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Journal

Journal of Intellectual Disability Research, 66(3)

ISSN

0964-2633

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Publication Date

2022-03-01

DOI

10.1111/jir.12911

Peer reviewed

HHS Public Access

Author manuscript

J Intellect Disabil Res. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

J Intellect Disabil Res. 2022 March ; 66(3): 282–296. doi:10.1111/jir.12911.

Co-occurring medical and behavioural conditions in children with Down syndrome with or without ADHD symptom presentation

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Abstract

Background: Co-occurring ADHD is a challenge to characterise in the presence of other medical conditions commonly present in children with Down syndrome (DS). The current study examined differences among children with DS with or without ADHD symptomatology in terms of demographics, developmental level, co-occurring medical conditions, and parent and teacher ratings of behaviour and executive functioning.

Methods: Parents and teachers of 108 school-age children with DS provided ratings of ADHD symptoms, behaviour problems, and executive functioning skills. Children with DS and ADHD symptom presentation, as identified by a scoring algorithm, were compared to those without ADHD symptom presentation on demographic characteristics, developmental level, co-occurring medical conditions, and parent- and teacher-report measures of behaviours and executive functioning.

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The authors have no conflicts of interest to disclose.

Results: Sleep disorders, Disruptive Behaviour Disorder, allergies, and seizures were more common in children with DS and ADHD symptom presentation than in children without ADHD symptom presentation. After controlling for ADHD medication use, children with DS and ADHD symptom presentation had poorer performance than those without ADHD symptom presentation on parent behaviour ratings, teacher behaviour ratings, and parent but not teacher ratings of executive functioning. No significant group differences in demographic characteristics or developmental level were identified.

Conclusions: Higher rates of co-occurring medical conditions present in children with DS and ADHD symptom presentation support the need for thorough differential diagnoses. The different pattern of group differences between parent- and teacher-report has implications for diagnostic practices across settings as well as for treatment.

Keywords

Down syndrome; trisomy 21; ADHD; behaviour; symptoms; co-occurring medical conditions

Down syndrome (DS) is the most prevalent chromosomal disorder (i.e., extra 21st chromosome), affecting 1 in 707 live births (Mai *et al.* 2019). Though most children with DS have an intellectual disability (ID), they display unique phenotypic profiles that differ in many ways from heterotypic ID. Children with DS can also have a number of medical and behavioural co-occurring conditions. Co-occurring medical conditions for children with DS are common and include congenital heart defects, sleep disturbances (e.g., sleep apnoea), hypothyroidism, hearing loss, and Alzheimer's disease (Bittles *et al.* 2007, Capone *et al.* 2006). Additionally, there is a higher rate of co-occurring neurodevelopmental conditions, including Attention Deficit Hyperactivity Disorder (ADHD), in individuals with DS (Ekstein *et al.* 2011, Oxelgren *et al.* 2017, Edvardson *et al.* 2014) compared to typically developing (TD) children.

Many children with DS also display relative difficulties with executive functioning and inattention. A common diagnostic dilemma is determining whether executive functioning deficits, inattention, and/or hyperactivity are explained by the diagnosis of DS and associated developmental delays, or whether co-occurring ADHD is present (Jopp and Keys 2001, Reiss and Szyszko 1983, Fletcher *et al.* 2016, Hendriksen *et al.* 2015, Barnhill and McNelis 2012). There are three ADHD presentations, including (1) Predominantly Inattentive Presentation, with primary difficulties in organization, attention to detail, following instructions, forgetting daily activities, and being easily distracted, (2) Predominantly Hyperactive-Impulsive Presentation, with primary difficulties with frequent fidgeting or squirming, excessive talking, and difficulties with turn taking, interrupting and sitting still, and (3) Combined Presentation, which is used to describe those children who have difficulties in both Inattentive and Hyperactive-Impulsive domains. However, recent evidence demonstrates that the occurrence of some of these ADHD symptoms are related to gestational age in both the TD and DS population, suggesting that ADHD symptoms are not simply inherent in DS (del Hoyo Soriano *et al.* 2020). Additionally, individuals with DS often have medical challenges that can impact attention and impulse control, including hypothyroidism, obstructive sleep apnoea, seizures, and hearing and visual impairments, all of which contribute to the presentation of symptoms of inattention and hyperactivity, and

thus should be taken into considerations when assessing for, and differentially diagnosing, ADHD (Edvardson et al. 2014).

Recent research suggests that some children with DS exhibit higher rates of ADHD symptoms compared to both children with ID and mental age-matched TD controls (Ekstein et al. 2011, Oxelgren et al. 2017, Edvardson et al. 2014). ADHD prevalence in ID is estimated to be 13–16% (Dekker and Koot 2003), considerably higher than the 6–8% estimated in the general population (Froehlich *et al.* 2007). As the phenotype of children with DS differs from those of children with heterotypic ID, so do the estimated prevalence rates of ADHD within the DS population. Previous studies have found that approximately 20–44% of children with DS meet ADHD diagnostic criteria (Ekstein et al. 2011). In one study of children with DS, only 7% of participants had a prior ADHD diagnosis; however, when assessed using standardised evaluation tools, 34% met ADHD diagnostic criteria (Oxelgren et al. 2017). Of the individuals with DS who had co-occurring ADHD, half met criteria for the predominantly inattentive presentation and half for the combined presentation. Similarly, another study of children *and* adults with DS lacking a previous ADHD diagnosis found that 31% met ADHD criteria based on a caregiver phone interview (Edvardson et al. 2014). In another study, 29% of the sample of children with DS scored above the threshold suggestive of ADHD based on parent report, while 26% of children with DS scored above the threshold based on teacher report (Ornoy *et al.* 2011). Together, these findings suggest that individuals with DS exhibit relatively high rates of ADHD-related symptoms, and that ADHD may be underdiagnosed and subject to diagnostic overshadowing (attributing ADHD symptoms to the intellectual disability phenotype seen with DS) in this population (Martínez *et al.* 2011, Ekstein et al. 2011, Capone et al. 2006, Reiss and Szyszko 1983).

Complicating the clinical diagnosis of ADHD in DS are several medical, developmental, and behavioural factors, including cognitive/adaptive delays, noncompliance, anxiety, negativity, level of social engagement (autism-related symptoms), sleep disturbance or sleep apnoea, hearing and/or vision loss, hypothyroidism, and medication side effects that are more common among individuals with DS (Capone et al. 2006). These co-occurring symptoms and conditions can mirror symptoms of inattention and hyperactivity, contributing to challenges with differential diagnosis of ADHD. Thus, a greater understanding of symptom presentation among children with DS and ADHD is needed to tailor supports or treatment. Studies to date have only identified a significant correlation between ophthalmologic problems and ADHD in children with DS (Ekstein et al. 2011). No correlation was found between the level of ID or adaptive skills and ADHD in DS (Hastings *et al.* 2005, Oxelgren et al. 2017, Ornoy et al. 2011, Ekstein et al. 2011). The lack of correlation between ADHD diagnosis and level of ID is contrary to findings among individuals with other forms of ID, as it has been found that individuals with ID and ADHD demonstrated more difficulties with cognitive skills compared to those without ADHD (Di Nuovo and Buono 2007).

To address these gaps and provide a better understanding of ADHD in children with DS, the present study was designed to compare differences between children with DS with ADHD symptom presentation (DS+ADHD) to those without ADHD symptom presentation (DS-ADHD) in terms of demographic characteristics, developmental/cognitive level, co-

occurring medical and mental health conditions, and behavioural presentation. Children were identified as having ADHD symptom presentation if they met criteria on a standardised diagnostic algorithm based on parent- and teacher-reports and/or had a prior ADHD diagnosis with concurrent ADHD medication use. First, we evaluated group (DS+ADHD versus DS-ADHD) differences across demographic characteristics and in levels of cognitive functioning and adaptive behaviour according to standardised assessments. Based upon findings from children with ID, we hypothesised that DS+ADHD would be linked to lower cognitive functioning and adaptive behaviour compared to DS-ADHD. Second, we evaluated group differences in rates of parent-reported co-occurring medical and mental health conditions. Based upon rates of co-occurring conditions in TD populations, we hypothesised that DS+ADHD would be linked to higher rates of Disruptive Behaviour Disorder and sleep disorders compared to DS-ADHD. Third, we evaluated group differences on parent- and teacher-report measures used to screen for behavioural and executive functioning concerns. We hypothesised that children with DS+ADHD, compared to DS-ADHD, would have higher scores on several measures of problem behaviour (anxiety/mood issues, social problems, attention problems, rule breaking, aggression, externalised problems, irritability, hyperactivity, and overall behavioural concerns) and executive functioning.

Method

Participants

The participants were 108 children with DS. Children with DS were between 6 to 18 years of age (M = 12.3 years, SD = 3.2), male (57.4%), and primarily White (88.9%). Respondents were primarily mothers (95.4%). Table 1 summarises the demographic and clinical characteristics of the children, their parents, and their teachers.

Procedures

Participant families were recruited through newsletters distributed by local DS associations and from medical settings into several single site or multi-site longitudinal community-based studies focused on measuring cognition and behaviour in DS. Data were extracted from the participants' first study visit for several multi-site longitudinal natural history studies conducted in Midwest and Western US cities, and from their screening visit to assess eligibility for single site or multi-site randomised clinical trials also conducted in Midwest and Western U.S. cities. Eligibility criteria included having a child with DS between the ages of 6–18 years and speaking English as a primary language. Parents provided consent for their own and their child's participation. Children older than 11 years of age provided assent. Teachers also provided consent for participation.

Children completed cognitive assessments. Parents completed forms collecting demographic and medical information (including the presence of co-occurring medical conditions and mental health diagnoses, such as sleep problems and Disruptive Behaviour Disorder), as well as a series of caregiver report forms evaluating adaptive behaviour, symptoms of ADHD, and behavioural concerns. Parents were also provided with forms to be completed by their child's teacher and returned by mail. As some study visits occurred during school breaks, teacher forms were obtained at the first study visit in the longitudinal studies when

the child was back in school. All study activities were approved and overseen by the Institutional Review Board at the medical centre.

Classifications of ADHD symptom presentation were made using the Vanderbilt ADHD Rating Scales – Parent and Teacher Forms (VADPRS and VADTRS), following diagnostic scoring algorithms similar to those used in trials of TD children. Children were considered to have met the criteria for a symptom domain (i.e., inattention and/or hyperactivity/impulsivity) if the VADPRS and VADTRS reported 6 non-overlapping symptoms in a symptom domain or both parent and teacher reported ≥4 symptoms in that domain. To meet criteria for ADHD symptom presentation, parents and teachers also had to endorse at least one area of functional impairment on the VADPRS/VADTRS. Children meeting criteria for predominantly inattentive type, predominantly hyperactive type, or combined type symptom presentation were categorised as DS+ADHD. Children not meeting the above criteria, but with a parent-reported ADHD diagnosis and concurrent ADHD medication, were also categorised as DS+ADHD to account for failure to meet diagnostic algorithm criteria due to effective medication treatment. Children meeting neither algorithm-based criteria nor clinician diagnosis and treatment-based criteria were categorised as DS-ADHD.

Measures

ADHD Rating Scales.—The VADPRS and VADTRS are DSM-based scales providing clinical information regarding the frequency and severity of ADHD symptoms across home and school domains (Wolraich *et al.* 2013, Bard *et al.* 2013). Originally developed for 6–12 year olds, the VADPRS/VADTRS is appropriate and commonly used with older adolescents (Makransky and Bilenberg 2014, Becker *et al.* 2020, Langberg *et al.* 2020). Internal consistency and reliability are excellent across the nine-item inattention and hyperactivity/impulsivity subscales among TD children (Wolraich et al. 2013, Bard et al. 2013). Internal consistency in the current sample was also high for the inattention (ICC = .89) and hyperactivity/impulsivity subscales (ICC = .88). Items are rated on a 4-point scale ranging from 0 (never) to 3 (very often). VADPRS and VADTRS subscales for Inattention (9 items), Hyperactivity (9 items), and Combined (18 items) were summed. The VADPRS provides additional subscales for Oppositional Defiant Disorder (ODD), Conduct Disorder, and Anxiety/Depression. The VADTRS combines Oppositional Defiant Disorder and Conduct Disorder into one category. The VADPRS/VADTRS are recommended for use in individuals with ID to differentiate children with and without parent-reported diagnoses of ADHD (Esbensen *et al.* 2017).

Cognition and Adaptive Behaviour.—Child cognitive ability was measured using the Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2). The KBIT-2 is a brief measure of cognitive ability appropriate for individuals aged 4–90 years and is recommended for studies of cognition among individuals with DS (Edgin *et al.* 2010, Kaufman 2004). Depending on the study from which the present data were drawn, adaptive behaviour was measured using either the Scales of Independent Behavior-Revised (SIB-R) or the Vineland Adaptive Behavior Scale-Third Edition (VABS-3). The SIB-R rates individuals from birth to 90 years on adaptive daily living skills and yields a standard score in four domains (motor skills, social interaction/communication skills, personal living skills, and community living

skills) and an overall Broad Independence score (Bruininks *et al.* 1996). The VABS-3 assesses adaptive function from birth to over 80 years in areas of social interaction and communication skills, personal living skills, community living skills, and motor skills (Sparrow *et al.* 2016). At the start of data collection, both the KBIT-II and SIB-R were recommended for use in children with DS, although the VABS-3 has been recommended more recently rather than the SIB-R (Esbensen et al. 2017, Edgin et al. 2010).

General Behaviour Rating Scales.—Two measures of maladaptive behaviour were used to assess general child behaviours: the Achenbach System of Empirically Based Assessment (ASEBA) checklists and the Aberrant Behavior Checklist (ABC). The ASEBA checklists include the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF). The CBCL and TRF obtain parent and teacher ratings, respectively, of 112 problem behaviours for children ages 6–18 years (Achenbach and Rescorla 2001). Items are rated on a 3-point scale from (0) not true to (2) very true, with t-scores created based on an age and gender normative sample. The CBCL and TRF assess symptoms on the Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior and Aggressive Behavior subscales. An Internalizing Problems score is derived from Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints subscale items; an Externalizing Problems score is derived from Rule-Breaking Behavior and Aggressive Behavior subscale items; and a Total Problems score is derived from all subscales. Internal consistency and one-week test-retest reliability ranges from good to excellent for each of the above subscales in samples of TD children (Achenbach and Rescorla 2001). Although not initially designed for use with children who have developmental disabilities, internal consistency is moderate to high for all subscales in samples of children who have ID or DS (Esbensen *et al.* 2018, Jacola *et al.* 2014, Esbensen et al. 2017).

Parents completed the ABC, a 58-item rating scale of maladaptive behaviours for children and adults with ID ages 5 years and over (Aman *et al.* 1985a, Aman *et al.* 1985b). Subscales assess Irritability, Lethargy, Stereotypic Behaviors, Hyperactivity, and Inappropriate Speech. Items are rated on a 4-point scale from (0) [not at all a problem] to (3) [problem is severe in degree]. Internal consistency is good to excellent, inter-rater reliability is moderate, and retest reliability extremely high (Aman et al. 1985b). The ABC has been recommended for use in individuals with ID (Esbensen et al. 2017).

Executive Functioning Rating Scales.—The Behavior Rating Inventory of Executive Function (BRIEF) is a rating scale of everyday skills measuring executive functioning of children ages 5–18 years completed by parents or teachers (Gioia 2000). The BRIEF Parent and Teacher Forms each consist of 86 items providing omnibus indices, including a Behavior Regulation Index (BRI) (comprised of the Inhibit, Shift, and Emotional Control subscales), a Metacognitive Index (MI) (comprised of the Initiate, Working Memory, Plan/Organize, Organizing Materials, and Monitoring subscales), and an overall Global Executive Composite (GEC). Items are rated on a 3-point scale of (1) Never, (2) Sometimes, and (3) Often, based on problems demonstrated over the last six months. T-scores are age- and gender-standardised, with a mean of 50 and a standard deviation of 10. Higher

scores indicate more problems, with scores ≥ 1.5 standard deviations above the mean (t-score above 65) reflecting clinically significant elevations. The BRIEF demonstrates excellent internal consistency, good interrater agreement, and good convergent validity with neuropsychological measures for some subscales when used with children with DS (Edgin et al. 2010, Esbensen *et al.* 2019).

Statistical Analysis

Demographic characteristics and medication use were compared across the DS+ADHD and DS-ADHD groups using t-tests and chi-square tests to identify potential covariates. Clinical characteristics, including cognitive/developmental level, presence of co-occurring Disruptive Behaviour Disorder, and presence of co-occurring sleep problems, were compared across the DS+ADHD and DS-ADHD groups using ANCOVA to control for identified covariates. In addition, we explored group differences for other co-occurring medical conditions to inform clinical practice. ANCOVAs compared the two groups on parent- and teacher-report measures related to anxiety, attention, hyperactivity, and impulsivity (VADPRS/VADTRS anxiety/mood and behaviour concerns; CBCL/TRF social problems, attention problems, rule breaking, aggression, externalised problems, total scores; ABC irritability, hyperactivity; all BRIEF subscales). We also explored group differences on other subscales of the CBCL/TRF and ABC using ANCOVA to potentially inform clinical practice. Missing items were deleted listwise within each analysis. Given that ADHD medications are expected to influence a range of behaviours, all analyses comparing behaviour rating scale scores controlled for ADHD medication status.

Results

Table 1 presents percentages, mean scores, and standard deviations for demographic and clinical characteristics for children, parents, and teachers. Forty-four children met criteria for DS+ADHD case identification, while 64 did not meet criteria (DS-ADHD). Of the children with DS+ADHD, 90.9% were identified by the scoring algorithm (with 59.1% meeting criteria for inattentive type, 2.3% with for hyperactive/impulsive type, and 29.5% for combined type), while 9.1% had a prior ADHD diagnosis plus ADHD medication treatment but did not meet the algorithm criteria. Table 2 presents mean scores and standard deviations for VADPRS and VADTRS Inattention, Hyperactivity, and Combined scores for the DS+ADHD and DS-ADHD groups.

Group comparison on demographic characteristics

Demographic characteristic percentages, mean scores, and standard deviations for children with DS+ADHD and DS-ADHD are shown in Table 2. There were no group differences on any child demographic variables (i.e., gender, race, ethnicity, or age). The male to female gender ratio was 1.7:1 for DS+ADHD and 1.1:1 for DS-ADHD. Over one-third of children with DS+ADHD (36.4%) were prescribed ADHD medication for ADHD. Of children with DS+ADHD prescribed medication for ADHD, most were prescribed methylphenidate preparations (e.g., Ritalin, Concerta, Focalin, Quillivant; 62.5%), followed by amphetamines (e.g., Adderall, Vyvanse; 37.5%). Children prescribed non-stimulants (alpha-agonists, 25%; atomoxetine, 6.2%) were also prescribed the stimulant medication methylphenidate for

ADHD. Subsequent analyses comparing rating scale scores were adjusted for ADHD medication status.

Group comparison on clinical characteristics

Table 2 presents percentages, mean scores, and standard deviations for each group's clinical characteristics. There were no group differences on KBIT-2 standard or raw scores, nor on the SIB-R or VABS-3 standard scores.

As hypothesised, children with DS+ADHD had more co-occurring diagnoses of Disruptive Behaviour Disorder [$\chi^2(1)=5.58$, $p=.018$] and sleep disorders [$\chi^2(1)=4.34$, $p=.037$] than children with DS-ADHD. Children with DS+ADHD also reported higher rates of allergies [$\chi^2(1)=3.84$, $p=.050$] and seizures [$\chi^2(1)=4.49$, $p=.034$] than children with DS-ADHD.

Group comparison on parent- and teacher-report measures

Table 3 presents estimated marginal means and standard errors for the DS+ADHD and DS-ADHD groups on parent- and teacher-report measures. On the Vanderbilt ADHD Rating Scales, as hypothesised, children with DS+ADHD had higher mean summed scores on the VADPRS ODD [$F(1,104)=11.18$, $p=.001$] and Conduct subscales [$F(1,104)=5.85$, $p=.017$], and the VADTRS ODD/Conduct subscale [$F(1,75)=7.00$, $p=.010$] than children with DS-ADHD. Counter to our hypotheses, no statistically significant group differences were identified on the VADPRS nor VADTRS Anxiety/Depression subscales.

On the ASEBA checklists, as hypothesised, children with DS+ADHD had higher t-scores on both the CBCL and TRF subscales for Attention Problems [$F(1,100)=35.11$, $p<.001$; $F(1,75)=4.00$, $p=.049$], Aggression [$F(1,100)=8.57$, $p=.004$; $F(1,75)=7.08$, $p=.010$], and Externalizing Problems [$F(1,100)=11.06$, $p=.001$; $F(1,75)=4.88$, $p=.030$] as well as the Total Problems scores [$F(1,100)=11.25$, $p=.001$; $F(1,75)=5.53$, $p=.021$] compared to DS-ADHD after controlling for medication use. Counter to our hypotheses, no statistically significant group differences were identified on the CBCL and TRF Social Problems or Rule-Breaking Behavior subscales. In exploratory group comparisons, children with DS+ADHD compared to DS-ADHD had higher t-scores on both the Somatic Complaints [$F(1,100)=4.06$, $p=.047$] and Thought Problems [$F(1,100)=3.94$, $p=.050$] CBCL subscales. No statistically significant group differences were identified for the CBCL and TRF Anxious/Depressed, Withdrawn/Depressed, or Internalizing Problems subscales.

On the ABC, as hypothesised, children with DS+ADHD compared to DS-ADHD had higher summed scores on the Irritability [$F(1,96)=11.39$, $p=.001$] and Hyperactivity [$F(1,96)=15.18$, $p<.001$] subscales. In exploratory comparisons, children with DS+ADHD had higher summed scores on the Lethargy subscale [$F(1,96)=6.02$, $p=.016$] than children with DS-ADHD. No statistically significant group differences were identified for the Stereotypy or Inappropriate Speech subscales.

On the BRIEF, as hypothesised, children with DS+ADHD compared to DS-ADHD had higher t-scores on the parent- and teacher-reported Inhibit subscale [$F(1,90)=6.97$, $p=.010$; $F(1,69)=6.08$, $p=.016$] and on the parent-reported subscales of Shift [$F(1,90)=11.86$, $p=.001$], Emotional Control [$F(1,90)=6.08$, $p=.016$], Initiate [$F(1,90)=9.90$, $p=.002$],

Working Memory [$F(1,90)=19.67$, $p<.001$], Plan/Organize [$F(1,90)=8.29$, $p=.005$], Organization of Materials [$F(1,90)=18.77$, $p<.001$], and Monitor [$F(1,90)=10.00$, $p=.002$], as well as the indices of BRI [$F(1,90)=11.30$, $p=.001$], MI [$F(1,90)=18.47$, $p<.001$], and GEC [$F(1,90)=22.69$, $p<.001$]. Counter to our hypotheses, no statistically significant group differences were identified for the other BRIEF teacher-report subscales.

Discussion

The current study examined differences among children with DS meeting ADHD symptom presentation criteria (DS+ADHD) versus children with DS not meeting clinical criteria (DS-ADHD) in terms of developmental level, co-occurring medical conditions, and ratings of behaviour and executive functioning, in order to gain further understanding of the impact of co-occurring ADHD symptomatology on screening and diagnostic evaluation practices. Both the rates of prior ADHD clinical diagnosis (15.7%) and of ADHD as determined by our diagnostic scoring algorithm (40.7%) were consistent with the prior literature (Ekstein et al. 2011, Oxelgren et al. 2017). The scoring algorithm indicated that most children with DS and ADHD had Inattentive Presentation, again consistent with the literature (Edvardson et al. 2014, Oxelgren et al. 2017). However, the scoring algorithm identified many more children with DS+ADHD than were reported to have a prior diagnosis, emphasizing potential under-diagnosis of ADHD in children with DS in the community.

We found no differences in levels of cognitive skills and adaptive behaviour using standard scores in children with DS+ADHD versus DS-ADHD, further supporting other reports in DS (Hastings et al. 2005, Oxelgren et al. 2017, Ornoy et al. 2011, Ekstein et al. 2011). As standard scores may demonstrate floor effects, group differences were corroborated with KBIT-2 raw scores. Although, contrary to findings for individuals with heterotypic ID (Di Nuovo and Buono 2007), there was no association between developmental level and the presence of ADHD in our sample of children with DS, it is still recommended clinical practice to consider symptoms in comparison to peers of comparable intellectual and chronological age when assessing for ADHD in individuals with ID or DS (Fletcher et al. 2016).

We also examined differences in demographic characteristics and rates of co-occurring medical conditions in children with DS+ADHD versus DS-ADHD. Study findings did not replicate a gender difference between these groups, although males are commonly reported in the general population and among children with ID to have higher rates of ADHD (Hastings and Beck 2004, Froehlich et al. 2007). Study findings also did not identify age differences between these groups, although symptoms are reported to worsen with age in the children with ID (Hastings and Beck 2004). However, the current findings are consistent with the findings of several other studies that have failed to find a gender difference or association with age within children with DS and co-occurring ADHD (Edvardson et al. 2014, Ornoy et al. 2011). These findings suggest that clinicians should monitor for symptoms of ADHD across childhood and adolescence, as well as equally in males and females, among individuals with DS.

We found that 36.4% of children with DS+ADHD were prescribed ADHD medications. Hence, in our sample the majority of children with DS+ADHD did not receive pharmaceutical interventions, which along with behavioural treatments, are evidence-based treatments recommended for children with ID and ADHD (Wolraich *et al.* 2019, Fletcher et al. 2016). This finding of low rates of ADHD medication treatment is consistent with reported rates for children with Down syndrome (Downes *et al.* 2015) and with concerns regarding prescribing stimulant medication in children with high rates of congenital heart defects (Vetter *et al.* 2008). Children with DS and ADHD were prescribed more methylphenidate preparations than amphetamines, which contrasts with their about equal use in typically developing children with ADHD (Bachmann *et al.* 2017). These finding may suggest under-treatment of ADHD symptoms among children with DS, although rates of behavioural treatment were not assessed. Efforts are needed to support paediatricians in screening all children with DS for ADHD symptoms in order to offer appropriate behavioural supports and medication management per best practice guidelines for treatment (Barbaresi *et al.* 2020). Efforts are also needed to better understand treatment practices following a diagnosis of ADHD, treatment strategies for presenting symptoms in the absence of a clinical diagnosis of ADHD, and guidance for how to assess treatment effectiveness.

As hypothesised, children with DS+ADHD versus DS-ADHD had higher rates of sleep disorders and Disruptive Behaviour Disorder. These findings are consistent with the high rates of co-occurring sleep and disruptive behaviour disorders observed in typically developing children with ADHD (Sung *et al.* 2008, Larson *et al.* 2011). Children with DS+ADHD were also found to have higher rates of both allergies and seizures than children with DS-ADHD, consistent with preliminary findings in TD children with ADHD (Hesdorffer *et al.* 2004, Wang *et al.* 2018). These higher rates of co-occurring medical conditions present in children with DS and ADHD symptom presentation underscore the importance of monitoring for seizures given concerns regarding potential risk of stimulant medication lowering the seizure threshold in children with poorly controlled epilepsy (Hemmer *et al.* 2001). A higher rate of allergies in children with DS and co-occurring ADHD is consistent with findings in typically developing children, with almost two-thirds of children with DS and ADHD reporting allergies (Miyazaki *et al.* 2017, Wang et al. 2018). The increased rate of allergies among TD children with ADHD is posited by some to be related to increased activity of the cholinergic/adrenergic system contributing to changes in the central nervous system that present as symptoms of ADHD (Chen *et al.* 2017). An alternative hypothesis is that conditions such as allergic rhinitis may produce nasal obstruction and resultant sleep disturbances that lead to some of the behavioural and cognitive patterns observed in ADHD (Brawley *et al.* 2004). The type of allergy (e.g., allergic rhinitis, atopic dermatitis) was not recorded in the current study and warrants further exploration to better understand the co-occurrence of ADHD and allergies among children with DS prior to making screening or treatment recommendations. These higher rates of co-occurring medical conditions present in children with DS and ADHD symptom presentation support the need for thorough evaluations of medical conditions to rule out their contribution to the presentation of inattention, hyperactive, and impulsive, consistent with the current guidelines for the health care of children with DS (Bull and Genetics 2011). However, we

did not replicate prior findings linking ophthalmological concerns to DS+ADHD (Ekstein et al. 2011), with both groups experiencing high rates of vision problems.

We also examined the hypothesis that children with DS+ADHD would have higher scores on specific parent- and teacher-reported measures of behavioural concerns. As hypothesised, children with DS+ADHD versus DS-ADHD had more reported oppositional and conduct behaviours on the VADPRS and VADTRS; inattention, aggression, and externalizing problems on the CBCL and TRF; and irritability and hyperactivity on the ABC. Of note, this pattern persisted across different measures and across both parent- and teacher-reports. However, counter to our hypotheses, group differences were not seen for social problems or rule-breaking behaviours as assessed by either parent- or teacher-reports, supporting a lack of association between these constructs and ADHD symptomatology in children with DS. In our exploratory analyses, group differences were identified for CBCL somatic complaints and thought problems subscales according to parent- but not teacher-report, underscoring the need to replicate these findings before drawing firm conclusions. On the ABC, children with DS+ADHD versus DS-ADHD had higher parent ratings of lethargy, consistent with studies of TD children showing a link between ADHD and ratings of sluggish cognitive tempo, which includes the symptom of lethargy (Becker *et al.* 2016). These subscales that discriminate DS+ADHD from DS-ADHD can be useful for differentially diagnosing ADHD in children with DS.

A different pattern of findings among raters was identified for executive functioning. Parents reported that children with DS+ADHD versus DS-ADHD had greater difficulties in *all* executive functioning domains. However, teachers only reported group differences in the inhibitory control domain, instead reporting substantial concerns across other executive function subscales for all children with DS regardless of ADHD status, with the estimated marginal mean scores for almost all domains falling around or above the clinical cut-off of 65 for both groups. Challenges with executive functioning may be more readily observed in the home environment for children with DS+ADHD versus DS-ADHD. Additionally, teachers may have more opportunities for making comparisons to other children for ratings of executive functioning; thus, teachers may identify difficulties across all domains of executive functioning for the entire population of children with DS.

Several study limitations should be noted. Data collection relied on parent report of co-occurring medical conditions. Future studies would benefit from evaluation of clinical charts to better understand how sleep disorders may be related to diagnoses of ADHD or symptoms of inattention and hyperactivity, as well as to clarify the contribution of allergies to ADHD symptom presentation. Information on behavioural treatments or supports for symptoms of ADHD or other behavioural concerns were also not collected for this study. Nonetheless, our study had several strengths. The large community-dwelling sample of children and adolescents ensures generalizability to other children with DS, yet future studies would benefit from analyses focused on smaller age ranges to identify presenting concerns among children versus adolescents. Sample sizes limited direct comparisons within children with DS+ADHD with or without medication yet were controlled for in comparisons to children with DS-ADHD. Further, the ADHD case definition scoring algorithm accounted for parent- and teacher-reports of ADHD symptoms as well as impairment, and analyses controlled for

the presence of ADHD medications, which helps account for effects of pharmacotherapy on outcomes. Although we did not have access to each child's ADHD clinical diagnosis, our confirmation of prior findings in the literature substantiates our use of the diagnostic scoring algorithm for ADHD case definition.

Our study corroborates prior findings regarding the rate of ADHD in DS and its associated demographic characteristics, and extends the literature by presenting the different profiles of children with DS with or without ADHD symptom presentation on specific subscales of parent- and teacher-measures. Identifying coexisting ADHD symptomatology in children with DS is important for identifying appropriate supports and for ongoing treatment and care. In treatment of children with complex ADHD, behavioural and educational interventions are considered the foundation of treatment; however, many children may respond best to these interventions when pharmacological treatments are also provided (Barbaresi et al. 2020). Stimulants are recommended for children with ADHD and ID when contraindications are not present, as 40–72% of children with ADHD and ID are beneficial responders to stimulant medications (Simonoff *et al.* 2013). However, children with DS have a unique neurophysiological profile and, therefore, may not respond to ADHD treatments in the same way as individuals with heterotypical ID. Thus, future research is needed to understand the most appropriate pharmaceutical and behavioural treatment options for children with DS and co-occurring ADHD.

Acknowledgments

This manuscript was prepared with support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health (Esbensen PI: R21 HD082307, R01 HD093754; Esbensen & Froehlich MPI: R61 HD100934), the Foundation Jérôme Lejeune (Esbensen PI), the Jack H Rubinstein Foundation (Esbensen PI), and the Emily Ann Hayes Research Fund (Esbensen PI). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research would not have been possible without the contributions of the participating families and the community support.

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Table 1.

Demographic and clinical characteristics of children, parents, and teachers.

	Children (n=108)	Parents (n=108)	Teachers (n=64)
Demographics	**Percent**	**Percent**	**Percent**
Gender (male)	57.4%	4.6%	10.9%
Race[a]			
White	88.9%	94.5%	93.7%
Black	5.6%	2.7%	3.2%
Asian	2.8%	2.7%	1.6%
Other	2.8%	0.0%	1.6%
Ethnicity (Hispanic)[a]	5.4%	1.4%	
Relationship[a]			
Biological parent		94.5%	
Adoptive parent		2.7%	
Grandparent		1.4%	
Other		1.4%	
Marital Status[a]			
Married		90.4%	
Divorced		4.1%	
Single		4.1%	
Domestic Partnership		1.4%	
Income (n=105)[b]			
<$24,999		5.7%	
$25,000-$49,999		8.0%	
$50,000-$74,999		5.7%	
$75,000-$99,999		20.7%	
>$100,000		46.0%	
refused		13.8%	
	M (SD) range	M (SD) range	M (SD) range
Age (years)	12.3 (3.2) 6–18	49.3 (6.7) 31–64	
KBIT-2 (n=103)	44.7 (7.5) 40–73		
SIB-R (n=32)	44.4 (23.3) 2–80		
VABS-3 (n=63)	69.1 (9.4) 44–95		
Years teaching experience			12.8 (9.1) 1–40
Medical and Mental Health	Percent		
Medication for ADHD	15.0%		
Co-occurring conditions			
Allergies	50.0%		

	Children (n=108)	Parents (n=108)	Teachers (n=64)
Demographics	**Percent**	**Percent**	**Percent**
ADHD	15.7%		
Anxiety	11.1%		
Autism Spectrum Disorder	3.7%		
Depression	1.9%		
Disruptive Behaviour Disorder	8.3%		
Feeding difficulties	11.1%		
Gastro-intestinal concerns	31.5%		
Hearing problems	24.5%		
Heart defect	37.9%		
Low birth weight	15.7%		
Recurrent otitis media	21.3%		
Recurrent pneumonia	5.7%		
Seizures	2.8%		
Sleep disorder	42.6%		
Thyroid problem	33.3%		
Vision problem	66.0%		

[a] n=73 for parents,

[b] n=87 for parents

ADHD = Attention Deficit Hyperactivity Disorder; KBIT-2 = Kaufman Brief Intelligence Test 2nd Edition; SIB-R = Scales of Independent Behavior-Revised; VABS-3 – Vineland Adaptive Behavior Scale 3rd Edition

Table 2.

Comparison between children with and without ADHD on potential covariates and clinical variables.

	DS+ADHD (n=44)	DS-ADHD (n=64)
Potential Covariates	**Percent**	**Percent**
Gender (male)	63.6%	53.1%
Race		
White	86.4%	90.6%
Black	9.1%	3.1%
Asian	0.0%	4.7%
Other	4.5%	1.6%
Ethnicity (Hispanic)	5.4%	5.4%
Medication for ADHD ***	36.4%	0.0%
	M (SD)	M (SD)
Age (years)	11.6 (3.0)	12.8 (3.3)
ADHD Symptoms	M (SD)	M (SD)
VADPRS Inattention	16.0 (4.3)	8.2 (3.6)
VADPRS Hyperactivity	10.2 (5.8)	3.8 (3.4)
VADPRS Combined	26.2 (8.0)	12.0 (5.7)
VADTRS Inattention (n=78)[a]	16.8 (5.5)	12.7 (5.2)
VADTRS Hyperactivity (n=78)[a]	9.4 (6.1)	4.9 (4.6)
VADTRS Combined (n=78)[a]	26.2 (9.8)	17.6 (8.4)
Cognitive/Developmental	M (SD)	M (SD)
KBIT-2 standard score (n=103)[b]	44.3 (6.7)	45.0 (8.0)
KBIT-2 raw score (n=103)[b]	92.1 (21.3)	97.0 (18.2)
SIB-R standard score (n=32)[c]	37.9 (25.0)	49.6 (21.2)
VABS-3 standard score (n=63)[d]	67.4 (9.4)	70.4 (9.3)
Medical and Mental Health	Percent	Percent
Allergies *	61.4%	42.2%
Anxiety	15.9%	7.8%
Autism Spectrum Disorder	3.7%	6.4%
Depression	2.8%	1.8%
Disruptive Behaviour Disorder *	15.9%	3.1%
Feeding difficulties	11.4%	10.9%
Gastro-intestinal concerns	34.1%	29.7%
Hearing problems	29.7%	21.1%
Heart defect	46.5%	31.7%

	DS+ADHD (n=44)	DS-ADHD (n=64)
Potential Covariates	**Percent**	**Percent**
Low birth weight	15.9%	15.6%
Recurrent otitis media	27.3%	17.2%
Recurrent pneumonia	9.3%	3.2%
Seizures *	6.8%	0.0%
Sleep disorder *	54.5%	34.4%
Thyroid Problem	30.6%	35.1%
Vision Problem	64.9%	66.7%

* Note: $p < .05$,

*** $p < .001$.

[a] DS+ADHD n=32, DS-ADHD n=46

[b] DS+ADHD n=43, DS-ADHD n=60

[c] DS+ADHD n=14, DS-ADHD n=18

[d] DS+ADHD n=27, DS-ADHD n=36

ADHD = Attention Deficit Hyperactivity Disorder; KBIT-2 = Kaufman Brief Intelligence Test 2nd Edition; SIB-R = Scales of Independent Behavior-Revised; VABS-3 – Vineland Adaptive Behavior Scale 3rd Edition; VADPRS =Vanderbilt ADHD Parent Rating Scale; VADTRS = Vanderbilt ADHD Teacher Rating Scale.

Table 3.

Comparison between children with and without ADHD on parent and teacher measures (Estimated Marginal Means (SE)).

	Parent report		**Teacher report**	
VANDERBILT (sum score)	**DS+ADHD (n=44)**	**DS-ADHD (n=63)**	**DS+ADHD (n=32)**	**DS-ADHD (n=46)**
ODD ***	6.1 (0.6)	3.3 (0.5)	-	-
Conduct Disorder **	1.7 (0.3)	0.7 (0.3)	-	-
Anxiety/Depression	2.3 (0.4)	1.3 (0.4)	3.3 (0.5)	2.1 (0.4)
ODD/Conduct Disorder ^^	-	-	5.2 (0.7)	2.8 (0.5)
CBCL/TRF (t-score)_	DS+ADHD (n=42)	DS-ADHD (n=61)	DS+ADHD (n=33)	DS-ADHD (n=45)
Anxious	53.4 (0.9)	52.0 (0.7)	56.3 (1.3)	55.1 (1.1)
Withdrawn	57.9 (1.4)	54.9 (1.1)	57.8 (1.4)	57.5 (1.1)
Somatic Complaints *	56.9 (1.0)	54.3 (0.8)	56.6 (1.2)	53.8 (1.0)
Social Problems	60.3 (1.0)	58.5 (0.8)	63.2 (1.5)	62.4 (0.9)
Thought Problems *	62.9 (1.4)	59.1 (1.1)	65.1 (1.5)	61.3 (1.3)
Attention Problems ***, ^	65.5 (1.1)	56.6 (0.9)	63.2 (1.3)	59.5 (1.1)
Rule Breaking	55.0 (0.8)	53.8 (0.6)	58.3 (1.2)	56.4 (1.0)
Aggression **,^^	58.7 (1.2)	54.0 (1.0)	63.1 (1.2)	58.6 (1.0)
Internalizing	52.2 (1.7)	48.1 (1.4)	56.0 (1.6)	55.0 (1.3)
Externalizing ***,^	56.3 (1.5)	49.2 (1.2)	62.0 (1.3)	57.9 (1.1)
Total ***,^	59.8 (1.6)	52.6 (1.3)	63.4 (1.3)	59.0 (1.1)
ABC (sum score)	DS+ADHD (n=40)	DS-ADHD (n=59)		
Irritability ***	6.6 (0.9)	2.4 (0.7)	-	-
Lethargy *	4.8 (0.8)	1.9 (0.7)	-	-
Stereotypy	2.1 (0.5)	1.2 (0.4)	-	-
Hyperactivity ***	10.9 (1.2)	4.7 (0.9)	-	-
Inappropriate Speech	1.4 (0.3)	1.3 (0.2)	-	-

	Parent report		Teacher report	
VANDERBILT (sum score)	**DS+ADHD (n=44)**	**DS-ADHD (n=63)**	**DS+ADHD (n=32)**	**DS-ADHD (n=46)**
BRIEF (t-score)	DS+ADHD (n=40)	DS-ADHD (n=53)	DS+ADHD (n=29)	DS-ADHD (n=43)
Inhibit $^{**,\wedge}$	63.6 (2.1)	55.8 (1.8)	77.3 (3.4)	65.7 (2.7)
Shift ***	65.8 (1.8)	56.9 (1.5)	74.8 (3.7)	68.9 (2.9)
Emotional Control *	53.8 (1.9)	47.2 (1.6)	69.7 (3.4)	62.0 (2.7)
BRI ***	62.0 (1.9)	53.2 (1.6)	76.7 (4.4)	69.3 (3.5)
Initiate **	61.2 (1.6)	54.2 (1.3)	75.9 (2.8)	73.0 (2.2)
Working Memory ***	68.5 (1.5)	59.4 (1.2)	79.3 (3.0)	75.4 (2.3)
Plan/Organize **	63.7 (1.8)	56.3 (1.5)	69.8 (3.2)	65.9 (2.5)
Organize Materials ***	56.4 (1.5)	47.2 (1.3)	69.9 (4.5)	63.6 (3.6)
Monitor **	68.5 (1.9)	60.1 (1.6)	79.2 (3.0)	72.4 (2.4)
MI ***	66.1 (1.5)	57.0 (1.3)	78.4 (2.9)	72.7 (2.3)
GEC ***	65.4 (1.5)	55.6 (1.2)	80.0 (3.0)	72.6 (2.4)

Note: For parent-report measure group comparisons

* $p < .05$,

** $p < .01$,

*** $p < .001$. For teacher-report measures group comparisons

$^{\wedge}$ $p < .05$,

$^{\wedge\wedge}$ $p < .01$,

$^{\wedge\wedge\wedge}$ $p < .001$

ABC = Aberrant Behavior Checklist; ADHD = Attention Deficit Hyperactivity Disorder; BRI = Behavior Regulation Index; BRIEF = Behavior Rating Inventory of Executive Function; CBCL = Child Behavior Checklist; GEC = Global Executive Composite; MI = Metacognitive Index; ODD – Oppositional Defiant Disorder; TRF = Teacher Report Form.