Received: 20 November 2020 | Revised: 18 May 2021 | Accepted: 2 June 2021

DOI: 10.1002/ppul.25535

PEDIATRIC PULMONOLOGY WILEY

Healthcare resource utilization and costs among children with cystic fibrosis in the United States

Teja Thorat MPH[1] | Lisa J. McGarry MPH[1] | Machaon M. Bonafede PhD[2,3] | Brendan L. Limone PharmD[3] | Jaime L. Rubin MPH[1] | Krutika Jariwala-Parikh PhD[3] | Michael W. Konstan MD[4,5]

[1]Vertex Pharmaceuticals Incorporated, Boston, Massachusetts, USA

[2]Veradigm Life Sciences, an Allscripts Healthcare LLC, Chicago, Illinois, USA

[3]Life Sciences, IBM Watson Health, Cambridge, Massachusetts, USA

[4]Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[5]Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, Ohio, USA

Correspondence
Teja Thorat, Vertex Pharmaceuticals Incorporated, 50 Northern Ave, Boston, MA 02210, USA.
Email: Teja_Thorat@vrtx.com

Funding information
Vertex Pharmaceuticals

Abstract

Background: Adverse health impacts of cystic fibrosis (CF) can be present in children before respiratory complications are observed. Children with CF show progressive health decline, with increasing lung function decline in adolescence. This study aims to quantify the healthcare resource utilization (HCRU) and costs attributable to CF by comparing children with CF with the general pediatric population.

Methods: This retrospective, cross-sectional, observational study compared HCRU and costs among children with CF in the US with demographically similar children without CF (comparison group) over a 12-month period using administrative claims data spanning 2010–2017. Analyses were conducted by insurance type (commercially insured [COM] and Medicaid insured [MED]) and stratified by age (<2 years, 2 to <6 years, 6 to <12 years, and 12–17 years).

Results: Children with CF (2831 COM and 1896 MED) were matched to children in the comparison group (8493 COM and 5688 MED). Higher prevalence of comorbidities was seen in children with CF versus the comparison group across all ages. Across all ages, HCRU attributable to CF was substantial (higher hospitalization rates, more outpatient and emergency room visits, and greater use of prescription medications), and there were higher associated costs (all p values < .05), in COM and MED populations. HCRU and costs attributable to CF were highest for children aged 12–17 years.

Conclusions: Substantial HCRU and costs are evident among children with CF across all ages, starting as young as infancy, with highest HCRU and costs among adolescents. Effective treatments from an early age are needed for children with CF.

KEYWORDS
administrative claims, burden of illness, cross-sectional study, healthcare costs

Dr. Bonafede was at Life Sciences, IBM Watson Health for the majority of the study conduct and is currently at Veradigm Life Sciences.

1 | INTRODUCTION

Cystic fibrosis (CF) is a rare genetic disease caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*).[1] There were approximately 30,000 people with CF (pwCF) in the United States in 2018, nearly half aged less than 18 years.[2] The signs of the disease may be present at birth, although pwCF can be asymptomatic during early childhood.[3,4] Young children with CF thus often appear healthy and may be assumed to have relatively low disease burden. The most common indicator of CF progression is lung function decline, which is not well documented in children aged less than 6 years due to challenges in conducting spirometry in this population; however, lung structure abnormalities can be present in the absence of symptoms and before lung function reduction is observed.[4,5] Infants with CF may have gastrointestinal abnormalities and pancreatic insufficiency leading to nutritional impairment and growth delay.[4,6] In children with CF aged 6 years or older, there is an annual lung function decline of 1–3 points in percent predicted forced expiratory volume in 1 second, with the highest decline in adolescents, implying health state deterioration and higher treatment burden.[7,8]

Recently, novel therapies such as CFTR modulators (CFTRms) that treat the underlying cause of CF, including potentiators (e.g., ivacaftor) and correctors (e.g., lumacaftor, tezacaftor, and elexacaftor) are available treatment options for children with CF.[9–16] Ivacaftor is available for children aged 4 months or older with approved mutations, lumacaftor/ivacaftor is available for those aged 2 years or older who are *F508del* homozygous, and tezacaftor/ivacaftor is available for those aged 6 years or older who are *F508del* homozygous or have more than or equal to 1 *CFTR* mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.[9,10,15,16] Recently, elexacaftor/tezacaftor/ivacaftor was approved in the United States for those aged 6 years or older who have at least 1 copy of the *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on in vitro data [13]. Indicated *CFTR* mutations and age ranges may vary by region.[10,12,15,16] With the advent of novel therapies, it is important to understand the HCRU and costs attributable to CF, especially among younger children before symptom manifestation, and demonstrate how HCRU and costs change with age as CF symptoms progress.

Our study aims to build on previously published evidence[17–21] on HCRU and costs of CF care by providing more recent comprehensive estimates of HCRU and costs, especially starting from birth, in the pediatric CF population. While there is general recognition that CF requires substantial HCRU in pediatric populations, in this study, we aimed to quantify real-world HCRU and costs attributable to CF before the initiation of CFTRms by comparing children with CF with demographically matched children without CF. Children without CF were used as a comparison group to represent the general pediatric population to appropriately estimate the HCRU and costs attributable to CF, an approach commonly used in burden-of-illness studies.[22–25]

2 | MATERIALS AND METHODS

2.1 | Data source

This retrospective, cross-sectional, observational study used data from the IBM® MarketScan® Commercial Claims and Encounters Database and the IBM® MarketScan® Multi-State Medicaid Database. The commercial database contains administrative health insurance claims (e.g., inpatient and outpatient services and outpatient prescription drug claims) of privately insured individuals covered under a variety of fee-for-service, fully capitated, and partially capitated health plans. The Medicaid database contains administrative health insurance claims of individuals covered by state Medicaid programs. The study did not involve primary data collection and used only deidentified data; thus, institutional review board approval was not necessary.

2.2 | Study population

Children with CF were identified on the basis of more than or equal to 1 inpatient medical claim with a primary diagnosis of CF (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]: 277.0x or *International Classification of Diseases, Tenth Revision, Clinical Modification* [*ICD-10-CM*]: E84) or more than or equal to 2 outpatient medical claims with primary or secondary diagnosis of CF more than or equal to 30 days apart between January 1, 2010, and June 30, 2017. Identified children with CF were required to have more than or equal to 12 months of continuous enrollment in medical and pharmacy benefits. For identified children with CF initiating CFTRms (ivacaftor or lumacaftor/ivacaftor), more than or equal to 12 months of continuous enrollment before initiation of CFTRms was required. Index date for this cohort was defined as the first day of the most recent 12 months before the end of continuous health plan enrollment or most recent 12 months of continuous enrollment before initiating CFTRms. Identified children with CF were required to be aged less than or equal to 17 years on the index date. The follow-up period was defined as the most recent 12 months of continuous enrollment in medical and pharmacy benefits post index date, described earlier. Identified children with CF were also required to have a qualifying CF diagnosis (inpatient, emergency room [ER], or outpatient claim) during the follow-up period. Among children with CF initiating CFTRms, we only included follow-up data before initiation of the CFTRm, as the objective was to evaluate HCRU before the advent of CFTRms. Moreover, only a small proportion of children with CF in the available study population was treated with CFTRms.

The comparison group was selected from individuals enrolled in the same health insurance plans to represent the general population. Identified individuals were required to have no diagnosis of CF in their available medical history and have more than or equal to 12 months of continuous health plan enrollment between January 1, 2010, and June 30, 2017. Index date for the matched comparison

group was the first day of the most recent 12 months of continuous enrollment (i.e., follow-up period). Identified individuals were required to be aged less than or equal to 17 years on the index date.

All eligible children with CF were matched directly (capped at a 1:3 ratio) to the comparison group by age, sex, geographic region (only available for commercially insured [COM] children), race (only available for Medicaid insured [MED] children), enrollment year (calendar year of the index date), and insurance plan type on index date to ensure balanced characteristics between the children with CF and comparison group. After matching, the children with CF and comparison children were treated as independent samples.

2.3 | Study measures

Baseline characteristics at the index date, including age, sex, geographic region (COM), race (MED), and insurance type, were reported for children with CF and the comparison group. Comorbid conditions during the follow-up period were identified by a claim with an *ICD-9-CM*/*ICD-10-CM* diagnosis code for the condition in the primary or secondary position. HCRU outcomes measured during the follow-up period included hospitalization-related outcomes defined as the annual occurrence of any hospitalization, rate of hospitalizations, mean length of stay per hospitalization in children with more than or equal to one admission, and an annual number of days in the hospital across all hospitalizations in children with more than or equal to one admission. The study also tallied annual rates and occurrence of outpatient and ER visits and prescription medication use over the follow-up period and evaluated the HCRU costs for the follow-up period. Total annual healthcare costs, including paid amounts and out-of-pocket costs on fully adjudicated claims for hospitalizations, outpatient visits, and prescription medication costs, were inflated to 2018 US dollars using the Medical Care Component of the Consumer Price Index.[26]

2.4 | Analysis

HCRU and costs were evaluated during the follow-up period. Categorical variables are presented by count and percentage, and continuous variables are summarized by the mean and standard deviation. Study measures were compared between children with CF and the comparison group. χ^2 tests were used to evaluate the statistical significance of differences for categorical variables; *t*-tests and analysis of variances were used for continuous variables. *p* Values < .05 were considered nominally significant because no multiplicity adjustments were conducted. All study measures were analyzed and reported separately for COM and MED populations. Within each insurance population, children were stratified by age on index date into four cohorts (0 to <2 years, 2 to <6 years, 6 to <12 years, and 12–17 years [i.e., adolescent cohort]). Differences between age cohorts were not statistically tested.

3 | RESULTS

A total of 2831 COM and 1896 MED children with CF were identified and met the eligibility criteria for inclusion in this study. These children were direct matched to 8493 COM and 5688 MED demographically similar children without CF, respectively. Within each insurer and age cohort, the CF and the comparison groups were well matched in terms of baseline demographics (Table 1).

3.1 | Comorbid conditions

Most comorbid conditions (occurring in ≥5% of children in any cohort) in the follow-up period were significantly more common in children with CF versus the comparison group for both COM and MED populations and across all age cohorts ($p < .05$; Table 1).

In children with CF in both the COM and MED populations, most CF-related comorbidities, such as pancreatic insufficiency, asthma, bronchiectasis, sinus disease, and pulmonary infection, developed early in life and tended to increase across the age cohorts (Table 1).

3.2 | Hospitalization

The rate of hospitalizations during the follow-up period, as measured by the proportion hospitalized and mean number of hospitalizations, was significantly higher among children with CF versus the comparison group in both the COM and MED populations ($p < .05$; Figure 1A,B). In the COM population, the mean annual number of hospitalizations among children with CF ranged from 0.19 to 0.82; in the comparison group, the mean annual number of hospitalizations was lower, ranging from 0.01 to 0.15. In the MED population, the mean annual number of hospitalizations among children with CF ranged from 0.33 to 1.25, while the comparison group had lower mean annual numbers of hospitalizations, ranging from 0.02 to 0.06 ($p < .05$; Figure 1B). Among children with a hospitalization, those with CF had longer mean lengths of stay per hospitalization and more mean annual total days of hospitalization than the comparison group across all four age cohorts of both COM and MED populations ($p < .05$; Figure 1C,D).

Furthermore, all hospitalization-related outcomes were notably higher in adolescents with CF than in the younger cohorts in both the COM and MED populations (Figure 1).

3.3 | Outpatient office visits and ER visits

Children with CF had a higher incidence of outpatient office visits and ER visits, as measured by the proportion of children with a visit and mean number of visits, versus the comparison group (Table 2). These differences were significant ($p < .01$) across all COM age cohorts and in nearly all MED cohorts (except for the proportion of visits in the youngest cohort). For both insurance populations, the

TABLE 1 Demographics at baseline and comorbid conditions over a 12-month period in the commercially insured (COM) and Medicaid-insured (MED) populations of children with cystic fibrosis (CF) and a matched comparison group (Comp) of children without CF

	(0 to <2 years)		(2 to <6 years)		(6 to <12 years)		(12–17 years)	
COM	CF (*n* = 273)	Comp (*n* = 819)	CF (*n* = 546)	Comp (*n* = 1638)	CF (*n* = 965)	Comp (*n* = 2895)	CF (*n* = 1047)	Comp (*n* = 3141)
Demographic information								
Mean age (*SD*), year	0.5 (0.5)	0.5 (0.5)	3.5 (1.1)	3.5 (1.1)	8.6 (1.7)	8.6 (1.7)	14.5 (1.7)	14.5 (1.7)
Male, *n* (%)	146 (53.5)	438 (53.5)	281 (51.5)	843 (51.5)	507 (52.5)	1521 (52.5)	536 (51.2)	1608 (51.2)
Health plan type, *n* (%)								
Comprehensive indemnity	5 (1.8)	15 (1.8)	2 (0.4)	6 (0.4)	8 (0.8)	24 (0.8)	7 (0.7)	21 (0.7)
EPO/PPO	172 (63.0)	516 (63.0)	329 (60.3)	987 (60.3)	614 (63.6)	1842 (63.6)	652 (62.3)	1956 (62.3)
POS/POS with capitation	18 (6.6)	54 (6.6)	31 (5.7)	93 (5.7)	48 (5.0)	144 (5.0)	67 (6.4)	201 (6.4)
HMO	29 (10.6)	87 (10.6)	66 (12.1)	198 (12.1)	97 (10.1)	291 (10.1)	121 (11.6)	363 (11.6)
CDHP/HDHP	33 (12.1)	99 (12.1)	73 (13.4)	219 (13.4)	140 (14.5)	420 (14.5)	140 (13.4)	420 (13.4)
Other/unknown	16 (5.9)	48 (5.9)	45 (8.2)	135 (8.2)	58 (6.0)	174 (6.0)	60 (5.7)	180 (5.7)
Region, *n* (%)								
Northeast	36 (13.2)	108 (13.2)	96 (17.6)	288 (17.6)	192 (19.9)	576 (19.9)	174 (16.6)	522 (16.6)
North Central	71 (26.0)	213 (26.0)	147 (26.9)	441 (26.9)	246 (25.5)	738 (25.5)	279 (26.6)	837 (26.6)
South	106 (38.8)	318 (38.8)	200 (36.6)	600 (36.6)	347 (36.0)	1041 (36.0)	402 (38.4)	1206 (38.4)
West	54 (19.8)	162 (19.8)	96 (17.6)	288 (17.6)	170 (17.6)	510 (17.6)	174 (16.6)	522 (16.6)
Unknown	6 (2.2)	18 (2.2)	7 (1.3)	21 (1.3)	10 (1.0)	30 (1.0)	18 (1.7)	54 (1.7)
Comorbidities occurring in ≥5% of children in any cohort over a 12-month period, *n* (%)[a,b]								
Anxiety	3 (1.1)	0 (0.0)	4 (0.7)^{NS}	3 (0.2)^{NS}	55 (5.7)	47 (1.6)	103 (9.8)	76 (2.4)
Asthma	39 (14.3)	50 (6.1)	108 (19.8)	111 (6.8)	302 (31.3)	183 (6.3)	346 (33.0)	117 (3.7)
Bronchiectasis	2 (0.7)	0 (0.0)	16 (2.9)	0 (0.0)	74 (7.7)	0 (0.0)	153 (14.6)	0 (0.0)
Constipation	35 (12.8)	29 (3.5)	90 (16.5)	38 (2.3)	168 (17.4)	45 (1.6)	111 (10.6)	15 (0.5)
Depression	0 (0.0)^{NS}	0 (0.0)^{NS}	2 (0.4)^{NS}	1 (0.1)^{NS}	28 (2.9)	18 (0.6)	102 (9.7)	93 (3.0)
Diabetes	0 (0.0)^{NS}	0 (0.0)^{NS}	2 (0.4)^{NS}	1 (0.1)^{NS}	43 (4.5)	7 (0.2)	206 (19.7)	14 (0.4)
Intestinal malabsorption	24 (8.8)	3 (0.4)	35 (6.4)	0 (0.0)	70 (7.3)	0 (0.0)	82 (7.8)	0 (0.0)
Nausea/vomiting	47 (17.2)	39 (4.8)	45 (8.2)	54 (3.3)	69 (7.2)	42 (1.5)	93 (8.9)	58 (1.8)
Pancreatic insufficiency[c]	186 (68.1)	0 (0.0)	355 (65.0)	0 (0.0)	706 (73.2)	1 (0.0)	809 (77.3)	0 (0.0)
Pulmonary infection	30 (11.0)	2 (0.2)	52 (9.5)	1 (0.1)	145 (15.0)	3 (0.1)	300 (28.7)	2 (0.1)
Sinus disease	14 (5.1)	19 (2.3)	84 (15.4)	43 (2.6)	280 (29.0)	55 (1.9)	348 (33.2)	39 (1.2)

MED	CF (*n* = 266)	Comp (*n* = 798)	CF (*n* = 454)	Comp (*n* = 1362)	CF (*n* = 639)	Comp (*n* = 1917)	CF (*n* = 537)	Comp (*n* = 1611)
Demographic information								
Mean age (*SD*), year	0.5 (0.5)	0.5 (0.5)	3.5 (1.1)	3.5 (1.1)	8.6 (1.7)	8.6 (1.7)	14.3 (1.7)	14.3 (1.7)
Male, *n* (%)	139 (52.3)	417 (52.3)	233 (51.3)	699 (51.3)	337 (52.7)	1011 (52.7)	295 (54.9)	885 (54.9)
Health plan type, *n* (%)								
Comprehensive indemnity	123 (46.2)	369 (46.2)	231 (50.9)	693 (50.9)	319 (49.9)	957 (49.9)	323 (60.1)	969 (60.1)
EPO/PPO	2 (0.8)	6 (0.8)	0 (0.0)	0 (0.0)	2 (0.3)	6 (0.3)	1 (0.2)	3 (0.2)
POS/POS with capitation	1 (0.4)	3 (0.4)	5 (1.1)	15 (1.1)	1 (0.2)	3 (0.2)	7 (1.3)	21 (1.3)
HMO	140 (52.6)	420 (52.6)	218 (48.0)	654 (48.0)	315 (49.3)	945 (49.3)	204 (38.0)	612 (38.0)
CDHP/HDHP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other/unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	6 (0.3)	2 (0.4)	6 (0.4)
Race, *n* (%)								
White	158 (59.4)	474 (59.4)	339 (74.7)	1017 (74.7)	458 (71.7)	1374 (71.7)	385 (71.7)	1155 (71.7)
Black	18 (6.8)	54 (6.8)	31 (6.8)	93 (6.8)	44 (6.9)	132 (6.9)	50 (9.3)	150 (9.3)
Hispanic	8 (3.0)	24 (3.0)	18 (4.0)	54 (4.0)	30 (4.7)	90 (4.7)	18 (3.4)	54 (3.4)
Other/unknown	82 (30.8)	246 (30.8)	66 (14.5)	198 (14.5)	107 (16.7)	321 (16.7)	84 (15.6)	252 (15.6)
Comorbidities occurring in ≥5% of children in any cohort over a 12-month period, *n* (%)[a,b]								
Anxiety	3 (1.1)	0 (0.0)	13 (2.9)	11 (0.8)	42 (6.6)	29 (1.5)	74 (13.8)	62 (3.8)
Asthma	46 (17.3)	71 (8.9)	106 (23.3)	106 (7.8)	240 (37.6)	188 (9.8)	199 (37.1)	135 (8.4)
Bronchiectasis	7 (2.6)	0 (0.0)	20 (4.4)	0 (0.0)	37 (5.8)	0 (0.0)	65 (12.1)	1 (0.1)
Constipation	58 (21.8)	27 (3.4)	122 (26.9)	52 (3.8)	146 (22.8)	56 (2.9)	98 (18.2)	41 (2.5)
Depression	1 (0.4)[NS]	0 (0.0)[NS]	4 (0.9)[NS]	7 (0.5)[NS]	24 (3.8)[NS]	49 (2.6)[NS]	101 (18.8)	85 (5.3)
Diabetes	3 (1.1)[NS]	1 (0.1)[NS]	3 (0.7)[NS]	4 (0.3)[NS]	45 (7.0)	8 (0.4)	133 (24.8)	14 (0.9)
Intestinal malabsorption	18 (6.8)	3 (0.4)	24 (5.3)	0 (0.0)	34 (5.3)	1 (0.1)	31 (5.8)	0 (0.0)
Nausea/vomiting	55 (20.7)	70 (8.8)	67 (14.8)	75 (5.5)	58 (9.1)	109 (5.7)	64 (11.9)	106 (6.6)
Pancreatic insufficiency[c]	167 (62.8)	0 (0.0)	310 (68.3)	0 (0.0)	482 (75.4)	0 (0.0)	413 (76.9)	0 (0.0)
Pulmonary infection	25 (9.4)	6 (0.8)	53 (11.7)	2 (0.1)	123 (19.2)	6 (0.3)	186 (34.6)	3 (0.2)
Sinus disease	16 (6.0)[NS]	38 (4.8)[NS]	56 (12.3)	43 (3.2)	144 (22.5)	46 (2.4)	154 (28.7)	37 (2.3)

Abbreviations: CDHP, consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; ICD, International Classification of Diseases; NS, not significant; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

[a]Comorbid conditions reported in ≥5% of children in any cohort are listed in alphabetical order.

[b]For comorbid conditions, $p < .05$ for children with CF versus the comparison group except where noted as NS.

[c]Calculated using ICD-9/10 diagnosis code for pancreatic insufficiency or the prescription use of digestive and pancreatic enzymes.

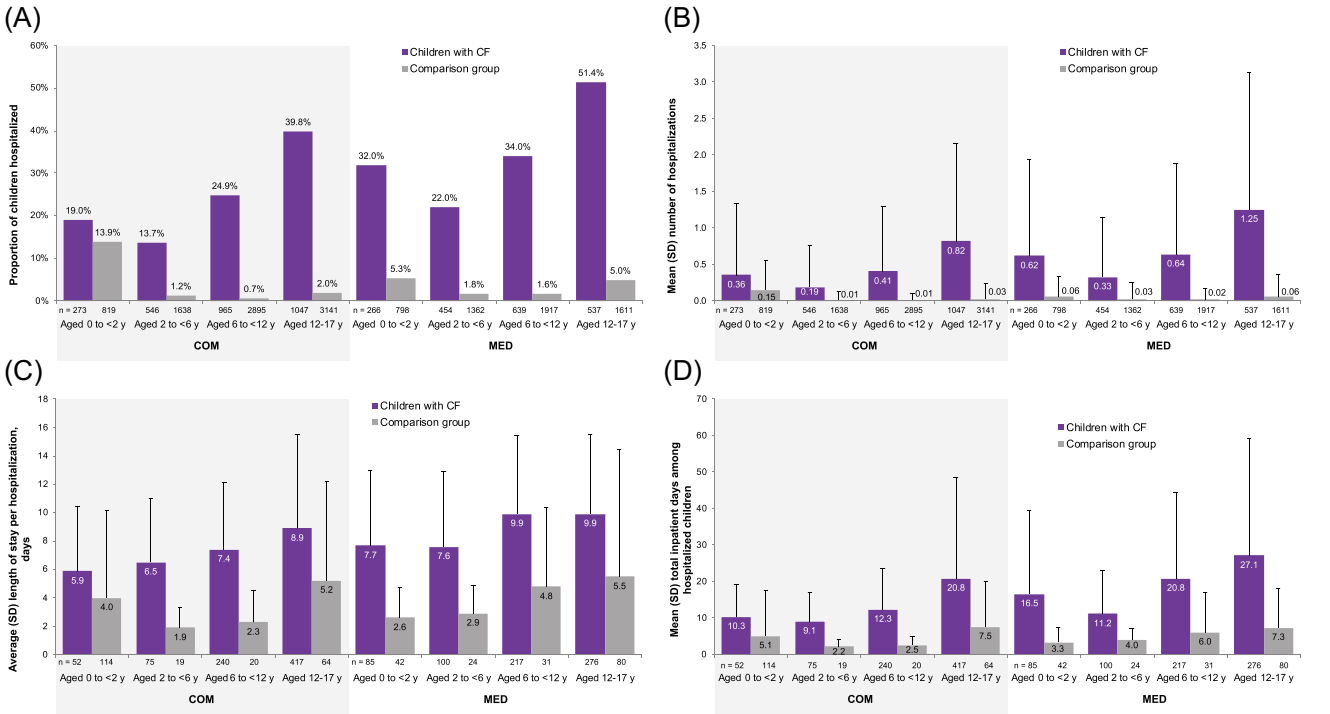


FIGURE 1 Proportion of children hospitalized (A), mean number of hospitalizations (B), average length of stay per hospitalization (C), and mean total inpatient days among hospitalized children (D) over a 12-month period in the commercially insured (COM) and Medicaid-insured (MED) populations of children with cystic fibrosis (CF) and a matched comparison group of children without CF. For children with CF versus the comparison group in all age cohorts for COM and MED children, $p < .05$ for the proportion of children hospitalized (A), $p < .001$ for the mean number of hospitalizations (B), $p < .05$ for the average length per hospitalization (C), and $p < .01$ for the mean total inpatient days among hospitalized children (D).

outpatient office and ER visits remained high across all age cohorts in children with CF, while outpatient office and ER visits tended to decrease with age in the comparison group (Table 2).

3.4 | Medication use

Children with CF were significantly more likely than the comparison group to receive an outpatient prescription medication in both the COM and MED populations, across all age cohorts ($p < .01$; Figure 2A). Children with CF also received significantly more unique prescription medications than the comparison group, ranging from approximately 2–3–fold in children with CF versus the comparison group (all p values < .01; Figure 2B). Additionally, in the comparison group for both insurance populations, the unique number of medications either decreased or remained the same with increasing age, whereas in children with CF, the unique number of medications increased across the age cohorts, with the highest medication use observed among adolescents (Figure 2B).

The proportion of children on prescription medications across different medication classes was significantly greater in children with CF than in the comparison group in both the COM and MED populations ($p < .05$). The high use of medications by medication class was observed even among the youngest cohort with CF and either increased with age or remained high across all age cohorts (Table S1).

3.5 | Healthcare costs

The annual healthcare costs among children with CF were significantly higher versus the comparison group in both the COM and MED populations across all age cohorts, ranging from approximately 9-fold in the youngest cohort to 42-fold in the adolescent cohort in the COM population and more than 12-fold in the youngest cohort to 25-fold in the adolescent cohort in the MED population (all p values < .01, Figure 3). The total annual healthcare costs for children with CF tended to increase with age, whereas the costs remained comparatively low and nearly consistent across the age cohorts in the comparison group (Figure 3).

In children with CF, outpatient prescription medications and hospitalizations comprised the largest category of total annual costs; outpatient prescription medications ranged between 39% and 63% of total costs for COM and 30% and 55% for MED, followed by hospitalization costs, ranging between 15% and 45% of total costs for COM and 27% and 55% for MED. Among children with CF in the COM population, the annual cost of hospitalizations per child ranged from $6500 to $53,678, the annual cost of outpatient prescriptions per child ranged from $20,373 to $47,494, and the annual cost for outpatient visits per child ranged from $9341 to $19,433. For the children with CF in the MED population, the annual cost of hospitalizations per child ranged from $10,460 to $64,327, the annual cost of outpatient prescriptions per child ranged from $13,265 to $45,082, and the annual cost for outpatient visits per child ranged

TABLE 2 Outpatient office visits and ER visits over a 12-month period in the commercially insured (COM) and Medicaid-insured (MED) populations of children with cystic fibrosis (CF) and a matched comparison group (Comp) of children without CF[a]

	(0 to <2 years)			(2 to <6 years)			(6 to <12 years)			(12–17 years)		
COM	**CF (*n* = 273)**	**Comp (*n* = 819)**	***p* value**	**CF (*n* = 546)**	**Comp (*n* = 1638)**	***p* value**	**CF (*n* = 965)**	**Comp (*n* = 2895)**	***p* value**	**CF (*n* = 1047)**	**Comp (*n* = 3141)**	***p* value**
Children with an office visit, *n* (%)	273 (100.0)	767 (93.7)	<.001	543 (99.5)	1455 (88.8)	<.001	963 (99.8)	2259 (78.0)	<.001	1040 (99.3)	2435 (77.5)	<.001
Office visits among all children per year, mean (*SD*)	14.3 (7.3)	7.5 (5.4)	<.001	9.3 (5.2)	3.6 (3.3)	<.001	9.7 (6.4)	2.6 (2.9)	<.001	10.5 (7.3)	2.8 (3.1)	<.001
Children with an ER visit, *n* (%)	92 (33.7)	207 (25.3)	.007	156 (28.6)	334 (20.4)	<.001	257 (26.6)	390 (13.5)	<.001	313 (29.9)	519 (16.5)	<.001
ER visits among all children per year, mean (*SD*)	0.6 (1.0)	0.4 (0.9)	.003	0.4 (0.8)	0.3 (0.6)	<.001	0.5 (1.3)	0.2 (0.5)	<.001	0.6 (1.3)	0.2 (0.6)	<.001
MED	**CF (*n* = 266)**	**Comp (*n* = 798)**	***p* value**	**CF (*n* = 454)**	**Comp (*n* = 1362)**	***p* value**	**CF (*n* = 639)**	**Comp (*n* = 1917)**	***p* value**	**CF (*n* = 537)**	**Comp (*n* = 1611)**	***p* value**
Children with an office visit, *n* (%)	262 (98.5)	766 (96.0)	.050[NS]	442 (97.4)	1245 (91.4)	<.001	626 (98.0)	1465 (76.4)	<.001	514 (95.7)	1199 (74.4)	<.001
Office visits among all children per year, mean (*SD*)	14.6 (9.0)	7.4 (5.8)	<.001	9.8 (6.4)	4.1 (3.7)	<.001	10.5 (7.8)	3.1 (3.8)	<.001	10.4 (8.2)	3.1 (3.9)	<.001
Children with an ER visit, *n* (%)	145 (54.5)	396 (49.6)	.167[NS]	214 (47.1)	480 (35.2)	<.001	241 (37.7)	543 (28.3)	<.001	212 (39.5)	519 (32.2)	.002
ER visits among all children per year, mean (*SD*)	1.3 (2.1)	1.0 (1.4)	.013	0.9 (1.3)	0.6 (1.0)	<.001	0.7 (1.4)	0.4 (0.9)	<.001	0.8 (1.6)	0.6 (1.2)	.000

Abbreviations: ER, emergency room; NS, not significant; SD, standard deviation.

[a]$p < .05$ for children with CF versus the comparison group in all age cohorts for COM and MED children except where noted as NS.

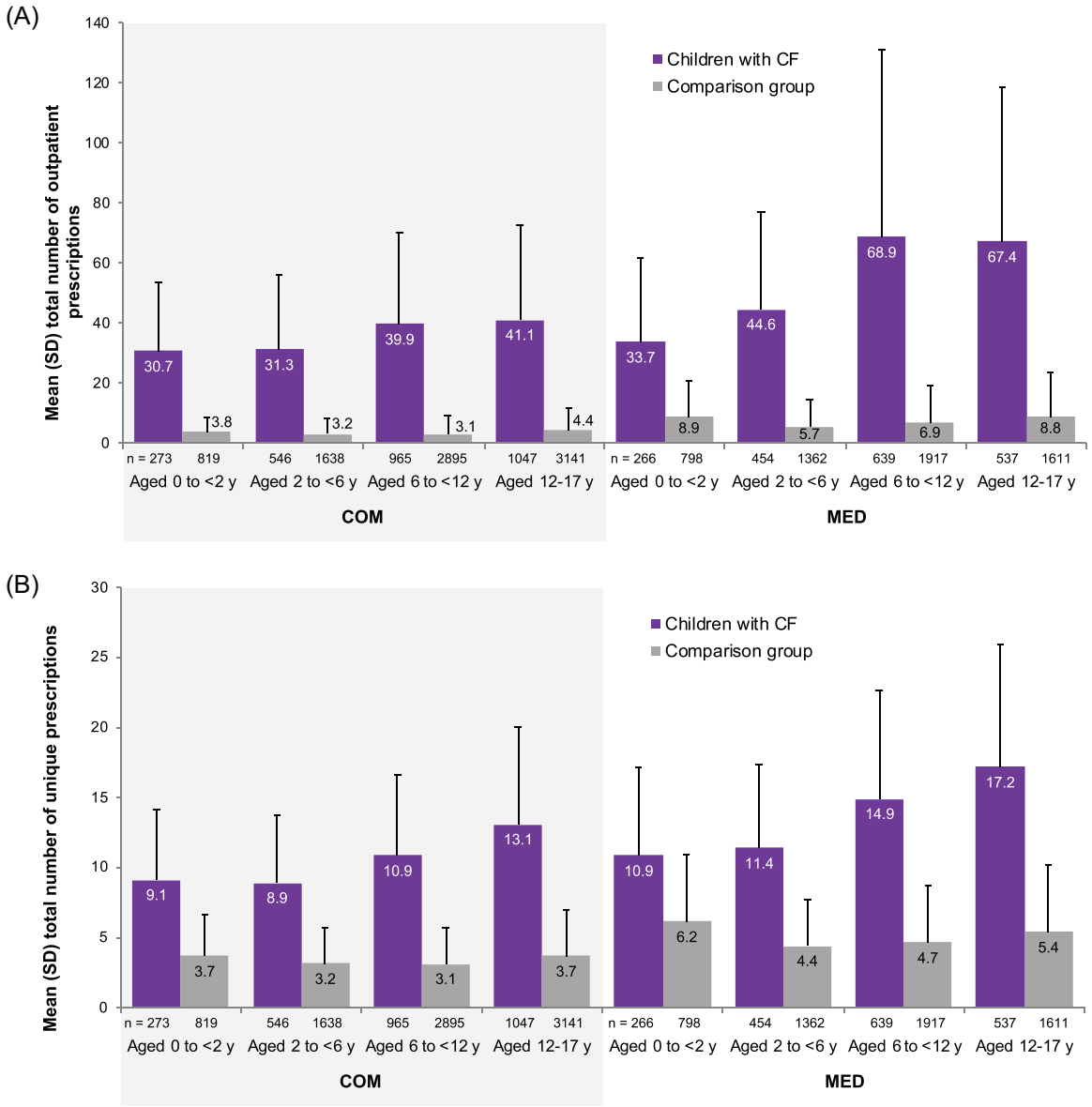
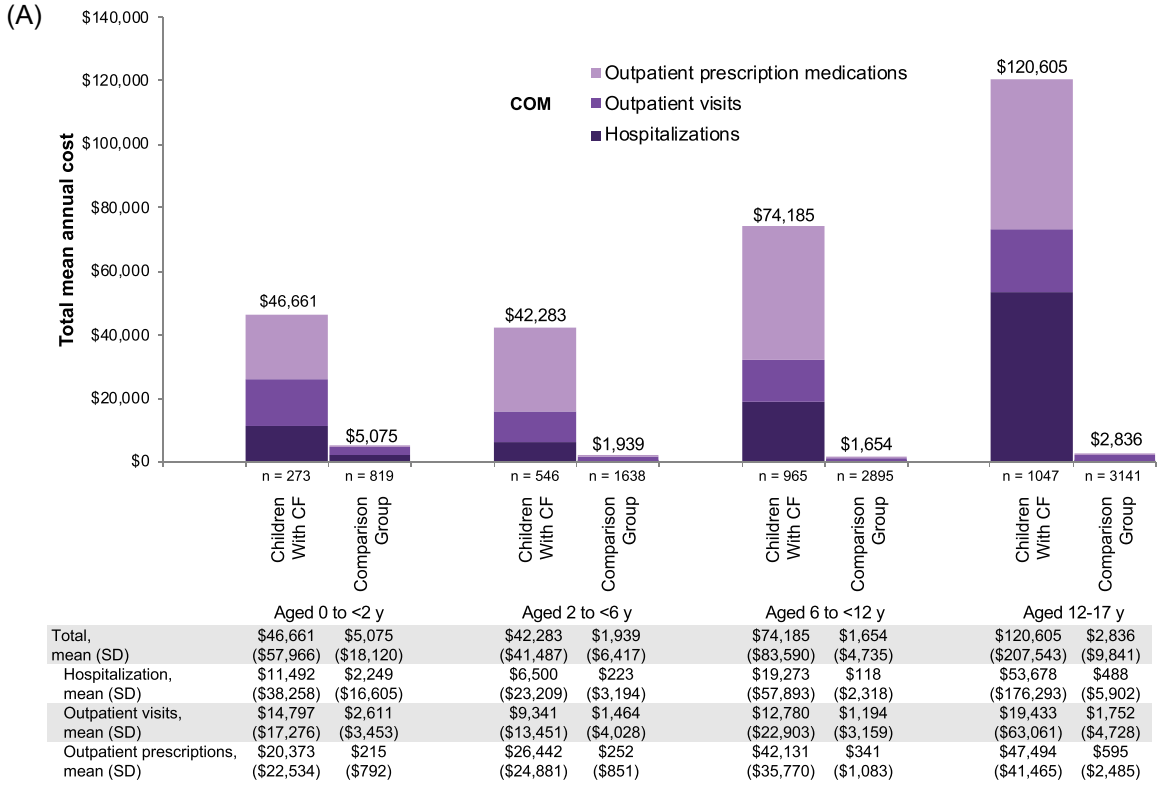


FIGURE 2 Prescription medication use: mean total number of outpatient prescription medications (A) and mean total number of unique prescription medications (B) over a 12-month period in the commercially insured (COM) and Medicaid-insured (MED) populations of children with cystic fibrosis (CF) and a matched comparison group of children without CF. $p < .001$ for children with CF versus the comparison group in all age cohorts for COM and MED children.

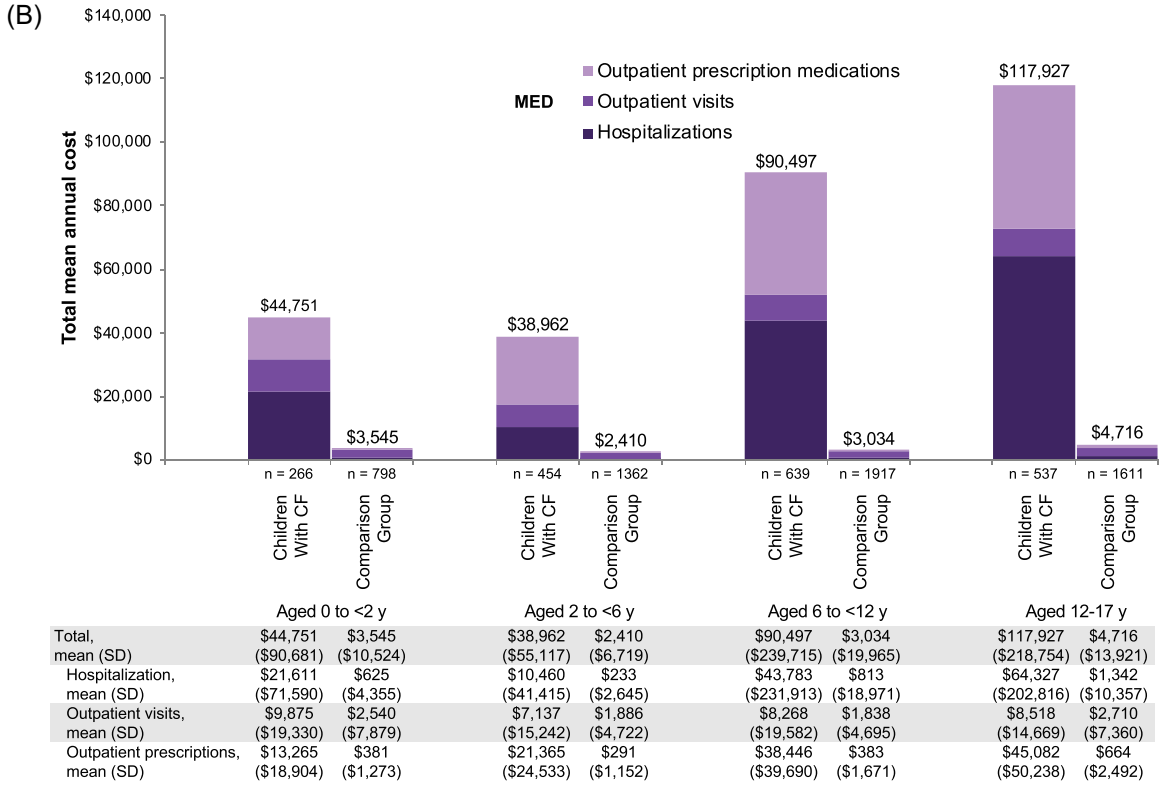
from $7137 to $9875. In contrast, the sum of total annual costs for hospitalizations, outpatient prescriptions, and outpatient visits was less than $5000 across all age cohorts and both insurance populations in the comparison group.

4 | DISCUSSION

This study quantified the real-world HCRU and costs attributable to CF versus those for the general pediatric population for both COM and MED populations in the United States. Children with CF had significant HCRU across all age cohorts and study measures. Over 12 months, they had a high hospitalization rate, higher proportion hospitalized, longer hospital stays, more ER and outpatient visits, and greater prescription medication use than children without CF. Consequently, healthcare costs associated with CF were up to 25-times higher than those in the comparison group. The biggest drivers of annual healthcare costs in children with CF were hospitalizations and prescription medications. Interestingly, the HCRU and costs tended to increase with age among children with CF, with the highest HCRU and costs observed in the adolescent cohorts, whereas among the comparison group the HCRU and costs decreased or remained low across all age cohorts. Notably, this study demonstrated considerable HCRU and costs attributable to CF at a young age, when respiratory impairment might not be visible, and illustrated the progressive nature of CF by documenting patterns of HCRU and costs attributable to CF from birth to age 17 years.



	Aged 0 to <2 y		Aged 2 to <6 y		Aged 6 to <12 y		Aged 12-17 y	
Total, mean (SD)	$46,661 ($57,966)	$5,075 ($18,120)	$42,283 ($41,487)	$1,939 ($6,417)	$74,185 ($83,590)	$1,654 ($4,735)	$120,605 ($207,543)	$2,836 ($9,841)
Hospitalization, mean (SD)	$11,492 ($38,258)	$2,249 ($16,605)	$6,500 ($23,209)	$223 ($3,194)	$19,273 ($57,893)	$118 ($2,318)	$53,678 ($176,293)	$488 ($5,902)
Outpatient visits, mean (SD)	$14,797 ($17,276)	$2,611 ($3,453)	$9,341 ($13,451)	$1,464 ($4,028)	$12,780 ($22,903)	$1,194 ($3,159)	$19,433 ($63,061)	$1,752 ($4,728)
Outpatient prescriptions, mean (SD)	$20,373 ($22,534)	$215 ($792)	$26,442 ($24,881)	$252 ($851)	$42,131 ($35,770)	$341 ($1,083)	$47,494 ($41,465)	$595 ($2,485)



	Aged 0 to <2 y		Aged 2 to <6 y		Aged 6 to <12 y		Aged 12-17 y	
Total, mean (SD)	$44,751 ($90,681)	$3,545 ($10,524)	$38,962 ($55,117)	$2,410 ($6,719)	$90,497 ($239,715)	$3,034 ($19,965)	$117,927 ($218,754)	$4,716 ($13,921)
Hospitalization, mean (SD)	$21,611 ($71,590)	$625 ($4,355)	$10,460 ($41,415)	$233 ($2,645)	$43,783 ($231,913)	$813 ($18,971)	$64,327 ($202,816)	$1,342 ($10,357)
Outpatient visits, mean (SD)	$9,875 ($19,330)	$2,540 ($7,879)	$7,137 ($15,242)	$1,886 ($4,722)	$8,268 ($19,582)	$1,838 ($4,695)	$8,518 ($14,669)	$2,710 ($7,360)
Outpatient prescriptions, mean (SD)	$13,265 ($18,904)	$381 ($1,273)	$21,365 ($24,533)	$291 ($1,152)	$38,446 ($39,690)	$383 ($1,671)	$45,082 ($50,238)	$664 ($2,492)

FIGURE 3 Healthcare costs over a 12-month period in the commercially insured (COM; A) and Medicaid-insured (MED; B) populations of children with cystic fibrosis (CF) and a matched comparison group of children without CF. $p < .001$ for children with CF versus the comparison group in all age cohorts for COM and MED children.

The results of this study are consistent with those of previous studies reporting healthcare costs of CF.[17,19,20,27–29] Studies evaluating costs of CF care showed that medications and hospital stays contribute to the majority of the total costs, similar to the findings from this study.[17,19,20,27–29] However, the previously published studies are limited to only COM populations in the United States, are outdated in terms of the years included in the analysis, are not reflective of developments in standard of care, did not exclusively evaluate costs in pediatric populations, or focused on evaluating costs for patients from ex-US countries.[17,19,20,27–29] Our study provides more recent estimates of costs of care in the pediatric CF population in the United States before the advent of CFTRms. Moreover, it establishes a benchmark that will allow us to determine the extent to which HCRU and costs change as younger children with CF are treated with CFTRms. Because CFTRms were only recently approved,[9–16] it is not yet possible to establish the HCRU and costs attributable to CF when CFTRms are started at a young age. However, this is an important area for future research.

To the extent we were able to compare patient characteristics in this study with those in the US CF Foundation Patient Registry (CFFPR), we were able to confirm broad similarities in the distribution by sex and age.[30,31] The HCRU among children with CF in this study is consistent with an analysis using the CFFPR in children aged less than 12 years that reported similar results for annual hospitalizations and use of medications such as bronchodilators, dornase alfa, hypertonic saline, and inhaled corticosteroids.[30] The early and intensive use of healthcare resources for children with CF is consistent with current treatment guidelines for management of the multisystemic impact of CF. Symptomatic management includes treatment with pancreatic enzyme replacement therapy, airway clearance techniques, antibiotics, and nutritional supplementation.[32,33] The results of this study showing increased HCRU as individuals age are consistent with published studies describing a substantial disease burden among older pwCF.[21,34] Moreover, the increasing HCRU as pwCF age reported in this study correlates with findings of variable lung function decline over time, with steep decline in adolescents compared with younger children with CF.[7,8] Lung function loss may lead to overall health status deterioration and, thus, higher HCRU and costs.

Early intervention is the cornerstone of treatment in pwCF and is supported by evidence from multiple studies showing early diagnosis and access to routine CF care to be associated with positive health outcomes extending over many years.[4,35–37] Although associated with improved outcomes, early symptomatic treatment remains inadequate, since predicted life expectancy for pwCF receiving symptomatic therapy is decades shorter than that of the general population.[2,38] In addition to standard symptomatic therapy, CFTRms treat the underlying cause of CF and can provide multisystemic clinical benefits, thereby improving prognosis from an early age.[9–16] Real-world evidence is emerging for the impact of CFTRms on lung function, nutrition, and pulmonary exacerbations.[9–16] As previously mentioned, further research evaluating the impact of CFTRms on HCRU among children with CF is warranted.

Results from this study help to demonstrate the considerable HCRU and costs attributable to CF among children as young as less than 2 years and emphasize the need for effective treatments in children starting at an early age.

5 | LIMITATIONS

This was an observational study, and there are inherent limitations to using previously collected real-world data. Also, the cross-sectional data should not be interpreted as describing trends for the same cohort of pwCF as they age. As this study aimed to describe the HCRU and costs attributable to CF, the comparator group was selected from children enrolled in the same health insurance plans to represent the general pediatric population. Future studies could compare HCRU in pwCF versus people with other severe and chronic healthcare conditions.

These analyses used administrative claims data, which are generated by the reimbursement process rather than for research purposes. Medical and prescription claims were used as a surrogate to identify comorbidities and concomitant medication use, which may have led to misclassification; clinical and laboratory test results, including spirometry and genotyping, were not available. Children with CF were identified through resource use claims, which may have led to misclassification of children included and excluded from the study. Moreover, children in the matched comparison group were not required to have any resource use to be included, which may have overestimated the observed differences between the two groups. However, any bias introduced by this is expected to be minimal because children with CF are highly managed (per CF care guidelines, pwCF should have regular healthcare visits for routine care[39]); moreover, although children were identified through their resource use, they did not necessarily incur that use during the analyzed 12-month follow-up period.

The study did not evaluate the difference in HCRU or costs between the COM and MED populations since unmeasured confounders make interpretation of these differences infeasible; however, results from this study indicate numerically higher HCRU in MED children across all age cohorts. Evidence suggests that MED populations tend to have worse health outcomes compared with COM populations.[40,41] This study did not examine differences across subgroups of pwCF, such as sex, race, and geographic region, which could impact HCRU and costs. Finally, these findings may not be generalizable to the entire US population of pwCF with commercial or Medicaid insurance, with other forms of insurance, or without insurance or pwCF outside the United States.

6 | CONCLUSIONS

This retrospective claims analysis in COM and MED populations of children with CF aged less than or equal to 17 years demonstrated significant HCRU and costs attributable to CF relative to a matched

comparison group without CF, observed through the following measures: higher hospitalization rates and longer hospital stays per admission; higher annual rates of outpatient office visits and ER visits; greater prescription medication use, with more total and unique prescription medications per year; and higher annual healthcare costs mainly associated with outpatient prescriptions and hospitalizations. The study also found considerable HCRU and costs in managing CF and its consequences compared with the general pediatric population starting as early as infancy, with higher HCRU and costs observed among older children with CF, especially adolescents. These results illustrate the substantial HCRU and costs attributable to CF and highlight the unmet need for effective treatment options starting from an early age in children with CF.

ACKNOWLEDGMENTS

Augustine Obi, PharmD, of Vertex Pharmaceuticals Incorporated, provided editorial coordination and assistance. Amos Race, PhD, and Samantha Keller, PhD, of ArticulateScience LLC, provided editorial assistance under the direction of the authors, with support from Vertex Pharmaceuticals Incorporated. This study was supported by Vertex Pharmaceuticals Incorporated. Data from this study (for children aged 0 to <6 years) have been presented in posters at the ECFS 2019 (Liverpool, UK) and ISPOR 2019 (New Orleans, LA, USA) conferences.

CONFLICT OF INTERESTS

All authors received nonfinancial support (assistance with manuscript preparation) from ArticulateScience LLC, which received funding from Vertex Pharmaceuticals Incorporated. TT, LM, and JLR are employees of Vertex and may own stock or stock options in that company. MMB was an employee of IBM Watson Health Company at the time the study was conducted, which received a research contract to conduct this study with and on behalf of Vertex, and is a current employee of Veradigm Life Sciences. BLL and KJ-P are employees of IBM Watson Health Company, which received a research contract to conduct this study with and on behalf of Vertex. MWK reports grants from Vertex, Laurent Pharmaceuticals, Anthera, Cystic Fibrosis Foundation, National Institutes of Health, and AzurRx; personal fees from Chiesi, Celtaxsys, Ionis Pharmaceuticals, Merck, Paranta Biosciences, Santhera, pH Pharma, Kala Pharmaceuticals, Vertex, Laurent Pharmaceuticals, Anthera, Cystic Fibrosis Foundation, and AzurRx; and serving on an advisory board for Vertex, Ionis Pharmaceuticals, Santhera, and Kala Pharmaceuticals, outside the submitted work.

AUTHOR CONTRIBUTIONS

Teja Thorat: conceptualization (equal); methodology (equal); project administration (lead); visualization (equal); writing original draft (lead); writing review & editing (lead). **Lisa McGarry**: conceptualization (equal); methodology (equal); writing original draft (equal); writing review & editing (equal). **Machaon M. Bonafede**: conceptualization (supporting); data curation (equal); formal analysis (equal); methodology (supporting); software (equal); validation (equal); visualization (equal); writing original draft (supporting); writing review & editing (equal). **Brendan L. Limone**: conceptualization (supporting); data curation (equal); formal analysis (equal); methodology (supporting); software (equal); validation (equal); visualization (equal); writing original draft (supporting); writing review & editing (equal). **Jaime L. Rubin**: conceptualization (equal); methodology (equal); writing original draft (equal); writing review & editing (equal). **Krutika Jariwala-Parikh**: conceptualization (supporting); data curation (equal); formal analysis (equal); methodology (supporting); software (equal); validation (equal); visualization (equal); writing original draft (supporting); writing review & editing (equal). **Michael Konstan**: conceptualization (equal); methodology (equal); writing original draft (supporting); writing review & editing (equal).

ORCID

Teja Thorat https://orcid.org/0000-0003-2856-752X
Michael W. Konstan https://orcid.org/0000-0002-0557-7277

REFERENCES

1. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989;245:1066-1073.
2. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report*. Bethesda, Maryland: Cystic Fibrosis Foundation; 2019.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181S:S4-S15.
4. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: a review of disease manifestation, progression, and response to early treatment. *J Cyst Fibros*. 2016;15:147-157.
5. Sly PD, Brennan S, Gangell C, et al. Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med*. 2009;180:146-152.
6. Schlüter DK, Griffiths R, Adam A, et al. Impact of cystic fibrosis on birthweight: a population based study of children in Denmark and Wales. *Thorax*. 2019;74:447-454.
7. Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *J Cyst Fibros*. 2010;9:250-256.
8. Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr*. 2007;151:134-139.
9. Orkambi (lumacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2019.
10. Kalydeco (ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2020.
11. Orkambi (lumacaftor/ivacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Limited; 2019.
12. Kalydeco (ivacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Limited; 2020.
13. Trikafta (elexacaftor/tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2021.

14. Kaftrio (ivacaftor/tezacaftor/elexacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Limited; 2021.
15. Symdeko (tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2019.
16. Symkevi (tezacaftor/ivacaftor) [summary of product characteristics]. Dublin, Ireland: Vertex Pharmaceuticals (Ireland) Limited; 2020.
17. Durieu I, Dalon F, Reynaud Q, et al. Temporal trends in healthcare resource use and associated costs of patients with cystic fibrosis [published online ahead of print April 14, 2021]. *J Cyst Fibros*. 2021.
18. Rubin JL, Thayer S, Watkins A, Wagener JS, Hodgkins PS, Schechter MS. Frequency and costs of pulmonary exacerbations in patients with cystic fibrosis in the United States. *Curr Med Res Opin*. 2017;33:667-674.
19. Grosse SD, Do TQN, Vu M, Feng LB, Berry JG, Sawicki GS. Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. *Pediatr Pulmonol*. 2018;53:1611-1618.
20. Van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. *Value Health*. 2013;16:345-355.
21. Hassan M, Bonafede MM, Limone BL, Hodgkins P, Sawicki GS. The burden of cystic fibrosis in the Medicaid population. *Clinicoecon Outcomes Res*. 2018;10:423-431.
22. Frey S, Stargardt T, Schneider U, Schreyögg J. The economic burden of cystic fibrosis in Germany from a payer perspective. *Pharmacoeconomics*. 2019;37:1029-1039.
23. Klein K, Soliman AM, Bonafede M, Nelson JK, Grubb E. Health care utilization and economic burden in patients with central precocious puberty: an assessment of the commercially insured and medicaid populations. *J Manag Care Spec Pharm*. 2019;25:836-846.
24. Thayer S, Bell C, McDonald CM. The direct cost of managing a rare disease: assessing medical and pharmacy costs associated with Duchenne muscular dystrophy in the United States. *J Manag Care Spec Pharm*. 2017;23:633-641.
25. Sieluk J, Slejko JF, Silverman H, Perfetto E, Mullins CD. Medical costs of alpha-1 antitrypsin deficiency-associated COPD in the United States. *Orphanet J Rare Dis*. 2020;15:260.
26. Consumer Price Index. https://www.bls.gov/cpi/tables/supplemental-files/home.htm. Accessed September 16, 2020.
27. Lieu TA, Ray GT, Farmer G, Shay GF. The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics*. 1999;103:e72.
28. Ouyang L, Grosse SD, Amendah DD, Schechter MS. Healthcare expenditures for privately insured people with cystic fibrosis. *Pediatr Pulmonol*. 2009;44:989-996.
29. Briesacher BA, Quittner AL, Fouayzi H, Zhang J, Swensen A. Nationwide trends in the medical care costs of privately insured patients with cystic fibrosis (CF), 2001-2007. *Pediatr Pulmonol*. 2011;46:770-776.
30. Bresnick K, Arteaga-Solis E, Millar SJ, Laird G, Lecamus C. *Burden of Illness Among Children Aged <12 Years with Cystic Fibrosis. AMCP Nexus 2019; October 29-November 1*. Maryland: National Harbor; 2019.
31. Cystic Fibrosis Foundation. *Cystic Fibrosis Foundation Patient Registry 2017 Annual Data Report*. Bethesda, Maryland: Cystic Fibrosis Foundation; 2018.
32. Clinical Care Guidelines. Cystic Fibrosis Foundation. https://www.cff.org/Care/Clinical-Care-Guidelines/. Accessed September 16, 2020.
33. Proesmans M. Best practices in the treatment of early cystic fibrosis lung disease. *Ther Adv Respir Dis*. 2017;11:97-104.
34. O'Sullivan AK, Wagener J, Berthiaume Y, et al. Multi-country comparison of reported disease burden among patients (pts) with cystic fibrosis (CF) who are homozygous for the F508del-CFTR mutation. *J Cyst Fibros*. 2016;15:S87. Abstract 141.
35. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373:1891-1904.
36. Dijk FN, Fitzgerald DA. The impact of newborn screening and earlier intervention on the clinical course of cystic fibrosis. *Paediatr Respir Rev*. 2012;13:220-225.
37. Tridello G, Castellani C, Meneghelli I, Tamanini A, Assael BM. Early diagnosis from newborn screening maximises survival in severe cystic fibrosis. *ERJ Open Res*. 2018;4:00109-02017.
38. European Cystic Fibrosis Society. European Cystic Fibrosis Society Patient Registry: annual data report 2017. Karup, Denmark: European Cystic Fibrosis Society; 2019.
39. Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137:e20151784.
40. Stephenson AL, Sykes J, Stanojevic S, et al. Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. *Ann Intern Med*. 2017;166:537-546.
41. Tumin D, Crowley EM, Li SS, Wooten W, Ren CL, Hayes D Jr. Patterns of health insurance coverage and lung disease progression in adolescents and young adults with cystic fibrosis. *Ann Am Thorac Soc*. 2021;18:290-299.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Thorat T, McGarry LJ, Bonafede MM, et al. Healthcare resource utilization and costs among children with cystic fibrosis in the United States. *Pediatric Pulmonology*. 2021;56:2833-2844. https://doi.org/10.1002/ppul.25535