



## Original Article

## Prevalence and factors associated with overweight and obesity in adults with cystic fibrosis: A single-center analysis

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## ARTICLE INFO

## Article history:

Received 17 June 2019

Revised 5 October 2019

Accepted 7 October 2019

Available online 11 November 2019

## Keywords:

Obesity

Cystic Fibrosis

Prevalence

## ABSTRACT

**Background:** The relation between malnutrition and pulmonary death in patients with cystic fibrosis (CF) has resulted in intensive nutritional intervention over the last few decades, leading to a significant decline in underweight and the emergence of overweight/obesity as a potential new problem.

**Methods:** We performed a cross-sectional database analysis of 484 adults with CF seen at the University of Minnesota CF Center between January 2015–January 2017, to determine the prevalence and pulmonary/cardiovascular risk factors associated with overweight and obesity in this population.

**Results:** Mean age was  $35.2 \pm 11.6$  years. 5.2% were underweight ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ), 62.6% normal weight ( $\text{BMI} \geq 18.5\text{--}24.9 \text{ kg/m}^2$ ), 25.6% overweight ( $\text{BMI} \geq 25\text{--}29.9 \text{ kg/m}^2$ ) and 6.6% obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ). In the subgroup with severe genotypes, 25% had  $\text{BMI} \geq 25 \text{ kg/m}^2$ . In the entire cohort, overweight/obese were likely to be older ( $\text{OR} = 1.04$ ,  $p < 0.0001$ ) and to have a mild CFTR genotype ( $\text{OR} = 3.33$ ,  $p = 0.0003$ ) and modestly elevated triglyceride levels ( $\text{OR} = 1.008$ ,  $p < 0.0001$ ). The prevalence of hypertension was higher in overweight (25%) and obese (31%) than normal (17%) or underweight (16%),  $p = 0.01$ . Total cholesterol levels were higher in overweight/obese versus normal/underweight (144–147 vs 123–131 mg/dL,  $p = 0.04$ ) as were LDL levels (70–71 vs 53–60 mg/dL,  $p = 0.02$ ), but all were within the normal range. Percent predicted FEV1 was higher in overweight/obese (78–81%) versus underweight (59%) and normal (70%),  $p < 0.0001$ , and overweight/obese experienced significantly fewer acute pulmonary exacerbations.

**Conclusions:** Overweight/obesity is common in adults with CF including those with severe genotypes. Lung function is better in the overweight/obese and lipid levels are within the normal range, albeit higher than in normal/underweight.

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## 1. Introduction

Cystic fibrosis (CF), the most common autosomal recessive disease in Caucasians, is caused by mutations of the CF transmembrane regulator protein (CFTR) gene. Loss of function mutations of CFTR-mediated chloride and bicarbonate transport in the apical membrane of epithelial cells lead to impaired mucociliary clearance and accumulation of mucus in various organs, resulting in chronic airway disease, pancreatic insufficiency, malabsorption, biliary cirrhosis, and infertility [1–2]. Individuals with CF are classically at risk for malnutrition, which is related to inadequate intake, increased energy expenditure, and malabsorption [3]. Malnutrition is well-known to be associated with declining pulmonary function

and high morbidity and mortality in this population [4–7], and multiple studies have demonstrated that achieving an adequate weight is associated with improved pulmonary function and survival [8–9]. This has long been a focus of CF management, and European and North American CF guidelines recommend maintaining a BMI above  $22 \text{ kg/m}^2$  in females and  $23 \text{ kg/m}^2$  in males [10–11].

Intensive efforts to promote adequate nutrition in CF with a high caloric diet, pancreatic enzyme replacement therapy, fat-soluble vitamin supplementation and, more recently, CFTR modulator therapy have significantly reduced the prevalence of malnutrition. At the same time, an increase in the number of CF patients who are overweight/obese, previously almost unheard of in this population, has been recognized. In Toronto, the proportion of underweight adults with CF decreased from 20% before 1990 to 11% in the 2000s, whereas the proportion of overweight/obese patients increased from 7% in the 1980s to 18% in the 2000s [12]. In

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Pittsburgh, 23% of children with CF seen in 2012 were reported to be overweight or obese [13].

Overweight/obesity is a major global health concern. It is associated with high morbidity and mortality in the general population, primarily because of the risk of hyperlipidemia, hypertension, and atherosclerotic cardiovascular disease [14–15]. Atherosclerotic cardiovascular disease is rare in CF and their cholesterol levels tend to be low. Overall the CF population is relatively young, so it is not clear if overweight/obesity poses the same risk in CF as in the general population. The following study was performed to assess the prevalence of obesity/overweight in adults at the large Minnesota CF center, and to determine its association with cardiovascular risk factors and pulmonary health.

## 2. Methods

### 2.1. Patients

This cross-sectional study included adults age  $\geq 18$  years followed at the University of Minnesota Cystic Fibrosis Center from January 1st, 2015 to January 31st, 2017. All data including demographics (age, ethnicity, gender, age at CF diagnosis), body mass index (BMI), CF genotype classification, lung function, cystic fibrosis related diabetes (CFRD) status, CFRD duration, presence of hypertension, supplemental feeding (oral supplements, gastrostomy or nasogastric tube overnight drip feeding), and specific medications (pancreatic enzymes, insulin, corticosteroids, CFTR modulators) were obtained through the CF Foundation patient registry database. The lipid profile was obtained from the University of Minnesota CF Center Access database. BMI was calculated as weight (kg)/height ( $m^2$ ) and categorized using the WHO adult criteria, where underweight is defined as BMI  $< 18.5$  kg/ $m^2$ ; normal weight BMI  $\geq 18.5$  to 24.9 kg/ $m^2$ ; overweight BMI  $\geq 25$  to 29.9 kg/ $m^2$  and obesity BMI  $\geq 30$  kg/ $m^2$ . CFRD was diagnosed according to standard criteria [16]. CF patients who had undergone lung transplantation were included in this analysis. Lung function was assessed as the forced expiratory volume in 1 s (FEV1), expressed as a percentage of the normal predicted values for height and sex using the Hankinson reference norms [17]. Cholesterol, HDL, and triglyceride level were measured by an enzymatic, colorimetric method with the Dimension Vista<sup>®</sup> system (Siemens Healthcare Diagnostics Inc, Newark, DE). LDL was calculated according to the Friedewald equation. Clinical and laboratory parameters from the most recent outpatient clinic visit during the study period were used in the analyses. However, for pancreatic enzymes and CFTR modulators, patients were considered to be on these medications if they took them at any time during the study period.

CFTR genotype was classified as severe or mild based on the predicted effect on gene expression (e.g., nonsense mutation, splice junction) or protein function, and using the rate of pancreatic insufficiency among individuals with that genotype in the CFTR2 study [18]. Patients with both CFTR alleles having severe mutations (severe/severe) were considered to have a severe genotype, whereas those with at least one mild mutation (severe/mild, mild/unclassified, mild/unknown or mild/mild) were considered to have a mild genotype. Patients with severe/unclassified, severe/unknown, unclassified/unclassified, and unknown mutations were “unclassified.” For example, F508del/F508del and F508del/W1282X were classified as severe mutations, whereas F508del/R117C and G542X/4005+2T->C were classified as mild genotypes. The specific alleles defined by this classification are listed in the online supplement Table 1 in Lewis et al. [19]. This study was approved by the University of Minnesota’s Institutional Review Board.

### 2.2. Statistical analysis

Baseline characteristics were summarized and presented as mean  $\pm$  SD or median (minimum and maximum) as appropriate for continuous variables, and frequency and percentage for categorical variables. In bi-variate analysis, groups were compared using the analysis of variance (ANOVA) with Tukey’s multiple comparisons adjustment for continuous variables and Chi-square test (or Fisher’s exact test if indicated) for categorical variables. Multi-variate analyses were conducted using logistic regression models. Variables that were significant at the 0.10 level in bi-variate analysis were included in multi-variate analysis. The backward model selection method was used to select the best set of factors associated with overweight and obesity. The Loess method and weighted least squares were used to examine the relationship between BMI and FEV1% predicted and to determine the BMI cut-off at which BMI is no longer associated with increased FEV1% predicted. Statistical analyses were performed in SAS 9.3 (SAS Institute, Cary, NC). *P* values  $< 0.05$  were considered statistically significant.

## 3. Results

### 3.1. Prevalence of overweight/obesity

A total of 484 adults with CF were included. Mean age was  $35.2 \pm 11.6$  years, 95% were white, and 55% were male. Eighty-five percent of patients were pancreatic insufficient, 46% had CFRD, 15% had history of lung transplantation and 29% were on supplemental feeding (Table 1). The majority of patients in this cohort (70%) had severe CFTR genotypes.

In the entire cohort, mean BMI was  $23.9 \pm 4.4$  kg/ $m^2$ . Only 5.2% of patients were underweight, and 62.6% had normal weight. Thus, the University of Minnesota CF Center has been highly effective in minimizing malnutrition in the CF population. However, 25.6% of patients were overweight and 6.6% were obese. As might be expected, patients in the overweight and obese categories were more likely to be older, male, diagnosed with CF at a later age, pancreatic sufficient, and to have a mild CFTR genotype compared to patients who were normal or underweight (Table 1). The prevalence of a severe CFTR genotype in patients with a BMI  $\geq 25$  kg/ $m^2$  was 56%, while 80% of patients who were underweight had a severe CFTR genotype. Sixty percent of overweight/obese and 100% of underweight CF patients were on pancreatic enzyme therapy. Underweight/normal weight patients were more likely to be on supplemental feeding compared to overweight/obese patients (36.4% vs 13.0%; *P*  $< 0.0001$ ) (Table 1). Of the overweight/obese patients on supplemental feeding, the majority used oral supplements (80%), with 4 patients in this group using gastrostomy tube. The indication for gastrostomy tube was to support nutritional status during exacerbation of chronic pulmonary disease secondary to infection. History of lung transplant, use of corticosteroids, prevalence and duration of diabetes, duration of insulin treatment, and treatment with CFTR modulators were not different amongst BMI categories.

In a subgroup analysis of patients with a severe CFTR genotype, 25% had a BMI  $\geq 25$  kg/ $m^2$ . The mean BMI for the severe CFTR genotype group was similar to the total cohort at  $23.2 \pm 3.7$  kg/ $m^2$ . Patients in this group who were overweight or obese were more likely to be older and male. Almost all of them were diagnosed with CF at a very early age and were pancreatic insufficient (Table 2). Thus, overweight/obesity was highly prevalent even in this group of CF patients with “classic” severe disease.

### 3.2. Cardiovascular risk factors

The prevalence of hypertension in our CF cohort was 31% in overweight and 25% in obese patients compared to 17% in nor-

**Table 1**  
Characteristics of adult patients with CF by body mass index category (N = 484).

	Underweight (N = 25)	Normal weight (N = 303)	Overweight (N = 124)	Obesity (N = 32)	P-value
Age (years)	30.7 ± 9.9	33.4 ± 10.5	39.6 ± 13.0 <sup>a,b</sup>	39.1 ± 11.4 <sup>c,d</sup>	<0.0001
BMI (kg/m <sup>2</sup> ) <sup>e</sup>	17.7 ± 0.8	21.9 ± 1.8	27.0 ± 1.3	34.8 ± 5.7	<0.0001
Male	8 (32%)	156 (51%)	78 (63%)	22 (69%)	0.006
Caucasian	23 (92%)	292 (96%)	117 (94%)	30 (94%)	0.37
Age at CF diagnosis (years)	1.8 ± 3.9 median 0.3 (0–16.5)	5.1 ± 9.3 median 0.7 (0–70.3)	11.4 ± 14.7 <sup>a,b</sup> median 4.5 (0–64.7)	12.5 ± 15.1 <sup>a,b</sup> median 4.6 (0–42.9)	<0.0001
CFTR genotype classification (n = 477)					<0.001
-Mild	2 (8%)	31 (10%)	38 (31%)	15 (48%)	
- Severe	20 (80%)	230 (77%)	73 (59%)	11 (35%)	
-Unclassified	3 (12%)	37 (12%)	12 (10%)	5 (16%)	
Homozygous F508del	15 (60%)	142 (48%)	60 (49%)	10 (32%)	0.20
History of lung transplant	4 (16%)	37 (12%)	18 (15%)	1 (3%)	0.30
Percent of patients taking pancreatic enzyme (n = 417)	20 (100%)	240 (91%)	77 (73%)	16 (57%)	<0.001
Percent of patients using supplemental feeding (n = 477)	13 (52%) (n = 25)	105 (35%) (n = 299)	18 (15%) (n = 121)	2 (6%) (n = 32)	<0.001
- Oral supplement	7 (54%)	88 (84%)	15 (83%)	1 (50%)	
-Gastrostomy tube	4 (31%)	9 (9%)	3 (17%)	1 (50%)	
-Nasogastric tube	0 (0%)	1 (1%)	0 (0%)	0 (0%)	
-Both oral and gastrostomy tube	2 (15%)	7 (7%)	0 (0%)	0 (0%)	
Percent of patients using corticosteroid					0.76
- Inhaled	8 (32%)	108 (36%)	44 (35%)	8 (25%)	
- Oral	3 (12%)	155 (51%)	60 (48%)	21 (66%)	
- None	14 (56%)				
Percent of patients who have CFRD (n = 483)	15 (60%)	144 (48%)	52 (42%)	10 (31%)	0.11
Duration of CFRD (years)	13.6 ± 5.9 median 13.5 (3–25.5)	13.2 ± 7.4 median 12.5 (1–41.6)	13.5 ± 6.9 median 14.3 (1.9–26.4)	14.9 ± 8.9 median 14.5 (5–32.4)	0.90
Duration of insulin treatment (years)	10.9 ± 6.1	11.3 ± 7.2	10.4 ± 5.4	14.4 ± 8.1	0.46
HbA1c (%)	6.5 ± 2.2	6.2 ± 1.0	6.3 ± 1.1	6.3 ± 1.3	0.43
Hypertension	4 (16%)	50 (17%)	38 (31%)	8 (25%)	0.01
Percent of patients who receive CFTR modulators	9 (36%)	103 (34%)	39 (31%)	10 (31%)	0.94
Duration of CFTR modulator treatment (years)	1.6 ± 0.9	1.7 ± 0.6	1.7 ± 0.7	1.5 ± 0.8	0.85
FEV1 (% predicted)	58.7 ± 27.8	69.8 ± 23.5 <sup>c</sup>	78.0 ± 23.4 <sup>a,b</sup>	81.4 ± 18.9 <sup>a,b</sup>	<0.0001
Frequency of pulmonary exacerbations over 3 years	8.4 ± 7.5 median 6.0 (0–29.0)	5.3 ± 5.4 <sup>c</sup> median 3.0 (0–32.0)	3.8 ± 4.7 <sup>a,d</sup> median 2.0 (0–30.0)	3.2 ± 4.5 <sup>a</sup> median 1.5 (0–20.0)	0.0004
Total Cholesterol (mg/dL) (n = 455)	122.7 ± 29.2	130.7 ± 36.3	144.1 ± 37.4 <sup>c,d</sup>	146.9 ± 34.7 <sup>c</sup>	0.04
HDL-C (mg/dL) (n = 455)	49.7 ± 16.2	51.5 ± 17.1	48.9 ± 14.1 <sup>d</sup>	43.8 ± 14.1 <sup>d</sup>	0.048
LDL-C (mg/dL) (n = 455)	53.4 ± 23.7	59.5 ± 26.1	70.5 ± 31 <sup>d</sup>	71.4 ± 29.7	0.02
Triglyceride (mg/dL) (n = 455)	99.4 ± 47.5	98.2 ± 58.3	124.3 ± 60.6 <sup>b</sup>	158.2 ± 87.6 <sup>a,b,f</sup>	<0.0001
VLDL-C (mg/dL) (n = 398)	21.7 ± 11.2	20.2 ± 10.6	23.6 ± 13.5	26.9 ± 17.0 <sup>d</sup>	0.09

<sup>a</sup> P ≤ 0.01 when compared to underweight group.<sup>b</sup> P ≤ 0.01 when compared to normal weight group.<sup>c</sup> P ≤ 0.05 when compared to underweight group.<sup>d</sup> P ≤ 0.05 when compared to normal weight group.<sup>e</sup> P ≤ 0.001 for all group comparisons.<sup>f</sup> P ≤ 0.05 when compared to overweight group BMI; Body mass index, CFRD; Cystic fibrosis related diabetes, CFTR: Cystic fibrosis transmembrane regulator, FEV1; forced expiratory volume in 1 s.

mal weight CF adults ( $P = 0.01$ ). Overweight and obese patients had statistically higher total cholesterol, LDL-C and triglyceride levels compared to underweight and normal weight patients after adjusting for sex and age (Table 1). HDL-C levels were significantly lower in overweight/obese compared to normal weight patients. However, it should be noted that all cholesterol values remained within the normal range across all BMI categories, and the triglyceride elevation seen in the overweight/obese group was modest.

In the severe CFTR genotype subgroup, only triglyceride levels were statistically higher in overweight/obese compared to normal weight patients. Other lipid values including total cholesterol, LDL-C, VLDL and HDL-C were similar between BMI groups (Table 2).

Lung transplantation adversely impacted the cardiovascular risk profile in CF. Transplanted patients had a markedly increased prevalence of hypertension (86.7% vs 11.3%;  $P < 0.0001$ ) and higher total cholesterol ( $155.5 \pm 39.9$  mg/dL vs

$131.6 \pm 35.3$  mg/dL;  $P < 0.0001$ ) and triglyceride ( $157.9 \pm 69.5$  mg/dL vs  $101.3 \pm 58.4$  mg/dL;  $P < 0.0001$ ) levels compared to non-transplanted patients. Interestingly, HDL-C was also elevated in transplanted recipients ( $58.6 \pm 19.7$  mg/dL vs  $49.0 \pm 15.3$  mg/dL;  $P = 0.0006$ ).

### 3.3. Lung function

In the natural history of CF, the majority of patients eventually die from respiratory failure. The mean percent predicted FEV1 in this cohort was  $72.1 \pm 23.9\%$ . FEV1 was significantly higher (better) in patients who were obese and overweight compared to normal and underweight patients after adjusting for sex and age. There was no significant difference in lung function between the overweight and obese groups. FEV1% predicted positively correlated with BMI, but there was no further improvement in FEV1% pre-

**Table 2**  
Characteristics of adult patients with CF who had a severe CFTR genotype, by body mass index category (N = 334).

	Underweight (N = 20)	Normal weight (N = 230)	Overweight (N = 73)	Obesity (N = 11)	P-value
Age (years)	31.6 ± 10.3	32.6 ± 9.6	37.2 ± 11.3	42.4 ± 8.0 <sup>a</sup>	0.0002
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	17.6 ± 0.9	21.9 ± 1.7	26.9 ± 1.3	34.4 ± 6.2	<0.0001
Male	5 (25%)	126 (55%)	50 (68%)	7 (64%)	0.0045
Caucasian	19 (95%)	224 (97%)	71 (97%)	9 (82%)	0.07
Age at CF diagnosis (years)	1.4 ± 3.7	2.6 ± 4.8	3.5 ± 6.5	2.3 ± 3.9	0.38
	median 0.3	median 0.5	median 0.6	median 0.4	
	(0–16.5)	(0–32.1)	(0–33.3)	(0–11.8)	
Homozygous F508del	15 (75%)	141 (61%)	60 (82%)	10 (91%)	0.002
History of lung transplant	4 (20%)	29 (13%)	11 (15%)	0 (0%)	0.45
Percent of patients taking pancreatic enzymes (n = 280)	16 (100%)	195 (99%)	56 (97%)	9 (100%)	0.47
	(n = 16)	(n = 197)	(n = 58)	(n = 9)	
Percent of patients using corticosteroids					0.96
-Inhaled	6 (30%)	86 (37%)	25 (34%)	4 (36%)	
-Oral	3 (15%)	28 (12%)	11 (15%)	2 (18%)	
-None	11 (55%)	116 (50%)	37 (51%)	5 (45%)	
Percent of patients who have CFRD	12 (60%)	128 (56%)	45 (62%)	6 (55%)	0.82
Duration of CFRD (years)	13.8 ± 6.2	13.3 ± 7.1	13.9 ± 7.1	19.5 ± 8.6	0.22
	median 13.1	median 12.5	median 14.9	median 18.0	
	(3–25.5)	(1.5–41.6)	(1.9–26.4)	(7.5–32.4)	
Duration of insulin treatment (years)	11.1 ± 6.4	11.1 ± 6.7	10.7 ± 5.7	17.2 ± 8.3	0.15
HbA1c (%)	6.8 ± 2.4	6.3 ± 1.0	6.7 ± 1.2	6.7 ± 1.2	0.08
Hypertension	4 (20%)	36 (16%)	25 (34%)	3 (27%)	0.006
Percent of patients who receive CFTR modulators	9 (45%)	101 (44%)	38 (52%)	8 (73%)	0.21
Duration of CFTR modulator treatment (years)	1.6 ± 0.9	1.7 ± 0.6	1.7 ± 0.6	1.8 ± 0.7	0.91
FEV1 (% predicted)	59.6 ± 26.7	69.0 ± 23.5	75.5 ± 22.7 <sup>c</sup>	73.2 ± 18.3	0.04
Frequency of pulmonary exacerbations over 3 years	8.2 ± 7.2	5.9 ± 5.8	4.2 ± 3.8 <sup>d</sup>	6.5 ± 6.1	0.02
	median 5.5	median 4.0	median 3.0 (0–19.0)	median 5.0	
	(0–29.0)	(0–32.0)		(0–20.0)	
Total Cholesterol (mg/dL) (n = 324)	122.6 ± 29.1	127.3 ± 36.5	130.2 ± 28.3	135.5 ± 27.8	0.71
HDL-C (mg/dL) (n = 324)	50.8 ± 17.5	49.9 ± 16.6	47.5 ± 14.6	52.4 ± 16.1	0.63
LDL-C (mg/dL) (n = 324)	50.9 ± 21.5	57.3 ± 25.6	58.6 ± 23.6	55.5 ± 23.5	0.68
Triglyceride (mg/dL) (n = 324)	106.9 ± 50.7	100.3 ± 59.8	121.0 ± 57.7 <sup>e</sup>	137.0 ± 63.0	0.022
VLDL (mg/dL) (n = 291)	23.3 ± 12.4	20.4 ± 10.4	23.2 ± 12.6	26.2 ± 15.0	0.13

<sup>a</sup> P = 0.023 when compared to underweight group.

<sup>b</sup> P = < 0.001 for all group comparisons.

<sup>c</sup> P = 0.036 when compared to underweight group.

<sup>d</sup> P = 0.024 when compared to underweight group.

<sup>e</sup> P = 0.046 when compared to normal weight group. BMI; Body mass index, CFRD; Cystic fibrosis related diabetes, CFTR: Cystic fibrosis transmembrane regulator protein, FEV1; forced expiratory volume in 1 s.

dicted beyond a BMI of 28–29 kg/m<sup>2</sup> (Fig. 1). Patients with normal weight had significantly more pulmonary exacerbations than patients who were overweight, and those who were underweight experienced the greatest frequency of pulmonary exacerbations compared to all groups. There was a weak inverse relationship between BMI and frequency of pulmonary exacerbations (Spearman  $R = -0.24; P \leq 0.0001$ ).

Multivariate regression analyses showed the best set of factors associated with overweight and obesity (BMI  $\geq 25$  kg/m<sup>2</sup>) for the entire cohort of patients with CF included age (OR = 1.04;  $P < 0.0001$ ), mild CFTR genotype (OR = 3.33;  $P = 0.0003$ ), and triglyceride levels (OR = 1.008;  $P < 0.0001$ ). (Table 3), while the best set of factors associated with overweight and obesity in patients with severe CFTR genotypes were male gender (OR = 2.00;  $P = 0.014$ ), age (OR = 1.04;  $P = 0.002$ ), homozygous F508del (OR = 3.149;  $P = 0.0006$ ), and triglyceride level (OR = 1.005;  $P = 0.016$ ) (Table 3).

#### 4. Discussion

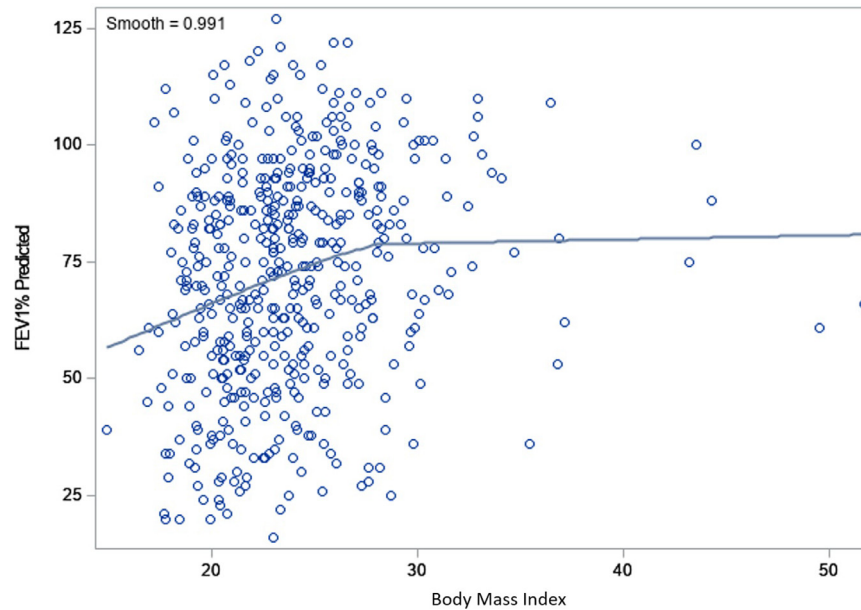
Overweight and obesity have become quite prevalent in CF, occurring in one-third of all adult CF patients at the University of Minnesota. It is particularly striking that 25% of those with severe CF mutations fall into this weight category. Only 5% of patients in

the total CF population were underweight, and, as expected, this was associated with worse clinical status.

In the general population, overweight/obesity is associated with significant risk of death from atherosclerotic cardiovascular disease [14–15]. Our data do not support a similar association in CF. While cholesterol levels were statistically higher in this group, they were still within normal limits. Triglyceride levels were modestly elevated and there was a higher prevalence of hypertension, but importantly, no patient (including the 30 [19%] patients age  $\geq 50$  years) had known cardiovascular disease. It is particularly relevant that overweight/obesity appeared to be associated with an improved prognosis in CF as lung function and episodes of acute pulmonary exacerbation were better in this group. However, there was no further benefit of higher BMI on lung function, beyond a BMI threshold of 28–29 kg/m<sup>2</sup>. This finding is in line with results from previous studies [12,20].

With the emphasis on nutritional augmentation [10–11], BMI in CF has increased over the past 30 years. Stephenson et al. observed an average BMI of 20.7 ± 2.7 kg/m<sup>2</sup> in the 1980s compared to 22.3 ± 3.4 kg/m<sup>2</sup> in the 2000s in a Toronto cohort of adults with CF followed from 1985 to 2011 [12]. Ten percent and 13% of adult patients were reported to have a BMI exceeding 25 kg/m<sup>2</sup> in a 2002 UK registry [20] and a 2004 Canadian database [21], respectively, and in 23% of Pittsburgh pediatric patients in 2012 [13]. Our observed prevalence of combined overweight and obesity





**Fig. 1.** Loess fit curve between body mass index (BMI) and FEV1% predicted in all study cohort. BMI; Body mass index, FEV1% predicted; forced expiratory volume in 1 s expressed as a percentage of the normal predicted values for height and sex.

**Table 3**

Multivariate logistic regression analysis of clinical variables and overweight/obesity in all study cohort ( $N=484$ ) and in patients with severe CFTR genotype ( $N=334$ ).

	Odds ratio	95% confidence interval	P value
All study cohort ( $N=484$ )			
Age	1.04	1.02, 1.06	<0.0001
CFTR genotype classification			
- mild vs severe	3.33	1.92, 5.80	0.0001
- unclassified vs severe	1.09	0.55, 2.19	0.15
Triglyceride	1.008	1.004, 1.011	<0.0001
Patients with severe CFTR genotype ( $N=334$ )			
Sex male vs female	2.00	1.15, 3.48	0.014
Age	1.04	1.02, 1.07	0.002
Homozygous F508	3.14	1.63, 6.04	0.0006
Triglyceride	1.005	1.001, 1.009	0.016

CFTR: Cystic fibrosis transmembrane regulator.

(32.2%) was remarkably greater than that previously reported from the United States and other European countries. Differences in the observed prevalence of overweight and obesity between the various studies (which included patients with similar gene mutations) might be explained by improvement in pulmonary and nutritional interventions over the years, and recently, by new CFTR modifier drugs that are changing the disease phenotype [22].

CFTR modifier drugs have been reported to increase weight in CF, sometimes dramatically [23]. In this cohort, we did not observe an association between body weight and treatment with CFTR modulators. However, since lumacaftor/ivacaftor was approved in July 2015, CF patients in the current study had been on this medication for a relatively short period (on average approximately 1.6 years), which could have limited our ability to examine the chronic impact of this CFTR modulator on body weight. The prevalence of overweight and obesity in our cohort is only 5–6% behind that found in the general population of US adults based on the 2015–2016 National Health and Nutrition Examination Survey (NHANES) [24], suggesting that soon the rate of overweight and obesity in CF may mirror that of the general US population.

This study cannot answer the “chicken and egg” relation between overweight/obesity and clinical status. Overweight/obesity

was associated with improved pulmonary function and reduced risk of acute pulmonary exacerbation. Is it just that a milder genotype (known to be associated with less severe pulmonary disease) allows patients to achieve a more “normal” (general population) rate of overweight/obesity, or could overweight/obesity be uniquely protective in CF? These data suggest that both may be true. Patients with less severe disease (mild CFTR mutation, later age of CF diagnosis and preserved pancreatic exocrine function and pulmonary function) were more likely to be overweight/obese, as might be expected [12,21,25]. More interesting is the fact that 54% of overweight/obese patients had severe CFTR genotypes, and the severe genotype subgroup, overweight/obesity was also associated with better pulmonary function. Thus, if there is no other important morbidity associated with excess weight in CF, it may actually be beneficial.

In the general population, excess morbidity and mortality in the overweight/obese population is related to atherosclerotic cardiovascular disease. Overweight (31%) and obese (25%) patients in our CF cohort were more likely to have hypertension as compared to normal weight CF adults (17%). We also confirmed previous studies suggesting that overweight/obese patients with CF have significantly higher levels of total cholesterol,

LDL-cholesterol [12,20–21] and triglyceride compared to those of normal/underweight [12,26]. This was largely a statistical consideration since cholesterol levels are generally abnormally low in the CF population. Thus, average total cholesterol levels (mg/dL) were in the 140's (compared to 120's) and LDL levels (mg/dL) in the 70's (compared to 50's) in the overweight/obese group, levels that are not typically associated with cardiovascular risk. Triglyceride levels were also significantly higher in overweight/obese CF patients but only in the 130–140 mg/dL range. One limitation of this analysis is that only about half of the triglyceride levels could be verified as fasting, as triglyceride levels can be elevated in the post prandial state. Thus, triglyceride levels may actually be lower than we have reported. Cardiovascular diseases are extremely rare in this population and no CF patient in the literature has yet been reported to have died from atherosclerotic cardiovascular disease, despite the fact that about 5% of CF population is now over 50 years of age [27]. While there are no data to date to suggest that overweight and obesity currently predispose CF patients to increased mortality, it is yet to be determined whether persistent metabolic risk over time could translate into development of cardiovascular disease similar to the general population.

The primary strength of this study is the size and richness of a large, prospectively collected adult CF population database at an accredited CF Center. This study has several limitations in addition to that mentioned for triglyceride measurement. Because the data were analyzed cross-sectionally, causal relationships cannot be inferred. The results from this single center study may not be generalizable to other CF populations, in particular because of the decades-long emphasis at the University of Minnesota on a high-calorie diet for people with CF. BMI, a tool used to classify patients' nutritional status, has its limitations since it does not reflect body composition— fat mass, muscle mass and fat distribution may influence metabolic and overall health and could be more important than BMI per se in CF patients. The diagnosis of hypertension was obtained from the CF Foundation patient registry database; therefore, it was not possible to verify what blood pressure threshold was used by individual providers to diagnose hypertension.

Nutritional counselling for the CF patients has historically focused on improving energy intake to achieve recommended calorie targets of 120–150% above the daily recommended intake for the general population [10–11]. Given the increasing prevalence of overweight/obesity in patients with CF, modern nutritional advice should take into consideration the patient's body weight category and potential cardiovascular risk factors. The 2017 Nutrition Guidelines for CF in Australia and New Zealand provide a framework for identification, assessment and management of dietary interventions in CF according to BMI in adults or BMI percentiles in children [28]. While acknowledging the lack of evidence for the management of overweight and obesity in the CF population, these guidelines suggest that nutritional consideration may shift from a high fat, high energy diet to a more nutrient dense, moderate energy diet in CF patients with a BMI > 27 kg/m<sup>2</sup> or a BMI percentile in the overweight/obese range [28]. These guidelines also recommend that nutritional counseling should take into account body composition, as CF patients are known to have sarcopenia and are at risk of losing lean body mass if they do not consume adequate calories [28]. It is unclear at this time whether weight management recommendations for the general population can be generalized to overweight and obese patients with CF, and thus this needs to be approached with caution.

In summary, the low prevalence of undernutrition, previously a source of major morbidity in adults with CF, reflects successful comprehensive multidisciplinary care over the last few decades. However, this success has been accompanied by a significant rise in obesity and overweight, which is beginning to resemble the global trend of obesity in the general population. Whether or not

this is harmful in CF remains to be determined since at present overweight/obese patients appear to have better pulmonary function than their normal and underweight peers. As there does not appear to be any further pulmonary advantage to being obese compared to simply being overweight, it seems reasonable to recommend a BMI < 30 kg/m<sup>2</sup> for adults with CF. Further longitudinal studies should address the consequences associated with overweight/obesity in adults and children with CF, to inform appropriate nutritional approaches and treatment plans. In the meantime, nutritional counselling for CF patients who are overweight or obese should be implemented carefully.

### Declaration of Competing Interest

T. Harindhanavudhi, A. Moheet, A. Moran and Q. Wang have no competing interests. J. Dunitz has received grants from Vertex Pharmaceuticals Inc, Hillrom, Proteostasis Therapeutics, Inc, and Cystic Fibrosis Foundation independent from the submitted work.

### CRedit authorship contribution statement

**Tasma Harindhanavudhi:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Qi Wang:** Data curation, **Jordan Dunitz:** Data curation, Writing - review & editing. **Antoinette Moran:** Data curation, Writing - review & editing. **Amir Moheet:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing.

### Acknowledgments

The authors would like to thank Ms. Catherine Moen from Department of Pediatrics, University of Minnesota for her assistance on database retrieval and technical support.

### Funding

A. Moheet has grant support by [Cystic Fibrosis Foundation](#) through the “[MOHEET16GE0-EnVision CF: Emerging Leaders in CF Endocrinology Program](#)”.

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