 0.001$)	X
Lind, R., et al. (2005)	Food Related (MHW) Health-Related (MHW)	Food-Related: PFI significantly more worried about food additives ($p < 0.05$), and genetically modified food ($P < 0.05$). Health-Related: Sum scores on the MHW did not differ significantly between PFI ($Mdn = 66.5$, IQR[46-85.5]) versus controls ($Mdn = 61.5$, IQR[44-75.5]) or general population ($Mdn = 57$, SD = 43-74), $p > 0.05$. PFI were significantly more worried about overuse of antibiotics ($p < 0.001$), amalgam in dental fillings ($p < 0.01$).	X X
* Cohen's d calculated where appropriate data was made available X: Impossible to calculate effect size based on reported results, NS: data was provided to calculate Cohen's d , but it was non-significant data			

Appendix E: EPHPP Quality Assessment Across Studies Included in 'Psychological Correlates'



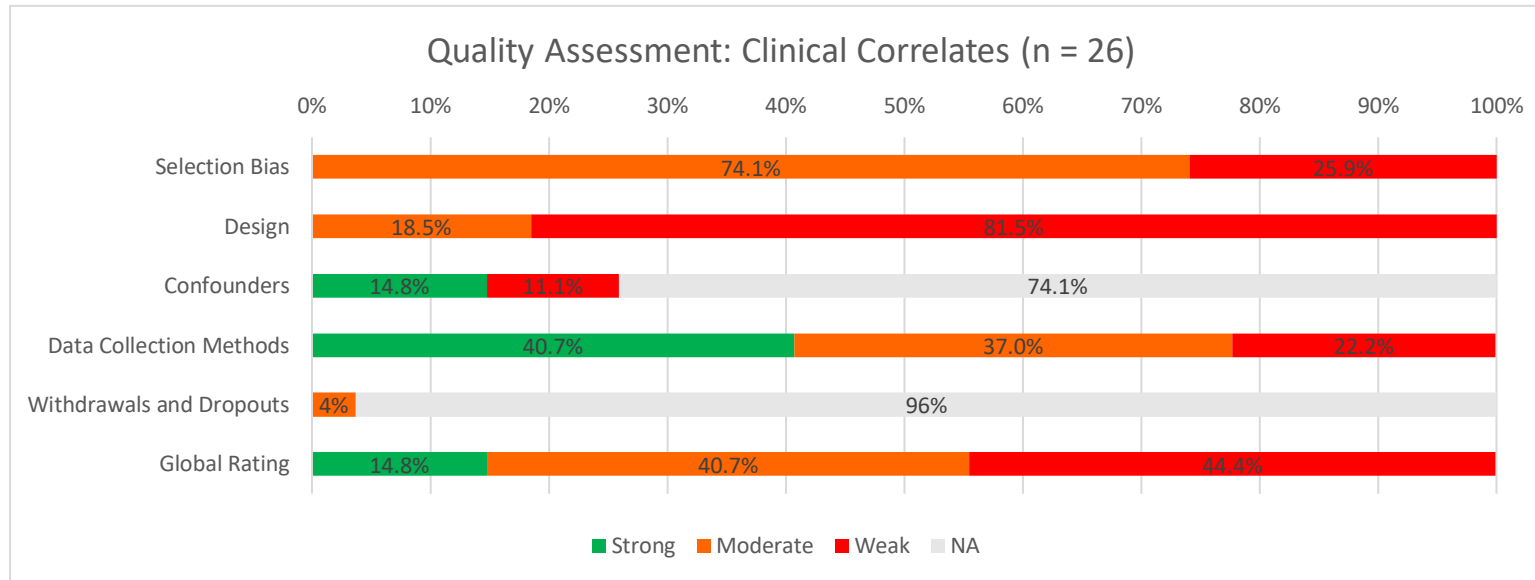
Appendix F: Clinical correlates summary of findings

Author (year)	Long-Term Conditions	Gastrointestinal	Atopy		
			Allergy	Skin-Related	Asthma
Berstad, A., et al. (2012)	Fibromyalgia (71%) Chronic fatigue (81%)	99% met IBS criteria	≥1 atopic disease (38%)		
Bohn, L., et al. (2013)		100% had IBS			
Cabrera-Chavez, F., et al. (2017)		IBS (14.3% vs. 4.7%, $p < 0.001$)			
Dainese, R., et al. (2014)		100% had IBS.	<i>Atopic disease and family history atopy NS</i>		
Gelincik, A., et al. (2008)			Nasal allergy (OR = 1.56, 95% CI [1.27-1.78], $p < 0.001$) Familial atopy (OR = 4.28, 95% CI [3.58-4.88], $p < 0.001$)	Dermatitis (OR = 3.88, 95% CI [3.29 4.48], $p < 0.001$)	OR = 1.45, 95% CI [1.18-1.78], $p < 0.001$
Golley, S., et al. (2015)		IBS (21.2% vs 8.7%, $p < 0.001$).	Food allergy ($p < 0.001$).		
Jakobsen, M. D., et al. (2016)	Muscle pain (OR = 1.80, $p < 0.001$) Fibromyalgia (OR = 1.72, $p < 0.001$) Back pain (OR = 1.24, $p < 0.001$) Hypothyroidism (OR = 1.61, $p < 0.001$) Chronic fatigue (OR = 2.55, $p < 0.001$) Odds of PFI increase with increasing number of concurrent comorbidities. 2 concurrent comorbidities (OR = 1.16, $p < 0.001$), 3 concurrent comorbidities (OR = 3.02, $p < 0.001$), 4 concurrent comorbidities (OR = 4.12, $p < 0.001$), 5 or 6 concurrent comorbidities (OR = 4.82, $p < 0.001$).				
Jansen, J. J. N., et al. (1994)			Other allergies ($p < 0.001$) Familial allergies ($p < 0.0001$)		
Lee, H. J., et al. (2019)		IBS Sample PFI+ IBS 79.2% vs. PFI in Control 44.8% $p < 0.001$			
Liden, M., et al. (2010)	100% had rheumatoid arthritis		Allergy ($p < 0.001$) childhood food allergy ($p < 0.05$)	Eczema $p < 0.05$	

Author (year)	Long-Term Conditions	Gastrointestinal	Allergy	Atopy Skin-related	Asthma
Lillestol, K., et al. (2010)		88.5% met IBS criteria			
Lind, R., et al. (2005)		71% met IBS criteria 18% dyspepsia			
Lind, R., Lied, G. et al. (2010)		94% met IBS criteria			
Lind, R., Lillestol, K. et al. (2010)		76.5% met IBS criteria			
Manu, P., et al. (1993)	100% had chronic fatigue. <i>Severity or duration of fatigue (NS).</i>				
Monsbakken, K. W., et al. (2006)	<i>State of health, fibromyalgia, musculoskeletal pain syndrome, musculoskeletal pain score (NS)</i>	100% IBS <i>h.pylori, abdominal symptom score (NS)</i>			
Nybacka, S., et al. (2018)		100% IBS PFI in IBS 19% vs. PFI in Control 6% $p = 0.025$	PFI & Atopic IBS prev. (28% vs. 9% $p = 0.002$).		
Parker, S. L., et al. (1990)			30% reported family history of food allergy.		
Patelis, A., et al. (2014)			Rhinitis ($p < 0.001$) IgE aeroallergens sensitisation ($p < 0.001$).	Eczema $p < 0.001$	$p = 0.001$ Further, 13-18% of sample had asthma.
Puente-Fernandez, C., et al. (2016)		Gastritis (OR = 4.26 95% CI [3.28-5.53], $p < 0.001$)	Allergic disease (OR = 2.09, 95% CI [1.03-4.24], $p = 0.04$) Allergic rhinitis (OR = 2.01, 95% CI [1.46-2.78], $p < 0.001$) Maternal ($p = 0.003$) and Parental ($p = 0.02$) history food allergy	Dermatitis (OR = 2.48, 95% CI [1.55-3.96], $p < 0.001$) Maternal history atopic dermatitis ($p = 0.03$) Parental history urticaria ($p = 0.03$)	
Rentzos, G., et al. (2015)					PFI prevalence: 53.1% vs. 29.8%, $p < 0.001$. Further, 38.2% asthmatics.
Saberi-Firoozi, M., et al. (2007)		IBS (OR = 1.47, 95% CI [1.09-1.98], $p = 0.011$)			
Soost, S., et al. (2009)			Allergic rhinitis (OR = 1.38; 95% CI (1.14-1.67) $p < 0.01$) in women only	Eczema (OR = 2.33; 95% CI (1.78–3.06), $p < 0.01$) in women only	

van Gils, T., et al. (2016)	Anaemia (OR = 3 95% CI [1.3-6.8], $p = 0.01$) Chronic headache (OR = 4.1 95% CI [1.6-10.6], $p < 0.01$)	37% of PFI-G reported IBS (OR = 5.9 95% CI [3.1-11.1], $p < 0.001$) Family: Celiac disease (OR= 3.4, 95% CI [1.4-10.5], $p < 0.05$)	
Vesa, T. H., et al. (1998)		IBS (OR = 4.6, [2.1-10.1])	
Woods, R. K., et al. (2001)		Atopy OR =1.38, 95% CI [1.23-1.55]	Wheeze in past 12 months (OR = 1.37, 95% CI [1.16-1.60]), Asthma history (OR = 1.71, 95% CI [1.09-2.66]) Current asthma medication (OR = 1.44, 95% CI [1.21-1.70]) all at $p < 0.05$.

Appendix G: EPHPP Quality Assessment Across Studies Included in 'Clinical Correlates'



Appendix H: Psychosocial correlates summary of findings

Author (year)	Sex	Age	Ethnicity	Socioeconomic
Barr, S. I. (2013)	PFI-L prevalence higher in females (20% vs. 12.3%, $p < 0.001$)	Younger Age (18.3% vs 13.3%, $p = 0.005$)	Not white (26% vs. 15.4% whites, $p = 0.002$)	
Bohn, L., et al. (2013)	Females reported more food items ($p = 0.06$).	NS		
Cabrera-Chavez, F., et al. (2017)	PFI-G prevalence higher in females (4.1% vs. 1.6%, $p < 0.001$).	NS		
Chen, J., et al. (2020)	Greatest prevalence of PFI reported amongst 'Other race' category (19.8%)			
Dainese, R., et al. (2014)	NS	NS		
Elieson, L. M., et al. (2017)	Significant, but not further described, $p < 0.001$	Significant, but not further described, $p < 0.001$		
Gelincik, A., et al. (2008)	NS	Younger age (OR = 1.32, 95% CI [1.19-1.49], $p = 0.03$)		
Golley, S., et al. (2015)	PFI-G prevalence higher in females (11% vs. 3%, $p < 0.001$), PFI predicted by female sex (OR = 0.26, 95% CI [0.14-0.46], $p < 0.001$)			
Hidese, S., et al. (2019)	PFI associated with female sex ($p < 0.001$)	Younger age ($p < 0.001$).		
Jakobsen, M. D., et al. (2016)	<i>Sample all female</i>	Younger age (OR = 0.97, $p < 0.001$)		Living in urban region (OR = 1.10, $p = 0.003$) >9 years of education (OR = 1.69, $p < 0.001$) Not in full-time work (OR = 1.3, $p < 0.001$) Poor childhood conditions (OR = 1.2, $p < 0.001$)
Jansen, J. J. N., et al. (1994)	PFI prevalence higher in female sex (15% vs. 9%, $p < 0.005$).	NS		Education, occupational group (NS)

Lee, H. J., et al. (2019)	NS	NS	Education, employment, (NS)
Lind, R., Lillestol, K. et al. (2010)			Part-time employed > health complaints ($p = 0.0005$).
Monsbakken, K. W., et al. (2006)	NS	NS	
Parker, S. L., et al. (1990)		Older age ($p < 0.05$)	Education, marital status, employment status (NS).
Patelis, A., et al. (2014)	PFI prevalence higher in female sex (61.6% $p < 0.001$)		
Puente-Fernandez, C., et al. (2016)	PFI prevalence higher in female (37.5% vs 19.8%), $p < 0.001$. PFI predicted by female sex (OR = 2.43, 95% CI [1.86-3.18], $p < 0.001$).		
Rix, K. J., et al. (1984)	NS	NS	PFI more likely 'professionals' ($p < 0.05$)
Saberi-Firoozi, M., et al. (2007)	PFI-L predicted by female sex (OR = 1.29, 95% CI [1.05-1.59], $p = 0.015$).	NS	
Soost, S., et al. (2009)	PFI predicted by female sex (OR = 1.83, 95% CI [1.39–2.39] $p < 0.001$)	Younger age (no p reported)	Higher education (OR = 1.92, [1.19–2.85], $p < 0.001$).
Tomba, C., et al. (2012)	NS		
van Gils, T., et al. (2016)	PFI-G predicted by female sex (OR = 2.8, 95% CI [1.4–5.7], $p < 0.01$)	Younger age ($p = 0.001$)	Living in urban region (OR = 2.5 95% CI [1.3–4.8], $p < 0.01$). Trend higher education
Vesa, T. H., et al. (1998)	PFI-L predicted by female sex (OR = 2.1, 95% CI [1.1 - 4.0])	NS	
Vierk, K. A., et al. (2007)	PFI prevalence higher in female sex (11.4% vs 6.5%, $p < 0.001$).	NS	NS Higher education (11.3% vs 6.6% high school or less, $p < 0.001$).
Woods, R. K., et al. (2001)	PFI predicted by female sex (OR = 1.47, 95% CI [1.24-1.74], $p < 0.05$)	NS	Living in Iceland, Norway, Sweden, Germany (OR = 1.72, 2.00, 1.98, 1.76 respectively) all $p < 0.05$.

Appendix I: EPHPP Quality Assessment Across Studies Included in 'Psychosocial Correlates'

