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Original Article

Diabetes is associated with increased burden of gastrointestinal symptoms in adults with cystic fibrosis

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ABSTRACT

Background: Individuals with diabetes mellitus (DM) are known to frequently experience gastrointestinal (GI) symptoms. In contrast, the impact of cystic fibrosis-related diabetes (CFRD) on accentuating GI symptoms in people with cystic fibrosis (pwCF) is unknown. We sought to examine this.

Methods: Abdominal symptoms were measured using the validated CF-specific GI symptom questionnaire - CFAbd-Score© - as part of a multicentre cohort study in pancreatic insufficient adults with CF, not on cystic fibrosis transmembrane conductance regulator (CFTR) modulators. The CFAbd-Score total score (0–100pts), its 5 domains, alongside nine specific GI symptoms associated with DM, were compared between the CFRD and non-CFRD groups.

Results: 27 (31%) and 61 (69%) participants with CF were recruited in the CFRD and non-CFRD groups respectively. Total CFAbd-Score and the two domains: gastroesophageal reflux disease and disorders of appetite were significantly higher in the CFRD group compared to the non-CFRD group ($p<0.05$), with the mean total CFAbd-Score being 25.4 ± 2.5 and 18.4 ± 1.5 in the CFRD and non-CFRD groups respectively. Among the nine GI symptoms commonly reported as elevated in DM, bloating and nausea were significantly more common in individuals with CFRD compared to those without ($p<0.05$).

Conclusions: Individuals with CFRD overall, have a higher GI symptom burden, according to CFAbd-Scores. Specifically, they experience significantly more bloating and nausea. Close monitoring and further research is needed to better understand and manage GI symptoms in this group.

1. Introduction

The prevalence of Cystic Fibrosis (CF) in Europe is estimated to be around 1 in 3500 live births, making it one of the most common life-limiting autosomal recessive genetic diseases to affect northern European populations [1]. In the United Kingdom (UK), median predicted survival is around 51 years, with median age of death being 36 years [2]. With the introduction of highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators, predicted life expectancy is likely to significantly rise over the next few decades.

The *CFTR* gene codes for an epithelial chloride and bicarbonate channel which is expressed in many organs including the lungs, gastrointestinal tract, pancreas and liver [3]. In CF, there is an absence, reduction or dysfunction of the CFTR protein which leads to significant disease-related complications, including recurrent and chronic respiratory tract infections, bronchiectasis, exocrine pancreatic insufficiency (EPI), CF-related liver disease (CFRLD), malnutrition, gastrointestinal (GI) symptoms and CF-related diabetes

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(CFRD) [2,4,5]. Lung disease remains the leading cause of morbidity and mortality [2].

Cystic fibrosis-related diabetes (CFRD) is the most common CF-related complication occurring in up to 40–50% of adults [6]. Risk factors for developing CFRD include increasing age, female sex, EPI, CFRLD, CFTR genotype, family history of type II diabetes and lung transplantation [7]. The pathogenesis of CFRD is complex [8] and it is associated with insulin deficiency, due to beta-cell loss and CFTR dysfunction [8,9]. Fluctuating insulin resistance can also occur due to pulmonary exacerbations, systemic inflammation and corticosteroid use [9]. Alongside this, glucagon secretion can increase due to reduced alpha-cell suppression [8,9]. The presence of CFRD is associated with reduced lung function, increased pulmonary exacerbations, poorer nutritional status, impaired health-related quality of life (QoL) and a higher mortality rate [10]. Mortality and the presence of CFRD has been reported to be higher in females than males [11]. However, in men, the presence of CFRD has been associated with an increased mortality risk [11].

Independent from CF, individuals with diabetes mellitus (DM) can experience a number of GI symptoms, which are often multifactorial in origin, and can be related to factors such as autonomic neuropathy, functional alterations to the peripheral and central nervous system (CNS), hyperglycaemia, psychological factors, altered intestinal transit times, gut dysbiosis, small intestinal bacterial overgrowth, EPI and medication side effects [12,13]. Gastrointestinal symptoms commonly experienced in people with DM include nausea, vomiting, early satiety, gastric reflux, abdominal bloating, abdominal pain, constipation, diarrhoea and faecal incontinence [12]. These GI symptoms can mirror those also described in people with CF (pwCF) [14,15]. The significantly higher prevalence of chronic GI symptoms in pwCF reflects the complex multisystem nature of the disease. In both CF and DM burdensome GI symptoms impact both GI-related and health-related QoL [16–18].

Given that both DM and CF are associated with significant GI symptoms, CFRD may itself potentially accentuate symptom burden in pwCF. We sought to test this hypothesis by comparing GI symptoms and their impact of QoL in a cohort of adults with CF with and without CFRD.

2. Methods

2.1. Data collection

Participants were recruited as part of an observational cohort study across four UK CF care centres (Leeds, Birmingham, Cambridge and Manchester). Pancreatic insufficient adults (≥18 years old), with two CF causing mutations, who were able to give informed consent were eligible. Individuals not meeting these criteria or those with other significant GI pathologies (such as inflammatory bowel disease, short bowel syndrome, colostomy or GI malignancy), lung transplant recipients, a prognosis < 6 months or pregnant were excluded. Participants were defined as pancreatic insufficient based upon a faecal elastase-1 test result of < 200 µg/g stool [19] and/or the requirement for exocrine pancreatic enzyme replacement therapy (PERT). A favourable ethical opinion from London – Bromley Research Ethics Committee was received (REC reference 18/LO/2241). Voluntary written informed consent was received from all participants.

This study comprises a sub-group of participants who completed the GI symptom questionnaire (CFAbd-Score©) and, to prevent confounding influences, were not on CFTR modulators or breastfeeding at the time of data collection (these data were collected April 2019- March 2020). Relevant clinical and sociodemographic data were collected from medical records and the UK CF registry, including sex, lung function (measured as percentage predicted forced expiratory volume in one second [ppFEV$_1$], body mass index (BMI), *CFTR* genotype, presence of a feeding tube and diagnosis of CFRD. The nearest BMI measurement to completion of abdominal symptom questionnaire was taken. For this unmatched case control study, participants were divided into two groups, those with CFRD and those without. A diagnosis of CFRD was confirmed through continuous glucose monitoring and/or oral glucose tolerance test (OGTT) confirmed by elevated blood glucose measurements. All included individuals with CFRD were on insulin therapy. Those with type I or II diabetes diagnosis or individuals only managed with diet or oral hypoglycaemic agents were excluded.

2.1.1. Gastrointestinal symptom assessment

Abdominal symptoms were measured with the validated CFAbd-Score© (v4.0) questionnaire [15,20,21]. The questionnaire was developed in line with United States (US) Food and Drug Administration (FDA) recommendations for developing a Patient Reported Outcome Measure (PROM), including focus groups, multidisciplinary CF specialists, pwCF and their families [15,20-22]. This questionnaire is comprised of 28 questions pertaining to five domains: abdominal pain, bowel movements, eating and appetite, gastroesophageal reflux symptoms and the impact of GI symptoms on QoL [21]. The format of response for the majority of abdominal symptoms was a six-point Likert scale - ranging from 'not at all' to 'always' [15]. Assessment of abdominal pain and pain on defecation were on a 0–10 scale [21]. Stool consistency was measured on a modified Bristol Stool chart, frequency of defecation and length of abdominal pain were measured in six discrete categories (ranging from 0 to 1 up to >5 times a day for stool frequency and 0 to >360 min for abdominal pain), colour of stool was recorded in 12 discrete colour categories [15,21]. The impact of GI symptoms on QoL was measured on a six-point Likert scale, rating from 'no problem' to 'problem is as bad as it can be' [21].

2.2. Data analysis

Participants were divided into those with CFRD (CFRD group) and those without a current diagnosis of CFRD (non-CFRD group). Dependent on data type, either an independent Mann-Whitney, Chi-squared or Fisher's Exact test, was employed to test for differences between the two groups with respect to the baseline clinical characteristics. The CFAbd-Score was formally scored based on binary logistical regression coefficients to weigh the domains, in line with FDA recommendations [21]. The resulting calculated score ranges from 0 to 100 points, with a higher score indicating more frequent and/or severe symptoms [21]. Factorial analysis of variance (ANOVA) tests were conducted to test for differences between CFRD and non-CFRD groups in the total CFAbd-Score and its five domains, which was the primary outcome. To test for sex differences and the influence of any medication found to be significantly different between the two groups, a factorial ANOVA model was considered for each domain, as well as for the total CFAbd-Score. Each model included the total CFAbd-Score or a single domain score as dependent variable and the factors representing medication and sex as independent variables, including a binary variable representing CFRD and two-way interaction terms between the variable representing CFRD and the other factors. For this, days of intravenous (IV) antibiotics in the last 12 months was grouped into 'high' (≥14) or 'low' (<14) based on the overall group median of 14 days. ANOVA assumptions on homogeneity of variance and normality of residuals were verified with Levene's test and normal quantile-quantile (Q-Q) plots, respectively. Results are reported as mean and standard error of mean (SEM).

As a secondary outcome, nine GI symptoms were identified from the literature as highly prevalent in people with DM, who do not additionally have CF: abdominal pain, bloating, heartburn

/ acid reflux, nausea, vomiting, constipation, stool frequency ≥3 bowel motions/day and loose stool [12]. These items were selected from the tool and differences between CFRD and non-CFRD groups were tested using Mann-Whitney U, Chi-squared or Fisher's Exact tests. Stool frequency and loose stool were measured as binary outcomes (yes/no) with the remaining seven items measured on a six-point scale, ranging from 'not at all' to 'always'. A $p<0.05$ was considered statistically significant. As analysis for the secondary outcomes was constrained to pre-specified GI symptoms along with the sample size and preliminary nature of this study, Bonferroni correction was not applied. Instead, multiple testing was addressed using Benjamini-Hochberg approach based on limiting the false discovery rate control [23,24], an alternative to Bonferroni-like approaches which may lead to higher type II error rates. Data were analysed in R version 3.6.3 [25], IBM SPSS version 23 and 26 (Chicago, Illinois) and figures were created with GraphPad Prism (GraphPad Software Inc, LA Jolla, CA, USA).

3. Results

3.1. Clinical and demographic characteristics

From the initial cohort of 175 participants, 87 did not meet the eligibility criteria for this study. Reasons included withdrawal at baseline ($n = 18$), non-completion of the abdominal symptom questionnaire ($n = 4$), presence of *CFTR* modulator therapies ($n = 61$), prescribed an oral hypoglycaemia agent ($n = 1$) or dietary management of CFRD without insulin therapy ($n = 2$), and breastfeeding ($n = 1$). In total 88 adults with EPI were therefore eligible for this study. The CFRD group comprised 27 (31%) participants and the non-CFRD group 61 (69%) participants, with significantly more females in the CFRD group ($p<0.01$). The CFRD group also had a higher proportion of participants prescribed H2 blockers, with a current history of laxative use and higher median number of days of IV antibiotics received in the last year compared to the non-CFRD group ($p<0.05$ for all), Table 1. In total, 13 participants had a history of GI surgery, 3 of whom were in the CFRD group and the remaining 10 were in the non-CFRD group. The most common surgeries were laparotomies, often for meconium ileus, hernia repairs and appendectomies. Detailed demographic and clinical characteristics are shown in Table 1.

3.2. Gastrointestinal symptom scores with cystic fibrosis-related diabetes

Overall, there was a high burden of GI symptoms in both groups (Table 2). However, individuals with CFRD had a significantly higher prevalence of GI symptoms, compared to those without CFRD, with mean total CFAbd-Score being 25.4 ± 2.5 and 18.4 ± 1.5 points in CFRD and no-CFRD groups respectively (main effect $p = 0.01$), Table 2. Furthermore, independent of CFRD status, the mean total CFAbd-Score was also significantly higher in participants prescribed H2 blocker medication, compared to those not (30.4 ± 2.5 points and 18.0 ± 1.4 points respectively; main effect $p = 0.0014$). However, no significant interaction was found between CFRD and H2 blocker use. There was also no significant difference in total CFAbd-Score according to sex, recent history of laxative use and history of IV antibiotic therapy or any significant interaction between these factors and CFRD.

Scores for two of the five CFAbd-Score domains were significantly higher in the CFRD group compared to the non-CFRD group (Fig. 1). These domains were 'gastroesophageal reflux disease' (35.3 ± 4.8 points and 19.2 ± 2.1 points in CFRD and non-CFRD group respectively, $p = 0.0003$) and 'disorders of appetite' (15.9 ± 2.8 points in CFRD and 7.4 ± 1.2 points in non-CFRD group, $p = 0.001$). For these two domains there was no significant relation between CFRD and the variables sex, H2 blocker medication, history of laxative use and IV antibiotic therapy. Scores for the 'disorders of appetite' domain were not significantly different between the other groups analysed. However, the mean score for the 'gastroesophageal reflux disease' domain was also markedly higher in participants on H2 blocker medication compared to those not prescribed this medication (H2 blocker: 40.7 ± 5.6 points, no H2 blocker: 19.7 ± 2.0 points; $p = 0.002$). This is likely to simply reflect the use of H2 blockers in people with more severe gastroesophageal reflux symptoms and disease.

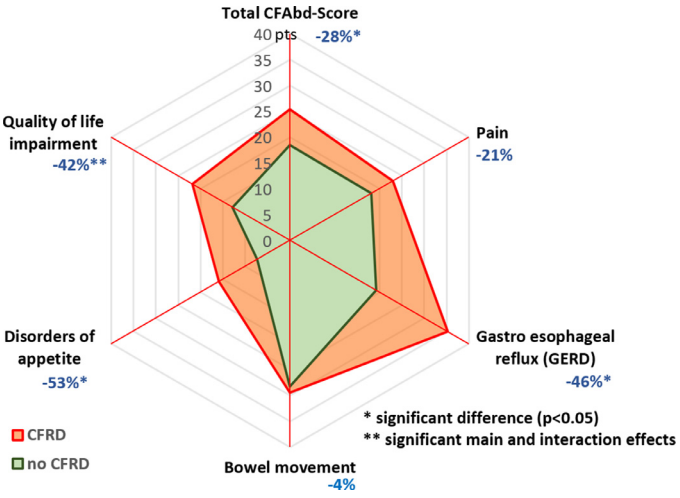


Fig. 1. Comparison of means for total score CFAbd-Score and its domains for PI adults with CF-related diabetes (CFRD) and without CFRD. Significance is indicated according to results of main effect comparisons conducted with factorial analysis of variance (ANOVA).

For the remaining three domains, symptoms of 'pain' were non-statistically significantly higher in the CFRD group (23.0 ± 3.4 points) compared to the non-CFRD group (18.2 ± 2.4 points), with no significant difference according to sex, or with H2 blocker, recent laxative or IV antibiotic use. There was also no statistically significant difference in 'disorders of bowel movement' scores between the CFRD and non-CFRD groups. However, for this domain, there was a significant difference between scores from participants with and without H2 blocker medication (H2 blocker: 36.5 ± 2.8 points, no H2 blocker: 26.5 ± 1.8 points; $p = 0.01$), with no significant interaction between CFRD and H2 blocker use found.

Lastly, for the 'GI-related quality of life' domain, a significant interaction between CFRD and H2 blocker medication was found (interaction effect: $p = 0.02$; main CFRD effect: $p = 0.01$). Further analyses revealed that the CFRD group on H2 blocker medication had the highest mean score for this domain (33.9 ± 5.3 points), which was significantly higher than the mean score from the CFRD group without H2 blocker medication (13.6 ± 3.7 points; $p = 0.005$), the mean score from the non-CFRD group with H2 blocker medication (13.9 ± 5.6 points; $p = 0.03$), and the mean score from the non-CFRD group without H2 blocker medication (12.7 ± 2.1 points; $p = 0.0004$). However, the sole presence of either H2 blocker medication or CFRD was not observed to induce significantly higher scores in this domain, Table 2. Furthermore, 'GI-related quality of life' scores from participants with current history of laxative use were significantly higher (indicating a greater impact of GI symptoms on quality of life) compared to those without (20.5 ± 3.1 points versus 11.9 ± 1.9 points; $p = 0.04$).

3.3. Specific gastrointestinal symptoms in adults with CF with and without cystic fibrosis-related diabetes

The frequency of responses to individual items on the CFAbd-Score in the CFRD and non-CFRD groups are shown in Fig. 2. According to the literature, the following symptoms are more com-

Table 1
Clinical and demographic characteristics according to CF-related diabetes (CFRD) status in pancreatic insufficient adults with cystic fibrosis.

	CFRD (n = 27)	No CFRD (n = 61)	p-value
Sex[a]			
Female	21 (78%)	16 (26%)	
Male	6 (22%)	45 (74%)	<0.01*
Age[b]	34 (28, 43)	33 (27, 39)	0.33
Body Mass Index[b]	22.76 (20.57, 27.22)	23.08 (21.78, 26.67)	0.35
***CFTR* genotype**[a]			
F508del homozygous	15 (56%)	34 (56%)	
F508del heterozygous	11 (41%)	21 (34%)	0.64
Other mutations	1 (4%)	6 (10%)	
ppFEV1[b]	51 (43, 80)	66 (49, 88.5)	0.09
Lung Microbiology[a]**:**			
Chronic *Pseudomonas aeruginosa* growth	21 (78%)	31 (51%)	0.03*
Burkholderia cepacia complex growth	2 (7%)	8 (13%)	0.72
Aspergillus fumigatus	12 (44%)[c]	22 (36%)	0.48
Days of IV antibiotics in the preceding 12 months[b]	28 (14, 42)	0 (0, 16)	<0.01*
Previous gastrointestinal surgery	3 (11%)	10 (16%)	0.75
Enteral feeding tube[a]	1 (4%)	5 (8%)	0.66
Relevant medications[a]**:**			
Proton pump inhibitors	20 (74%)	36 (59%)	0.23
H2 blocker	11 (41%)	7 (12%)	<0.01*
Current history of laxative use	17 (63%)	20 (33%)	0.02*
Pancreatic enzyme replacement therapy[d]	26 (96%)	58 (95%)	1.00
Oral Steroids	2 (7%)	0 (0%)	0.09
Duration of CFRD (years)[e]	9 (1, 28)	N/A	n/a

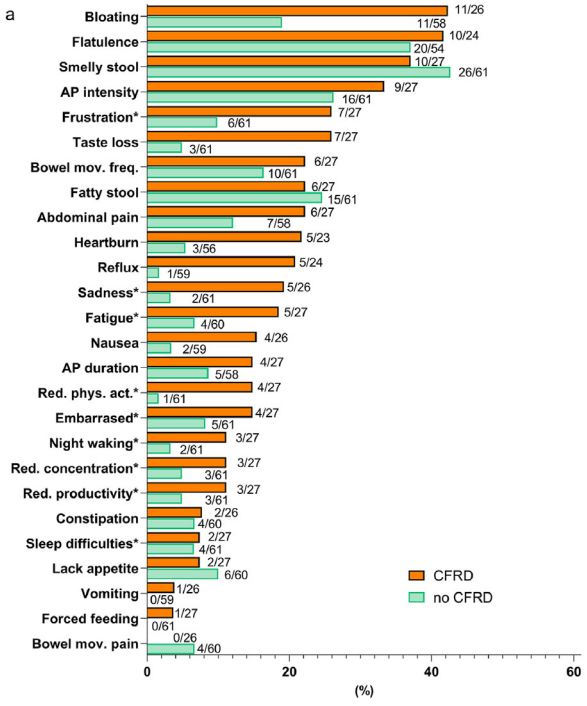
CF – cystic fibrosis, CFRD – cystic fibrosis related diabetes, CFTR – cystic fibrosis transmembrane conductance regulator;.
* statistically significant (p<0.05).
[a] N (%).
[b] Median (interquartile range).
[c] one of which intermittent growth, all other participants chronic.
[d] All participants had a clinical diagnosis of pancreatic insufficiently; however a small number of participants declined pancreatic enzyme replacement therapy.
[e] Median (range).

Table 2
Total and Domain CFAbd-Scores in PI adults with CF according to CF-related diabetes (CFRD) status.

		CFRD (mean ± SEM)	No CFRD (mean ± SEM)	Statistical significance *p<0.05
Total CFAbd-Score		25.4 ± 2.5	18.4 ± 1.5	***p* = 0.01***
5 domains of the CFAbd-Score	**Pain**	23.0 ± 3.4	18.2 ± 2.4	p = 0.264
	Gastroesophageal reflux disease	35.3 ± 4.8	19.2 ± 2.1	***p* = 0.0003***
	Disorders of bowel movement	29.4 ± 2.7	28.2 ± 2.0	p = 0.709
	Disorders of appetite	15.9 ± 2.8	7.4 ± 1.2	***p* = 0.001***
	GI-related quality of life[a]			
	H2 Blocker	33.9 ± 5.3	13.9 ± 5.6	***p* = 0.03***
	No H2 Blocker	13.6 ± 3.7	12.7 ± 2.1	p = 0.99
	Cross-tabulation categories:			
	CFRD + H2 vs CFRD + no H2			**p = 0.005***
	CFRD + H2 vs no CFRD + no H2			***p* = 0.0004***
	CFRD + no H2 vs no CFRD + H2			p = 0.99
	no CFRD + H2 vs no CFRD + no H2			p = 0.99

[a] Pairwise comparisons for the 'GI-related quality of life' were conducted via Tukey HSD (honestly significant differences) analysis; H2 = H2 blocker medication.

mon in non-CF individuals with diabetes: abdominal pain, bloating, heartburn, acid reflux, nausea, vomiting, constipation, stool frequency ≥3 bowel motions/day and loose stool. Consequently, we assessed whether these key GI symptoms with a higher prevalence in people with DM were also more frequent in pwCF with CFRD compared to pwCF without CFRD. Percentages of pwCF reporting to be experiencing these key GI symptoms - excluding loose stool - at least 4–7 times over the previous two weeks were higher in pwCF with CFRD than in pwCF without CFRD (Fig. 2b). We found that bloating and nausea were significantly higher in those with CFRD (p<0.05) Table 3. Eighty-five percent of those with CFRD experienced some level of bloating compared to 71% in those without CFRD. There was a non-significant trend towards a higher prevalence of acid reflux (p = 0.050) and abdominal pain in those with CFRD, with 70% of the CFRD group experiencing some degree of abdominal pain compared to 60% in the non-CFRD group (Table 3).



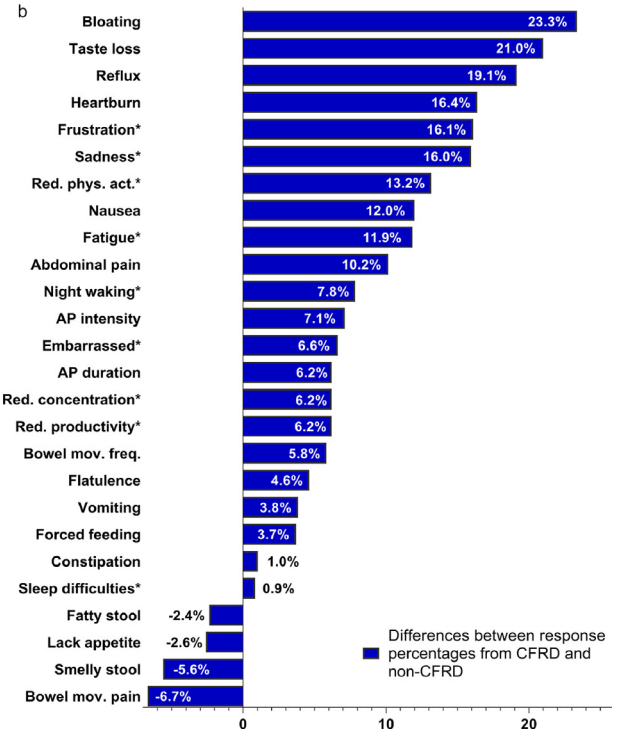


Fig. 2a. Frequency of responses for the CFAbd-Score single items for 27 pwCF with CF-related diabetes (CFRD) and 61 pwCF without CFRD. Percentages of participants reporting symptoms with a frequency of at least 4-7 times during the past 2 weeks are listed. Frequency of bowel movement includes individuals reporting at least 3-4 stools/day.
AP: abdominal pain; Bowel mov.: bowel movement; Red.phys.act.: Reduced physical activity.
*Items regarding quality of life were assessed as relating to abdominal symptoms.
Fig. 2b Differences in response frequencies for the CFAbd-Score single items from 27 people with CF (pwCF) with CF-related diabetes (CFRD) and 61 pwCF without CFRD. Positive percentages indicate higher prevalence of symptoms in pwCF with CFRD, reported as at least frequently (4-7 times during the past 2 weeks). Stool colour and consistency were excluded. For frequency of bowel movement, changes regard those reporting at least 3-4 stools/day. AP: abdominal pain; Bowel mov.: bowel movement; Red.phys.act.: Reduced physical activity.
*Items regarding quality of life were assessed as relating to abdominal symptoms.

Table 3
Specific diabetes-related GI symptoms measured on a six-point scale on the CFAbd-Score in PI adults with CF according to CFRD status.

	Response (n)		Not at all n (%)		Rarely n (%)		Occasionally n (%)		Frequently n (%)		Almost always n (%)		Always n (%)		Statistical Significance *$p<0.05$
	CFRD ($n = 27$)	No CFRD ($n = 61$)	CFRD	No CFRD	CFRD	No CFRD	CFRD	No CFRD	CFRD	No CFRD	CFRD	No CFRD	CFRD	No CFRD	
Abdominal pain	27	53	8 (30)	21 (40)	7 (26)	9 (17)	6 (22)	16 (30)	6 (22)	6 (11)	–	–	–	1 (2)	$p = 0.468$
Bloating	26	58	4 (15)	17 (29)	1 (4)	12 (21)	10 (39)	18 (31)	6 (23)	7 (12)	1 (4)	3 (5)	4 (15)	1 (2)	$\mathbf{p = 0.006}$*
Heartburn	23	56	9 (39)	30 (54)	4 (17)	14 (25)	5 (22)	9 (16)	3 (13)	2 (4)	2 (9)	1 (2)	–	–	$p = 0.075$
Acid Reflux	24	59	10 (42)	33 (56)	5 (21)	18 (31)	4 (17)	7 (12)	5 (21)	1 (2)	–	–	–	–	$p = 0.050$
Nausea	26	59	10 (39)	39 (66)	6 (23)	9 (15)	6 (23)	9 (15)	4 (15)	2 (3)	–	–	–	–	$\mathbf{p = 0.011}$*
Vomiting	26	59	19 (73)	50 (85)	6 (23)	7 (12)	–	2 (3)	1 (4)	–	–	–	–	–	$p = 0.188$
Constipation	26	60	10 (39)	25 (42)	4 (15)	11 (18)	10 (39)	20 (33)	2 (8)	4 (7)	–	–	–	–	$p = 0.685$

Multiple testing was addressed using Benjamini-Hochberg method to control false discovery rate at the 0.05 level.

There was no significant difference in degree of heartburn, vomiting or constipation (Table 3). There were also no significant differences in the binary outcomes of stool frequency (≥3 bowel motions/day) or loose stool consistency between the two groups.

4. Discussion

To our knowledge, this is the first study to identify a higher prevalence of GI symptoms in people with cystic fibrosis-related diabetes compared to those without. This highlights the value of comprehensive GI symptom assessments to identify pwCF particularly at risk so that they can receive appropriate support and GI management. Overall, in pwCF the reported GI symptom burden was high, as has been previously reported in the literature and highlights why relieving GI symptoms in pwCF is the second highest James Lind Alliance research priority [5,26]. The mean total CFAbd-Score was significantly higher in individuals with CFRD, being 25.4 ± 2.5 compared to 18.4 ± 1.5 points in those without CFRD. This level of difference (7%) exceeds the estimated change of 3–4/100 points in scores which would be considered to be the minimal clinically relevant difference based on previous studies [21,27-29]. Of note, the CFAbd-Scores from both groups were significantly higher than previously reported in healthy controls, resulting in an absolute difference of 8.0 ± 0.7 points [21]. The CFAbd-Score has been validated and shown to be sensitive in detecting differences between groups, with a higher CFAbd-Score previously being associated with a history of abdominal surgery, pancreatic insufficiency and intestinal inflammation in pwCF [15,28]. A reduction in CFAbd-Scores after commencing elexacaftor-tezacaftor-ivacaftor therapy has also been demonstrated [27]. The mechanisms driving GI symptoms in pwCF are likely to be multifactorial, reflecting a complex interplay between pancreatic maldigestion and intestinal malabsorption and a milieu of intestinal inflammation, gut dysbiosis, altered small intestinal transit time and small intestinal bacterial overgrowth (SIBO), as well as an impaired enterohepatic circulation [14,15,30].

We noted similarities between the reported GI symptoms in our participants with CFRD to those identified in the literature as commonly experienced by people with DM (pwDM). Of the nine specific symptoms previously reported as being more frequent in pwDM, we identified higher symptoms of nausea and bloating in pwCFRD compared to those without [12]. There was a trend towards higher levels of abdominal pain and acid reflux in pwCF with CFRD, symptoms which have an increased prevalence in pwDM [12]. The lack of statistical significance may reflect the small sample size. Interestingly, certain symptoms, which have a higher prevalence in pwDM, such as heartburn, vomiting, constipation, stool frequency ≥3 bowel motions/day or loose stool consistency occurred at similar rates in pwCF with and without CFRD [12]. This may simply reflect the presence of pancreatic maldigestion and other CF-disease specific factors such as altered pH, gastrointestinal transit times [30], inflammation [31], gut dysbiosis [32] and abnormal mucus in the GI tract [33], all of which still occur in the absence of CFRD [34]. In addition, all study participants had PI; if pancreatic enzyme replacement therapy (PERT) dosing is not optimal, then symptoms, such as diarrhoea and constipation, can arise [35].

Several factors may be driving this reported increase in GI symptom burden in pwCF and CFRD. For instance, DM is associated with autonomic and peripheral neuropathy and central nervous system (CNS) structural and functional changes, all of which can increase the presence and/or perception of GI symptoms [12]. In contrast, progressive neuropathy may also lead to reduced perception of symptoms which may influence findings.

It is also important to recognize the potential role of CFTR on neurological function as the protein is expressed in both the myenteric ganglia and CNS, where it can impact on neural innervation and autonomic function [36]. Potentially, pwCF and CFRD may have greater peripheral and CNS impairments resulting in accentuation of any impairments in GI motility and function. As altered intestinal transit times and SIBO are associated with both DM and CF, the combination of diabetes with CF may be accentuated in the presence of both pathologies and further drive symptoms [13,30,37]. These areas require further investigation, particularly whether the duration of CFRD is associated with a higher GI symptom burden.

Although there were significantly more females in the CFRD group, the increase in GI symptoms associated with CFRD was not attributable to sex differences. The number of IV antibiotic days, in the previous year, did not appear to exacerbate GI symptoms in either group. Independent to CFRD status, the use of H2 blockers resulted in an increased total CFAbd-Score as well as the 'disorders of bowel movement' and 'gastroesophageal reflux disease' domains. The sole presence of either H2 blocker medication or CFRD did not appear to induce significant differences in the 'GI-related quality of life' domain. The subgroup which included participants with both CFRD and H2 blockers, had the highest mean score in 'GI-related quality of life' domain with respect to the other three subgroups (CFRD without H2 blockers, non-CFRD with H2 blockers and non- CFRD without H2 blockers). Furthermore, no significant interaction was found between CFRD and H2 blocker medication for the total CFAbd-Score and the two domains ('gastroesophageal reflux disease' and 'disorders of appetite') which were significantly higher in those with CFRD compared to those without CFRD. This suggests that the presence of CFRD was increasing the burden of GI symptoms independent to H2 blocker use. There was no statistically significant difference in a number of variables including BMI and $ppFEV_1$ between the CFRD and non CFRD groups, which could have explained differences in GI scores. Other variables, such as diet as well as adherence to the use of PERT, were not accounted for in this study and may also be driving differences between the two groups. These findings are preliminary in nature and re-investigating these associations in a larger study would be valuable and allow for more detailed exploration of potential confounding factors and covariates, such as *CFTR* genotype, IV antibiotic exposure, enteral feeding, age, meconium ileus at birth, lung microbiology (including Aspergillus), impact of GI medications and long term exposure to glucocorticoids. We limited the number of statistical tests based on a priori-framework and addressed multiple testing with an approach based on controlling the false discovery rate control [23,24], however, we cannot preclude the risk of type I error with findings. Furthermore, when comparing the percentages of pwCF with CFRD and without CFRD reporting on experienced symptoms at least 4–7 times over the previous two weeks, marked differences were observed in other symptoms not included in the 9 key GI symptoms herein addressed. Although we did not perform exploratory analyses, those findings may serve as a reference for subsequent studies with larger cohorts and in longitudinal setups. Future studies could also compare differences in GI symptoms between those with normal glucose tolerance, impaired glucose tolerance and CFRD. A key strength of this study was the use of a validated CF-specific questionnaire with high content and construct-validity and known-groups validity [15,20,21].

5. Conclusion

In conclusion, the CFAbd-Score, as a validated CF-specific GI questionnaire, reveals for the first time, that people with CF and CFRD have a particularly high prevalence of GI symptoms. Future research is needed to further characterise these differences, assess changes with CFTR modulators, investigate the underlying causes and implement appropriate treatment strategies.

Conflict of interest

JGM reports independent grants and speaker/board honoraria from Vertex, Chiesi and Viatris outside the submitted work. DP speaker/board honoraria from Vertex. HW: Received previous funding from Gilead, which was not directly related to this research project and from Health Education England for simulated placement delivery funding. LRC, DS, AMJ, JB, JLW, RAF, CZ and FD declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT authorship contribution statement

L.R. Caley: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Project administration, Writing – original draft. **C. Zagoya:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. **F. Duckstein:** Writing – review & editing. **H. White:** Supervision, Writing – review & editing, Funding acquisition. **D. Shimmin:** Writing – review & editing. **A.M. Jones:** Resources, Writing – review & editing. **J. Barrett:** Investigation, Resources, Writing – review & editing. **J.L. Whitehouse:** Resources, Writing – review & editing. **R.A. Floto:** Writing – review & editing, Funding acquisition. **J.G. Mainz:** Conceptualization, Methodology, Writing – review & editing. **D.G. Peckham:** Conceptualization, Methodology, Writing – original draft, Supervision, Funding acquisition.

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