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Sleep disturbance and school engagement in children with cystic fibrosis during the COVID-19 pandemic

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Background: Alterations in sleep limit quality of life of children with chronic diseases, especially those in vulnerable patient populations, such as children with cystic fibrosis (CF). Children with CF are more likely to have disrupted sleep and diminished sleep quality than those without even when corrected for measures of disease severity. Parents of children with CF have also been shown to have insufficient sleep duration and daytime sleepiness that positively correlates with the sleep disturbances in their children [1]. No published studies describe the relationship between sleep disturbance and school engagement in pediatric CF populations during the COVID-19 pandemic.
Methods: A pilot prospective cross-sectional observational study in school-aged children with CF was initiated at Cincinnati Children's Hospital Medical Center in July 2021, with planned ongoing enrollment until May 2022. A COVID-19-specific school engagement questionnaire was developed, and data were collected. Information on patient diagnoses, medications, demographic characteristics, Epworth Sleepiness Score for Children and Adolescents (ESS-CHAD), Pediatric Insomnia Severity Index (PISI), Pittsburgh Sleep Quality Index (PSQI), sleep diaries, and academic report card data is being recorded. Descriptive statistics were performed.
Results: Of 23 school-aged children with CF enrolled, 11 children aged 5 to 18 (median age 10; 63.6% female) have available data. Eight (72.7%) had insufficient sleep duration according to American Academy of Sleep Medicine consensus guidelines. Mean ESS-CHAD was 7 (range 2–12), and two (18.2%) met criteria for subjective mild excessive daytime sleepiness. Median range of absences during a given academic year was 6 to 10 days. Subjects had participated in a variety of learning methods during the past academic year: virtual (n = 6), in-person (n = 4), hybrid (n = 4), home-school (n = 1). Five (45.5%) parents reported being afraid of their child becoming sick or contracting COVID-19 through school-related activities, two (18.2%) believed that the pandemic had worsened their child's sleep and affected their academic performance, and all 11 (100%) felt that their child's academic performance was stable or improving after a transition to mostly in-person instruction this academic year.
Conclusions: Preliminary data from ongoing enrollment in this pilot study suggest that the COVID-19 pandemic has harmed sleep and school engagement in some children with CF. Academic performance subjectively improved after a return to mostly in-person instruction. Sleep disturbance may be an underappreciated aspect of the pediatric CF care model. We have limited understanding of the approaches needed for sleep-related screening, diagnosis, and clinical management. Additional data and analyses will be reported at the 2022 North American Cystic Fibrosis Conference.
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Characteristics of 225 infants with cystic fibrosis screen positive, inconclusive diagnosis and cystic fibrosis transmembrane conductance regulator–related metabolic syndrome identified in New York State over a 3-year period

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Background: New York State (NYS) added third-tier sequencing to its immunoreactive trypsinogen (IRT)–deoxyribonucleic acid (DNA) cystic fibrosis (CF) newborn screening (CF NBS) algorithm on December 1, 2017, to reduce false-positive referrals. NYS refers infants with high IRT and two or more CF transmembrane conductance regulator *(CFTR)* variants, including variants of potential clinical significance for diagnostic evaluation, to one of 10 CF specialty care centers (SCCs). Findings of intermediate or normal sweat chloride (Cl^-) levels (<60 mmol/L) in these infants, consistent with published criteria for CF screen positive, inconclusive diagnosis (CFSPID)/*CFTR* transmembrane conductance regulator–related metabolic syndrome (CRMS), poses challenges to clinicians and families. The aim of this descriptive study is to describe NYS CF NBS results and findings from initial and follow-up evaluations of CFSPID/CRMS infants identified since the algorithm change.
Methods: As part of long-term follow-up, a clinical and demographic dataset was compiled from SCCs for infants with high IRT and at least two *CFTR* variants (with one or more not clearly CF-causing) referred between December 1, 2017, and November 30, 2021. Genotypes and *CFTR* phasing were abstracted from NYS NBS records. Sweat Cl^-, oropharyngeal culture (OPS), fecal elastase, CF status, and race and ethnicity data were requested from the SCCs. The NYS Department of Health Institutional Review Board considered the project exempt.
Results: Over the 3-year period, *CFTR* phasing was determined for 193 of 290 infants that the NBS identified as not having CF, 14.5% (28/193) were confirmed in cis and reclassified as likely carriers, 5.5% (16/290) were determined to be carriers after variant reclassification, 5.8% (17/290) were lost to follow-up or parental refusal, and 77% (225/290) were evaluated at least once at a SCC and classified as CFSPID/CRMS. The most common variant was 5T-12TG (40% (90/225) carried at least one copy). Sweat Cl^- values for CFSPID/CRMS infants were higher than for carriers, although there was overlap. None of the infants with *CFTR* variants in cis had sweat Cl^- greater than 25 mmol/L, two had insufficient quantity of specimen, and three were not sweat tested. For the highest reported sweat Cl^- value for each infant classified as CFSPID/CRMS, most infants had low sweat Cl^- (39% (88/225) <20 mmol/L; 42% (95/225) 20–29 mmol/L; 11.5% (26/225) 30–39 mmol/L; 5% (12/225) 40–49 mmol/L); 1.7% (4/225) had sweat Cl^- of 50 to 59 mmol/L (W1282X//5T-12TG, n = 3; R117H-5 T//5T-12TG, n = 1). Decreasing sweat Cl^- trend was seen in 5.3% (n = 12), increasing trend in 7.1% (n = 16), and variable trend in 0.9% (n = 2). Oropharyngeal swab cultures from two of 110 infants, who had sweat Cl^- levels of 12 mmol/L and 10 mmol/L, showed isolated *Pseudomonas aeruginosa*. Of 113 infants with fecal elastase values, 112 were reported as normal. One infant with sweat Cl^- of 28 mmol/L and 31 mmol/L at 17 days of life had a low initial value indicative of malabsorption; results were normal on repetition.
Conclusions: None of the 225 CFSPID/CRMS infants converted to a CF diagnosis during the 3-year period. Sweat Cl^- values remain low in most

cases. There is variability among SCCs, including rate of follow-up and repeat sweat Cl^- testing. Baseline data on CFSPID/CRMS infants in the large racially and ethnically diverse population of NYS indicate the need for ongoing evaluation to determine the conversion rate to CF.

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Cystic fibrosis in the United States by 2040: A population landscape analysis

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Background: The network of Cystic Fibrosis Foundation–accredited care programs partner with people with cystic fibrosis (CF) and their families to provide specialized disease management using a multidisciplinary approach. There are 128 pediatric, 119 adult, and 40 affiliate CF programs in the United States. In the past decade, the introduction of highly effective modulator therapies (HEMT) ivacaftor (IVA) and elexacaftor/tezacaftor/ivacaftor, in combination with other advances in CF care, has increased survival for persons living with CF, with approximately 57% of people with CF being aged 18 and older. In 2020, estimated median predicted survival was 50 for individuals born between 2016 and 2020, compared with 30 in the early 1990s. Given the potential for slower lung function decline with HEMT, it is likely that survival will increase, requiring CF care programs to serve a growing adult population. The objective of this analysis was to forecast the CF population in the United States through 2040 and predict the distribution of lung function and first transplants to inform planning for the future of CF care.
Methods: We implemented a simulation to predict the size and characteristics of the CF population from 2021 to 2040, simulating percentage predicted forced expiratory volume in 1 second (FEV_1pp), lung transplantation, and survival status. We used data from the Cystic Fibrosis Foundation Patient Registry to characterize the distribution of persons with CF according to age, sex, race, ethnicity, HEMT eligibility, and prescription status. We applied those distributions to a simulated 2020 prevalent population and projected CF births to 2040. The microsimulation used estimates of the probability an individual would transition between lung function categories defined according to FEV_1pp (high: >90%; moderate: 69–90%; low: 40–70%; severe: <40%), undergo lung transplant, or die derived from logistic regression models using longitudinal data for 2010 to 2020, with transition probabilities dependent on HEMT prescription status.
Results: By 2040, we estimate that adults with CF will comprise more than 70% of the total CF population. The proportion of adults classified as greater than 90% FEV_1pp will range from 35% to 40% over this period, with nearly 80% of children with FEV_1pp at this level or higher. Age at first transplant will increase over the next 20 years, with more than half of first transplants occurring in individuals aged 35 and older, compared with 37% reported in 2020.
Conclusions: Although CF has historically been characterized as a pediatric disease, we predict continued growth of the adult CF population over the next 20 years because of longer survival and a decline in CF births. Because of slower decline in lung function, age at time of lung transplant will increase, resulting in an older post-lung transplant population. It is likely that this growing, aging adult CF population will be more medically complex because of extra-pulmonary and age-related comorbidities, so coordination of care between CF care teams, subspecialists, and transplant centers will remain critical. The need to expand the workforce knowledgeable in the nuances of multidisciplinary adult CF care is more important than ever.
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Effect of pregnancy on lung function in women with cystic fibrosis in the United States and United Kingdom: A registry-based study, 2003–2017

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Background: Women with cystic fibrosis (CF) are living longer, healthier lives and increasingly having children [1]. Lung function is known to decrease with age, but little is known about how pregnancy affects lung function decline. To address this, we assessed the impact of pregnancy on lung function trajectory in women with CF in the United States and United Kingdom.
Methods: This was a longitudinal registry study of 11,366 women aged 15 to 44 with CF contributing 331,724 lung function measures between 2003 and 2017 in the United States and 3,433 women contributing 24,394 measures in the United Kingdom over the same period. Pregnancy was recorded as a binary event in annual review records. We used previously developed mixed-effects models (random intercept and slope) to assess whether rate of decline of lung function changed after pregnancy, adjusting for clinically important covariates including age at diagnosis, genotype, and birth cohort [2,3].
Results: A total of 1,637 first pregnancies were recorded in the United States and 596 in the United Kingdom, with most occurring in the pre-modulator era (before 2013: United States, 65%, United Kingdom, 60%). Baseline clinical and demographic characteristics were similar for both population groups. After a record of pregnancy, the overall rate of lung function decline increased by 0.31 percentage points (95% CI, 0.23–0.39 percentage points) in percentage of forced expiratory volume in 1 second per year in the United States and 0.37 percentage points (95% CI, 0.18–0.56 percentage points) in the United Kingdom.
Conclusions: Our preliminary analysis suggests that pregnancy may be associated with greater decline of lung function of approximately one-third of a percentage point per year in the United States and the United Kingdom. Further robustness checks using alternative model specifications are required, along with studies in cohorts of women who have benefited from modulator therapy.
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