A Systematic Review of Attention-Deficit/Hyperactivity Disorder in People Living with Cystic Fibrosis

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Abstract

Background: There is a lack of research that has focused on ADHD in people with cystic fibrosis (pwCF). Given ADHD is associated with executive functioning impairments, exploring ADHD in the context of living with CF is of great importance. The purpose of the current systematic review was to examine ADHD in pwCF across the lifespan in terms of its prevalence, its impact on various health outcomes, and treatments for managing ADHD.

Methods: This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Articles reporting studies of any design that focused on ADHD in pwCF were included. Studies were excluded if they did not meet this criterion and if they were written in languages other than English. PsycINFO, MEDLINE, EMBASE, and CINAHL databases were searched. Search items were based on three concepts: 1) terms related to CF, 2) terms related to ADHD, and 3) terms related to age.

Results: Ten studies were included in this systematic review. Reported prevalence rates of ADHD in people with CF ranged from 5.26% to 21.9%. The reported relationships between ADHD in pwCF and other health outcomes is also inconsistent. In terms of treatment considerations, pharmacological interventions and behavioural strategies for managing ADHD in the context of living with CF have been reported as being successful.

Conclusions: The presence of ADHD in pwCF should be evaluated when symptoms are impacting treatment adherence and health outcomes. Additional research is needed to further explore ADHD in the CF population and health variables that may be associated with CF prognosis.

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Submitted to: Pediatric Pulmonology

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Keywords: cystic fibrosis, attention-deficit/hyperactivity disorder, mental health, health outcomes, executive functions

Background

Cystic fibrosis (CF) is a progressive, genetic disease that causes a buildup of mucus in the lungs and digestive abnormalities [1]. People with CF (pwCF) require daily, time-consuming treatments, making CF one of the most challenging illnesses for families to manage [1-2]. In addition to the physical challenges of the disease, pwCF have been found to experience elevated psychological symptoms (e.g., depression, anxiety) [3], as well as impairments in quality of life [4]. Over the past decade, significant advances have been made in the care of people with CF, including major steps toward systematically promoting mental health and well-being [5]. International guidelines have recommended universal screening of people with CF for depression and anxiety [6]. More recently, the research on mental health in pwCF has been directed to also include Attention-Deficit Hyperactivity Disorder (ADHD) [7].

ADHD is a neurodevelopmental disorder [8]. People with ADHD demonstrate a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development [8]. Examples of inattentive symptoms may include failing to give close attention to details, having trouble paying attention, forgetfulness, and difficulty listening. Hyperactivity symptoms may include but not be limited to fidgeting, interrupting others, and feeling restless. Impairment in executive functioning is a hallmark of ADHD making daily tasks challenging to plan, coordinate, and execute. Moreover, although not primary symptoms of ADHD, people with ADHD often experience emotion regulation and externalizing behaviour challenges [9]. While varied estimates of prevalence of ADHD exist, a recent worldwide estimate of the prevalence was 5% to 7% [10].
Experiencing symptoms of ADHD and/or deficits in executive functioning such as task avoidance, procrastination, disorganization, poor inhibitory control, and difficulty paying attention may make managing treatment of a chronic illness increasingly challenging [11]. This is a new area of research and no previous reviews have been published to summarize the documented literature on ADHD in pwCF. Given ADHD is associated with deficits in executive skills that are critical when managing an illness and functional impairment in several areas (e.g., paying attention, organizing, planning), exploring ADHD in the context of managing CF is warranted [12]. The purpose of the current study was to explore attentional difficulties in pwCF across the lifespan. We sought to provide a synthesis of the most up-to-date literature regarding the prevalence of ADHD in pwCF, health outcomes for pwCF with ADHD, and considerations for treating ADHD in the context of CF. As there is a paucity of research in this area, we were broad in our inclusion of studies to not only include those with a diagnosis of ADHD, but also those studies that assessed attentional deficits within executive functioning in pwCF.

Methods

2.1. Search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were utilised to inform the review process [13]. A research librarian was consulted when developing the selection criteria and search strategy. A systematic literature search was performed to identify studies on CF, ADHD, and attention. PsychINFO, MEDLINE, EMBASE, and CINAHL databases were searched from inception until December 17, 2022 and related articles were identified. An a priori defined search strategy was utilised to identify relevant articles that were systematically screened against inclusion and exclusion criteria. The search strategy was developed by combining subject heading terms with keywords and text words and individually tailored for each database. Search terms were based on three concepts with terms related to a) CF, b) ADHD, and c) age. The full list of search terms and search strategy is detailed in the Appendix. The published protocol can be accessed via the PROSPERO database.

Two independent reviewers (HP, MR) screened the titles and abstracts of all retrieved references. Studies eligible for inclusion were: a) original research articles of any study design, b) articles assessing ADHD in individuals with CF across the lifespan with, and c) articles assessing ADHD diagnoses and/or symptomology (i.e., attention, executive function, inhibition). Studies were excluded if they did not meet this criterion, if the full text was unavailable, and if they were written in languages other than English. The article screening process was independently conducted by the first and second authors (HP, MR) based on the aforementioned search strategy. Duplicate and non-relevant studies, as well as case studies, abstracts, editorials, and correspondence were eliminated. Full-text versions of potentially relevant studies were obtained and analyzed to determine whether the inclusion criteria were met. Disagreements over inclusion were resolved by consensus with a third reviewer (JK). References of included papers were screened, although this did not yield any additional articles.

2.2. Data extraction

Data for the final qualitative analysis were extracted independently and analyzed in accordance with the PRISMA guidelines. Though no disagreements occurred, a third author (JK) was available if needed. The following variables were extracted where applicable: article characteristics (e.g., year of publication, authors), sample characteristics (e.g., sample size, demographics, comparison groups), study methodology (i.e., study design, measures used, ADHD-related outcomes, other outcomes), and information for assessment of the risk of bias.

2.3. Risk of bias assessment

The potential risk of bias in included studies was assessed by assigning a level of evidence, from level I (strong evidence) to level V (weak evidence), based on the quality of the study’s design [14]. For the purpose of this systematic review, only level I-III evidence was considered. Level I comprised high quality RCT’s, prospective studies investigating disease outcomes, and systematic reviews of level-I studies. Level
II comprised prospective comparative studies, retrospective prognostic studies, and systematic reviews of level-II studies or level-I studies with inconsistent results. Level III encompasses case control studies, retrospective comparative studies for treatment efficacy, and systematic reviews of level-III studies.

2.4 Data synthesis

A narrative synthesis was used to describe the data in three sections: 1) prevalence of ADHD and/or attentional difficulties in pwCF, 2) health outcomes for pwCF with ADHD, and 3) treatment considerations for pwCF with ADHD.

Results

3.1 Study characteristics

Our search identified 1303 articles; there were no additional studies identified from reference lists of retrieved studies and reviews (see Figure 1). Of the total 1303 articles, 774 remained for screening after duplicates were removed. Titles and abstracts were screened to exclude 737 articles presented in abstract form, conference posters, editorials, correspondence, or were not within the scope of our search criteria. Thirty-seven full-text articles were assessed for eligibility for the inclusion and exclusion criteria. The ten studies that met all the criteria for systematic review are presented in Table 1.

Of the ten studies, four were retrospective chart reviews and six were cross-sectional studies. These studies were published between 2011 and 2020. In terms of geographical region, six studies were conducted in the United States, one in Canada, one in Turkey, one in Israel, and one in Poland. All studies focused on different age ranges of people living with CF. Of the ten studies, six included children only (i.e., below age 18 years), two included children, adolescents and young adults (i.e., ages ranging up to 19 or 21 years), one included adults only (i.e., above age 18 years), and one assessed pwCF across the lifespan (i.e., ages 6 years and up). Presence or lack thereof of comparison group(s) also varied across studies (see Table 1 for summary).

3.2 Risk of bias within studies

Two reviewers (HP, MR) independently assessed the risk of bias within the included studies using the level of evidence (Table 1). All six cross-sectional studies demonstrated a low risk of bias (level I). Three retrospective studies showed a moderately low risk of bias (level II), with none of them reaching low risk level (level I). Additionally, one of the retrospective studies showed moderately high risk of bias (level III) as they were investigating treatment outcomes by means of a retrospective cohort chart review.

Outcome measures

While some studies focused on those with an ADHD diagnosis, others simply examined the presence of problems with attention and/or hyperactivity. Tools to measure attention deficits, hyperactivity problems, and/or ADHD symptoms were highly variable across studies. Of the six studies that included pediatric patients (i.e., below age 18 years), one relied on a previous diagnosis of any subtype of ADHD [15], one used the Kiddie Schedule for Affective Disorders and Schizophrenia-Scale (KSADS: a structured diagnostic interview for parents of children and adolescents and children and adolescents themselves) to diagnose ADHD [16], and another used the ADHD-Rating Scale (ADHD-RS; a self-report questionnaire that assesses ADHD criteria outlined in the Diagnostic Statistical Manual for Mental Disorders), to diagnose ADHD [12]. The other three studies did not use an ADHD diagnosis and instead looked at attention functioning and/or presence of hyperactivity problems. Measures included the attention and hyperactivity problems subscales on the Behaviour Assessment System for Children-2nd edition (BASC-II), the Behaviour Rating of Executive Functioning (BRIEF), the Test of Everyday Attention for Children (TEA-Ch), Delis Kaplan Executive Function System (D-KEFS)[17], the d2 test [18], and the Barkley Deficits in Executive Functioning-Scale-Children and Adolescents (BDEFS-CA) [19].

Of the two studies that included children, adolescents, and young adults, one study relied on a previous diagnosis of any type of ADHD, and another used the attention and hyperactivity subscale scores of the BASC-II [20-21]. For the study that included only adult participants, the ADHD Self Report Scale-v.1.1
Symptoms Checklist was used to diagnose ADHD [22]. Finally, for the study that assessed participants across the lifespan, the ADHD-RS was used, as well as a Continuous Performance Task (CPT) [23].

**Prevalence**

Of the ten studies included in the review, six examined the prevalence of ADHD in pwCF. Variable prevalence rates for ADHD in pwCF were reported across studies ranging from 5.26% to 21.9%. Whereas some studies reported a substantially higher prevalence of ADHD in pwCF compared to the general population, others reported comparable prevalence estimates. It should be noted and considered when interpreting the results that the prevalence estimates for the general population that were used to compare against pwCF varied across studies and ranged from 4% to 11%.

Of 188 pwCF aged 5 to 18 included in Georgiopoulos and Hua’s (2011) study, 18 (9.6%) participants were diagnosed with ADHD [12]. The authors concluded that this prevalence rate was comparable to the general population. In another study, Eworuke et al. (2015) reported a prevalence of ADHD in pwCF aged 3 to 18 years of 5.26% in 1999 and 8.16% in 2006. These authors also concluded these estimates to be comparable to the general population [15]. Spitzer and colleagues (2018) reported a prevalence rate of 8.3% for pwCF aged 6 to 21 years and concluded that this was comparable to the general population [20].

Gundogu et al. (2019) compared several psychological diagnoses in 32 pwCF aged 8 to 16 years and 33 healthy, age- and sex-matched control children [16]. They found that 21.9% of pwCF met criteria for ADHD compared to 12.1% in healthy children. It was highlighted that those with CF in the preadolescent age range were especially more likely to meet criteria for an ADHD diagnosis compared to healthy control children. Cohen-Cymberknoh et al. (2018) reported a prevalence rate of 17.7% in their study of ADHD in pwCF across the lifespan, indicating a substantially higher rate of ADHD symptoms among pwCF compared to the general population [23]. Similarly, Georgiopoulos et al. (2018) reported that 15% of pwCF scored in the elevated range for ADHD symptoms and also reported that this rate was substantially higher than that observed in the general population [22]. In terms of sex, five of the studies reporting prevalence of ADHD in pwCF demonstrated that males were more likely to be diagnosed with ADHD and/or have elevated scores on symptom-measures of ADHD than females [12, 15-16, 20, 23]. One study demonstrated no significant differences between sexes on levels of ADHD symptoms or proportion of diagnoses [22].

Three studies included in the review assessed the prevalence of deficits in attention and/or hyperactivity through examining executive functioning. The results among these studies were variable. For example, Borshuk et al. (2019) found that a sample of 19 pwCF aged 6 to 18 years did not demonstrate elevated rates of executive functioning deficits compared to the general population [19]. Piasecki et al. (2017) reported that compared to a control group of healthy children, pwCF aged 7 to 17 years demonstrated reduced attention span, lesser work stability requiring mental alertness, and committed more mistakes on a test of attention [18]. In another study, Gold et al. (2020) compared neurocognitive outcomes in pediatric lung transplant recipients aged 2.5 to 18 years with and without CF pre- and post-transplant [17]. The results demonstrated that executive functioning skills were higher in the CF group as reported by their caregivers. Further, behavioural improvements in attention, hyperactivity, and behavioral regulation were observed post-transplant.

**Health outcomes**

3.5.1 **Treatment Adherence**

The impact of ADHD on treatment adherence was assessed in three studies. One study found no differences in self-reported treatment adherence between pwCF and ADHD versus pwCF without ADHD [22]. Two studies found ADHD symptoms to be related to poorer treatment adherence. For example, Georgiopoulos and Hua (2011) found that in a sample of 18 pwCF and ADHD, 61% showed low adherence to treatment at the time of their initial evaluation [12]. Similarly, Borshuk et al. (2019) found worse executive functioning in pwCF was moderately associated with poorer adherence [19].

3.5.2 **Hospitalizations**
Two studies explored disease severity using frequency of hospitalizations as an indicator. One study explored differences in CF-related hospitalizations between pwCF with ADHD versus pwCF without ADHD [20]. pwCF with ADHD showed more frequent hospitalizations than pwCF only. Differently, pwCF with ADHD were less likely to be recently hospitalized and had a lower average of outpatient clinic visits compared to pwCF only [15].

3.5.3 Pulmonary Function

Four studies examined the association between pulmonary function and elevated symptoms of or diagnosis of ADHD. Each of these studies used FEV1%predicted to assess the pulmonary function of participants. One study demonstrated that pwCF with ADHD had a higher average FEV1%predicted compared to those with CF only [20]. In contrast, another study showed that worse executive functioning was significantly associated with worse lung function [19]. Two studies reported no difference between lung function in pwCF with ADHD versus pwCF without ADHD [22-23].

3.5.4 Nutritional Status

Of the four studies that examined the association between nutritional status as measured by Body Mass Index (BMI) and elevated symptoms of or diagnosis of ADHD, no significant associations were reported [19-20, 22-23].

3.5.5 Sleep Habits

One study explored sleep habits in pwCF (aged 6 to 19 years) and their association with behavioural patterns, including attention and hyperactivity [21]. In their sample of 50 participants, they found that 80% of participants demonstrated poor sleep as characterized by poor sleep efficiency measured using wrist actigraphy and wake time after onset (WASO). The results demonstrated that lower sleep efficiency was associated with increased attention and hyperactivity problems as measured by scores on the BASC-II.

3.5.6 Quality of Life

Two studies examined associations between quality of life and elevated symptoms of or diagnosis of ADHD in pwCF. Borshuk et al. (2019) found that worse executive functioning was unrelated to overall quality of life in pwCF; however, worse executive functioning was related to increased treatment burden [19]. Georgiopoulos et al. (2018) used the Cystic Fibrosis Questionnaire-Revised (CFQ-R) to assess quality of life. The results showed that pwCF with higher ADHD symptom scores had lower scores on subscales of the CFQ-R including Physical Functioning, Role Functioning, and Respiratory Symptoms [22].

3.5.7 Social Factors

Two studies examined various social factors that may be related to pwCF with ADHD. One study showed that when compared with pwCF only, pwCF with ADHD demonstrated a higher proportion of cases living in poverty and in foster care [15]. Race was not reported as a significant predictor of CF [15]. Further, executive functioning and family functioning were significantly related with a strong magnitude correlation [19]. That is, those with lower executive functioning abilities exhibited increased difficulties with family cohesion and communication.

Treatment considerations

While some studies hypothesized about treatment considerations for ADHD in pwCF, only one study directly assessed this. In their retrospective chart review, Georgiopoulos and Hua (2011) described treatment for ADHD in pwCF aged 5 to 18 [12]. Results demonstrated that all patients were offered psychosocial interventions for ADHD that may have included educational supports, psychoeducation, and individual and/or family psychotherapy. Psychopharmacological interventions were trialled in 13 of the 18 pwCF with ADHD. The authors reported that stimulants, nonstimulants, and combination therapies were viable treatment options. Side effects reported by participants in this study included weight loss, tics, feeling moody, weight gain, sleep disturbance, hypomania, and sedation. In this study, non-stimulant medications were less likely
related to significant weight loss and less likely to require discontinuation when compared with stimulant medications.

Discussion

To our knowledge, the present study represents the first, most up-to-date, and comprehensive review of the available studies examining attentional difficulties in pwCF across the lifespan. Our review identified ten articles that were focused on attentional difficulties and/or ADHD in pwCF. The limited articles generated from our search demonstrates that the paucity of research in this area is pronounced.

Our review demonstrated that measures used to assess ADHD, attentional difficulties, and associated symptoms (i.e., executive functioning) were inconsistent across studies. A variety of approaches to symptom assessment or measure was employed including chart review to confirm diagnosis, self-report measures (e.g., ADHD-RS, ADHD Self-Report Scale v.1.1, BASC-II, BDEFS-CA) [12, 19, 22], caregiver report measures (e.g., BASC-II, BRIEF) [20-21], structured diagnostic interviews (e.g., KSADS) [16], and direct neurocognitive or computer measures of attention (e.g., TEA-Ch, D-KEFSd2 test, CPT) [17, 23]. While all studies included used psychometrically validated measures, the inconsistency in use of measures across studies makes it difficult to compare results across studies. Further, it is important to note that comprehensive ADHD assessments include clinical interviews, direct observations, cognitive and neuropsychological testing, and self-report and/or caregiver ratings of symptoms [23]. The majority of studies in this review used elevated ADHD symptom scores to indicate probable ADHD diagnosis and unless completed elsewhere in a previous psychiatric consultation, participants did not receive a comprehensive assessment for ADHD. Determining a “best-practice” measure for examining ADHD symptoms in each age group (i.e., children, adolescents, and adults) to apply across future studies would be useful in making cross-study comparisons and accumulating evidence regarding pwCF with ADHD.

The prevalence estimates of pwCF with ADHD as reported in the studies included in this review were inconsistent. Of the 10 studies included in the review, six studies assessed prevalence of pwCF with ADHD and prevalence estimates ranged from 5.26% to 21.9%. Three studies reported comparable prevalence rates to the general population [12, 15, 20], while three other studies reported a higher prevalence in pwCF with ADHD [16, 22-23]. It is also important to reiterate that across the reviewed studies prevalence estimates for the general population that were used to compare against pwCF prevalence rates varied across studies and ranged from 4% to 11%. As such, this may have impacted the authors’ conclusions on whether pwCF have a comparable or higher prevalence rate of ADHD compared to the general population. Further, in one study estimates of ADHD in pwCF may have been inaccurate as the study only included those who were referred for psychiatric evaluation, excluding those who were not referred, those who declined a referral for psychiatric evaluation, and those outside of the study institution [12]. In spite of the inconsistency of results, it is evident that pwCF are experiencing similar to higher rates of ADHD than those in the general population. Future studies, employing a “best-practice” (as suggested above) assessment approach will likely aid in garnering a more accurate picture of the prevalence rate of ADHD in pwCF.

Although the exact mechanism is unknown, several hypotheses exist as to why ADHD may be highly prevalent among the CF population. ADHD is highly genetic [24] and it is possible that CF creates risk for the phenotypic expression of ADHD. Inflammatory responses in the brain due to different postnatal environments have been suggested to play a role in ADHD [25]. Studies have indicated increased inflammatory markers in ADHD, suggesting that associations with chronic inflammatory illnesses, such as CF, may exist [26]. Respiratory issues such as hypoxia or hypercapnia have been proposed as early mechanisms of cognitive dysfunction in other pulmonary diseases such as asthma [27], and may also apply to CF. Other contributing factors that may promote the manifestation of ADHD in CF include early malnutrition [28], psychosocial stress from chronic illness, and high psychiatric comorbidity [12].

The results summarized in this review regarding health outcomes for pwCF with ADHD were also inconsistent. One of the more acknowledged topics in ADHD in CF is treatment adherence. In managing a chronic illness that is complex like CF, people must have the ability to transition easily between activities,
self-initiate treatments, self-monitor symptoms and adjust treatments as needed, organize one’s treatments, manage time well during medical appointments, retain and recall information provided by various health care providers, and regulate the challenging emotions that may be associated with managing a chronic illness [19]. The results that suggest ADHD symptoms impact treatment adherence may be explained by the fact that the aforementioned skills necessary to plan, organize and complete treatments are challenged by ADHD symptoms.

Identifying and treating ADHD in pwCF may become increasingly important because of the increased complexity of treatment for CF and the necessity of treatment adherence for positive CF prognosis. One study that directly assessed treatment success in pwCF with ADHD showed that psychopharmacological interventions and psychosocial interventions appeared to be effective in pwCF [12]. The authors highlighted the importance of considering each patient’s unique medical status and psychiatric history when determining the best regimen of psychosocial and psychopharmacological interventions for treating ADHD in pwCF. Importantly, as stimulant medications may be associated with weight loss, discontinuation of the medication may be necessary given the adverse impact of having a BMI under the 50th percentile may have on pulmonary function [12]. Given the potential deficits in executive functioning in pwCF with ADHD, other tangible supports may be useful for pwCF and their families. These may include implementing automated systems (e.g., appointment reminders, calendars, automatic pharmacy refills), plans of care to address exacerbations, directly supporting access to resources, as well as role-playing skills in clinic. Further, in children with CF it may be necessary to focus on the development of problem-solving skills to counteract specific executive function deficits that may be encountered in CF such as transitioning from homework to treatments [19].

This review has several limitations. First, the number of articles included in this review was small and as such, the results should be interpreted cautiously. Second, the range of outcomes assessed across studies was highly variable. As noted previously, it would be beneficial to seek more consistency in use of outcome measures or “best practice” assessment approach to be able to compare results across studies. Third, most of the articles identified were conducted in the United States. Initiation of studies in other countries is important to fully understand the difficulties faced by pwCF in different geographical regions. Fourth, evaluation of some study fundings should be viewed conservatively in light of many of the studies employing small sample sizes and heterogenous demographic factors. For example, recruitment and inclusion of participants relied heavily on pwCF with ADHD that attended clinic regularly. This may indicate a sample bias as those pwCF with ADHD who attend clinic regularly are likely attend to self-care and adhere to treatments as well, as compared to those who do not attend clinic regularly [22]. Overall, future studies should seek to employ more robust methodologies (i.e., larger sample sizes, consistent outcomes) and improve accessibility to participate.

Conclusions

This is the first systematic review to summarize the literature on attentional difficulties in pwCF. The presence of ADHD in pwCF should be evaluated, in particular when symptoms are impacting treatment adherence and health outcomes. ADHD may be easily looked over in pwCF as caregivers may attribute difficulties in functioning to behavioural challenges associated with the illness [19]. Health care providers should monitor pwCF and families who may struggle with planning, organization, and adherence. When concerns regarding ADHD arise, a comprehensive psychological assessment should be recommended. Additional research is needed to further explore ADHD in the CF population and health variables that may be associated with CF prognosis.

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Conflict of interest

The authors declare that there are no conflicts of interest.

APPENDIX Search Strategy (Medline)
1. Cystic Fibrosis
2. (1)
3. Attention Deficit Hyperactivity Disorder
4. ADHD
5. Attention Deficit Disorder or Attention Deficit*
6. Attent* or Inattent*
7. (3 or 4 or 5 or 6)
8. Infant*
9. Toddler*
10. Child* or Youth*
11. Adolescent* or Teen*
12. Pre-school* or School-age*
13. Young adult* or Emerging adult* or Adult*
14. Parent* or Guardian* or Caregiver*
15. Mother* or mom
16. Father* or dad
17. (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16)
18. (2 AND 7 AND 17)

References

adherence: A different perspective. *International Journal of Psychiatry Medicine, 42* (2), 105-115. https://doi.org/10.2190/PM.42.2.a


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<tr>
<th>Author(s), year</th>
<th>Level of evidence</th>
<th>Study design</th>
<th>Population n, age</th>
<th>Comparison group(s)</th>
<th>Measure(s) used</th>
<th>Outcome(s) related to attention</th>
<th>Other outcome(s)</th>
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<tr>
<td><strong>Gold et al., 2020</strong></td>
<td>II</td>
<td>RCR</td>
<td>21, 2.5-18 yrs</td>
<td>CF, Age-matched norms</td>
<td>WPPSI; WISC-IV or V; WASI or WASI II, RCFT; TEA-Ch; D-KEFS; CVLT-C; CMS; WIAT II or III; BRIEF; BASC-II; SIB-R</td>
<td>Executive function, working memory, processing speed</td>
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<tr>
<td><strong>Spitzer et al., 2018</strong></td>
<td>II</td>
<td>RCR</td>
<td>46, 6-21 yrs</td>
<td>CF, CF/ADHD</td>
<td>n/a</td>
<td>ADHD diagnosis</td>
<td>BMI, FEV1%, hospital admissions</td>
</tr>
<tr>
<td><strong>Georgiopoulos &amp; Hua, 2011</strong></td>
<td>III</td>
<td>RCR</td>
<td>188, 5-18 yrs</td>
<td>CF</td>
<td>ADHD-RS, CGI-S, CGI-I</td>
<td>ADHD improvement, ADHD severity</td>
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<td>II</td>
<td>RCR</td>
<td>6940, 3-18 yrs</td>
<td>CF, CF with ADHD</td>
<td>n/a</td>
<td>ADHD incidence, ADHD prevalence</td>
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<tr>
<td><strong>Cavanaugh et al., 2016</strong></td>
<td>I</td>
<td>CS</td>
<td>50, 6-19 yrs</td>
<td>CF</td>
<td>Wrist actigraphy,</td>
<td>Attention, hyperactivity</td>
<td>Sleep efficiency, nighttime awakenings, behavioral symptoms, HRQoL,</td>
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<td>Type</td>
<td>Design</td>
<td>Age</td>
<td>Measures</td>
<td>Outcome Measures</td>
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<tr>
<td>Borshuk et al., 2019</td>
<td>I</td>
<td>CS</td>
<td>19, 6-18 yrs</td>
<td>CF, BDEFS-CA, CFQ-R, TARS, FAD</td>
<td>Executive function, n/a, BMI, FEV1%, CF treatment adherence, HRQoL, family functioning, social support</td>
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<tr>
<td>Gundogu et al., 2019</td>
<td>I</td>
<td>CS</td>
<td>65, 8-16 yrs</td>
<td>CF, age-sex-matched control, KSAD, CDI, SCARED, SSAS, PedsQL</td>
<td>ADHD diagnosis, n/a, FEV1%, hospital admissions, psychiatric comorbidity, social support, child and parent QoL</td>
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<tr>
<td>Georgiopoulos et al., 2018</td>
<td>I</td>
<td>CS</td>
<td>53, 18+ yrs</td>
<td>CF, ASRS-v1.1, CFQ-R, CES-D, HADS</td>
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<td>Cohen-Cymberknoh et al., 2018</td>
<td>I</td>
<td>CS</td>
<td>175, 6-18+ yrs</td>
<td>CF, CF with ADHD, ADHD-RS, MOXO-CPT</td>
<td>ADHD diagnosis, BMI, FEV1%, CF severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piasecki et al., 2017</td>
<td>I</td>
<td>CS</td>
<td>88, 7-17 yrs</td>
<td>CF, IBD, age-sex-matched control, d2 test, BVRT, Trail of 10 words, RPM</td>
<td>Attention, Intellectual functioning, visual and auditory memory</td>
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</table>

BMI = body mass index; CS = cross sectional study; FEV% = forced expiratory volume percentage; IBD = inflammatory bowel disease; n/a = not applicable; RCR = retrospective chart review; ADHD-RS = ADHD Rating Scale; ASRS-v.1.1 = Adult ADHD Self-Report Scale-v.1.1 Symptom Checklist; BASC = Behaviour Assessment System for Children; BDEFS-CA = The Barkley Deficits in Executive Functioning Scale—children and adolescents; BRIEF = Behavioural Rating of Executive Functioning; BVRT = Benton Visual Retention Test; CDI = Children’s Depression inventory; CES-D = Center for Epidemiologic Studies Depression Scale; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CGI-I = Clinical Global Impression Improvement subscale; CGI-S = Clinical Global Impression Severity subscale; CMS = Children’s Memory Scale; CVLT-C = California Verbal Learning Test for Children; D-KEFS = Delis Kaplan Executive Function System; FAD = Family Functioning; FEV1% = Forced Expiratory Volume Percentage; HRQoL = Health Related Quality of Life; ICS = cross sectional study; KSAD = Kinder SAD; MOXO-CPT = Modified Osterrieth’s Complex Figure Test; RPM = Revised Paced Reading; SSD = Social Support; TARS = Teacher’s Assessment Rating Scale; VBQ = Visual Behaviour Questionnaire; VLS = Visual and Language Skills; WISC = Wechsler Intelligence Scale for Children; WMS = Wechsler Memory Scale.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HRQoL</td>
<td>health related quality of life</td>
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<td>KSADS</td>
<td>Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version</td>
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<td>MOXO-CPT</td>
<td>MOXO Continuous Performance Task</td>
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<td>Pediatric Quality of Life Questionnaire</td>
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<td>SCARED</td>
<td>Screen for Child Anxiety and Related Disorders</td>
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<td>SIB-R</td>
<td>Scale of independent Behaviour-Revised</td>
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<td>SSAS</td>
<td>Social Support Appraisals Scale</td>
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<tr>
<td>TARS</td>
<td>Treatment Adherence Rating Scale</td>
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<tr>
<td>TEA-Ch</td>
<td>Test of Everyday Attention for Children</td>
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<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scales of Intelligence</td>
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<tr>
<td>WIAT</td>
<td>Wechsler Individual Achievement Test</td>
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<tr>
<td>WISC</td>
<td>Wechsler Intelligence Scale for Children</td>
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<tr>
<td>WPPSI</td>
<td>Wechsler Preschool and Primary School Scale of Intelligence</td>
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Records identified through database search 
(n = 1303) 
[Medline n = 436, PsycINFO n= 61, EMBASE 
n = 682, CINAHL n = 124]

Duplicates removed 
(n = 529)

Records screened 
(n = 774)

Records excluded based on title or abstract 
(n = 737)

Full-text articles assessed for eligibility 
(n = 37)

Full-text articles excluded 
(n = 27)

Studies included in qualitative synthesis 
(n =10)

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of study.