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The Dutch Gastrointestinal Symptom Tracker for People With Cystic Fibrosis: Associations With Anxiety, Depression, and Health-Related Quality of Life

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ABSTRACT

Background: People with CF (pwCF) frequently have gastrointestinal symptoms (GI), including abdominal pain and irregular bowel movements. These are often embarrassing, difficult to report, and frequently missed. Thus, a GI Symptom Tracker was created and validated in the USA and translated and validated in Dutch. This questionnaire consists of four subscales: Eating Challenges, Stools, Adherence Challenges, and Abdominal Symptoms. The aim of this study was to investigate the relationship between GI symptoms, anxiety/depression, and health-related quality of life (HRQoL) in Dutch pwCF.

Methods: In this prospective, cross-sectional single-center pilot study, pwCF completed the Dutch GI Symptom Tracker, GAD-7 (anxiety), PHQ-9 (depression), and CFQ-R (HRQoL) from September 2021 to June 2022. Regression analyses were used to analyze the univariable associations between GI symptoms, anxiety/depression, and HRQoL.

Results: A total of 51 pwCF were enrolled consecutively ($n = 41$ adults, 66% female, mean age (y) [range] = 32.7 [19–71] and $n = 10$ adolescents, 70% female, mean age (y) [range] = 14.2 [12–17]). Elevated levels of anxiety (scores ≥ 10 on GAD-7) were found in 17% of adults and 0% of adolescents. Elevated depression scores (≥ 10 on PHQ-9) were found in 9% of adults and 20% of adolescents. GI scales "Abdominal Symptoms" and "Stools" were significantly, positively associated with elevated symptoms of anxiety and depression. Most GI scales were associated with lower HRQoL.

Conclusion: This is the first study investigating the link between GI symptoms assessed by the Dutch GI Symptom Tracker and anxiety/depression and HRQoL in Dutch pwCF. More GI symptoms were associated with higher anxiety and depression scores and worse HRQoL. Additional research is needed to better understand how mental and physical health are linked in GI symptoms in CF.

Marieke Verkleij, Ageeth Hofsteenge, Alexandra Quittner - Dutch Translation of the Gastrointestinal (GI) Symptom Tracker for People with Cystic Fibrosis. (P247 Poster presentation by Verkleij) European Cystic Fibrosis Conference 2022, Rotterdam, the Netherlands, June 2022. Published: Journal of Cystic Fibrosis. DOI: 10.1016/S1569-1993(22)00576-8.

1 | Introduction

People with CF (pwCF) have frequent gastrointestinal (GI) symptoms, including abdominal pain and irregular bowel movements [1–3], which might contribute to significant morbidity and mortality [4, 5]. Modulator therapy has been shown to improve lung function and body weight in pwCF, however, the impact of these modulators on GI symptoms is ambiguous and relatively unknown [5–7].

Discussing GI symptoms can be embarrassing, since they are challenging to assess and often not reported to CF care team members. Besides, addressing GI symptoms during a pulmonary clinic visit might be challenging due to limited time and lack of standardized measurements. In case of any red flags related to GI symptoms or laboratory-radiological abnormalities, the (pediatric) gastroenterologist is consulted.

Despite the high prevalence of GI symptoms in this population there is little systematic data on the mechanisms underlying the development of these symptoms [1, 8]. Several pathophysiological mechanisms have been proposed, including malabsorption, altered GI motility, psychological factors, diet, and microbial dysbiosis [4, 9]. The majority of pwCF suffer from pancreatic insufficiency, leading to fat malabsorption, malnutrition, and abdominal discomfort, particularly when not appropriately treated [10]. The presence of biological factors, such as malabsorption, dysmotility, and microbial dysbiosis, but also related pain and discomfort, has been associated with the development of neurophysiological and behavioral symptoms [11], such as anxiety/depression and health-related quality of life (HRQoL) [12]. It is well-established that pwCF are at increased risk for developing symptoms of anxiety/depression with negative consequences for CF disease management, health outcomes, adherence to treatment, and HRQol [13–16]. This relationship between biological, GI-related factors and development neurophysiological and behavioral symptoms can be explained by the gut–brain axis theory, describing the bidirectional linkage between the nervous system and the GI tract. The gut–brain axis links emotional and cognitive centers with the peripheral intestinal functions [11, 17]. More studies are needed to examine the potential links between GI symptoms, psychological symptoms, and HRQoL in pwCF [18].

Given that GI symptoms may be embarrassing to report, difficult to assess, and often accompanied by substantial pain and disruptions of daily activities [19–24], a standardized instrument to measure these symptoms in pwCF, the GI Symptom Tracker, was developed by Dr. Quittner in collaboration with AbbVie Inc. (2017). This questionnaire consists of four subscales: Eating Challenges (4 items), Stools (8 items), Adherence Challenges (5 items), and Abdominal Symptoms (7 items). It has been developed to facilitate a standardized method of assessing the frequency and impact of GI symptoms, to improve communication between patient and provider, to open a dialog about strategies to reduce GI symptoms, improve medication adherence, and maintain increased calorie intake, all with the goal of improving patients' health outcomes. It was developed and validated in 11 CF centers in the USA ($n = 179$), demonstrating good reliability and validity [1]. The Dutch translation was recently completed [20].

The aim of this study was to investigate the relationship between GI symptoms, as measured by the Dutch GI Symptom Tracker, anxiety/depression, and HRQoL in Dutch pwCF. We hypothesized that GI symptoms would be associated with elevated levels of anxiety and depression and worse HRQoL.

2 | Methods

2.1 | Study Design

This was a cross-sectional pilot study conducted at a single CF center in the Netherlands. The medical ethics committee of Amsterdam University Medical Centers (Amsterdam UMC), the Netherlands, approved the study (METc_2021.0469). For this study, self-report questionnaires were completed by the participants and analyzed to asses GI symptoms (Dutch GI Symptom Tracker), anxiety (GAD-7), depression (PHQ-9), and HRQoL (CFQ-R).

2.2 | Participants and Procedure

All adolescents (12–17 y) and adults (aged $\geq$ 18 y) with CF visiting the outpatient clinic at the Amsterdam UMC between September 2021 and June 2022 were consecutively invited to participate in this prospective, cross-sectional observational study. All participants provided written informed consent.

Exclusion criteria included: unable to read or poor command of the Dutch language, established diagnosis of a nonfunctional gastrointestinal disease, such as inflammatory bowel disease, celiac disease, history of bowel surgery, and severe psychiatric dysfunction, including acute safety risk to self or others. Patients reporting suicidality on question 9 on the Patient Health Questionnaire (PHQ-9) were assessed further. Those reporting suicidal intent were excluded from this study and referred to their care provider.

All participants received either online questionnaires (see Section 2.3) through the clinical data management platform [25] or paper questionnaires through a member of their CF-multidisciplinary care team (pediatric psychologist, dietician, specialized nurse, or pediatrician).

2.3 | Measures

2.3.1 | Demographic and Clinical Variables

Variables such as age, gender, type of CFTR mutation, body mass index (BMI), and pancreatic insufficiency status were obtained from pwCF using a demographic questionnaire which was then verified with the medical record. Lung function (forced expiratory volume in 1 s) was assessed using the MasterScreen (Jaeger, CareFusion Corporation) during clinical visits. Before assessing lung function, short- or long-acting β_2-adrenergic agonists were stopped for 12 h.

2.3.2 | Questionnaires

2.3.2.1 | GI Symptom Tracker: Dutch Translation. The GI Symptom Tracker, a standardized instrument, has been developed and validated for ages ≥ 12 years through adulthood, demonstrating good reliability and validity [1]. The four subscales are as follows: Eating Challenges (4 items), Stools (8 items), Adherence Challenges (5 items), and Abdominal Symptoms (7 items), see Supporting Information S2: Supplement X. Scores are standardized on a 0–100 scale with higher scores indicating more symptoms/problems over the recall period, which was 1 week. Symptoms are rated using a 4-point scale ranging from 1 (*never/not at all*) to 4 (*almost always/a great deal*).

As a next step, two native Dutch speakers who also speak English, experts in CF (psychologist and dietician) translated the GI Symptom Tracker from English into Dutch [21].

Discrepancies were resolved to produce the "consensus forward" Dutch version, focusing on cultural equivalence and medical terms used by pwCF. The consensus measure was back-translated into English by two Dutch speakers with strong English skills, followed by a discussion to ensure the instructions, items, and rating scales conveyed the original meaning ("harmonization"). It was administered to 10 pwCF (aged 14–47) to perform cognitive testing to assess clarity of items and comprehensiveness.

The GI Symptom Tracker underwent all steps recommended by international Guidelines, viz. FDA Guidance on Patient-Reported Outcome Measures (2009). Participants reported that the GI Symptom tracker was brief (average of 4 min, ranging from 2 to 8 min), with most items perceived as relevant and providing valuable insights into GI symptoms. They recommended adding options "variable" and "Panzytrat" to the first question asking for a dose of enzymes per meal/snack, which have now been added to the Dutch version [21].

The Dutch GI Symptom Tracker, "Signaleringslijst maagdarmsymptomen voor mensen met CF" is now ready for clinical and research purposes, see Supporting Information S1: Supplement Y [21].

This is the first standardized measure of GI symptoms, enzyme, and nutrition adherence for Dutch pwCF. It provides a systematic assessment to increase effective treatment.

2.3.2.2 | Generalized Anxiety Disorder 7-Item (GAD-7, Dutch Version) [26]. The GAD-7 assesses anxiety symptoms. It consists of 7 items, each scored as 0 ("not at all"), 1 ("several days"), 2 ("more than half of the days"), or 3 ("nearly every day"). Total scores range from 0 to 21; scores of 5, 10, and 15 points are used as cut-off points for mild, moderate, and severe anxiety, respectively. The GAD-7 has excellent psychometric properties, including strong internal consistency (Cronbach's $\alpha = 0.85$) and convergent validity with DSM-V diagnostic criteria. Using a cut-off score of 10 or higher, sensitivity was 0.89 and specificity 0.82 [26, 27].

2.3.2.3 | Patient Health Questionnaire-9 (PHQ-9, Dutch Version) [28]. The PHQ-9 assesses depressive symptoms and consists of 9 items corresponding to DSM-V diagnostic criteria for major depression. It has demonstrated strong psychometric properties. Items are scored on a 4-point Likert scale: 0 ("not at all"), 1 ("several days"), 2 ("more than half of the days") or 3 ("nearly every day"). Scores range from 0 to 27, with higher scores indicating more severe depressive symptoms. Scores can be divided according to the level of severity: "minimal" (Scores 0–4), "mild" (Scores 5–9), "moderate" (Scores 10–14), "moderately severe" (Scores 15–19) and "severe" (Scores 20–27). The PHQ-9 also assesses suicidal ideation (question #9) which can accompany more severe depressive symptoms. Studies have shown that using a threshold score of 10 or higher has a sensitivity of 0.85 and a specificity of 0.89 [29].

2.3.2.4 | Quality of Life (CFQ-R, Dutch Version) [30]. The Cystic Fibrosis Questionnaire Revised (CFQ-R) is a self-report questionnaire to measure the physical, emotional, and social impact of CF and includes the following 12 domains: physical functioning, emotional functioning, social functioning, role functioning, body image, eating disturbances, treatment burden, health perceptions, respiratory symptoms, digestive symptoms, weight, and vitality. In this study two different versions of the CFQ-R, adapted for the age of the patient, were used: CFQ-R 12–13 yrs and CFQ-R 14–adulthood. This instrument is considered the "gold standard" quality of life measure for CF. It has well-established reliability and validity [31], differentiating those with mild, moderate, and severe CF and showing a response to therapeutic interventions [32, 33]. The Dutch version of the CFQ-R has been shown to have robust internal consistency and psychometric properties [30]. Higher scores indicate a better quality of life.

2.4 | Statistical Analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 28. Due to multiple testing, p values of < 0.001 (two-sided) instead of $p < 0.05$ were considered statistically significant.

Descriptive statistics were used to evaluate and summarize the demographic and clinical characteristics of the participants and the mean scores for the GI Symptom Tracker, GAD-7, PHQ-9, and CFQ-R.

Independent t-tests were used to examine differences in GI symptoms, anxiety, depression, and HRQoL between adults and adolescents. Regression analyses were used to analyze the univariable associations between GI symptoms, anxiety, depression, and HRQoL across the two groups. All regression analyses were adjusted for age, gender, BMI, and lung function.

3 | Results

3.1 | Participant Characteristics

A total of 106 participants (89 adults and 17 adolescents) with a confirmed diagnosis of CF were invited to participate in the study. This represented 48% of those eligible: 40 adults and 3

adolescents did not respond or return the questionnaires; 8 adults and 3 adolescents were not willing to participate and 1 adolescent died within the study period. Nonresponders were comparable in their demographic and medical characteristics. Thus, a total of 51 adults and adolescents completed the study.

Table 1 presents the demographic characteristics of adults and adolescents with CF. The mean lung function of adults was below average (< 80%). The majority of participants used CFTR modulators and were pancreatic insufficient.

3.1.1 | Prevalence of Anxiety and Depression

Table 2 shows mean scores and classification of anxiety and depression in adults and adolescents with CF. Elevated scores on anxiety (scores ≥ 10 on GAD-7) were reported by 17% of adults and 0% of adolescents, elevated scores on depression (scores ≥ 10 on PHQ-9) by 9% of adults and 20% of adolescents with CF. Adults reported more symptoms of anxiety ($p = 0.16$) and fewer symptoms of depression ($p = 0.58$) than adolescents, however, no significant differences were found in mean anxiety and depression scores between adults and adolescents.

3.1.2 | Gastrointestinal Symptoms and Health-Related Quality of Life

Table 3 shows mean scores of the Dutch GI Symptom Tracker and HRQoL in adults and adolescents. "Eating Challenges" and "Stools" had the highest/worst scores, highlighting the severity of these symptoms. No significant differences between adults and adolescents were found in mean scores across all GI-tracker domains and HRQoL (all CFQ-R domains).

As hypothesized, GI symptoms were significantly, positively associated with elevated symptoms of anxiety, depression, and worse HRQoL, see Table 4. More GI "Abdominal Symptoms" were significantly associated ($p < 0.001$) with elevated symptoms of anxiety and worse "Role Functioning" and "Digestive Symptoms." More GI "Stools" were significantly associated with elevated symptoms of anxiety and depression and worse "Physical Functioning," "Social Functioning," "Role Functioning," and "Digestive Symptoms." More GI "Eating Challenges" were significantly associated with worse "Role Functioning" and "Vitality." GI "Adherence Challenges" were not significantly associated.

4 | Discussion

This is the first study investigating associations between GI symptoms—assessed by the Dutch GI Symptom Tracker—, anxiety/depression and HRQoL in Dutch pwCF.

Elevated levels of GI symptoms and anxiety/depression were prevalent in pwCF. As hypothesized, more GI symptoms were associated with more symptoms of anxiety, depression, and worse HRQoL. In our data, "Eating Challenges" and "Stools" had the highest/worst scores, highlighting the severity of these symptoms; and the scales "Abdominal Symptoms" and "Stools" were significantly, positively associated with elevated anxiety/depression and worse HRQoL. In general, this study provided strong evidence of convergent and divergent validity, finding statistically significant relationships between GI symptoms and related domains of HRQoL, but no relationship to CFQ-R Respiratory Symptoms.

Recent studies have recognized the synergies between psychological symptoms, specifically depression, and changes in inflammation in the gut microbiota [12]. Our results suggest new targets for treatment (depression) that may reduce inflammation in the gut and improve HRQoL in pwCF and vice versa: targeting gut symptoms might reduce anxiety/depression and improve HRQoL. The treatment of CF has been transformed by the development of highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators, such as elexacaftor/tezacaftor/ivacaftor [34]. For many patients, this has led to improvements in lung function, respiratory symptoms, and sweat chloride concentrations [35]. However, the impact of modulators on GI symptoms is relatively unknown [7, 36]. Several studies on gastrointestinal patient-reported outcome measures (GI-PROMs) in relation to epithelial transport inhibitors (ETIs) and CFTR modulators in CF have shown promising results, including improved intestinal function, hepatobiliary complications, and decreased episodes of GI inflammation, illustrated by decreased fecal calprotectin levels [37, 38]. Nevertheless, PROMISE findings showed minimal change in GI symptoms after ETI [39].

Although quality of life may improve for many who started modulator treatment [40], a variety of negative side effects with potential impacts on safety and well-being have been reported, including neuropsychiatric changes [41]. In our study sample, the majority (68.2% of adults and 90% of adolescents) used modulators. Large epidemiologic studies are needed to better characterize these relationships.

Strengths and limitations should be considered. This is an innovative pilot study with clinical implications regarding assessing and treating GI symptoms. This study was limited by a relatively small sample size, especially of adolescents. A larger sample size would increase the statistical power of our analyses and improve their generalizability. However, even with this relatively small sample and an adjustment for multiple testing by using a significance cut-off value < 0.001, the predicted relationships between GI symptoms and mental health and quality of life were found to be statistically significant.

Another limitation is that some participants completed the measures online whereas others completed them in clinic; differences in the mode of administration may have led to response biases. An additional limitation is that only Dutch speakers participated in the study. Besides, there is a possibility of ascertainment bias, given that individuals with fewer symptoms or lower socioeconomic status may have been less inclined to share their screening outcomes for research purposes.

TABLE 1 | Demographic characteristics of adults and adolescents with CF, $n = 51$.

	Mean (SD), range	
	Adults ($n = 41$)	**Adolescents 12–18 yrs ($n = 10$)**
Age in years	32.7 (12.6), 19–71	14.2 (1.6), 12–17
Gender, % female	66%	70%
Genetic mutation (*n* %)		
F508del/F508del	21 (51.2)	10 (100)
F508del/other	13 (31.7)	
Other	7 (17.1)	
Use of CFTR modulator(s) (*n* %)	28 (68.3)	9 (90)
Tezacaftor + Ivacaftor (Symkevi)	2 (4.9)	
Lumacaftor + Ivacaftor (Orkambi)	1 (2.4)	
Ivacaftor + Tezacaftor + Elexacaftor (Kaftrio/Trikafta)	24 (58.5)	9 (90)
Ivacaftor (Kalydeco)	1 (2.4)	
No	13 (31.7)	1 (10)
Pancreatic function (*n* %)		
Sufficient	8 (19.5)	1 (10)
Insufficient, exocrine	17 (41.4)	9 (90)
Insufficient, both endocrine and exocrine	16 (39)	
GI-related diagnosis (*n* %)		
None	23 (56.1)	6 (60)
Constipation	6 (14.6)	3 (30)
Liver cirrhosis	4 (9.8)	
(Focal) steatosis hepatic	3 (7.3)	1 (10)
Crohn's disease	1 (2.4)	
Cyclic vomiting	1 (2.4)	
Chronic diarrhea	1 (2.4)	
Pancreatic cyst	1 (2.4)	
Gastroparesis	1 (2.4)	
Medication related to GI disease (*n* %)		
Laxatives *(including macrogol, lactulose, picroprep)*	8 (19.5)	1 (10)
Ursochol	5 (12.2)	4 (40)
Loperamide	1 (2.4)	
Ustekinumab	1 (2.4)	
Mean FEV_1 in % of predicted (SD)	72.1 (23.8)	83.6 (15.90)
BMI	22.2 (2.6), 18.6–28.4	20.2 (2.2), 17.1–24.4
Highest level of education	*N* (%)	
Low/Middle/High[a]	9 (23)/21 (54)/9 (23)	10 (100)
Average working hours per week[b]	*N* (%)	
0	17 (42)	NA
1–12	6 (15)	NA
13–24	7 (17)	NA
≥ 25	9 (22)	NA
Unknown	2 (5)	NA

(Continues)

TABLE 1 | (Continued)

	Mean (SD), range	
	Adults ($n = 41$)	**Adolescents 12–18 yrs ($n = 10$)**
Relational status[b]		
Single	21 (51)	NA
Married	10 (24)	NA
Living together with partner	10 (24)	NA
Use of medication other than CF medication		
Yes	14 (34)	2 (20)
No	27 (66)	8 (80)
Sport	*N* (%)	
Yes	30 (76)	7 (70)
No	10 (24)	3 (30)
Unknown	1 (2)	
Probiotic	*N* (%)	
Yes	11 (27)	0 (0)
No	30 (73)	10 (100)

Note: Endocrine pancreatic insufficiency was defined as impaired OGTT and CFRD. Exocrine insufficiency was defined as the use of PERT. In all patients using PERT, low fecal elastase or fat malabsorption as determined by fat balance had been established early at diagnosis.
Abbreviations: BMI = body mass index, FEV_1 = forced expiratory volume in 1 s, expressed as a percentage of the predicted value. Normal values of FEV_1 range between 80% and 120%.
[a]Education level, "Low": primary school or lower vocational secondary education, "Middle": intermediate general secondary education or intermediate vocational education, and "High": higher general secondary education, higher vocational education, or university education. High school ($N = 10$ adolescents).
[b]Question not asked in adolescents.

TABLE 2 | Anxiety and depression scores and categories.

	Adults ($n = 41$)	**Adolescents ($n = 10$)**	**Total group ($n = 51$)**
Anxiety (GAD-7)			
Total score (Mean (SD))	6.2 (4.8)	4.0 (2.9)	5.8 (4.5)
Category score, n (%)			
Normal range (score ≤ 4)	15 (37)	6 (60)	21 (41)
Mild range (score 5–9)	19 (46)	4 (40)	23 (45)
Moderate range (score 10–14)	4 (10)		4 (8)
Severe range (score ≥ 15)	3 (7)		3 (6)
Depression (PHQ-9)			
Total score (Mean (SD))	4.3 (5.1)	5.3 (4.1)	4.5 (4.9)
Category score, n (%)			
Normal range (score ≤ 4)	32 (78)	6 (60)	38 (74)
Mild range (score 5–9)	5 (12)	2 (20)	7 (14)
Moderate range (score 10–14)	1 (2)	2 (20)	3 (6)
Severe Moderate Severe (score 15–19)	2 (5)		2 (4)
Severe (score ≥ 20)	1 (2)		1 (2)

Abbreviations: GAD-7 = Generalized Anxiety Disorder 7-Item, PHQ-9 = Patient Health Questionnaire-9.

Moreover, in this study, no mechanism for the relationship between GI symptoms and mental health was examined. Therefore, additional studies are needed to identify and address factors that might influence GI symptoms, anxiety/depression, and HRQoL in pwCF. In a future study, we plan to investigate the gut microbiome and the influence of dietary intake to gain insights into their relationship to GI symptoms. Another future study should examine the complex interplay between GI

TABLE 3 | Scores of the Dutch GI Symptom Tracker and health-related quality of life (CFQ-R) in people with CF ($n = 51$).

	Adults ($n = 41$) Mean (SD)	Adolescents ($n = 10$) Mean (SD)	Total group ($n = 51$) Mean (SD)
Dutch GI Symptom Tracker domains			
Eating Challenges	53.3 (7.3)	50.2 (11.3)	52.7 (8.2)
Stools	44.7 (14.0)	46.2 (15.9)	45.0 (14.1)
Adherence Challenges	35.0 (12.0)	32.0 (13.8)	34.4 (12.3)
Abdominal Symptoms	39.0 (13.6)	35.2 (7.5)	38.3 (12.7)
Health-related quality of life (CFQ-R) domains			
Physical Functioning	79.9 (21.1)	85.4 (12.5)	81.0 (19.8)
Emotional Functioning	76.7 (19.8)	84.7 (15.1)	78.3 (19.1)
Social Functioning	74.3 (17.2)	66.7 (17.6)	72.8 (17.3)
Role Functioning	81.1 (18.2)	78.3 (23.3)	80.6 (19.1)
Body Image	87.8 (21.3)	82.2 (28.8)	86.7 (22.8)
Eating Disturbances	91.1 (15.0)	97.8 (7.0)	92.4 (14.0)
Treatment Burden	76.4 (22.7)	72.2 (7.9)	75.6 (20.6)
Health Perceptions	63.7 (19.2)	68.9 (27.1)	64.7 (20.8)
Respiratory Symptoms	84.3 (13.3)	82.8 (14.0)	84.0 (13.3)
Digestive Symptoms	74.8 (21.4)	81.1 (12.9)	76.0 (20.0)
Weight	81.3 (25.9)	86.7 (32.2)	82.4 (27.0)
Vitality	62.0 (18.4)	64.2 (14.2)	62.4 (17.5)

Note: Dutch GI Symptom Tracker, Dutch Gastrointestinal Symptom Tracker. Scores are standardized on a 0–100 scale; higher scores indicate more symptoms/problems over the past week. CFQ-R, Cystic Fibrosis Questionnaire Revised. Scores are standardized on a 0–100 scale; higher scores indicate less symptoms/problems over the past week.

symptoms, systemic inflammatory markers, and mood disorders in CF, given that these systems seemed to be linked in the gut–brain axis [12].

Studying the relationship between these systemic inflammatory markers, GI symptoms, and mood disorders can provide insight in the underlying mechanisms, identify biomarkers for disease activity and treatment response, and develop targeted therapeutic interventions. A clear relationship between gut and brain has been described in other diseases, like inflammatory bowel disease and functional GI disorders [42, 43], but data on CF and gut–brain axis are yet limited.

4.1 | Clinical Implications

Our results confirmed the association between GI symptoms and mental health (e.g. anxiety/depression) in pwCF. This reinforces the importance of mental health screening and psychological care, which is already embedded in many CF centers in the Netherlands with the inclusion of a psychologist/social worker as part of the multidisciplinary team [15]. In the CF mental health guidelines, annual mental health screening and treatment is recommended beginning at age 12 through adulthood [13]. National implementation of these guidelines has been highly successful [44], partly because of the development of a mental health "toolbox" and additional mental health training sessions at national conferences.

Although an association was observed between the presence of GI symptoms and mental health, any conclusions on causality could not be drawn because the underlying mechanism for this relationship was not examined in this study. This should be a target of future studies.

Further intensification of the collaboration with gastroenterologists is warranted for pwCF if these GI problems are complex and challenging to assess and address during routine pulmonary visits.

The Dutch GI Symptom Tracker is now available. It can be used to facilitate collaborative patient–provider discussions to manage GI symptoms, guide nutritional interventions, and improve adherence to pancreatic enzymes to improve outcomes in cystic fibrosis. Therefore, we recommend that the Dutch GI Symptom Tracker can be implemented into regular CF care in Dutch CF centers. GI screening can be incorporated into the International Mental Health Guidelines [13] as well.

In conclusion, this is the first study investigating the association between GI symptoms, assessed by the Dutch GI Symptom Tracker, anxiety/depression, and HRQoL in Dutch pwCF. We observed a significant, positive association between more GI symptoms and elevated anxiety, depression, and worse HRQoL Additional research is needed to better understand how mental and physical health are linked in CF.

TABLE 4 | Unstandardized regression coefficients, confidence interval, and *p* values regarding the associations between GI symptoms, anxiety, depression, and health-related quality of life in people CF ($n = 51$).

	GI abdominal symptoms	GI stools	GI eating challenges	GI adherence challenges
Anxiety (GAD-7)	1.13 (0.39 to 1.88) $p < 0.001$	1.22 (0.37 to 2.07) $p < 0.001$	0.13 (−0.42 to 0.68) $p = 0.63$	−0.47 (−1.21 to 0.27) $p = 0.21$
Depression (PHQ-9)	0.88 (0.16 to 1.60) $p = 0.02$	1.10 (0.30 to 1.90) $p < 0.001$	0.41 (−0.09 to 0.91) $p = 0.10$	−0.65 (−1.33 to 0.02) $p = 0.06$
Health-related quality of life (CFQ-R) Domains				
Physical Functioning	−0.24 (−0.42 to −0.06) $p = 0.01$	−0.32 (−0.52 to −0.12) $p < 0.001$*	−0.16 (−0.29 to −0.04) $p = 0.01$	0.02 (−0.16 to 0.20) $p = 0.87$
Emotional Functioning	−0.19 (−0.39 to −0.00) $p = 0.05$	−0.18 (−0.40 to 0.04) $p = 0.10$	−0.05 (−0.18 to 0.08) $p = 0.45$	0.12 (−0.07 to 0.30) $p = 0.21$
Social Functioning	−0.18 (−0.39 to 0.04) $p = 0.10$	−0.36 (−0.58 to −0.14) $p < 0.001$*	−0.13 (−0.27 to 0.02) $p = 0.08$	0.10 (−0.10 to 0.30) $p = 0.30$
Role Functioning	−0.29 (−0.47 to −0.12) $p < 0.001$*	−0.42 (−0.61 to −0.23) $p < 0.001$*	−0.23 (−0.35 to −0.12) $p < 0.001$*	−0.04 (−0.23 to 0.14) $p = 0.64$
Body Image	−0.14 (−0.30 to 0.03) $p = 0.12$	−0.02 (−0.21 to 0.17) $p = 0.85$	0.01 (−0.10 to 0.12) $p = 0.86$	0.16 (0.01 to 0.31) $p = 0.04$
Eating Disturbances	−0.32 (−0.59 to −0.04) $p = 0.02$	−0.24 (−0.56 to 0.08) $p = 0.13$	−0.11 (−0.30 to 0.08) $p = 0.23$	0.13 (−0.13 to 0.39) $p = 0.32$
Treatment Burden	−0.13 (−0.30 to 0.04) $p = 0.14$	−0.26 (−0.45 to −0.07) $p = 0.01$	−0.01 (−0.13 to 0.11) $p = 0.89$	0.09 (−0.07 to 0.25) $p = 0.26$
Health Perceptions	−0.25 (−0.43 to −0.08) $p = 0.01$	−0.21 (−0.42 to −0.01) $p = 0.04$	−0.02 (−0.15 to 0.10) $p = 0.70$	0.20 (0.03 to 0.36) $p = 0.02$
Respiratory Symptoms	−0.15 (−0.42 to 0.12) $p = 0.28$	−0.15 (−0.46 to 0.15) $p = 0.32$	−0.04 (−0.22 to 0.14) $p = 0.67$	−0.01 (−0.27 to 0.24) $p = 0.92$
Digestive Symptoms	−0.35 (−0.51 to −0.20) $p < 0.001$*	−0.36 (−0.55 to −0.18) $p < 0.001$*	−0.001 (−0.13 to 0.13) $p = 0.99$	0.02 (−0.15 to 0.20) $p = 0.79$
Weight	−0.17 (−0.29 to −0.04) $p = 0.01$	−0.09 (−0.24 to 0.06) $p = 0.23$	−0.01 (−0.10 to −0.08) $p = 0.81$	0.15 (0.03 to 0.26) $p = 0.02$
Vitality	−0.15 (−0.36 to 0.06) $p = 0.16$	−0.20 (−0.43 to 0.04) $p = 0.10$	−0.20 (−0.33 to −0.07) $p < 0.001$*	0.09 (−0.11 to 0.28) $p = 0.37$

*$p < 0.001$ considered as significant.
Note: Abbreviations: CFQ-R = Cystic Fibrosis Questionnaire Revised, GAD-7 = Generalized Anxiety Disorder 7-Item, PHQ-9 = Patient Health Questionnaire-9. Adjusted for BMI, age, gender, lung function.

Author Contributions

Marieke Verkleij: conceptualization, investigation, funding acquisition, writing – original draft, methodology, validation, visualization, writing – review and editing, formal analysis, project administration, data curation, supervision, resources. **Berber Vlieg-Boerstra:** conceptualization, writing – review and editing, formal analysis, supervision. **Geesje H. Hofsteenge:** conceptualization, writing – review and editing, resources, data curation. **Eric Haarman:** supervision. **Jos Twisk:** software, formal analysis, writing – review and editing, validation, methodology. **Alexandra L. Quittner:** writing – review and editing, conceptualization, supervision. **Tim de Meij:** conceptualization, investigation, funding acquisition, writing – review and editing, supervision.

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Conflicts of Interest

Marieke Verkleij reports grants from the Dutch Cystic Fibrosis Foundation and consulting and speaker's fees from Vertex Pharmaceuticals. Berber Vlieg-Boerstra reports research funding from Nutricia, consulting or speaker's fees from ViniMini, Nestlé, and Nutricia. Alexandra L. Quittner reports research funding from the FDA (Food and Drug Administration), CF Foundation; consulting and speaker's fees from Vertex Pharmaceuticals; licensing fees through IQVIA.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.