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Original Article

The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study

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Quality of life

BACKGROUND: Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by a deficiency of lipoprotein lipase leading to extreme hypertriglyceridemia. Patients' burden of illness and quality of life have been poorly addressed in the literature.

OBJECTIVE: To understand the ways in which FCS impacts patients' lives.

METHODS: Investigation of Findings and Observations Captured in Burden of Illness Survey (IN-FOCUS) was a global web-based survey open to patients with FCS. Survey questions captured information on diagnostic experience, symptoms, comorbidities, disease management, and impact on multiple life dimensions.

RESULTS: Of 166 patients in 10 countries, 62% were from the United States and 70% were male. Median age at the time of the survey was 33 years, and median age at diagnosis was 9 years. Patients saw a mean of 5 physicians from different specialties before their FCS diagnosis and experienced multiple physical, emotional, and cognitive symptoms on a daily to monthly basis; 40% were admitted to the hospital in the past year. A lifetime mean of 13 episodes occurred in the 40% of patients with FCS-related acute pancreatitis. Most patients (>90%) found managing fat intake to be difficult, and 53% experienced symptoms despite adherence to their diets. FCS impacted employment status (94%), emotional/mental well-being (58%–66%), and social relationships (68%–82%).

CONCLUSIONS: Patients with FCS experience significant clinical and psychosocial burdens that reduce their quality of life and limit employment and social interactions. Increased awareness among healthcare professionals of the multifaceted nature of the FCS disease burden may help expedite diagnosis and timely institution of treatment and broaden management considerations.

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Introduction

Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by extremely high serum levels of triglycerides (TG), on a persistent basis, caused by reduced or absent lipoprotein lipase (LPL) activity.[1] In 80% to 90% of patients, the function of LPL is limited or impaired because of loss-of-function mutations in the *LPL* gene encoding the LPL protein, but rarer mutations in genes such as *APOA5, APOC2, LMF1,* and *GPIHBP1* that encode for cofactors and transport proteins important for adequate LPL function have also been described.[1,2] LPL catalyzes the hydrolysis of plasma TG and uptake of fatty acids into peripheral tissues such as muscle and adipose tissue; in the absence of LPL activity, excessive levels of chylomicrons accumulate in plasma, with fasting plasma TG values usually being well in excess of 1000 mg/dL.[1]

Despite its rarity, FCS affects an estimated 3000 to 5000 patients globally, and its effects can be devastating and even fatal.[1] Patients with FCS present with a variety of signs and symptoms, such as nausea, vomiting, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, recurrent episodes of mild to incapacitating abdominal pain, failure to thrive, and severe and recurrent episodes of acute pancreatitis (AP).[1,2] The complication of greatest concern is AP, which not only may lead to chronic pancreatic functional impairment after a single attack but may also be life threatening.[3] Recurrent AP occurs in ≥50% of FCS patients; the overall associated mortality rate is 5% to 6%, but it increases to 30% in subgroups of markedly hypertriglyceridemic patients who experience pancreatic necrosis following an infected pancreatic abscess or persistent multiple organ failure.[2,4]

The mainstays of symptom management are dietary restriction of total fat intake, abstinence from alcohol, and avoidance of medications known to increase TG levels, such as thiazides, beta blockers, and exogenous estrogen.[1,5,6] Lipid-lowering agents such as fibrates, omega-3 fatty acids, and niacin are generally ineffective, primarily because they act by reducing the hepatic output of very low-density lipoproteins or by enhancing LPL activity.[2,5] To reduce plasma TG levels, patients must restrict their total fat intake to no more than 10% to 15% of calories. Adherence to dietary restrictions of this severity over a patient's lifetime is difficult, negatively impacts quality of life, and does not completely obviate the risk for pancreatitis in all patients.[2]

Acute clinical manifestations of FCS, such as AP, have been well documented, but other manifestations, such as pain, cognitive impairment, and psychosocial effects, have been less well described. Thorough description of these FCS indicators could improve physician's ability to recognize the signs and symptoms of the disease, understand the heterogeneity of the disease, and, ultimately, lead to better, more rapid disease management. The Investigation of Findings and Observations Captured in Burden of Illness Survey in FCS Patients (IN-FOCUS) was a multinational web-based survey conducted to characterize and quantify the burden of illness associated with FCS across all possible dimensions from the patient's perspective, add to the literature base of FCS, and inform more comprehensive description of FCS for the medical community. The survey collected data on initial experience with FCS, diagnosis, symptoms, comorbidities, management, and impact on different dimensions of life. Findings from an interim analysis of this study based on 60 patients from the United States have been published.[7] That initial report highlighted the difficulty of diagnosing FCS, its multiplicity of symptoms and comorbidities, its impact on patients' physical, emotional, and cognitive functioning, and its interference with patients' employment and productivity. The current report, which presents an updated analysis from IN-FOCUS, expands on the interim analysis to characterize the burden of illness in a larger global cohort.

Patients and methods

Study design

IN-FOCUS was an online, anonymous, quantitative research study consisting of a web-based survey, conducted in patients with diagnoses of FCS. The study design and patient selection have been detailed elsewhere[7] and are summarized here. All research materials were approved by the institutional review board of the University of Mississippi.

Data from the web-based survey were collected from respondents in 10 countries (Australia, Canada, Germany, India, Netherlands, Portugal, Spain, Sweden, United Kingdom, and United States) between June 24, 2016, and February 24, 2017. It was designed to capture current and retrospective data about the experience of living with FCS as self-reported by eligible patients with FCS. Survey questions were derived from established patient-reported outcomes assessments, including the Short-Form 36 Health Survey and the Pancreatitis Quality of Life Instrument, and from consultation with expert physicians, dieticians, and patients. A sampling of questions from the survey is shown in Supplementary Figure S1.

Patients

Patients were recruited through flyers, word of mouth, and social media outlets. Physicians with experience treating FCS were provided with informational flyers to share with eligible or interested patients. Patients

Table 1 Baseline demographics and characteristics

Patient characteristics	Patients (n = 166)
Sex (male)	116 (69.9)
Age at time of survey, y	
Median (range)	33 (18–59)
0–10	0 (0)
11–20	8 (4.8)
21–30	69 (41.6)
31–40	46 (27.7)
41–50	30 (18.1)
51–60	13 (7.8)
Age at FCS diagnosis, y	
Median (range)	9 (1–57)
0–10	121 (72.9)
11–20	28 (16.9)
21–30	5 (3.0)
31–40	5 (3.0)
41–50	5 (3.0)
51–60	2 (1.2)
Country of residence	
United States	103 (62.0)
Canada	37 (22.3)
Australia	9 (5.4)
United Kingdom	9 (5.4)
Germany	2 (1.2)
Sweden	2 (1.2)
India	1 (0.6)
Netherlands	1 (0.6)
Portugal	1 (0.6)
Spain	1 (0.6)
Family history of FCS	
Yes	119 (72)
No. of physicians seen before diagnosis, n	
Mean	5
1–3	37
4–6	85
7–9	1
≥10	8
Physician who made the diagnosis	
Endocrinologist	34 (20)
Pancreatologist	20 (12)
Pediatrician	16 (10)
Lipidologist	10 (6)
Cardiologist	6 (4)
Primary care physician	6 (4)
Metabolic specialist	6 (4)
Nephrologist	4 (2)
Dermatologist	3 (2)
Surgeon	1 (1)
Other	6 (4)
Unable to recall	54 (33)
Patients with genetically confirmed diagnosis	10 (6)
Patients with misdiagnoses	79 (48)
Most common misdiagnoses	
Hypertriglyceridemia	37 (47)
Acute pancreatitis of unknown cause	33 (42)

FCS, familial chylomicronemia syndrome.
Values are n (%) unless stated otherwise.

completed a series of screening questions online to determine their eligibility to participate.

Eligible patients met the following criteria: ≥18 years of age, diagnosis of FCS or Fredrickson type 1 Hyperlipoproteinemia or LPL deficiency or high TG level with a history of pancreatitis or high TG level with a history of severe abdominal pain requiring hospital admission, fasting TG level ≥750 mg/dL (8.4 mmol/L) determined by the most recent fasting TG test or fasting TG level <750 mg/dL determined by the most recent fasting TG test with self-reported diet management to minimize fat content, and no participation in a clinical trial for FCS investigational treatment(s) in the previous 6 months. In addition, 1 of the following 4 criteria had to be met: personal history of TG-induced AP in the absence of another known cause, history of recurrent abdominal pain requiring emergency department visit/hospital admission attributed to high TG levels in the absence of another known cause, family history compatible with FCS or Fredrickson type 1 Hyperlipoproteinemia in the absence of another known cause, or genetic diagnosis consistent with FCS.

Statistical analysis

The final data cutoff date for these analyses was February 24, 2017. Complete data are presented for all cohorts except that from the United Kingdom, which continued to accrue patients after the data cutoff date. Categorical variables were analyzed descriptively as frequencies and percentages of occurrence for each category. Continuous variables, including rating scales, were presented as means and standard deviations or as medians with ranges. Analyses were conducted using SPSS Statistics 22 (IBS, Armonk, NY).

Results

Patient sample

A total of 600 patients were screened (answered ≥1 question); of the 217 patients who qualified, 166 completed the questionnaire. Demographic and baseline characteristics of respondents are summarized in Table 1. Most respondents were from the United States (62.0%) and Canada (22.3%), and 70% of the population was male. Median (range) age of respondents was 33 years (18–59 years), and median (range) age at FCS diagnosis was 9 years (1–57 years). The diagnosis was made in nearly three-fourths of patients (72.9%) by the time they were 10 years of age.

Journey to FCS diagnosis

Patients were seen by a mean of 5 physicians before a diagnosis of FCS was made (Table 1). However, 8 patients reported visiting ≥10 physicians, and 1 patient visited up

to 30 physicians. The most common specialists to make the FCS diagnosis were endocrinologists, pancreatologists, and pediatricians. Misdiagnoses were common; 79 patients (48%) reported receiving a misdiagnosis before receiving a correct diagnosis. FCS was most commonly misdiagnosed as hypertriglyceridemia (47%) and AP of unknown cause (42%).

Symptoms

A list of 41 symptoms encompassing physical, emotional, and cognitive domains associated with FCS was developed through consultation with the published literature, medical experts, and patients. Patients rated the severity and frequency of symptoms on a Likert scale (range, 1–7; 1 = very mild, 7 = very severe) for the preceding 12 months.

The incidence, frequency, and severity at which patients experienced physical, emotional, and cognitive symptoms at their highest severity are shown in Figures 1–3, respectively. The size of each sphere on the figures reflects the rate at which each symptom was reported. The most commonly reported physical symptoms were generalized abdominal pain (41%), bloating (37%), feeling of physical weakness (asthenia, 30%), indigestion (27%), and fatigue (23%) (Table 2). In general, patients reported experiencing these symptoms twice a week to once every 2 weeks (Fig. 1). The 4 most common emotional symptoms were constant uncertainty about the possibility of an attack of AP or pain at any time (34%), anxiety/fear/worry about health because of FCS (26%), uncertainty about what or how much to eat (20%), and feeling out of control/helpless because of FCS (17%) (Table 2). Patients experienced these symptoms several times a week to once monthly (Fig. 2). Cognitive symptoms included difficulty in concentrating (16%), impaired judgment (11%), brain fog (8%), and forgetfulness (8%); patients experienced these symptoms daily or every other day (Fig. 3).

In general, sex differences were not observed in a majority of physical and emotional symptoms experienced by patients (Supplementary Table S1). However, there was a greater prevalence of selected physical and cognitive differences of FCS symptoms reported in females compared to males, including steatorrhea (22% vs 9%), difficulty in hearing (10% vs 2%), anxiety in food-related social situations (26% vs 13%), impaired judgement (22% vs 7%), and brain fog (16% vs 5%).

Comorbid conditions

Patients with FCS often have multiple comorbidities. At least one-third of the patients reported 2 or more comorbidities, including AP (40%), eating disorders (23%), diabetes (16%), chronic pancreatitis (11%), hepatomegaly (11%), splenomegaly (10%), hypertension (10%), lipemia retinalis (9%), peripheral neuropathy (7%), addiction to pain medication such as opioids (5%), other conditions (5%), and pancreatic calcification (2%) (data not shown). Overall, in the 12 months before the survey, patients with

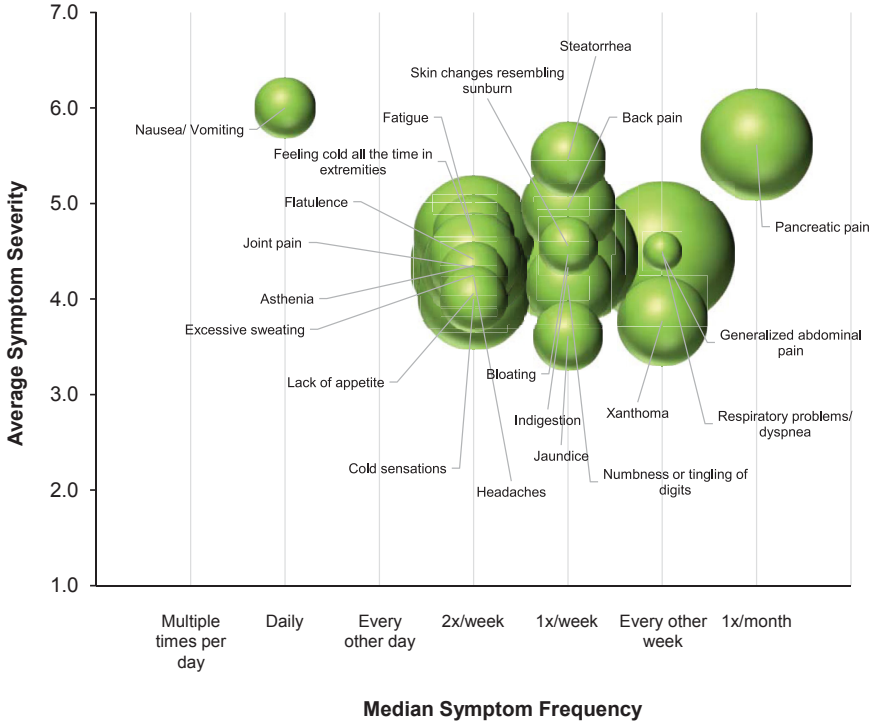

Figure 1 Physical symptoms at their worst or most severe. For each symptom selected, patients indicated symptom severity and frequency. Severity was recorded on a Likert scale (range, 1–7; 1 = very mild, 7 = very severe). Frequency was recorded by selection from the following options: multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size in the chart is proportional to the percentage of patients who selected each symptom.

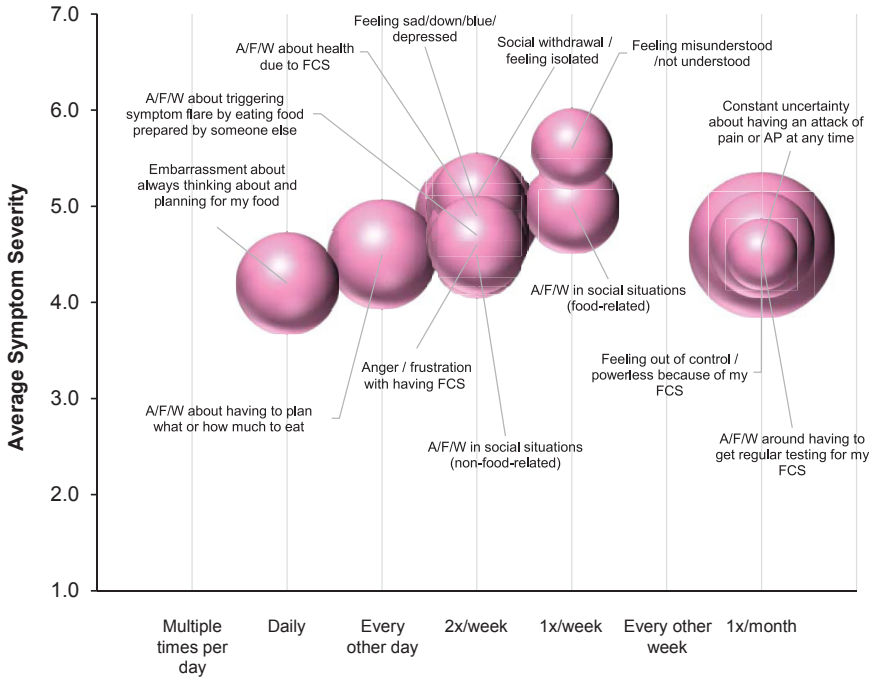

Figure 2 Emotional symptoms at their worst or most severe. For each symptom selected, patients indicated symptom severity and frequency. Severity was recorded on a Likert scale (range, 1–7; 1 = very mild, 7 = very severe). Frequency was recorded by selection from the following options: multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size in the chart is proportional to the percentage of patients who selected each symptom.

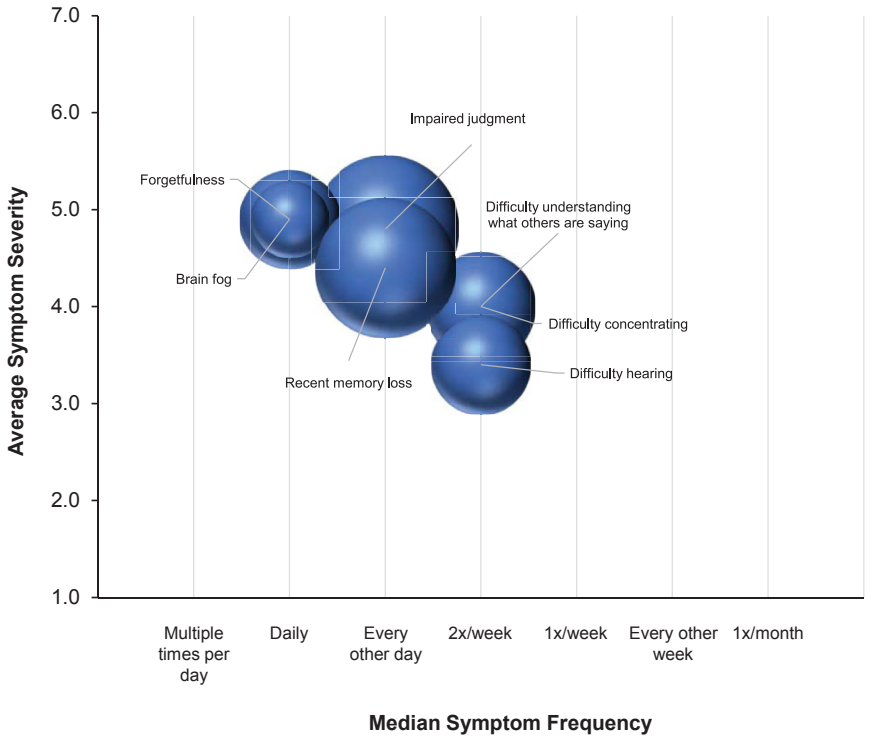

Figure 3 Cognitive symptoms at their worst or most severe. For each symptom selected, patients indicated symptom severity and frequency. Severity was recorded on a Likert scale (range, 1–7; 1 = very mild, 7 = very severe). Frequency was recorded by selection from the following options: multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size in the chart is proportional to the percentage of patients who selected each symptom.

FCS visited their doctors 7 times (routine visits), urgent care 2 times, hospital as outpatient 3 times, and hospital as inpatient 1 time (hospital stay, 4 nights) and underwent laboratory tests on a monthly basis (data not shown).

Forty percent of patients with FCS experienced ≥1 episode of AP; a mean of 2 episodes occurred in the past 12 months, and 13 episodes occurred in their lifetimes (Fig. 4). These patients visited the hospital as outpatients 5 times and as inpatients 6 times in their lifetimes. Approximately 50% of patients reported that they visited the hospital (as inpatients or outpatients) for every AP episode, and approximately 25% reported that they had been readmitted to the hospital within 30 days of discharge.

Disease management

Patients reported using a median of 6 different strategies to manage FCS. Most patients (91%) managed their disease by restricting fat intake, but one-third practiced routine fasting to avoid symptoms (Fig. 5). In addition, >50% of patients used TG-lowering medication or avoided alcohol or drugs known to increase TG levels. Most patients reported that managing their symptoms was extremely time-consuming (81%) and energy-draining (70%), and their approach was rigid/prohibitive (Supplementary Fig. S2). Although approximately two-thirds of patients (67%) reported that their current approach was effective, 53% experienced symptoms despite adherence to their diets.

Table 2 Frequency of symptoms when most severe: physical, emotional, and cognitive

Physical, % (21 symptoms)				Emotional, % (13 symptoms)				Cognitive, % (7 symptoms)	
Generalized abdominal pain	41	Back pain	16	Constant uncertainty about having an attack of pain or acute pancreatitis at any time	34	Feeling out of control/ powerless because of my FCS	17	Difficulty concentrating	16
Bloating	37	Numbness or tingling of digits	14	A/F/W about health due to FCS	26	Anger/frustration with having FCS	17	Impaired judgment	11
Asthenia	30	Headaches	14	A/F/W about having to plan what or how much to eat	20	A/F/W in social situations (nonfood related)	15	Brain fog	8
Indigestion	27	Steatorrhea	13	Embarrassment about always thinking about and planning for my food	20	Social withdrawal/ feeling isolated	13	Forgetfulness	8
Lack of appetite	25	Excessive sweating	11	Feeling sad/down/ blue/depressed	18	Feeling misunderstood/ not understood	11	Difficulty understanding what others are saying	5
Fatigue	23	Jaundice	10	A/F/W about triggering symptom flare by eating food prepared by someone else	18	A/F/W around having to get regular testing for my FCS	11	Recent memory loss	5
Joint pain	22	Cold sensations	9	A/F/W in social situations (food related)	17			Difficulty hearing	4
Pancreatic pain	19	Nausea/vomiting	8						
Feeling cold all the time in extremities	18	Skin changes resembling sunburn	8						
Flatulence	18	Respiratory problems/ dyspnea	4						
Xanthoma	17								

A/F/W, anxiety/fear/worry; FCS, familial chylomicronemia syndrome.

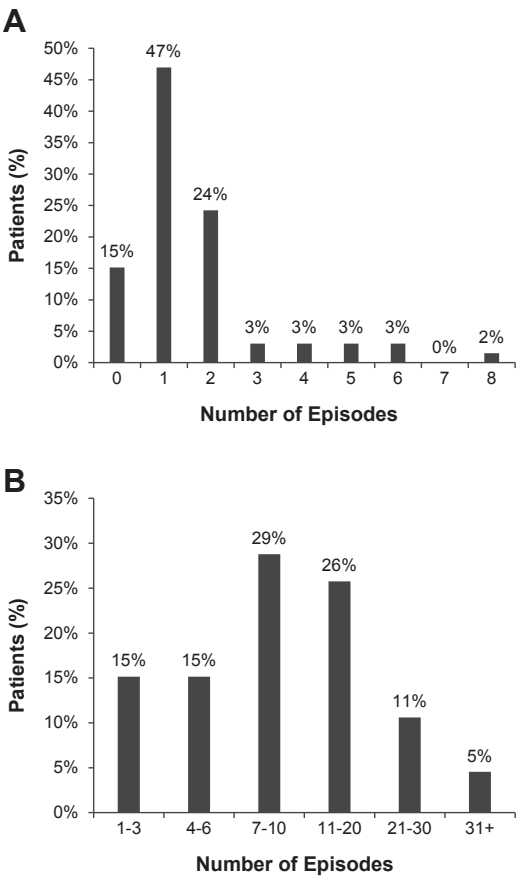

Figure 4 Number of acute pancreatitis episodes experienced by patients with FCS, who reported acute pancreatitis as a comorbidity. (A) Past 12 months. (B) Lifetime.

The recommended daily fat intake for the overall US population is 44 g to 78 g.[8] Most patients tried to limit their daily fat intake to 18 g to 25 g (equivalent to fat content of approximately 1–1.5 tbsp olive oil), but doing so was difficult for 93% of patients (Supplementary Fig. S2). When they exceeded the recommended dietary fat limit, patients most commonly reported feeling fearful, annoyed, anxious, helpless, or sick/ill (Supplementary Fig. S3).

In general, although patients were satisfied with their current treatment providers, they were less satisfied with their historical experience with FCS professionals (Supplementary Fig. S4). The proportion of patients who trusted their medical professionals to treat their condition properly and who felt they were more knowledgeable about their condition than most physicians were similar (46% and 45%, respectively). Between 26% and 45% of patients felt that some medical professionals did not understand their disease, made them feel guilty or responsible for their symptoms, gave advice that would have worsened symptoms, or seemed unsympathetic.

Impact of FCS on patients' employment and personal and social well-being

Thirty-two percent of patients reported that FCS significantly interfered with their lives (Fig. 6). Sixty percent of patients with FCS were employed full time or part time; among those who were unemployed or employed part time, 94% felt that their employment status was due, by varying extent, to FCS (Supplementary Fig. S5). Most of those who were unemployed (76%) had been employed in the past, and 65% of this group attributed their unemployment to FCS. Among homemakers, 40% felt their lack of employment opportunities was due to FCS.

When questioned about their relationships and social activities, patients said the greatest negative impacts of FCS were on their ability to travel for work or leisure (48%) and on whether to have children at all or on how many children to have (44%) (Fig. 7). Approximately 75% of respondents felt their social lives were restricted because of the need to plan in advance for food, stress from having to carry prepared food, not eating or not being able to share offered food, stress on their families, difficulty friends and families experienced in trying to understand FCS, exhaustion because of constantly having to explain FCS, difficulty being spontaneous, and feeling like a burden to others (Supplementary Fig. S6). By contrast, 70% of respondents reported that FCS strengthened their relationship with their spouse (Supplementary Fig. S7).

The mental and emotional well-being of nearly two-thirds of patients was significantly affected by FCS, particularly with respect to anxiety and feelings of self-worth (Supplementary Fig. S8). Most patients (71%–87%) expressed concern about the potential long-term impact of FCS on their health and other aspects of their lives, including worsening of their condition with age, long-term effects of FCS on health, ability to lead a normal life, and losing their jobs or becoming unable to work because of FCS (Supplementary Fig. S9).

Discussion

This report of the global IN-FOCUS study outlines the burden of FCS and the challenges associated with managing this disease throughout a patient's lifetime by providing a comprehensive inventory of the factors underlying the disease burden. These results highlight the difficulty of obtaining a correct diagnosis, the clinical burden of a disease with frequent and painful symptoms that often lead to hospital admission, and the limitations on employment and overall social and emotional function. This study expands on the interim report and on study-based patient interviews and discussions, all of which highlight the multidimensional impact of FCS on quality of life.[7,9] Furthermore, this report highlights the fact that FCS manifests itself not only through physical disease characteristics, including AP, but also describes the emotional, social, and cognitive symptoms many patients with FCS experience as a precursor to, or independent from, AP and other physical manifestations. This detailed report on the disease burden of FCS has the potential to impact the journey to diagnosis and to expedite the

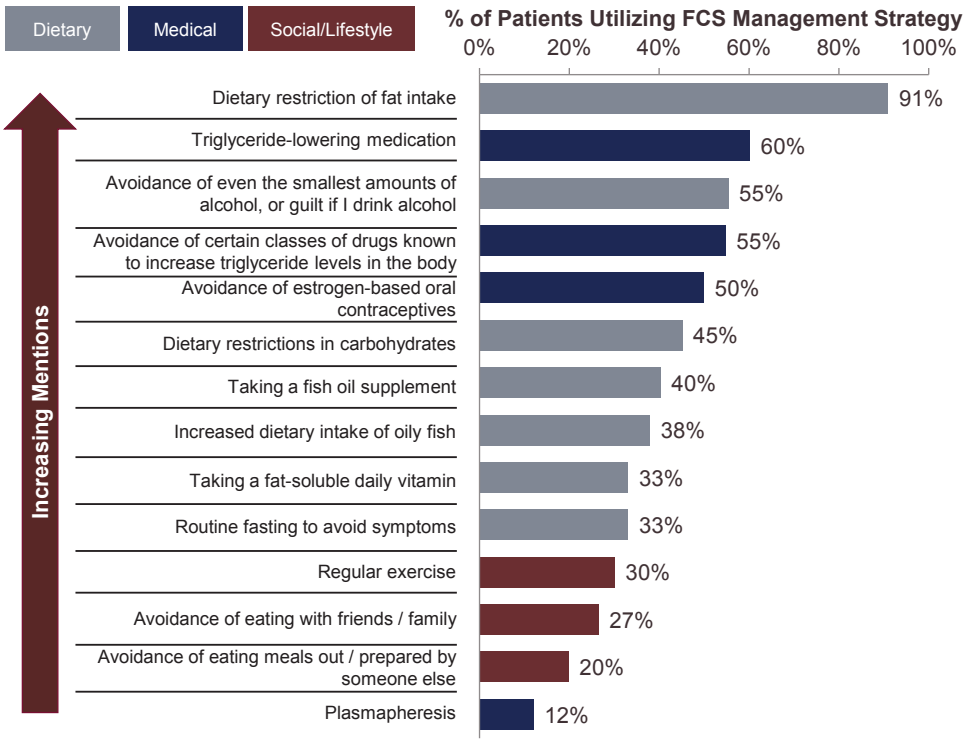

Figure 5 Management strategies used by patients with FCS. Response percentages may total >100% because respondents may use >1 strategy.

development of appropriate strategies for symptom and disease management.

As in the interim analysis,[7] patients in this study visited a mean of 5 physicians (range, 1–30) before receiving a definitive diagnosis of FCS, suggesting a potential delay in receiving appropriate care. The high frequency of both misdiagnosis and appropriate diagnosis from different medical specialists indicates a lack of awareness of FCS among medical practitioners and a need for stronger educational initiatives. Delay in diagnosis is a particular issue in rare diseases because it results in delayed treatment, increased morbidity, and potentially life-threatening complications.[10,11] The cycling of patients through multiple providers and sometimes extensive and repetitive testing and the possibility of conflicting recommendations for treatment may worsen symptoms and increase the psychological and emotional burden for patients.[11]

The emotional burden on patients is related to their uncertainty about the next attack of pain or AP, need for a highly restrictive diet, and search for a knowledgeable and empathetic physician. Managing the lifestyle events involved in such a restricted fat intake is draining and time consuming for almost all patients and can be associated with fear, anxiety, helplessness, and guilt when dietary fat limits are exceeded. Although FCS is usually diagnosed when patients are young, and they become accustomed to their symptom burden, diet, and lifestyle modifications over the years, they often experience lower quality of life than persons without FCS. Comorbid conditions can add to the physical and emotional burden imposed on patients with FCS. Physicians can better manage FCS if they have a better understanding of the nature and extent of common comorbid conditions.

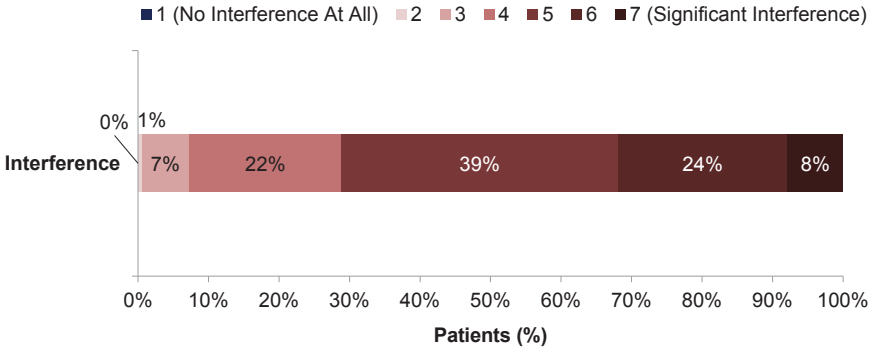

Figure 6 Overall interference of FCS with patients' life.

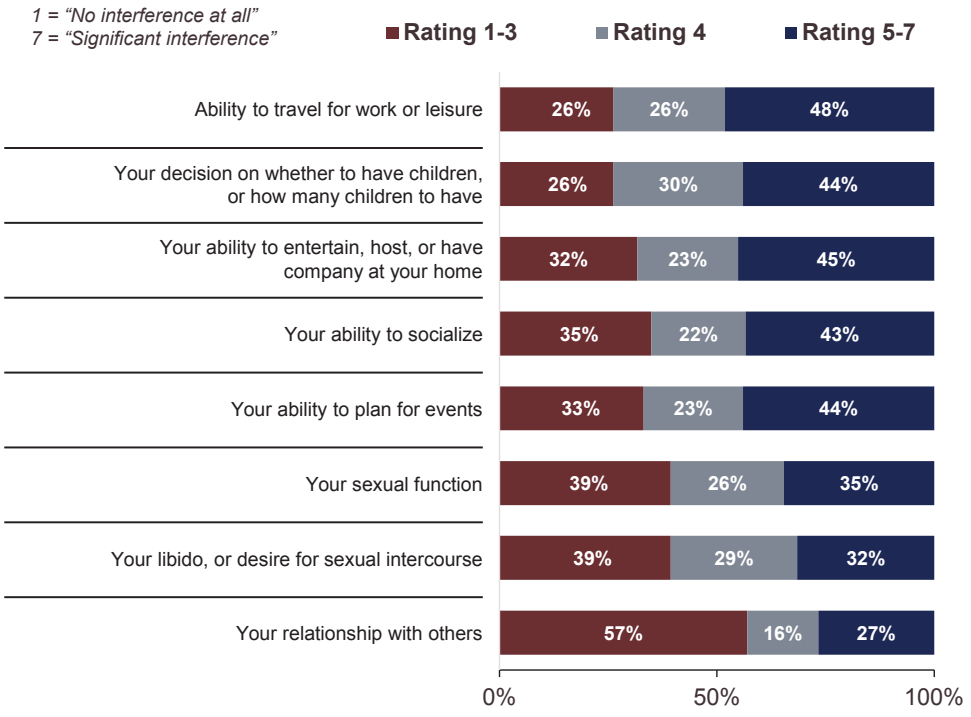

Figure 7 Impact of FCS on social relationships and activities.

Although the patients surveyed said they were generally satisfied with their current providers, almost one-third to one-half considered themselves more knowledgeable than their medical professionals, most likely because physicians are not familiar with the strict dietary fat restrictions needed for effective control. Moreover, patients reported a lack of understanding and sympathy and said they received conflicting or incorrect advice from providers. This underscores the importance of a detailed report of the FCS manifestations beyond the physical manifestations described in the extant literature. Much of the mental and emotional burden for these patients stemmed from the difficulty of following a strict diet and living with the constant fear and anxiety that they could experience symptoms despite that diet. Nearly two-thirds of patients stated that FCS interfered significantly with their self-worth, emotional well-being, sleep, and mental functioning. In addition, a large majority of patients were not optimistic about the future and were worried about their condition worsening, long-term health effects, potential job loss, and ability to live a normal life. The impact of FCS on employment was shown in the interim results[7] and was corroborated here in the global sample.

Although these results provide a window into the true burden of FCS, several limitations should be considered based on the study design. Because the findings were self-reported, independent verification of facts and experiences is not possible. For example, patients with secondary hypertriglyceridemia (eg, diabetes related) could not be excluded. In addition, this study was not longitudinal, which meant the evolution of symptoms over time and with longer disease experience could not be evaluated. The fact that the survey was administered online suggests the potential for selection bias favoring younger patients, more digitally knowledgeable patients, or sicker patients who are more engaged with their disease and willing to take the time to participate. Selection bias may be one of the factors limiting the general applicability of the results of the survey because of the nonrepresentative nature of the internet population and the self-selection bias of the respondents. Because recruitment was conducted primarily by word of mouth and by referrals within FCS patient groups and organizations, this study sample may represent only a subset of the FCS population. Finally, because the study lacks a comparator group, such as a group of patients with a different rare disease, it was not possible to dissect which symptoms are specific to patients with FCS. Secondary analyses are required to determine whether there are groups of patients who experience worse manifestations and whether any clustering of symptoms may predict a prognostic pathway.

In conclusion, this study of 166 patients—the largest to examine the burden of illness in FCS—reflects the patient perspective on the burden FCS places on patients' lives. By characterizing the effect of FCS on multiple dimensions of patients' lives, these findings provide a comprehensive and accurate picture of the wide-ranging ramifications of the disease. These results highlight the need not only for more effective treatments but also for broader clinical management considerations for these heterogeneous symptoms. This work should contribute to increased awareness among health care providers about the burden of symptoms associated with FCS, help improve current diagnosis and

management of FCS, and spur the development of more effective treatment options.

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Authors' contributions: Conception and design of the study was performed by M.D., M.S., A.H., J.R.v.L., C.C. Acquisition of data was performed by M.D., J.R.v.L., C.C. Analysis and interpretation of data was performed by M.D., Z.A., J.R.v.L., J.L.W., M.S., A.H., C.C. Drafting the article or revising it critically for important intellectual content was performed by M.D., M.S., Z.A., J.L.W., J.R.v.L., A.H., C.C. Final approval of the version to be submitted was performed by Z.A., J.L.W., J.R.v.L., A.H., M.S., M.D., C.C.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jacl.2018.04.009.

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Appendix

Supplementary Table S1 Typical symptom experience by sex

Physical, % (21 symptoms)			Emotional, % (13 symptoms)			Cognitive, % (7 symptoms)		
Male								
Generalized abdominal pain	41	Back pain	13	Constant uncertainty about having an attack of pain or acute pancreatitis at any time	35	Feeling out of control/powerless because of my FCS	16	Difficulty concentrating	16
Bloating	34	Numbness or tingling of digits*	9	A/F/W about health due to FCS*	21	Anger/frustration with having FCS	16	Impaired judgement*	7
Asthenia	28	Headaches	12	A/F/W about having to plan what or how much to eat	17	A/F/W in social situations (nonfood related)	13	Brain fog*	5
Indigestion	28	Steatorrhea*	9	Embarrassment about always thinking about and planning for my food	17	Social withdrawal/ feeling isolated	10	Forgetfulness	5
Lack of appetite	26	Excessive sweating	9	Feeling sad/down/blue/ depressed	17	Feeling misunderstood/ not understood	9	Difficulty understanding what others are saying	5
Fatigue	21	Jaundice	8	A/F/W about triggering symptom flare by eating food prepared by someone else	16	A/F/W around having to get regular testing for my FCS	9	Recent memory loss	3
Joint pain	19	Cold sensations	7	A/F/W in social situations (food related)*	13			Difficulty hearing*	2
Pancreatic pain	18	Nausea/Vomiting	6						
Feeling cold all the time in extremities*	14	Skin changes resembling sunburn	9						
Flatulence	18	Respiratory problems/dyspnea	3						
Xanthoma	17								
Female									
Generalized abdominal pain	40	Back pain	22	Constant uncertainty about having an attack of pain or acute pancreatitis at any time	30	Feeling out of control/powerless because of my FCS	20	Difficulty concentrating	18
Bloating	46	Numbness or tingling of digits*	26	A/F/W about health due to FCS*	38	Anger/frustration with having FCS	18	Impaired judgement*	22
Asthenia	32	Headaches	16	A/F/W about having to plan what or how much to eat	28	A/F/W in social situations (nonfood related)	20	Brain fog*	16
Indigestion	24	Steatorrhea*	22	Embarrassment about always thinking about and planning for my food	26	Social withdrawal/ feeling isolated	18	Forgetfulness	14
Lack of appetite	22	Excessive sweating	14	Feeling sad/down /blue/depressed	20	Feeling misunderstood/ not understood	16	Difficulty understanding what others are saying	6

(*continued on next page*)

Supplementary Table S1 (*continued*)

Physical, % (21 symptoms)			Emotional, % (13 symptoms)			Cognitive, % (7 symptoms)	
Fatigue	28	Jaundice	16	A/F/W about triggering symptom flare by eating food prepared by someone else	24	A/F/W around having to get regular testing for my FCS	14	Recent memory loss	8
Joint pain	28	Cold sensations	14	A/F/W in social situations (food related)*	26			Difficulty hearing*	10
Pancreatic pain	22	Nausea/Vomiting	12						
Feeling cold all the time in extremities*	28	Skin changes resembling sunburn	4						
Flatulence	18	Respiratory problems/dyspnea	6						
Xanthoma	18								

*Indicates significant difference in proportion of respondents between genders at 95% CI.