The Prevalence and Effect of Comorbid Cystic Fibrosis and Attention Deficit Hyperactivity Disorders on Hospitalizations: A Retrospective Analysis

Nicole Spitzer 1, Timothy B. Legare 2, Priyanshi Patel 3, Nicholas Toselli 4, Floyd Livingston 5

1. Ophthalmology, University of Central Florida College of Medicine, Orlando, USA  
2. Surgery, University of Central Florida College of Medicine, Orlando, USA  
3. Pediatrics, University of Central Florida College of Medicine, Orlando, USA  
4. Miscellaneous, University of Central Florida College of Medicine, Orlando, USA  
5. Pediatric Pulmonology, Nemours Children’s Hospital, Orlando, USA

Corresponding author: Nicole Spitzer, nicolespitzer@knights.ucf.edu

Disclosures can be found in Additional Information at the end of the article

Abstract

Introduction: The prevalence of attention-deficit/hyperactivity disorder (ADHD) in pediatric cystic fibrosis (CF) patients is comparable to the general population, but the effects of ADHD on CF treatment and the outcomes have been minimally investigated.

Methods: Two cohorts were retrospectively reviewed, pediatric patients with comorbid CF/ADHD and patients with CF only. Each patient with CF/ADHD was age and sex-matched to a CF-only patient based on their most recent pulmonary office visit. Each patient was reviewed for forced expiratory volume in one-second percent predicted (FEV1%pred), body mass index (BMI) percentile, and hospitalizations for one year prior to the last pulmonary visit.

Results: A total of 624 patients with CF were identified, with 52 having co-morbid CF/ADHD (8.3%). Of those identified, 46 met inclusion criteria and were analyzed in the CF/ADHD cohort. The mean total hospital admissions between the CF/ADHD cohort and the CF-only cohort were not statistically significant (2.22 vs 1.834, p=.467). The difference between the BMI percentiles was not statistically significant (48.634 vs 38.634, p=.135). The difference between FEV1%pred was statistically significant at 84% for the CF/ADHD group and 74% for the CF-only group (p=.042).

Conclusion: The difference in total hospital admissions between the CF/ADHD cohort and the CF-only cohort did not reach statistical significance, but the study was underpowered. There was a significant difference between FEV1%pred between the two groups, in favor of the comorbid CF/ADHD population. More research is needed to further evaluate the effects of a comorbid ADHD diagnosis on outcomes in the CF pediatric population.

Categories: Pediatrics, Psychiatry, Pulmonology

Keywords: cystic fibrosis, attention deficit hyperactivity disorder, treatment compliance, adhd, adherence, adherence

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder that is caused by a mutation in the CF transmembrane conductance regulator (CFTR) protein [1]. The CFTR protein is a
cycloadenosine monophosphate regulated chloride channel that regulates sodium and water transport in and out of epithelial cells [1]. A defect in this channel leads to thick secretions in many locations in the body such as the respiratory system, gastrointestinal tract, sweat glands, and various other places [1,2]. CF is the most common autosomal recessive life-shortening disorder amongst Caucasians [3]. Patients experience recurrent bronchopulmonary infections, malabsorption, pancreatic insufficiency, and nutritional derangements [1]. CF has been described as a life-shortening disorder, however, recent changes in disease management over the past 20 years have increased life expectancy from an average age of 28 to 37 [1,4]. Improvement in life expectancy is due to the increased availability and treatment of the manifestations of CF, as there currently is no cure.

The multisystem effect of CF leads to treatments being complex, and treatments may utilize a variety of different strategies: airway clearance, inhalants to alter airway surface liquids and mucus, antimicrobials for infections, anti-inflammatory medications, medications that target the defective CFTR protein, and nutritional therapy [1]. A review of the literature in 2014 showed that the average number of self-administered home treatments for a CF patient is seven, taking an average of 108 minutes per day to perform [4]. Due to this complexity, treatment adherence has varied widely amongst pediatric CF patients [4]. Treatment adherence has been shown to decrease morbidity, mortality, and hospitalizations [4-5]. As CF patients grow older and the prognosis of CF improves, it becomes imperative for physicians to determine the barriers to adherence and the risk factors for non-adherence and determine how best to intervene in non-adherent patients.

Another area currently being investigated is the effect of chronic illnesses on developing psychiatric illnesses. In general, patients with chronic diseases are at a greater risk for psychiatric, emotional, and behavioral disorders, given the complexity surrounding therapy and the burden of the disease [6-7]. Pediatric CF patients appear to have a significant risk of developing psychological manifestations, such as depression and anxiety [8-9]. Patients with CF associated with other co-morbidities, such as depression, have an increased hospitalization risk [10].

Attention-deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder found in the pediatric population and should be considered as a diagnosis for any child older than four years old who presents with distractibility, hyperactivity, impulsiveness, poor academic performance, behavioral problems, or poor attention spans [11]. The ADHD diagnosis is based upon the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and is further defined by three subtypes: primarily inattentive, primarily hyperactive, and combined subtypes [11]. Most recent data suggests the prevalence of ADHD is increasing, from 7.8% in 2005 to 9.5% in 2007 [11-13]. According to the Centers for Disease Control and Prevention, as of 2011, approximately 11% of children four to 17 years of age have been diagnosed with ADHD in the United States [14].

The current data on comorbid ADHD and CF is sparse. To date, our team identified three articles that address ADHD in the pediatric CF population. The first, published in 2011, found that the prevalence of ADHD diagnoses in the CF population at Massachusetts General Hospital (9.6%) mirrored the prevalence in the general pediatric population (10%) [15]. The second study reported the prevalence of ADHD diagnoses in the CF population of Medicaid patients from 1999-2006 [16]. This study reported an increase in the prevalence of CF/ADHD patients from 5.26% in 1999 to 8.16% in 2006 [16]. Finally, the most recent study, in 2018, found that in their pediatric and adult CF population, there was a higher rate (17%) of ADHD symptoms than in the general population [17]. Diagnosing and managing ADHD in CF patients may become paramount because of the increased complexity of treatment for CF and the impact that treatment adherence has on outcomes in this population. It has been found that ADHD is associated with impairment of self-care, and data has suggested that the impulsivity of ADHD
may be associated with early mortality [15,18]. Most children with ADHD present with poor attention spans, task avoidance, distractibility, deficits in impulse control and executive function, and other behavioral problems [12,15]. Deficiencies in executive functioning can present as forgetfulness and difficulty in planning and coordinating everyday tasks [19]. This may result in trouble following complex directions and may create a risk for errors in managing difficult treatment plans [11-12,20]. These associations warrant investigations into the effects of comorbid CF/ADHD and its impacts on healthcare outcomes. In this study, we will report the prevalence of ADHD in our pediatric CF population at a multisite tertiary care pediatric hospital system. We hypothesize that there will be significant differences in the number of hospitalizations, BMI percentiles, and pulmonary function tests between patients with comorbid ADHD/CF and patients with CF only.

Materials And Methods

Methods

Following institutional review board approval by the Nemours Office of Human Subjects Protection (741996), a retrospective cohort study of all patients diagnosed with CF and comorbid CF/ADHD from 1/1/04 to 12/31/14 was conducted. As a first step, the extraction of patients with the ICD-9 code for CF was performed. Additionally, the medical records extracted (n = 624) were queried for the presence of the ICD-9 code for ADHD (n=52). Data were extracted from medical records from all four children’s hospitals in our institution. CF and CF/ADHD patients were matched by age, sex, and most recent clinic visit (within ±6 months of matched cohort) to a patient who had CF without an ADHD diagnosis (CF-only cohort). Of the 52 comorbid CF/ADHD patients, one patient was unable to be matched to a CF only patient, two had incomplete spirometry records for comparison, and three patients were determined from the chart review to not have ADHD. The incomplete records were consistently seen in patients who either transferred care or only had one office visit.

Inclusion criteria for the CF/ADHD arm of the study were as stated: age greater than six years old, diagnosis of cystic fibrosis with pulmonary manifestations, and a diagnosis of any subtype of ADHD. Inclusion criteria for the CF-only arm were as stated above, without a diagnosis of any subtype of ADHD.

Variables

For each patient that met the inclusion criteria, the following variables were extracted: the CF/ADHD cohort was reviewed at their most recent clinic date for age, sex, race, BMI percentile, and forced expiratory volume at one-second percent predicted (FEV1%pred). Additional variables included: number of hospitalizations within one year, along with whether the patient had visited the emergency room (ER) with no admission to the hospital, was seen in the emergency room, and had been admitted to the hospital (ER-ADM), and whether the patient had been admitted to the hospital without visiting the emergency room (ADM). Each patient was then grouped into categories based upon severity using their FEV1%pred at the most recent office visit, with categories defined as: Mild CF = FEV1%pred >70%, Moderate CF = FEV1%pred <70%, but >40%, and Severe CF = FEV1%pred <40%.

Data management and statistical analyses

Sex and ethnicity are reported as frequency and percentage. BMI, FEV1%pred, and number of hospitalizations are reported as means with standard deviation. An independent t-test was used to assess group differences for hospitalization data. A Pearson Chi-square test (X2) was used to assess the associations of sex, FEV1%pred, and BMI. The alpha level for significance was set at .05. All statistical analysis were two-tailed and conducted in SPSS (IBM Corp). Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, IBM Corp.)
Results

There were a total of 624 patients identified with CF at our institution. A total of 52 patients (8.3%) were identified to have comorbid CF/ADHD. Of the 572 CF-only patients, 358 (54.2%) were male and 286 (45.8%) were female. Of the 52 patients with comorbid CF and ADHD, 39 (75%) were male and 13 (25%) were female. This is statistically significantly different from the male to female distribution in the CF-only cohort (52.3% male vs. 45.8% female, p=.002).

CF/ADHD arm

A total of 46 patients with CF/ADHD were identified and met the inclusion criteria. There were 36 males with CF/ADHD and 10 females with a mean age of 14.7 years (range 6-21 years) at the initial office visit. The mean BMI percentile was 48.634% (SD= 31.736). Amongst the CF/ADHD group, there were 39 (84.8%) Caucasians, three (6.5%) African-Americans, three (6.5%) Hispanic patients, and 1 (2.2%) designated as "other; race not specified." A compilation of demographic statistics is shown in Table 1. The average FEV1%pred of the CF/ADHD group was 84.70% (SD=21.637). Of the 46 patients in the CF/ADHD arm, 35 (76.1%) fell into the Mild CF category, 10 (21.7%) in the Moderate CF, and 1 (2.2%) with Severe CF. Pulmonary function and BMI percentile comparisons are illustrated in Table 2.

|                | CF/ADHD | CF Only |
|----------------|---------|---------|
| Total Patients (n=92) | 46      | 46      |
| Female          | 10 (21.7%) | 10 (21.7%) |
| Male            | 36 (78.3%) | 36 (78.3%) |
| African American| 3 (6.5%)  | 4 (8.7%) |
| Caucasian       | 39 (84.8%) | 39 (84.8%) |
| Hispanic        | 3 (6.5%)  | 2 (4.3%) |
| Other (not specified) | 1 (2.2%) | 1 (2.2%) |
| Mean age (range)| 14.7 years (6-21) | 14.8 years (6-21) |

TABLE 1: Matched Patient Demographics

CF: Cystic Fibrosis; ADHD: Attention-Deficit/ Hyperactivity Disorder
CF arm

A total of 46 patients were analyzed that met inclusion criteria: There were 36 males and 10 females with an average age at the time of analysis of 14.8 years (range 6-21 years) and a mean BMI percentile of 38.643% (SD=28.536). Amongst the CF-only group, there were 39 (84.8%) Caucasians, four (8.7%) African-Americans, two (4.3%) Hispanic patients, and one (2.2%) patient designated as "other; race not specified"; see also Table 1. The mean FEV1%pred for the CF only arm was 74.76% (SD=24.377). Of the 46 patients in the CF-only arm, 32 (69.6%) fell into the Mild CF category, 9 (19.6%) in the Moderate CF category, and 5 (10.9%) into the Severe CF category; see also Table 2.

CF/ADHD to CF comparisons

Since the groups were matched based on age and sex, the differences were non-significant (p=.995 and p=1.0, respectively). The race and BMI percentile, which were not matched variables, were also not statistically significant between the two groups (p=.952 and p=.135, respectively). With regards to hospital admissions, only the most recent pulmonary visit was a statistically significant difference in the mean FEV1%pred between CF/ADHD (mean=84.70% (SD=21.637) predicted) patients and CF-only (mean=74.76% (SD=24.377) predicted, p=.042) patients. The mean total admissions for the CF/ADHD arm was 2.22 (SD=2.34) and for the CF-only group was 1.826 (SD=.984). Other hospital admission data is represented in Table 2.

Discussion

The prevalence of ADHD in the pediatric CF population at our institution was 8.3%, which is comparable to that of the general population per previous data that suggest a range of

| | ADHD/CF | CF Only |
|---|---|---|
| Mean BMI percentile (%) | 48.634% (SD=31.736) | 38.643% (SD=28.536) |
| Mean FEV1%pred | 84.70% (SD= 21.637) | 74.76% (SD=24.377) |
| Mild CF (FEV1%pred>70%) | 35 (76.1%) | 32 (69.6%) |
| Moderate CF (FEV1%pred =40-70%) | 10 (21.7%) | 9 (19.6%) |
| Severe CF (FEV1%pred <40%) | 1 (2.2%) | 5 (10.9%) |
| Average Total Hospital Admissions | 2.22 (n=18, SD 2.340) | 1.826 (n=23, SD .984) |
| ADM | 16 (34.6%) | 19 (41.3%) |
| ER-ADM | 4 (8.7%) | 7 (15.2%) |
| ER | 4 (8.7%) | 1 (2.2%) |
| No Hospital Visit | 22 (47.8%) | 19 (41.3%) |

TABLE 2: BMI Percentile, Pulmonary Function, and Hospital Admission Statistics

| BMI: Body Mass Index percentile; FEV1%pred: forced expiratory volume in one second percentile; ADM: Direct hospital admission; ER-ADM: Emergency room to hospital admission; ER: Emergency room visit with no hospital admission |
prevalence from 7.8%-11% [13-15]. Without being able to see immediate results, managing an increasingly more difficult and time-intensive treatment regimen every day for life becomes a burden for adolescent patients with CF [21]. On average, CF patients exhibit poor treatment adherence and this is correlated with a decrease in lung function and an increase in lung exacerbations [22]. In patients with comorbid ADHD and CF, the underlying changes in executive functioning and behavior can impair self-care skills and disrupt treatment adherence. A key motivating factor in the treatment adherence of CF patients is the early development of self-care skills through repeated practice and encouragement [21]. ADHD can interfere with the development of self-care skills, potentially removing an integral treatment motivator and possibly leading to worse outcomes in CF patients. An ADHD diagnosis in the CF population may not be recognized immediately by caregivers because they may attribute the behavioral changes to symptoms of the disease or complications from treatments of the chronic illness that interfere with the patient’s activities of daily living [15]. The early identification and treatment of ADHD in CF patients may improve healthcare management and increase treatment adherence. There is a need for a better understanding of the impact that traditional ADHD treatment has on the progression of CF, including treatment adherence and changes in life expectancy and/or quality of life. Evidence shows that drug therapies, such as stimulants, non-stimulants, and combination therapies, are good treatment options for ADHD, but the literature is lacking on how each of these treatments would affect CF patients with differing disease severities [15].

While the primary outcome of total hospital admissions was not statistically significant between the CF/ADHD group and the CF-only group, the data yielded results that warrant further investigation. The CF/ADHD group had statistically significantly better FEV1%pred, which is generally considered to be a clinical indicator of good pulmonary health in CF but had more non-statistically significant frequent hospitalizations [23-25]. This is paradoxical because treatment adherence in CF is already known to be difficult and ADHD has been thought to increase the difficulty [4,26-27]. Additionally, a recent study has shown that increasing treatment adherence reduces pulmonary exacerbations and may lead to fewer hospitalizations [22]. Since the treatment of CF is complex and time-consuming, ranging from 108 minutes a day to two hours per day, and because patients do not see immediate benefits, treatment adherence is a major concern in the CF population [4,21]. Many factors ultimately determine treatment adherence, including socioeconomics, clinician-patient relationship, education about the consequences and sequelae of non-adherence, development of self-care skills, and others [28-29]. ADHD may be increasing or decreasing the adherence in CF patients, leading to the increased hospitalizations and increased FEV1%pred. The answer is not known at this time and, ultimately, the answer to this difference in hospitalizations may be multifactorial and complex.

Admittedly, there are some limitations to our work: we did not investigate whether or not the patients with comorbid CF/ADHD were being treated for their ADHD symptoms, but the pharmacotherapy for ADHD can result in weight loss and loss of appetite, which is opposite of the BMI percentile data we found [50], thus further inquiry into these findings is needed. Although our institution is a multi-site, not for profit children’s specialty care hospital operating in two states, we only identified 46 patients with CF/ADHD and complete records; with more data, we could address the issue of sample size, which has affected our study power.

**Conclusions**

As more children with CF are living longer, it has become imperative to identify and treat comorbidities. Our work contributes to the limited research done on the prevalence of ADHD and CF, which shows that ADHD is diagnosed in the same percentage of the pediatric CF population as in the general pediatric population. There were differences in lung function, hospitalizations, and BMI between the two groups, although not statistically significant.
Subsequent studies are needed to further elucidate the effect of a CF/ADHD co-morbid diagnosis on CF outcomes.

**Additional Information**

**Disclosures**

**Human subjects**: Consent was obtained by all participants in this study. Nemours Office of Human Subjects Protection issued approval 741996. Thank you for your submission of New Retrospective Project materials for this research study. Your submission received expedited review based on the applicable federal regulation and meets all DHHS criteria for approval. The above-referenced research retrospective study is approved per expedited category 5. The IRB has determined that: • This is ‘Research not involving greater than minimal risk per 45CFR46.404’. • All approved documents can be found under ‘Board Documents’. The requirement for obtaining informed consent/parental permission and assent and authorization for use and disclosure of protected health information is waived based on the applicable federal regulation. • The approved research is retrospective. The data or samples that will be used in this research must have been in existence prior to approval date of the initial submission of this study. Research use of future data or samples, i.e., those that are not in existence at the time of the initial approval, requires prospective IRB review and approval and may require Informed Consent or Parental Permission. • To continue, the research requires IRB review and approval on an annual basis. May 31, 2016 is the last day that research may be conducted. Per Nemours NOHSP Policy HSP-093, as this is a retrospective study, it will automatically expire at the end of the approval period noted in this letter, and will be closed by the Administrative Staff of NOHSP. To avoid closure of your study the Investigator needs to take one of the following actions: Submit an application for continuing review on a timely basis (prior to the expiration date with sufficient lead time to assure IRB review before expiration) OR Submit a closure report at an earlier date. The Principal Investigator is responsible for the timely submission of the continuing review application. Please post this date on your research calendar. Please be reminded that applications for continuing review need to be submitted at least 2 weeks ahead of the expiration date to give sufficient lead time for IRB review. Reviewed/approved documents in this submission: • Application Form - IRB Proposal Application Retrospective Chart Analysis (UPDATED: 04/21/2015) • Data Collection - Data Collection Form (UPDATED: 04/13/2015) - 2 - Generated on IRBNet • Investigator Agreement - Sub-I Investigator Agreement Dr. Schaeffer (UPDATED: 05/5/2015) • Investigator Agreement - Sub-I Investigator Agreement Dr. Elishemir (UPDATED: 05/5/2015) • Investigator Agreement - Sub-I Investigator Agreement Dr. Chidekel (UPDATED: 05/4/2015) • Investigator Agreement - PI Research Agreement Dr. Livingston (UPDATED: 04/14/2015) • Investigator Agreement - Sub-I Investigator Agreement Nicole Spitzer (UPDATED: 04/6/2015) Investigator Agreement: As the PI, you have agreed to assure that this research is conducted in compliance with Nemours policy and all applicable federal regulations and [ICH standards], which also includes the following: • All research must be conducted in accordance with this approved submission. Any revision to approved materials must be approved by the IRB prior to initiation. • Remember that informed consent/parental permission is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document. • All serious and unexpected adverse events and unanticipated problems affecting participants must be reported promptly to the IRB according to NOHSP policy. • All non-compliance issues or complaints regarding this study must be reported to the Director, NOHSP. • All research records must be retained for a minimum of three years. • A Closure Report must be submitted to the IRB when this protocol is completed. If you have any questions, please contact Laurie Ward at Nemours Children’s Specialty Care, 807 Children’s Way, Jacksonville, FL 32207 at (904) 697-3415 or lward@nemours.org. Please include your study title and reference number in all correspondence with this office. **Animal subjects**: All authors have confirmed that this study
did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**Acknowledgements**

Our group would like to thank the Nemours Hospital System for allowing us space and time to conduct this research. A special thank you is given to Mrs. Bertha Ben Khallouq of the University of Central Florida, College of Medicine (UCF COM), for her assistance in statistics, support, and study management. Finally, we thank the faculty and staff at UCF COM and the Focused Inquiry Research Experience (FIRE) Module for their feedback and support at the early stages of this project.

**References**

1. Martiniano SL, Hoppe JE, Sagel SD, Zemanick ET: Advances in the diagnosis and treatment of cystic fibrosis. Adv Pediatr. 2014, 61:225-245. 10.1016/j.yapd.2014.03.002
2. Strausbaugh SD, Davis PB: Cystic fibrosis: a review of epidemiology and pathobiology. Clin Chest Med. 2007, 28:279-288. 10.1016/j.ccm.2007.02.011
3. Baiardini I, Steinhilber G, F DIM, Braido F, Solidoro P: Anxiety and depression in cystic fibrosis. Minerva Med. 2015, 106:1-8.
4. O’Donohoe R, Fullen BM: Adherence of subjects with cystic fibrosis to their home program: a systematic review. Respir Care. 2014, 59:1731-1746. 10.4187/respcare.02990
5. Briesacher BA, Quittner AL, Saiman L, Sacco P, Fouayzi H, Quittell LM: Adherence with tobramycin inhaled solution and health care utilization. BMC Pulm Med. 2011, 11:5. 10.1186/1471-2466-11-5
6. Wells KB, Golding JM, Burnam MA: Psychiatric disorder in a sample of the general population with and without chronic medical conditions. Am J Psychiatry. 1988, 145:976-981. 10.1176/ajp.145.8.976
7. Knapp PK, Harris ES: Consultation-liaison in child psychiatry: a review of the past 10 years. Part I: clinical findings. J Am Acad Child Adolesc Psychiatry. 1998, 37:17-25. 10.1097/00004583-199801000-00012
8. Turkel S, Pao M: Late consequences of chronic pediatric illness. Psychiatr Clin North Am. 2007, 30:819-855. 10.1016/j.psc.2007.07.009
9. Quittner AL, Barker DH, Snell C, Grimley ME, Marciel K, Cruz I: Prevalence and impact of depression in cystic fibrosis. Curr Opin Pulm Med. 2008, 14:582-588. 10.1097/MCP.0b013e3283121cf1
10. Snell C, Fernandes S, Buioreau IS, Garcia G: Depression, illness severity, and healthcare utilization in cystic fibrosis. Pediatr Pulmonol. 2014, 49:1177-1181. 10.1002/ppul.22990
11. Felt BT, Biermann B, Christner JG, Kochhar P, Harrison RV: Diagnosis and management of ADHD in children. Am Fam Physician. 2014, 90:456-464.
12. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA: ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014, 43:434-442. 10.1093/ije/dyt261
13. Morbidity and Mortality Weekly Report (MMWR). (2010). Accessed: March 8, 2014: http://2010.
14. Attention-Deficit/Hyperactivity Disorder (ADHD): Data and Statistics. Accessed: March 8, 2014: https://www.cdc.gov/ncbddd/adhd/data.html.
15. Georgiopoulos AM, Hua LL: The diagnosis and treatment of attention deficit-hyperactivity disorder in children and adolescents with cystic fibrosis: a retrospective study. Psychosomatics. 2011, 52:160-166. 10.1016/j.psym.2010.12.016
16. Eworuke E, Zeng QY, Winterstein AG: Clinical and sociodemographic factors associated with
attention-deficit/hyperactivity disorder in patients with cystic fibrosis. Psychosomatics. 2015, 56:495-505. 10.1016/j.psym.2014.09.001

17. Cohen-Cymberknoh M, Tanny T, Breuer O, et al.: Attention deficit hyperactivity disorder symptoms in patients with cystic fibrosis. J Cyst Fibros. 2018, 17:281-285. 10.1016/j.jcf.2017.11.020

18. Thapar A, Cooper M: Attention deficit hyperactivity disorder. Lancet. 2015, 387:1240-1250. 10.1016/s0140-6736(15)00238-x

19. Tarver J, Daley D, Sayal K: Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. Child Care Health Dev. 2014, 40:762-774. 10.1111/chc.12139

20. Floet AM, Scheiner C, Grossman L: Attention-deficit/hyperactivity disorder. Pediatrics in review. J Pediatrics. 2010, 31:56-69. 10.1542/pir.31-2-56

21. Sawicki GS, Heller KS, Demars N, Robinson WM: Motivating adherence among adolescents with cystic fibrosis: youth and parent perspectives. Pediatr Pulmonol. 2015, 50:127-136. 10.1002/ppul.23017

22. Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA: Longitudinal association between medication adherence and lung health in people with cystic fibrosis. J Cyst Fibros. 2011, 10:258-264. 10.1016/j.jcf.2011.03.005

23. Sass LA, Hair PS, Perkins AM, Shah TA, Krishna NK, Cunnion KM: Complement effectors of inflammation in cystic fibrosis lung fluid correlate with clinical measures of disease. PloS One. 2015, 10:0144723. 10.1371/journal.pone.0144723

24. Hulzebos EH, Bomhof-Roordink H, van de Weert-van Leeuwen PB, Twisk JW, Arets HG, van der Ent CK, Takken T: Prediction of mortality in adolescents with cystic fibrosis. Med Sci Sports Exerc. 2014, 46:2047-2052. 10.1249/mss.0000000000000344

25. Morgan WJ, VanDevanter DR, Pasta DJ, Foreman AJ, Wagener JS, Konstan MW: Forced expiratory volume in 1 second variability helps identify patients with cystic fibrosis at risk of greater loss of lung function. J Pediatrics. 2016, 169:116-121. 10.1016/j.jpeds.2015.08.042

26. Pugatsch T, Shoseyov D, Cohen-Cymberknoh M, Hayut B, Armoni S, Griese M, Kerem E: Adherence pattern to study drugs in clinical trials by patients with cystic fibrosis. Pediatr Pulmonol. 2015, 51:143-146. 10.1002/ppul.23544

27. Harpin VA: The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. Arch Dis Child. 2005, 90:2-7. 10.1136/adc.2004.059006

28. Oates GR, Stepanikova I, Gamble S, Gutierrez HH, Harris WT: Adherence to airway clearance therapy in pediatric cystic fibrosis: socioeconomic factors and respiratory outcomes. Pediatr Pulmonol. 2015, 50:1244-1252. 10.1002/ppul.23517

29. Kettler LJ, Sawyer SM, Winefield HR, Greville HW: Determinants of adherence in adults with cystic fibrosis. Thorax. 2002, 57:459-464. 10.1136/thorax.57.5.459

30. Konikowska K, Regulska-Ilow B, Rozanska D: The influence of components of diet on the symptoms of ADHD in children [Article in Polish]. Rocz Panstw Zakl Hig. 2012, 63:127-134.