NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD AGOSTO 2018

Acta Neurol Belg. 2018.
DISTAL 1Q21.1 AND PROXIMAL 1Q21.2 MICRODUPLICATION IN A CHILD WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Veerapandiyan A, Oh D, Kornitzer J .

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ADHD Atten Deficit Hyperact Disord. 2018;10:177-88.
FACTOR STRUCTURE AND CLINICAL CORRELATES OF THE 61-ITEM WENDER UTAH RATING SCALE (WURS).
Calamia M, Hill BD, Musso MW, et al.
The objective of this study was to assess the factor structure and clinical correlates of a 61-item version of the Wender Utah Rating Scale (WURS), a self-report retrospective measure of childhood problems, experiences, and behavior used in ADHD assessment. Given the currently mostly widely used form of the WURS was derived via a criterion-keyed approach, the study aimed to use latent variable modeling of the 61-item WURS to potentially identify more and more homogeneous set of items reflecting current conceptualizations of ADHD symptoms. Exploratory structural equation modeling was used to generate factor scores which were then correlated with neuropsychological measures of intelligence and executive attention as well as a broad measure of personality and emotional functioning. Support for a modified five-factor model was found: ADHD, disruptive mood and behavior, negative affectivity, social confidence, and academic problems. The ADHD factor differed somewhat from the traditional 25-item WURS short form largely through weaker associations with several measures of personality and psychopathology. This study identified a factor more aligned with DSM-5 conceptualization of ADHD as well as measures of other types of childhood characteristics and symptoms which may prove useful for both research and clinical practice

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Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

ADHD Atten Deficit Hyperact Disord. 2018;10:237-43.

EXPLORATORY STUDY OF BARRIERS TO SUCCESSFUL OFFICE CONTACTS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hooven JT, Fogel BN, Waxmonsky JG, et al.

The American Academy of Pediatrics published attention deficit hyperactivity disorder (ADHD) guidelines, but significant variability exists in care. This exploratory study aimed to understand barriers to compliance with primary care office contacts for ADHD medication management. The study was conducted at a single academic medical center via retrospective chart review between 6/1/15 and 5/31/16 in combination with telephone interviews. Participants included 306 children 6ΓÇô12-áyears old with an ADHD-related ICD-9/ICD-10 diagnosis. Factors affecting compliance were assessed via multivariable linear regression using the outcome of unsuccessful office contacts based on the percentage of missed, canceled, or rescheduled appointments. ADHD patients averaged 28.3% (SD 23.8%) unsuccessful office contacts. Unsuccessful contacts significantly increased by 15% for Hispanic ethnicity, 8% for public insurance, 8% for inattentive subtype, and 3% for every 10 miles additional distance from the office. Telephone interviews were attempted for those missing ΓëÑ-á3 appointments, which represented 18.3% (56/306) of the sample. Interviews were successfully completed with 37.5% (21/56). Of these, 52.3% (11/21) of parents preferred in-person visits. Structural barriers were not a concern, but 52.3% (11/21) reported high caregiver strain and fatigue. The results indicate that-ácultural barriers to understanding of ADHD and its management must be reconsidered. Use of Internet-based platforms may be a novel approach to address issues of distance, financial difficulty, and parental stress

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ADHD Atten Deficit Hyperact Disord. 2018.

EVALUATING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER USING ECOLOGICAL MOMENTARY ASSESSMENT: A SYSTEMATIC REVIEW.

Miguelez-Fernandez C, de Leon SJ, Baltasar-Tello I, et al.

Ecological momentary assessment is an excellent tool for the measurement of different day-to-day domains in patients and capturing real-world and real-time data. The purpose of this review is to evaluate feasibility in current ecological momentary assessment studies on emotional and behavioral functioning, functional impairments, and quality of life patients with an attention-deficit/hyperactivity disorder diagnosis. This systematic review follows the recommendation of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines selecting articles published from January 1, 1990, up to the latest access on May 2018, identifying a pool of 23 eligible studies. Twenty-three studies demonstrate the validity of ecological momentary assessment methodology in evaluating different aspects of patients with attention-deficit/hyperactivity disorder. Fifteen studies focus on the childΓÇÖs or adolescentΓÇÖs daily behavior, while eight studies only focus on adults. The studies presented in this review monitored patients and their families over a maximum period of 28-ádays. We can conclude that ecological momentary assessment can be successfully implemented with attention-deficit/hyperactivity disorder patients to evaluate diverse backgrounds. However, more studies are needed with a longer monitoring period, especially in adolescents, to determine the effectiveness of ecological momentary assessment on patients with attention-deficit/hyperactivity disorder

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Am J Occup Ther. 2018 May;72:7203205040p1-p9.

COMPARISON OF CHILDREN WITH AND WITHOUT ADHD ON A NEW PICTORIAL SELF-ASSESSMENT OF EXECUTIVE FUNCTIONS.

Bar-Ilan RT, Cohen N, Maeir A.

OBJECTIVE: We examined the Pictorial Interview of Children's Metacognition and Executive Functions' (PIC-ME's) reliability and validity, targeting children's appraisal of their executive function (EF) in daily life.

METHOD: One hundred children with attention deficit hyperactivity disorder (ADHD) and 44 typically developing children (ages 5-10 yr) completed the PIC-ME. Parents completed the PIC-ME and Behavior Rating Inventory of Executive Function (BRIEF).
RESULTS: Cronbach's alpha for the child PIC-ME was .914. A high correlation was found between the parent PIC-ME total and the BRIEF (r = .724). Comparisons between groups revealed significant differences on the parent PIC-ME (p < .0001) but none on the child PIC-ME. Children with ADHD identified a median of eight EF challenges they wanted to set as treatment goals.
CONCLUSION: Results support the PIC-ME's initial reliability and validity among children with ADHD. Children were able to identify several EF challenges and engage in goal setting

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Am J Addict. 2018;27:309-10.

STIMULANT MISUSE IN ADULT ADHD WITH COMORBID SUBSTANCE USE DISORDER (OR STIMULANT USE DISORDER): MISSING "DUE DILIGENCE": A CASE REPORT AND LITERATURE REVIEW.

Thusius N, Schneekloth T, Sinha S.

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood (4-8% of children in the general population). The majority of patients continue to be impaired by ADHD symptoms, leading to prevalence of 1-5% in adulthood. Pharmacological treatment with stimulants is by far the most described treatment modality. Several studies have shown that children with ADHD have a greater risk of developing substance use disorders (SUD) later in life than children without ADHD. The prevalence of ADHD in SUD patients is estimated to be 23.1%. Stimulants have a significant potential for misuse. Recent studies indicate non-medical use of Dextroamphetamine-amphetamine in adults went up by 67% and emergency department visits by 155.9%. There fore concerns have been raised that stimulants prescribed to treat ADHD could affect an individual's vulnerability to developing substance use disorder(s). The studies conducted have found no differences in later substance use for children with ADHD who received treatment and those that did not suggesting treatment with a stimulant appears not to affect an individual's risk for developing a substance use disorder. Here we describe a case of very severe misuse of prescription stimulant medications in a patient with adult ADHD.
Methods: We describe a 66-year-old, married, retired Foreign Service officer of European descent, who presented to the outpatient clinic with depressive symptomatology and prescription stimulant abuse issues. In 2000 he was prescribed Amphetamine-Dextroamphetamine (Adderall) 15 mg/day. The dose was increased to 20 mg/day in 2008. In 2010 he started taking Adderall for mood enhancement and within the last seven years the dose escalated to 420 mg of Lisdexamfetamine dimesylate (Vyvanse) and 240 mg of AmphetamineDextroamphetamine (Adderall) per day, prescribed by two independent psychiatrists and filled by two different pharmacies. He has been prescribed Alprazolam (Xanax) for anxiety up to 4 mg/day for the past three years. Psychiatrically, he carries diagnoses of depressive and anxiety disorder and has been on combination of Bupropion (Wellbutrin) and Desvenlafaxine (Pristiq) for the past five years. He has significant family history of addictive disorders. His brother and father had alcoholism. His 26-year-old son died of drug overdose in 2016. Upon admission to our intensive addiction treatment program (outpatient with residing) the initial cardiac work up was unremarkable. Lisdexamfetamine dimesylate and AmphetamineDextroamphetamine were tapered off without significant withdrawal symptoms. Bupropion and Desvenlafaxine doses were optimized and Alprazolam was tapered off slowly. He has developed skills and strategies to effectively cope with the death of his son. He continues to struggle to identify maladaptive thoughts and behaviors and the skills to decrease his symptoms of depression and anxiety. This is in part due to his difficulty with focusing, concentrating and remembering the skills he learned. With his permission, both outpatient psychiatrists were notified of the lethal doses of stimulants the patient had been taking for mood enhancement.
Results: Patient reported symptoms of depression since 1985 and life-long anxiety. He has been on medications for mental health for the past five years, he denied feeling any positive effects from the antidepressant medications (Desvenlafaxine and Bupropion) to improve his mood or decrease his anxiety. He reported that he had been seeing two psychiatrists in an effort to "double up" on his medications and had been taking 400% of the maximum approved doses of Lisdexamphetamine and Amphetaminedextroamphetamine. He has not been honest with his providers about the other, or the amount

of medication he was taking daily. He shared that he needed to self-medicate to get out of bed in the morning and through the day. He felt that his Adderall use has been an attempt to also self-medicate his depression. Our patient had limited insight into the relationship between substance use and mental health. Our patient is an example of lack of healthy coping skills and impulse control secondary to depression and ADHD.
Conclusions: The presentation of ADHD in adults may be influenced by the longevity of their ADHD, associated sequelae (eg, low self-esteem and interpersonal, educational, and occupational difficulties), and comorbid disorders. There are neither reliable biomarkers nor neuropsychological tests for diagnosis, and persons with ADHD typically have a complex presentation with at least one comorbidity. While stimulants are generally more efficacious for ADHD symptoms than nonstimulants, they are associated with misuse and diversion. The precautions, to be applied to all adult ADHD patients for whom stimulants are being considered, include careful diagnosis and consideration of comorbidities, baseline risk stratification, informed consent processes, treatment agreements, periodic reassessments of treatment response, and meticulous documentation. Summary: The above mentioned principles help to risk stratify patients at baseline and should be applied to all adult ADHD patients for whom stimulants are being considered. With concerns for comorbid substance use disorder(s), the patients should ideally be first evaluated by an addiction psychiatrist before stimulants are prescribed and should be monitored closely for any aberrant behavior

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Asia-Pacific Psychiatry. 2018;10.
PARENTAL SMOKING AND DEPRESSION, AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: KOREAN NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2005-2014.
Cho YJ, Choi R, Park S, et al.
Introduction: We aimed to investigate the risk factors associated with attention-deficit hyperactivity disorder (ADHD) in children and adolescents using a nationally representative sample of the Korean population.
Methods: Data from children and adolescents aged less than 18-áyears (n-á=-á23-á561) were obtained from the Korean National Health and Nutrition Examination Survey, 2005 to 2014. ADHD was assessed using a self-reported diagnosis of ADHD. We estimated the annual prevalence and number of Korean children and adolescents with physician-diagnosed ADHD from 2005 to 2014. We considered various risk factors including demographics, obesity, and family environment (household income, parental age, depression in adults in the household, and exposure to environmental smoke at home). The relationship between ADHD and the considered risk factors was evaluated using multiple logistic regression.
Results: The annual prevalence of physician-diagnosed ADHD showed a 4-fold increase (0.35% in 2005 and 1.36% 2014) over the study period. Among ADHD patients, boys and girls constituted 78% and 22%, respectively. Total smoking amounts and depression in adults in the household were significantly associated with children's ADHD. When the analysis was limited to parental effects, only the father's smoking amount and depression were associated with the children's ADHD.
Discussion: This study identified adults' smoking and depression as family environmental factors associated with children's ADHD. From a public health care perspective, this result illuminates the need for awareness programs emphasizing a parent's conditions that may influence the development of ADHD in children

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Biol Psychol. 2018;138:35-40.
THE IMPACT OF SNAP25 ON BRAIN FUNCTIONAL CONNECTIVITY DENSITY AND WORKING MEMORY IN ADHD.
Wang C, Yang B, Fang D, et al.
Attention deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopment disorder. The deficit in working memory is a central cognitive impairment in ADHD. The SNAP-25 is a neurotransmitter vesicular docking protein whose MnlI polymorphism (rs3746544) is located in the 3ΓÇ¦-untranslated region (3ΓÇ¦-UTR) and known to be linked to ADHD, but the underlying mechanism of this polymorphism remains unclear. Using a functional connectivity density (FCD) mapping method based on resting-state functional magnetic resonance imaging in a sample of male children diagnosed with ADHD, we first investigated the correlation between SNAP-25 rs3746544 and FCD hubs. Compared with rs3746544 G-allele carriers, TT homozygous,

which confers a high risk for ADHD, exhibited significantly decreased local and long-range FCD in anterior cingulate cortex, and decreased local FCD in the dorsal lateral prefrontal cortex. Moreover, both higher local and long-range FCD could predict better WM capacity. The current findings provide new insights into the underlying neural mechanisms linking SNAP-25 rs3746544 with the risk for ADHD via the endophenotype of brain functional connectivity

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BMC Psychiatry. 2018;18.

MINDFULNESS FOR CHILDREN WITH ADHD AND MINDFUL PARENTING (MINDCHAMP): PROTOCOL OF A RANDOMISED CONTROLLED TRIAL COMPARING A FAMILY MINDFULNESS-BASED INTERVENTION AS AN ADD-ON TO CARE-AS-USUAL WITH CARE-AS-USUAL ONLY.

Siebelink NM, B+Âgels SM, Boerboom LM, et al.

Background: Self-control in childhood has been linked to long-term and cascading effects on health, academic, criminality, wealth and parenting outcomes. Hence it is important to target self-control deficits early in life. Self-control deficits are a hallmark of Attention Deficit/Hyperactivity Disorder (ADHD). Even after receiving care-as-usual (CAU) for ADHD, impaired self-control often remains. Pharmacotherapy can be hampered by side-effects, low adherence and short-term effectiveness. Other limitations of CAU are decreased effectiveness when parents have ADHD and little effect on parental well-being. Mindfulness-Based Interventions (MBIs) are an emerging non-pharmacological approach with potential to improve self-control and well-being in both children and parents. However, there is a lack of sufficiently powered randomised controlled trials (RCTs) to establish their effects in families with ADHD. This study protocol describes an RCT to investigate the effectiveness of a family MBI as an add-on to CAU in treatment of youth with ADHD, and is described in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Methods/design: An RCT will be conducted in N = 100 children (aged 8-16 years) with ADHD and their parents. The experimental condition will consist of a family MBI (MYmind): 8-week group-based MBI for youth combined with parallel group-based Mindful Parenting for their parents, as an add-on to CAU. The control condition will consist of CAU-only. Assessments will take place at baseline, end of treatment (3 months later), 2 and 6 months' follow-up. Primary outcome measure will be an ecologically valid assessment of child self-control with the parent-rated Behaviour Rating Inventory of Executive Function (BRIEF). Secondary child outcome measures will be teacher-rated BRIEF, computerised self-control tasks and questionnaires on psychological symptoms (e.g. ADHD, symptoms of autism), well-being and mindfulness. For parental outcomes, secondary measures will be self-rated BRIEF, computerised self-control tasks and questionnaires on psychological symptoms, well-being and mindful parenting.

Discussion: The proposed RCT will take account of methodological limitations of previous studies on MBIs in child ADHD populations. The current study will provide valuable information on family MBI as a potential effective intervention in targeting self-control deficits for youth with ADHD and their parents

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BMJ (Online). 2018;362.

ADHD: METHYLPHENIDATE SHOULD BE FIRST LINE DRUG TREATMENT IN CHILDREN, REVIEW CONFIRMS.

Iacobucci G.

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Child Neuropsychol. 2018.

CONFIRMATORY FACTOR ANALYSIS OF THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION IN A NEURO-PEDIATRIC SAMPLE AND ITS APPLICATION TO MENTAL DISORDERS.

Halvorsen M, Mathiassen B, Amundsen T, et al.

The construct validity of the 9-scale version of the Behavior Rating Inventory of Executive Function (BRIEF) parent form was examined in a clinical sample of children and adolescents with neurological and

neurodevelopmental disorders (N-á=-á281). Confirmatory factor analysis supported a three-factor model separating the inhibitory behavioral control dimension from the emotional control and metacognitive problem-solving dimensions. The Metacognitive factor was also related to a diagnosis of attention deficit/hyperactivity disorder (ADHD) after controlling for age, gender, IQ, adaptive functioning, and a conventional behavioral rating scale, which included inattention-hyperactivity symptoms. The Emotional Regulation factor was related to a diagnosis of oppositional defiant disorder. Correlational analyses indicated that child comorbid emotional and behavioral problems may exacerbate parental BRIEF reporting. Accordingly, when assessing executive function among children with neurological and neurodevelopmental disorders, the BRIEF should be complemented with assessments of mental health problems

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Clin Drug Investig. 2018 May;38:449-55.

ANTIPSYCHOTIC PRESCRIBING AND SAFETY MONITORING PRACTICES IN CHILDREN AND YOUTH: A POPULATION-BASED STUDY IN ALBERTA, CANADA.

Chen W, Cepoiu-Martin M, Stang A, et al.

BACKGROUND AND OBJECTIVE: Antipsychotic medication use has steadily increased in Canada, with an expansion in the profile of users and the diagnoses for which they are used. The use of antipsychotics is associated with a number of adverse effects for which routine monitoring is recommended. The objectives of this study were to determine the most common diagnoses associated with antipsychotic use in children in Alberta, Canada and the proportion who receive recommended laboratory tests for adverse effects.

METHODS: Data on dispensed antipsychotics, diagnoses, prescribers, and laboratory testing were obtained from provincial data sources. To assess the frequency of metabolic and hormonal laboratory baseline and/or follow-up testing, the sample was divided into an antipsychotic-naive cohort and an antipsychotic non-naive cohort.

RESULTS: In 2014, 6916 children were dispensed at least one second- or third-generation antipsychotic. The most frequently dispensed antipsychotics were risperidone (3908 children), quetiapine (2140 children), and aripiprazole (1302 children). The majority of children prescribed risperidone were diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) or conduct disorder. Quetiapine was mainly prescribed for neurotic disorder or depression, while aripiprazole was prescribed most frequently for conduct disorder or neurotic disorders. Among antipsychotic-naive patients, 17% had at least one laboratory test done at baseline, and 35% had at least one laboratory test done at follow-up. In the non-naive patients, 42% had at least one follow-up laboratory test. Lipid and glucose testing were done in less than 5% of the naive cohort at baseline, and in less than 15% at follow-up. In the non-naive cohort, less than 22% received lipid or glucose testing during the year 2014.

CONCLUSIONS: The majority of antipsychotic use in children in Alberta is off-label and associated with disruptive behavior disorders, depression, and anxiety disorders. The vast majority of children prescribed antipsychotic medications do not undergo recommended laboratory tests

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Clin Pharmacol Ther. 2018.

THE JURY IS STILL OUT ON THE BENEFITS AND HARMS OF METHYLPHENIDATE FOR CHILDREN AND ADOLESCENTS With Attention-Deficit/Hyperactivity Disorder.

Storeb OJ, Faltinsen E, Zwi M, et al.

Much remains unclear about the benefits and harms of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Between 2012 and 2018, we conducted two Cochrane systematic reviews on methylphenidate for ADHD. This article explores the main findings in relation to evidence-based practice and our current understanding of ADHD

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Dev Med Child Neurol. 2018;60:933-41.

INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH CORE SETS FOR CEREBRAL PALSY, AUTISM SPECTRUM DISORDER, AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Schiariti V, Mahdi S, B+Âlte S.

Aim: Capturing functional information is crucial in childhood disability. The International Classification of Functioning, Disability and Health (ICF) Core Sets promote assessments of functional abilities and disabilities in clinical practice regarding circumscribed diagnoses. However, the specificity of ICF Core Sets for childhood-onset disabilities has been doubted. This study aimed to identify content commonalities and differences among the ICF Core Sets for cerebral palsy (CP), and the newly developed Core Sets for autism spectrum disorder (ASD) and attention-deficit-hyperactivity disorder (ADHD).

Method: The categories within each Core Set were aggregated at the ICF component and chapter levels. Content comparison was conducted using descriptive analyses.

Results: The activities and participation component of the ICF was the most covered across all Core Sets. Main differences included representation of ICF components and coverage of ICF chapters within each component. CP included all ICF components, while ADHD and ASD predominantly focused on activities and participation. Environmental factors were highly represented in the ADHD Core Sets (40.5%) compared to the ASD (28%) and CP (27%) Core Sets.

Interpretation: International Classification of Functioning, Disability and Health Core Sets for CP, ASD, and ADHD capture both common but also unique functional information, showing the importance of creating condition-specific, ICF-based tools to build functional profiles of individuals with childhood-onset disabilities. What this paper adds: The International Classification of Functioning, Disability and Health (ICF) Core Sets for cerebral palsy (CP), autism spectrum disorder (ASD), and attention-deficit-hyperactivity disorder (ADHD) include unique functional information. The ICF-based tools for CP, ASD, and ADHD differ in terms of representation and coverage of ICF components and ICF chapters. Representation of environmental factors uniquely influences functioning and disability across ICF Core Sets for CP, ASD and ADHD

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Dev Neurosci. 2018;1-12.

DIFFERENT DEVELOPMENTAL PATTERN OF BRAIN ACTIVITIES IN ADHD: A STUDY OF RESTING-STATE FMRI.

Tang C, Wei Y, Zhao J, et al.

There are distinct symptoms for attention deficit hyperactivity disorder (ADHD) at different ages. To explore the developmental mechanism of ADHD from childhood to adolescence, patients from different age groups with ADHD drawn from a large dataset should be investigated. In this study, we hypothesized that there are significant differences in the developmental patterns of local and global brain activities between ADHD and typically developing (TD) individuals. Three voxel-based measurements and the functional connectivity (FC) of the brain networks were extracted from resting-state functional magnetic resonance imaging (fMRI) of both ADHD and TD participants 7ΓÇô16 years of age. The topological properties of brain networks in both groups were also analyzed, including hubs, hemispheric symmetry, together with local and global efficiency. The results showed, from the local perspective, that the ADHD group had abnormal amplitude of low-frequency fluctuation, fractional amplitude of low-frequency fluctuation, and regional homogeneity in the medial orbital frontal cortex, anterior cingulate cortex, postcentral gyrus, thalamus, precuneus, and cerebellum compared with the TD group. From the global perspective, the aberrant FC between multiple networks, such as the default mode network (DMN), the attention network, and the executive control network, might directly contribute to symptom differences in childhood and adolescence in ADHD patients. Finally, from the developmental perspective, there was delayed maturation of brain networks in the ADHD group, especially in the DMN. Overall, we presented the differences in brain networks between the ADHD and TD group from multiple perspectives and demonstrated the developmental abnormality of brain networks in ADHD patients, contributing to the study of the etiology of ADHD

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Drugs and Therapy Perspectives. 2018;34:411-19.

AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (ADZENYS ER) AND ORALLY DISINTEGRATING TABLETS (ADZENYS XR-ODT) IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A PROFILE OF THEIR USE.

Lyseng-Williamson KA .

Amphetamine extended-release oral suspension (Adzenys ERΓäó) and extended-release orally disintegrating tablets (Adzenys XR-ODT-«) are easy-to-administer, long-acting, and convenient CNS stimulant options for treating attention-deficit hyperactivity disorder (ADHD) in children aged 6-years, adolescents, and adults. The bioavailability of d- and l-amphetamine with Adzenys ER suspension and XR-ODT-« is equivalent to that of a corresponding dose of the reference product [i.e. mixed amphetamine salt extended-release capsules (MAS ER)], which has well-established efficacy, tolerability, and safety profiles. As Adzenys ER suspension/XR-ODT contain both immediate- and extended-release amphetamine particles, plasma concentrations of d- and l-amphetamine increase rapidly, remain relatively stable for several hours, then slowly decline, allowing for once-daily administration. The use of Adzenys ER suspension/XR-ODT may be of particular benefit in individuals who require a rapid onset and prolonged reduction in ADHD symptoms, as well as those who have difficulty swallowing tablets or capsules whole (neither formulation requires swallowing whole tablets/capsules, and both may be taken without regard to food)

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Dusunen Adam. 2018;31:222-24.

EMERGENCE OF STUTTERING IN AN ATTENTION DEFICIT HYPERACTIVITY DISORDER PATIENT TREATED WITH METHYLPHENIDATE.

Copur M, Copur S.

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Early Hum Dev. 2018;124:11-16.

INFANT REGULATORY PROBLEMS, PARENTING QUALITY AND CHILDHOOD ATTENTION PROBLEMS.

Breeman LD, Jaekel J, Baumann N, et al.

Background and aims: To determine the combined impact of infant multiple/persistent regulatory problems (RPs), parenting quality and maternal mental health on childhood attention problems.

Study design: A prospective, population-based cohort study including 16 paediatric hospitals in Southern Bavaria (Germany).

Subjects: 1459 infants were followed from birth to 8 years of age.

Outcome measures: RPs were assessed at 5 and 20 months using interviews by trained paediatricians; parenting quality was assessed between birth and 5 months using parent interviews and nurses observations; maternal mental health was assessed at birth and 5 months using standardized parents interviews; childhood data on attention problems were collected at 8 years, using parent reports and expert behaviour observation ratings.

Results: After correction for gestational age, sex, and socioeconomic status, early RPs (= 0.079) and low parenting quality (= 0.175) predicted later attention problems (R2 = 0.272). Their impact was additive, such that infants with both multiple/persistent RPs and poor parenting quality showed the highest attention problems 8 years later. However, the impact of RPs on attention was strongest for preterm children. Maternal mental health was a significant moderator of the relationship between parenting quality and attention problems. With adequate maternal mental health, good parenting quality was related to lower attention problems, yet with mental health problems present, the effect of good parenting on attention problems diminished.

Conclusions: Guidance and support for parents of infants with multiple/persistent crying, sleeping or feeding problems may be essential to prevent the development of childhood attention problems, especially when maternal mental health problems are present

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Eating Weight Disord. 2018;23:507-12.

TESTING THE DUAL PATHWAY MODEL OF ADHD IN OBESITY: A PILOT STUDY.

Van der Oord S, Braet C, Cortese S, et al.

Introduction: There may be shared neuropsychological dysfunctions in ADHD and obesity. This study tested a neuropsychological model of ADHD (reward/executive dysfunctioning) in individuals with obesity. Furthermore, the association between co-morbid binge eating and reward/executive dysfunction was explored.

Methods: Reward/executive dysfunctioning was assessed using both neuropsychological measures and questionnaires in individuals (aged 17-68) with obesity (N = 39; mean BMI = 39.70) and normal weight (N = 25; mean BMI = 22.94).

Results: No significant differences emerged between individuals with and without obesity on the outcome measures. However, individuals with obesity and binge eating showed significantly more self-reported delay discounting and inattention than those individuals with obesity but without binge eating. When controlling for inattention, this difference in delay discounting was no longer significant.

Discussion: Not obesity alone but obesity with binge eating was specifically associated with a mechanism often reported in ADHD, namely delay discounting. However, this effect may be more driven by inattention

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Eating Weight Disord. 2018;23:513-19.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND PSYCHOLOGICAL COMORBIDITY IN EATING DISORDER PATIENTS.

Sala L, Martinotti G, Carenti ML, et al.

PURPOSE: There is some evidence that eating disorders (ED) and Attention-deficit/hyperactivity disorder (ADHD) share common clinical features and that ADHD might contribute to the severity of eating disorders. A greater understanding of how the presence of comorbid ADHD may affect the psychopathological framework of eating disorder seems of primary importance. The aim of our study was to evaluate rates of ADHD in three ED subgroups of inpatients: anorexia nervosa restricting type (AN-R), anorexia nervosa binge-eating/purging type (AN-BP) and bulimia nervosa (BN). The secondary aim was the evaluation of the associated psychological characteristics.

METHOD: The sample consisted of 73 females inpatients (mean age 28.07 ± 7.30), all with longstanding histories of eating disorder (ED). The presence of a diagnosis of ADHD was evaluated in a clinical interview based on DSM-IV-TR criteria. The following psychometric instruments were used: the eating attitude test (EAT-40), the Bulimic Investigatory Test, Edinburgh (BITE), the Eating Disorder Inventory (EDI-2), the Wender Utah Rating Scale (WURS), the Brown Attention Deficit Disorder Scale (BADDS), the Hamilton scales for Anxiety (HAM-A) and Depression (HAM-D), and the Barrat Impulsivity Scale (BIS-10).

RESULTS: Among the three ED subgroups, 13 patients reported comorbidity with ADHD; three in the AN-R subtype, nine in the AN-BP and one in the BN. The remaining 60 patients (n = 34 AN-R; n = 19 AN-BP; n = 7 BN) presented only a diagnosis of ED. The EAT (p = 0.04) and HAM-A (p = 0.02) mean scores were significantly higher in patients with comorbid ADHD.

CONCLUSIONS: In our study the comorbidity between ADHD and ED appeared to be frequent, particularly among patients with AN-BP. ED inpatients with higher level of anxiety and more abnormal eating attitudes and bulimic symptoms should be assessed for potentially associated ADHD

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Epilepsy and Behavior Case Reports. 2018;10:82-85.

LONG-TERM USE OF METHYLPHENIDATE IN A BOY WITH HYPOTHALAMIC TUMOR, DRUG-RESISTANT EPILEPSY AND ADHD.

Socanski D, Jovic N, Beneventi H, et al.

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Eur J Paediatr Neurol. 2018 May;22:488-97.

BRAIN-RELATED COMORBIDITIES IN BOYS AND MEN WITH DUCHENNE MUSCULAR DYSTROPHY: A DESCRIPTIVE STUDY.

Hendriksen RGF, Vles JSH, Aalbers MW, et al.

AIM: Duchenne Muscular Dystrophy (DMD) is more than a muscle disease since there is a higher prevalence of neuropsychological comorbidities. Similarly, the prevalence of epilepsy is increased. Given the nowadays-increasing interest in brain-related comorbidities in DMD, this study aimed to evaluate the relationship between DMD, epilepsy, and associated neurodevelopmental disorders in an international sample of DMD patients.

METHOD: Using a questionnaire-based study we investigated the occurrence of self/by-proxy reported brain-related comorbidities in a group of 228 DMD patients. We evaluated the presence of epilepsy and other brain-related comorbidities, but also the specific mutation in the dystrophin gene. With respect to epilepsy, all individually reported epilepsy cases as based on the questionnaire results including information provided on epilepsy treatment, EEG abnormalities, and a description of how a typical seizure would look like, were independently and blindly re-assessed by two external paediatric neurologists (Cohen's kappa of 0.85).

RESULTS: Based on the latter, 18 (7.9%) DMD patients were considered to have epilepsy. In patients with both DMD and epilepsy, certain other brain-related comorbidities (i.e. attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety disorders and sleep disorders) were significantly more prevalent.

CONCLUSION: This study is supportive of a high occurrence of epilepsy and other brain-related comorbidities in DMD. Furthermore this study shows for the first time that the frequency of some of these disorders appear to be further increased when epilepsy is present next to DMD. As this study is limited by the self/by proxy setup and the lack of response rates, future studies should elucidate the true incidence of the (triangular) cooccurrence between epilepsy, neurodevelopmental deficits, and DMD

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Eur Child Adolesc Psychiatry. 2018.

SEX DIFFERENCES IN PREDICTING ADHD CLINICAL DIAGNOSIS AND PHARMACOLOGICAL TREATMENT.

Mowlem FD, Rosenqvist MA, Martin J, et al.

In youth, ADHD is more commonly diagnosed in males than females, but higher male-to-female ratios are found in clinical versus population-based samples, suggesting a sex bias in the process of receiving a clinical diagnosis of ADHD. This study investigated sex differences in the severity and presentation of ADHD symptoms, conduct problems, and learning problems in males and females with and without clinically diagnosed ADHD. We then investigated whether the predictive associations of these symptom domains on being diagnosed and treated for ADHD differed in males and females. Parents of 19,804 twins (50.64% male) from the Swedish population completed dimensional assessments of ADHD symptoms and co-occurring traits (conduct and learning problems) when children were aged 9-years. Children from this population sample were linked to Patient Register data on clinical ADHD diagnosis and medication prescriptions. At the population level, males had higher scores for all symptom domains (inattention, hyperactivity/impulsivity, conduct, and learning problems) compared to females, but similar severity was seen in clinically diagnosed males and females. Symptom severity for all domains increased the likelihood of receiving an ADHD diagnosis in both males and females. Prediction analyses revealed significant sex-by-symptom interactions on diagnostic and treatment status for hyperactivity/impulsivity and conduct problems. In females, these behaviours were stronger predictors of clinical diagnosis (hyperactivity/impulsivity: OR 1.08, 95% CI 1.01, 1.15; conduct: OR 1.43, 95% CI 1.09, 1.87), and prescription of pharmacological treatment (hyperactivity/impulsivity: OR 1.24, 95% CI 1.02, 1.50; conduct: OR 2.20, 95% CI 1.05, 4.63). Females with ADHD may be more easily missed in the ADHD diagnostic process and less likely to be prescribed medication unless they have prominent externalising problems

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Eur J Integr Med. 2018;22:62-68.

EFFICACY OF ADDING ACUPUNCTURE TO METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RANDOMIZED CLINICAL TRIAL.

Moharreri F, Khorsand VA, Soltanifar A, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is the most prevalent finding in children with behavioral issues. It has been shown that acupuncture, as a complementary medicine, may have some beneficial effects in ADHD treatment; however, the available evidence of its effectiveness are inadequate. This study aimed to investigate the effectiveness of acupuncture treatment in patients with ADHD.

Methods: This double blind randomized sham controlled trial was conducted on patients with confirmed ADHD referred to Ibn-e-Sina Psychiatric Hospital, Mashhad, Iran between January 2017 and June 2017. Patients were randomly allocated into either an acupuncture (experimental group) or a sham acupuncture (control group). All patients received a standard treatment of 0.3-1 mg/kg of Methylphenidate (Ritalin) in 2 or 3 divided doses. Within 4 weeks the intervention group received acupuncture treatment 3 times a week. Sham acupuncture was used for the control group within the same duration as acupuncture group. The treatment outcomes were measured using home version of ADHD-rating scale (RS) and the Continuous Performance Test after 3 weeks. Independent-samples t-test, Pearson Chi-square test, and Paired-samples t-test were used for data analysis with SPSS version 16.0.

Results: This study was conducted on 59 patients (52 males) with a mean age of 10.64 ± 2.46 years in two groups of experiment (n = 31) and control (n = 28). ADHD-RS total score was significantly more decreased in acupuncture group after 3 weeks (-6.29 ± 7.1 vs. -1.96 ± 6.7; p = 0.007). Also, the hyperactivity and impulsivity was significantly more decreased in the acupuncture group compared to the sham control group (-3.29 ± 3.7 vs. -0.45 ± 4.1; p = 0.005). Furthermore, acupuncture did not considerably change Omission error, Commission error, Reaction Time and Correct hit (p > 0.05).

Conclusion: Our study showed that acupuncture can significantly improve the parent-report ADHD-RS. Nevertheless, it did not improve the attention deficit. We recommend further investigations with larger sample sizes and longer follow-up. The adverse effects of acupuncture on ADHD patients were not assessed in this study, but should be measured in future studies

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Eur Neuropsychopharmacol. 2018.

DISTINGUISHING THE EFFICACY AND SEDATIVE EFFECTS OF GUANFACINE EXTENDED RELEASE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Huss M, McBurnett K, Cutler AJ, et al.

The present study investigated whether symptom reduction in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) treated with guanfacine extended release (GXR) can be explained by sedative effects of the medication. Data from four double-blind, randomized, placebo-controlled, phase 3 trials of GXR monotherapy (1-7 mg/day; morning administration) in children (aged 6-12 years) and adolescents (aged 13-17 years) with ADHD were analyzed post hoc. Two studies used forced-dose titration and two used flexible-dose titration. Efficacy was determined using ADHD Rating Scale IV (ADHD-RS-IV) scores. Sedative treatment-emergent adverse events (TEAEs) included somnolence, sedation and hypersomnia. The proportion of responders (30% reduction in ADHD-RS-IV total score) increased from weeks 1 to 4 and remained stable to study endpoint. Sedative TEAEs generally peaked at the first week in which the target dose was achieved and then declined. In subgroup analyses, significant placebo-adjusted improvements in ADHD-RS-IV total scores were observed in participants without any sedative TEAEs in the forced-dose and flexible-dose studies (nominal p < 0.001). In addition, GXR was associated with significant improvements in both inattentive and hyperactive-impulsive symptoms, as assessed by the ADHD-RS-IV subscale scores (nominal p < 0.001) and by the ADHD-RS-IV total score in participants with different ADHD subtypes (nominal p < 0.05). Thus, the efficacy of GXR in children and adolescents with ADHD is not primarily due to sedation, although some contribution to symptom reduction cannot be excluded, especially early in treatment when rates of sedative TEAEs are at their highest

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Exp Dermatol. 2018.

X-LINKED ICHTHYOSIS: CLINICAL AND MOLECULAR FINDINGS IN 35 ITALIAN PATIENTS.

Diociaiuti A, Angioni A, Pisaneschi E, et al.

Recessive X-linked ichthyosis (XLI), the second most common ichthyosis, is caused by mutations in the STS gene encoding the steroid sulfatase enzyme. A complete deletion of the STS gene is found in 85%-90% of cases. Rarely, larger deletions involving contiguous genes are detected in syndromic patients. We report the clinical and molecular genetic findings in a series of 35 consecutive Italian male patients. All patients underwent molecular testing by MLPA or aCGH, followed, in case of negative results, by next-generation sequencing analysis. Neuropsychiatric, ophthalmological and paediatric evaluations were also performed. Our survey showed a frequent presence of disease manifestations at birth (42.8%). Fold and palmoplantar surfaces were involved in 18 (51%) and 7 (20%) patients, respectively. Fourteen patients (42%) presented neuropsychiatric symptoms, including attention-deficit hyperactivity disorder and motor disabilities. In addition, two patients with mental retardation were shown to be affected by a contiguous gene syndrome. Twenty-seven patients had a complete STS deletion, one a partial deletion and 7 carried missense mutations, two of which previously unreported. In addition, a de novo STS deletion was identified in a sporadic case. The frequent presence of palmoplantar and fold involvement in XLI should be taken into account when considering the differential diagnosis with ichthyosis vulgaris. Our findings also underline the relevance of involving the neuropsychiatrist in the multidisciplinary management of XLI. Finally, we report for the first time a de novo mutation which shows that STS deletion can also occur in oogenesis

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Front Human Neurosci. 2018 Jul;12.

EFFECTS OF THE 2-REPEAT ALLELE OF THE DRD4 GENE ON NEURAL NETWORKS ASSOCIATED WITH THE PREFRONTAL CORTEX IN CHILDREN WITH ADHD.

Qian A, Tao J, Wang X, et al.

Objective: Genetic variation, especially polymorphism of the dopamine D4 receptor gene (DRD4), has been linked to deficits in self-regulation and executive functions and to attention deficit hyperactivity disorder (ADHD), and is related to the structural and functional integrity of the default mode network (DMN), the executive control network (ECN) and the sensorimotor network (SMN). The aim of this study was to explore the effects of the 2-repeat allele of the DRD4 gene on brain network connectivity and behaviors in children with ADHD.

Methods: Using independent component analysis (ICA) and dimension analyses, we examined resting-state functional magnetic resonance imaging (fMRI) data obtained from 52 Asian medicine-naive children with ADHD (33 2-repeat absent and 19 2-repeat present).

Results: We found that individuals with 2-repeat absent demonstrated increased within-network connectivity in the right precuneus of the DMN, the right middle frontal gyrus (MFG) of the SMN compared with individuals with 2-repeat present. Within the ECN, 2-repeat absent showed decreased within-network connectivity in the left inferior frontal gyrus (IFG) and the left anterior cingulate cortex. A deeper study found that connectivity strength of the left IFG was directly proportional to the Stroop reaction time in 2-repeat absent group, and as well as the right MFG in 2-repeat present group.

Conclusion: Polymorphisms of the DRD4 gene, specifically 2-repeat allele, had effects on the ECN, the SMN and the DMN, especially in the prefrontal cortex (PFC) circles. ADHD children with DRD4 2-repeat allele have aberrant resting-state within-network connectivity patterns in the left IFG and the right MFG related to dysfunction in inattention symptom. This study provided novel insights into the neural mechanisms underlying the effects of DRD4 2-repeat allele on ADHD

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Gait Posture. 2018.

P 070 INVESTIGATION OF BILATERAL COORDINATION IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Demircioglu A, Balci G, Ipek F, et al.

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Genes and Genomics. 2018.

GENETIC ASSOCIATIONS BETWEEN ADHD AND DOPAMINERGIC GENES (DAT1 AND DRD4) VNTRS IN KOREAN CHILDREN.

Hong JH, Hwang IW, Lim MH, et al.

It is well known that dopaminergic genes affect the development of attention deficit hyperactivity disorder (ADHD) in various populations. Many studies have shown that variable number tandem repeats (VNTRs) located within the 3ΓÇ¦-untranslated region of DAT1 and in exon 3 of DRD4 are associated with ADHD development; however, these results were inconsistent. Therefore, we investigated the genetic association between two VNTRs and ADHD in Korean children. We determined the VNTRs using PCR. We examined genotype and allele frequency differences between the experimental and control groups, along with the odds ratios, using Chi square and exact tests. We observed a significant association between the children with ADHD and the control group in the 10R/10R genotype of DAT1 VNTRs ($p = 0.025$). In addition, the 11R allele of DAT1 VNTRs showed a higher frequency in the control group than in the ADHD group ($p = 0.023$). Also, the short repeat (without 11R) and long repeat alleles (including 11R) were associated with ADHD ($p < 0.05$). The analysis of DRD4 VNTRs revealed that the 2R allele is associated with ADHD ($p = 0.025$). A significant result was also observed in long and short repeats ($p < 0.05$). Additionally, ADHD subtypes showed that the DRD4 VNTRs are associated with combined and hyperactive-impulsive subtype groups ($p < 0.05$). Therefore, our results suggest that DAT1 VNTRs and DRD4 VNTRs play a role in the genetic etiology of ADHD in Korean children

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Harefuah. 2018 Apr;157:219-24.

CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): ACCESSIBILITY AND AVAILABILITY OF SERVICES IN ISRAEL.

Ornoy A, Rivkin D, Barlev L.

INTRODUCTION: The prevalence of Attention Deficit Hyperactivity Disorder (ADHD) among children ranges from 8% -12% and is more common in males. Most ADHD children suffer from related disorders such as learning disabilities and behavioral problems. Treatment with stimulants improves the learning and social abilities of most children and the addition of non-pharmaceutical treatments induces further improvement.

OBJECTIVES: Our previous study, four years ago, screened 1,129 1st and 2nd grade children in Jerusalem and identified 105 with high risk for ADHD. Currently we evaluated the contribution of the screening and the availability and utilization of services for these children.

METHODS: Interviews were conducted with 85 parents of identified children, now in 5th and 6th grades (response rate 81%) and 12 education and health professionals. Research tools consisted of a structured questionnaire for parents completed by phone and semi-structured interviews with professionals.

RESULTS: A total of 87% of parents reported that they were aware of the child's attention difficulties before the screening; 68% reported that the screening had encouraged them to pursue diagnosis. Only 49% of the children were diagnosed by the HMO's and 51% privately. Waiting time at HMO's was 3 times that of private services. Only 52% of the ADHD children received pharmacological treatment, most of them also received "supportive treatment".

CONCLUSIONS: HMO's do not provide sufficient services to ADHD children and parents have to seek help privately. HMO's should find the way to make better use of the services of psychiatrists and pediatricians permitted to diagnose and treat such children and furthermore, they must improve services and public awareness of ADHD

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Harefuah. 2018 Apr;157:225-27.

CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): CLINICAL ACTIVITY IN ISRAEL.

Bloch Y.

INTRODUCTION: This editorial relates to the study published in the current issue on how our current knowledge is practiced in screening, diagnosing and treating children suffering from ADHD in Israel. It seems that there is an awareness of the disorder by parents and teachers, thus there is no need for community screening. The roles of the different medical professions: pediatricians (after receiving training on ADHD), child neurologists and child psychiatrists are not clear enough and thus services are not utilized properly. The diagnosis demands a physical, developmental, psychosocial and mental evaluation, including information from multiple settings (home and school) and the use of validated questionnaires. The extremely common psychiatric differential diagnosis and comorbidities point to the importance of psychiatric consultation, just as neurological comorbidities demand a neurological evaluation in complex cases. The recommended treatment plan combines psychoeducation and a collaborative and flexible decision about the combination of pharmacological (most commonly stimulants) and evidence-based non-pharmacological treatments (mainly parent training and cognitive behavioral therapies). Since ADHD is a chronic and complex neurodevelopmental disorder, continuous and long term medical follow-up relating to both treatment targets and side effects are crucial, and are not adequately stressed in clinical practice

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Italian Journal of Pediatrics 2018;44:108

ADHD PREVALENCE ESTIMATES IN ITALIAN CHILDREN AND ADOLESCENTS: A METHODOLOGICAL ISSUE

Reale L, Bonati M.

Background Attention deficit hyperactivity disorder (ADHD) is recognized as the most common, and most studied, developmental age disorder. Basic information, such as the most appropriate case definition and the best way to evaluate the disorder's prevalence rate, however, remains an open issue.

Methods A comprehensive meta-analysis on the epidemiology of ADHD in Italy, which was lacking from the literature, was therefore performed to attempt to estimate the actual prevalence rate of ADHD, highlighting conceptual and quantitative differences between clinical-diagnosis and survey-based symptoms studies. The Medline, Embase, and PsycINFO databases, and the grey literature, were searched up to January 2018. The review was laid out in three main sections: an overall prevalence estimate, an epidemiological profile of ADHD symptoms, and an attempt to define the actual rate of ADHD diagnosis, as emerged from Italian studies.

Results A total of 15 unique studies were included. These contributed to estimating the prevalence of ADHD in 67,838 subjects aged 5–17, representing 9 of the 20 regions (45%) of Italy. Overall, the pooled prevalence of ADHD was 2.9% (range: 1.1–16.7%). When distinguishing studies based on case definition, however, we found an average prevalence estimate, based on symptoms criteria, of 5.9% (range: 1.4 to 16.7%) and a best-estimate prevalence rate of 1.4% (range: 1.1 to 3.1%).

Conclusions Following the case definition for epidemiological studies of ADHD, counting only subjects with an ADHD diagnosis performed and confirmed by clinical assessment would reduce the wide variability in prevalence estimates, and, above all, would both describe the real rate of subjects suffering from ADHD disorder and avoid misdiagnosis.

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J Affect Disord. 2018 May;232:41-47.

EMOTIONAL DYSREGULATION IS A PRIMARY SYMPTOM IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Hirsch O, Chavanon M, Riechmann E, et al.

BACKGROUND: Clinical observations suggest that adults have more diverse deficits than children with Attention Deficit/Hyperactivity Disorder (ADHD). These seem to entail difficulties with emotionality, self-concept and emotion regulation in particular, along with the cardinal symptoms of inattention, impulsivity, and hyperactivity for adult patients. Here, we probed a model that explicitly distinguished positive and negative

affect, problems with self-concept and emotion regulation skills as distinct but correlating factors with the symptom domains of inattention, hyperactivity, and impulsivity.
METHODS: Participants were 213 newly diagnosed adults with ADHD (62.9% male, mean age 33.5 years). Symptoms were assessed via self-report on the Conners' Adult ADHD Rating Scales, a modified version of the Positive and Negative Affect Scale and the Emotion Regulation Skill Questionnaire. A confirmatory factor analysis with the R package lavaan, using a robust Maximum Likelihood estimator (MLR) for non-normal data, was conducted to test our new non-hierarchical 7-factor model.
RESULTS: All calculated model-fit statistics revealed good model-fit (chi(2)/df ratio=2.03, robust RMSEA=.07). The SRMR in our model reached .089, indicating an acceptable model fit. Factor loadings on the postulated factors had salient loadings >/=.31 except for one item on the hyperactivity factor. Latent factor associations were especially salient between emotional dysregulation and problems with self-concept, and also partially with impulsivity/emotional lability.
LIMITATIONS: The three models of ADHD and emotion regulation as suggested by Shaw et al. (2014) could not be disentangled in this study, though the overall results support the model with shared neurocognitive deficits. Further, we did not separately analyze ADHD with or without comorbid disorders. As our sample of clinical cases with ADHD is highly comorbid (47.9%), other disorders than ADHD might account for the emotion regulation deficits, though a sensitivity analysis revealed no such differences.
CONCLUSIONS: Our model adequately characterizes the relations between and among clinically and therapeutically relevant symptoms in adult ADHD, thus potentially informing future therapeutic interventions by targeting the successful and flexible use of adaptive emotion regulation skills

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J Clin Pediatr Dent. 2018;42:208-11.
DENTAL AGE DIFFERENCE IN CHILDREN WITH ADHD.
Wadhwa P, Yu Q, Zhu H, et al.
OBJECTIVE: The purpose of this study was to determine if changes in dental development are associated with Attention Deficit Hyperactivity Disorder (ADHD) or ADHD medications.
STUDY DESIGN: This retrospective chart review evaluated the dental age of 128 patients between 6 and 16 years of age using the Demirjian method from the following two groups a) children with ADHD b) unaffected children. The ADHD group was further stratified into four groups according to the medication type. The impact of ADHD on dental age difference (the difference between dental age and chronologic age) was analyzed using T-test and the association between medication type and dental age difference was analyzed through one way ANOVA.
RESULTS: The mean difference between estimated dental age and chronologic age (dental age difference) for all subjects was 0.80 years. There was no significant dental age difference in subjects with ADHD and the control group (0.78+/-1.28vs. 0.84 +/-1.09 years respectively; P=0.75) and there was no significant difference in dental age difference and type of medication (P=0.84).
CONCLUSION: No significant difference was found between children with ADHD and unaffected children with respect to dental age difference. No significant differences were found in dental age difference in the four medication groups

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J Clin Pediatr Dent. 2018;42:212-16.
THE PREVALENCE OF ADHD PATIENTS AMONG PEDIATRIC DENTISTS IN ISRAEL AND KNOWLEDGE OF DENTAL AND BEHAVIORAL ASPECTS OF TREATING THEM.
Blumer S, Khoury RS, Peretz B.
OBJECTIVE: There are no clear guidelines for managing the dental treatment of children with attention deficit hyperactivity disorder (ADHD). The use of sedation in combination with chronic ADHD medication use is also not well defined. This study surveyed the prevalence of ADHD children, management techniques and knowledge of pharmacologic therapies of these children among Israeli dentists.

STUDY DESIGN: A specially designed questionnaire was distributed to all Israeli dentists attending a national conference in 2016.
RESULTS: Of the 160 dentists who attended the conference, 96 completed the survey (60% response rate), and they included 46 (51%) pediatric dental specialists and 50 (49%) general dental practitioners. The medications Ritalin and Concerta were most familiar to the respondents (98.9%). Eighty-seven (91.1%) of the practitioners responded that their ADHD patients take their usual doses of any drug for treating ADHD symptoms, regardless of whether or not the dentists intended to use sedatives. The practitioners invented their own behavior management techniques with varying degrees of success.
CONCLUSIONS: There are no specific guidelines for the most effective pharmacologic protocol (co-administration of ADHD drugs and dental sedatives) or behavior management techniques for the provision of optimal dental care to children with ADHD

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J Am Med Assoc. 2018;320:255-63.

ASSOCIATION OF DIGITAL MEDIA USE WITH SUBSEQUENT SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG ADOLESCENTS.

Ra CK, Cho J, Stone MD, et al.

IMPORTANCE Modern digital platforms are easily accessible and intensely stimulating; it is unknown whether frequent use of digital media may be associated with symptoms of attention-deficit/hyperactivity disorder (ADHD).
OBJECTIVE To determine whether the frequency of using digital media among 15- and 16-year-olds without significant ADHD symptoms is associated with subsequent occurrence of ADHD symptoms during a 24-month follow-up.
DESIGN, SETTING, AND PARTICIPANTS Longitudinal cohort of students in 10 Los Angeles County, California, high schools recruited through convenience sampling. Baseline and 6-, 12-, 18-, and 24-month follow-up surveys were administered from September 2014 (10th grade) to December 2016 (12th grade). Of 4100 eligible students, 3051 10th-graders (74%) were surveyed at the baseline assessment.
EXPOSURES Self-reported use of 14 different modern digital media activities at a high-frequency rate over the preceding week was defined as many times a day (yes/no) and was summed in a cumulative index (range, 0-14).
MAIN OUTCOMES AND MEASURES Self-rated frequency of 18 ADHD symptoms (never/rare, sometimes, often, very often) in the 6 months preceding the survey. The total numbers of 9 inattentive symptoms (range, 0-9) and 9 hyperactive-impulsive symptoms (range, 0-9) that students rated as experiencing often or very often were calculated. Students who had reported experiencing often or very often 6 or more symptoms in either category were classified as being ADHD symptom-positive.
RESULTS Among the 2587 adolescents (63%eligible students; 54.4%girls; mean [SD] age 15.5 years [0.5 years]) who did not have significant symptoms of ADHD at baseline, the median follow-up was 22.6 months (interquartile range [IQR], 21.8-23.0, months). The mean (SD) number of baseline digital media activities used at a high-frequency rate was 3.62 (3.30); 1398 students (54.1%) indicated high frequency of checking social media (95%CI, 52.1%-56.0%), which was the most common media activity. High-frequency engagement in each additional digital media activity at baseline was associated with a significantly higher odds of having symptoms of ADHD across follow-ups (OR, 1.11; 95%CI, 1.06-1.16). This association persisted after covariate adjustment (OR, 1.10; 95%CI, 1.05-1.15). The 495 students who reported no high-frequency media use at baseline had a 4.6%mean rate of having ADHD symptoms across follow-ups vs 9.5%among the 114 who reported 7 high-frequency activities (difference; 4.9%; 95%CI, 2.5%-7.3%) and vs 10.5%among the 51 students who reported 14 high-frequency activities (difference, 5.9%; 95%CI, 2.6%-9.2%).
CONCLUSIONS AND RELEVANCE Among adolescents followed up over 2 years, there was a statistically significant but modest association between higher frequency of digital media use and subsequent symptoms of ADHD. Further research is needed to determine whether this association is causal

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J Am Med Assoc. 2018;320:237-39.
DIGITALMEDIA AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADOLESCENTS.
Radesky J.

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JAMA. 2018 Jul;320:16-18.
ADAM GAZZALEY, MD, PHD: DEVELOPING PRESCRIBABLE VIDEO GAMES.
Abbasi J.

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JAMA. 2018 Jul;320:255-63.
ASSOCIATION OF DIGITAL MEDIA USE WITH SUBSEQUENT SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG ADOLESCENTS.
Ra CK, Cho J, Stone MD, et al.
Importance: Modern digital platforms are easily accessible and intensely stimulating; it is unknown whether frequent use of digital media may be associated with symptoms of attention-deficit/hyperactivity disorder (ADHD).
Objective: To determine whether the frequency of using digital media among 15- and 16-year-olds without significant ADHD symptoms is associated with subsequent occurrence of ADHD symptoms during a 24-month follow-up.
Design, Setting, and Participants: Longitudinal cohort of students in 10 Los Angeles County, California, high schools recruited through convenience sampling. Baseline and 6-, 12-, 18-, and 24-month follow-up surveys were administered from September 2014 (10th grade) to December 2016 (12th grade). Of 4100 eligible students, 3051 10th-graders (74%) were surveyed at the baseline assessment.
Exposures: Self-reported use of 14 different modern digital media activities at a high-frequency rate over the preceding week was defined as many times a day (yes/no) and was summed in a cumulative index (range, 0-14).
Main Outcomes and Measures: Self-rated frequency of 18 ADHD symptoms (never/rare, sometimes, often, very often) in the 6 months preceding the survey. The total numbers of 9 inattentive symptoms (range, 0-9) and 9 hyperactive-impulsive symptoms (range, 0-9) that students rated as experiencing often or very often were calculated. Students who had reported experiencing often or very often 6 or more symptoms in either category were classified as being ADHD symptom-positive.
Results: Among the 2587 adolescents (63% eligible students; 54.4% girls; mean [SD] age 15.5 years [0.5 years]) who did not have significant symptoms of ADHD at baseline, the median follow-up was 22.6 months (interquartile range [IQR], 21.8-23.0, months). The mean (SD) number of baseline digital media activities used at a high-frequency rate was 3.62 (3.30); 1398 students (54.1%) indicated high frequency of checking social media (95% CI, 52.1%-56.0%), which was the most common media activity. High-frequency engagement in each additional digital media activity at baseline was associated with a significantly higher odds of having symptoms of ADHD across follow-ups (OR, 1.11; 95% CI, 1.06-1.16). This association persisted after covariate adjustment (OR, 1.10; 95% CI, 1.05-1.15). The 495 students who reported no high-frequency media use at baseline had a 4.6% mean rate of having ADHD symptoms across follow-ups vs 9.5% among the 114 who reported 7 high-frequency activities (difference; 4.9%; 95% CI, 2.5%-7.3%) and vs 10.5% among the 51 students who reported 14 high-frequency activities (difference, 5.9%; 95% CI, 2.6%-9.2%).
Conclusions and Relevance: Among adolescents followed up over 2 years, there was a statistically significant but modest association between higher frequency of digital media use and subsequent symptoms of ADHD. Further research is needed to determine whether this association is causal

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JAMA Pediatr. 2018;172:749-56.

ASSOCIATION OF GESTATIONAL AGE AT BIRTH WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Ask H, Gustavson K, Ystrom E, et al.

IMPORTANCE Preterm birth is associated with an increased risk of attention-deficit/ hyperactivity disorder (ADHD); however, it is unclear to what extent this association can be explained by shared genetic and environmental risk factors and whether gestational age at birth is similarly related to inattention and hyperactivity/impulsivity and to the same extent in boys and girls.

OBJECTIVES To investigate the association between gestational age at birth and symptoms of ADHD in preschool and school-age children after adjusting for unmeasured genetic and environmental risk factors.

DESIGN, SETTING, AND PARTICIPANTS In this prospective, population-based cohort study, pregnant women were recruited from across Norway from January 1, 1999, through December 31, 2008. Results of a conventional cohort design were compared with results from a sibling-comparison design (adjusting for genetic and environmental factors shared within families) using data from the Norwegian Mother and Child Cohort Study. Data analysis was performed from October 1, 2017, through March 16, 2018.

EXPOSURES Analyses compared children and siblings discordant for gestational age group: early preterm (delivery at gestational weeks 22-33), late preterm (delivery at gestational weeks 34-36), early term (delivery at gestational weeks 37-38), delivery at gestational week 39, reference group (delivery at gestational week 40), delivery at gestational week 41, and late term (delivery after gestational week 41).

MAIN OUTCOMES AND MEASURES Maternally reported symptoms of ADHD in children at 5 years of age and symptoms of inattention and hyperactivity/impulsivity at 8 years of age. Covariates included child and pregnancy characteristics associated with the week of delivery and the outcomes.

RESULTS A total of 113 227 children (55 187 [48.7%] female; 31 708 [28.0%] born at gestational week 40), including 33 081 siblings (16 014 female [48.4%]; 9705 [29.3%] born at gestational week 40), were included in the study. Children born early preterm were rated with more symptoms of ADHD, inattention, and hyperactivity/impulsivity than term-born children. After adjusting for unmeasured genetic and environmental factors, children born early preterm had a mean score that was 0.24 SD (95% CI, 0.14-0.34) higher on ADHD symptom tests, 0.33 SD (95% CI, 0.24-0.42) higher on inattention tests, and 0.23 SD (95% CI, 0.14-0.32) higher on hyperactivity/impulsivity tests compared with children born at gestational week 40. Sex moderated the association of gestational age with preschool ADHD symptoms, and the association appeared to be strongest among girls. Early preterm girls scored a mean of 0.8 SD (95% CI, 0.12-1.46; P = .02) higher compared with their term-born sisters.

CONCLUSIONS AND RELEVANCE After accounting for unmeasured genetic and environmental factors, early preterm birth was associated with a higher level of ADHD symptoms in preschool children. Early premature birth was associated with inattentive but not hyperactive symptoms in 8-year-old children. This study demonstrates the importance of differentiating between inattention and hyperactivity/impulsivity and stratifying on sex in the study of childhood ADHD

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J Abnorm Child Psychol. 2018 Jul;46:965-77.

SPECIFICITY OF REWARD SENSITIVITY AND PARASYMPATHETIC-BASED REGULATION AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY AND DISRUPTIVE BEHAVIOR DISORDERS.

Tenenbaum RB, Musser ED, Raiker JS, et al.

Attention-deficit/hyperactivity disorder (ADHD) is associated with disruptionsin reward sensitivity and regulatory processes. However, it is unclear whether these disruptions are better explained by comorbid disruptive behavior disorder (DBD)symptomology. This study sought to examine this question using multiple levels of analysis (i.e., behavior, autonomic reactivity). One hundred seventeen children (aged 6 to 12 years; 72.6% male; 69 with ADHD) completed the Balloon-Analogue Risk Task (BART) to assess external reward sensitivity behaviorally. Sympathetic-based internal reward sensitivity and parasympathetic-based regulation were indexed via cardiac pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA), respectively. Children with ADHD exhibited reduced internal reward sensitivity (i.e.,lengthened PEP; $F(1,112) = 4.01$, $p = 0.047$) compared to healthy controls and were characterized by greater parasympathetic-based dysregulation (i.e., reduced RSA augmentation $F(1,112) = 10.12$, $p = 0.002$). However, follow-up analyses

indicated the ADHD effect was better accounted for by comorbid DBD diagnoses; that is, children with ADHD and comorbid ODD were characterized by reduced internal reward sensitivity (i.e., lengthened PEP; t = 2.47, p = 0.046) and by parasympathetic-based dysregulation (i.e., reduced RSA augmentation; t = 3.51, p = 0.002) in response to reward when compared to typically developing youth. Furthermore, children with ADHD and comorbid CD exhibited greater behaviorally-based external reward sensitivity (i.e.,more total pops; F(3,110) = 5.96, p = 0.001) compared to children with ADHD only (t = 3.87, p = 0.001) and children with ADHD and ODD (t = 3.56, p = 0.003). Results suggest that disruptions in sensitivity to reward may be better accounted for, in part, by comorbid DBD

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J Abnorm Child Psychol. 2018 Jul;46:979-92.

EIGHT-YEAR LATENT CLASS TRAJECTORIES OF ACADEMIC AND SOCIAL FUNCTIONING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

DuPaul GJ, Morgan PL, Farkas G, et al.

We examined trajectories of academic and social functioning in children with attention-deficit/hyperactivity disorder (ADHD) to identify those who might be at risk for especially severe levels of academic and social impairment over time. We estimated a series of growth mixture models using data from two subsamples of children participating in the NIMH Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) including those with at least baseline and 96-month data for reading and mathematics achievement (n = 392; 77.3% male; M age = 7.7; SD = 0.8) or social skills ratings from teachers (n = 259; 74.9% male; M age = 7.6; SD = 0.8). We compared latent trajectories for children with ADHD to mean observed trajectories obtained from a local normative (i.e., non-ADHD) comparison group (n = 289; 80.6% male; M age = 9.9; SD = 1.1). Results indicated six latent trajectory classes for reading and mathematics and four classes for teacher social skills ratings. There was not only a relationship between trajectories of inattention symptoms and academic impairment, but also a similarly strong association between trajectory classes of hyperactive-impulsive symptoms and achievement. Trajectory class membership correlated with socio-demographic and diagnostic characteristics, inattention and hyperactive-impulsive symptom trajectories, externalizing behavior in school, and treatment receipt and dosage. Although children with ADHD display substantial heterogeneity in their reading, math, and social skills growth trajectories, those with behavioral and socio-demographic disadvantages are especially likely to display severe levels of academic and social impairment over time. Evidence-based early screening and intervention that directly address academic and social impairments in elementary school-aged children with ADHD are warranted

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J Adolesc Health. 2018.

PARENT PERCEPTIONS OF THEIR COLLEGE STUDENTS SELF-MANAGEMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schaefer MR, Wagoner ST, Young ME, et al.

Purpose: The present study examines parents perspectives of the experiences and challenges surrounding self-management of Attention-Deficit/Hyperactivity Disorder (ADHD) in their college students.

Methods: Participants were parents of emerging young adults with ADHD prescribed daily medication for their condition. Thirteen individual interviews were conducted using a semistructured interview script guided by the Health Belief Model. The qualitative data were analyzed via directed content analysis.

Results: Five themes emerged from the interviews: (1) parents are heavily involved in their child's self-management prior to college, and the abrupt transition of responsibilities is difficult for parents; (2) parents worries about their child's self-management and functioning are exacerbated by privacy laws and poor communication from child and university; (3) volitional nonadherence is high; (4) obtaining academic accommodations is difficult; and (5) parents recommend a gradual transition, desire enhanced communication from the college, and wish for social support resources in the college setting for their children.

Conclusions: Parents of college students with ADHD are distressed and frustrated by the transition to college. They express the desire to remain continually involved in their child's self-management of ADHD,

but several barriers hinder their ability to do so, resulting in fear of the potential consequences on their child's functioning. This collateral information from parents regarding the challenges associated with ADHD self-management experiences in college should result in the development of comprehensive interventions to improve the quality of life in college students with ADHD

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J Autism Dev Disord. 2018.

PARENT AND TEACHER REPORTS OF COMORBID ANXIETY AND ADHD SYMPTOMS IN CHILDREN WITH ASD.

Llanes E, Blacher J, Stavropoulos K, et al.

This study examined the prevalence of ADHD symptoms and anxiety as reported by parents and teachers for 180 preschool children (ages 4ΓÇô5) and school-aged children (ages 6ΓÇô7) with ASD using the Child Behavior ChecklistΓÇöParent and Teacher Report Forms (Achenbach and Rescorla, Manual for ASEBA school-age forms & profiles, Research Center for Children, Youth, and Families, University of Vermont, Burlington, VT, 2001). Parents reported elevated anxiety symptoms in 31% of preschool children and 50% of school-aged children, while teachers reported lower rates of 5 and 30%, respectively. Parents reported elevated ADHD symptoms in 22% of preschool children and 45% of school-aged children, while teachers reported elevations in 20 and 24%, respectively. There was low concordance between parents and teachers, with teachers reporting fewer problems overall. Specific behaviors endorsed by parents and teachers are also discussed

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J Autism Dev Disord. 2018.

PHYSICAL HEALTH IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Alabaf S, Gillberg C, Lundstr+Âm S, et al.

With increasing numbers of children being diagnosed with neurodevelopmental disorders (NDDs) attention has been drawn to these childrenΓÇÖs physical health. We aimed to identify the prevalence of defined physical problems (epilepsy, migraine, asthma, cancer, diabetes, psoriasis, lactose intolerance, celiac disease, diarrhea, constipation, daytime enuresis, encopresis) in a nationwide population of 9- and 12-year-old twins subdivided into those with and without indications of NDDs. Parents of 28,058 twins participated in a well-validated telephone interview regarding their childrenΓÇÖs mental health and answered questions about their physical problems. The results indicate a high rate of physical problems in children with NDDs, particularly in those with indications of the presence of combinations of several NDDs

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J Child Psychol Psychiatry. 2018 Jun;59:692-702.

SUBSTANCE USE THROUGH ADOLESCENCE INTO EARLY ADULTHOOD AFTER CHILDHOOD-DIAGNOSED ADHD: FINDINGS FROM THE MTA LONGITUDINAL STUDY.

Molina BSG, Howard AL, Swanson JM, et al.

Background: Inconsistent findings exist regarding long-term substance use (SU) risk for children diagnosed with attention-deficit/hyperactivity disorder (ADHD). The observational follow-up of the Multimodal Treatment Study of Children with ADHD (MTA) provides an opportunity to assess long-term outcomes in a large, diverse sample.

Methods: Five hundred forty-seven children, mean age 8.5, diagnosed with DSM-IV combined-type ADHD and 258 classmates without ADHD (local normative comparison group; LNCG) completed the Substance Use Questionnaire up to eight times from mean age 10 to mean age 25.

Results: In adulthood, weekly marijuana use (32.8% ADHD vs. 21.3% LNCG) and daily cigarette smoking (35.9% vs. 17.5%) were more prevalent in the ADHD group than the LNCG. The cumulative record also revealed more early substance users in adolescence for ADHD (57.9%) than LNCG (41.9%), including younger first use of alcohol, cigarettes, marijuana, and illicit drugs. Alcohol and nonmarijuana illicit drug use

escalated slightly faster in the ADHD group in early adolescence. Early SU predicted quicker SU escalation and more SU in adulthood for both groups.
Conclusions: Frequent SU for young adults with childhood ADHD is accompanied by greater initial exposure at a young age and slightly faster progression. Early SU prevention and screening is critical before escalation to intractable levels

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J Neural Transm. 2018;125:1395-400.
INVESTIGATION INTO THE PLASMA CONCENTRATION OF ¤Ë3 POLYUNSATURATED FATTY ACIDS IN JAPANESE ATTENTION-DEFICIT HYPERACTIVITY DISORDER PATIENTS.
Yonezawa K, Nonaka S, Iwakura Y, et al.
Several studies report that patients with attention-deficit hyperactivity disorder (ADHD) have a low plasma concentration of polyunsaturated fatty acids (PUFAs). Since fish intake varies among countries and is high in Japan, those results may not apply to Japanese patients with ADHD. However, there is currently not enough evidence to support this. We compared the plasma PUFAs levels of patients with ADHD with the standard reference levels for healthy subjects, and examined the relationship between those PUFAs levels and the subjectΓÇÖs psychological evaluation. The subjects were 24 patients (age < 20-áyears) previously diagnosed with ADHD (according to the DSM-IV-TR criteria) at the psychiatric department of the Nagasaki University Hospital, between November 2010 and November 2015. The plasma concentrations of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) were measured using gas chromatography. Data pertaining to global assessment of functioning (GAF), clinical global impressions, ADHD Rating Scale-IV, and the drug used for treatment (atomoxetine or methylphenidate) were obtained from the medical records. The plasma concentrations of DHA, EPA, and EPA/AA were significantly lower than the normal reference range, indicating that ADHD patients present an imbalance in PUFAs levels. This trend is similar to ADHD patients in other countries and replacement therapy in Japanese ADHD patients may be useful

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J Neurosci. 2018;38:6779-86.
ORBITOFRONTAL SIGNALING OF FUTURE REWARD IS ASSOCIATED WITH HYPERACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Tegelbeckers J, Kanowski M, Krauel K, et al.
Alterations in motivated behavior are a hallmark of attention-deficit/hyperactivity disorder (ADHD), one of the most common psychiatric disorders in children and adolescents. The orbitofrontal cortex (OFC) plays a key role in controlling goal-directed behavior, but the link between OFC dysfunction and behavioral deficits in ADHD, particularly in adolescence, remains poorly understood. Here we used advanced high-resolution functional magnetic resonance imaging(fMRI) of the human OFC in adolescents with ADHD and typically developing (TD) controls (N = 39, age 12ΓÇô16, all male except for one female per group) to study reward-related OFC responses and how they relate to behavioral dysfunction in ADHD. During fMRI data acquisition, participants performed a simple decision-making task, allowing us to image expectation-related responses to small and large monetary outcomes. Across all participants, we observed significant signal increases to large versus small expected rewards in the OFC. These responses were significantly enhanced in ADHD relative to TD participants. Moreover, stronger reward-related activity was correlated with individual differences in hyperactive/impulsive symptoms in the ADHD group, whereas high cognitive ability was associated with normalized OFC responses. These results provide evidence for the importance of OFC dysfunctions in the neuropathology of ADHD, highlighting the role of OFC-dependent goal-directed control mechanisms in this disorder

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J Am Acad Child Adolesc Psychiatry. 2018;57:593-602.

PARENT TRAINING FOR PRESCHOOL ADHD IN ROUTINE, SPECIALIST CARE: A RANDOMIZED CONTROLLED TRIAL.

Lange A-M, Daley D, Frydenberg M, et al.

Objective: Parent training is recommended for attention-deficit/hyperactivity disorder (ADHD) in preschool children. Evidence-based interventions are important, but only if they produce better outcomes than usual care.

Method: The authors conducted a multicenter, 2-arm, parallel-group, randomized controlled trial in routine specialist ADHD clinics in the Danish Child and Adolescent Mental Health Services. Children (N = 164, 3-7 years old) with ADHD received a well-established parent training program (New Forest Parenting Programme; n = 88) or treatment as usual (n = 76). The primary outcome was parent ratings of child ADHD symptoms. Secondary outcomes included teacher ratings and direct observations of ADHD symptoms. Outcomes were measured at baseline, after treatment, and at follow-up (36 weeks later). Representativeness of participants was evaluated against the total national cohort of children (N = 1,378, 3-7 years old) diagnosed with ADHD during the same period using the Danish Civil Registration System. Statistical analysis used a repeated measure model.

Results: After treatment, the parent training program was superior to treatment as usual on parent-rated ADHD symptoms (p =.009; effect size d = 0.30) and on parenting self-efficacy and family strain. Effects persisted to 36 weeks after treatment. There were no effects on teacher ratings or direct observations of ADHD or on ratings of conduct problems or parenting. The clinical sample was similar to the national cohort of young children with ADHD.

Conclusion: Evidence-based parent training has value as an intervention for preschool ADHD in routine clinical settings. As in previous trials, effects were restricted to parent-reported outcomes. Surprisingly, there were no effects on child conduct problems.

Clinical trial registration information: A Controlled Study of Parent Training in the Treatment of ADHD in Young Children (D'SNAPP). http://clinicaltrial.gov/; NCT01684644

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J Am Acad Child Adolesc Psychiatry. 2018;57:571-82.

PREDICTING THE ADULT FUNCTIONAL OUTCOMES OF BOYS WITH ADHD 33 YEARS LATER.

Ramos-Olazagasti MA, Castellanos FX, Klein RG.

Objective: Little is known of the factors that influence the course of childhood attention-deficit/hyperactivity disorder (ADHD). Objectives were to identify early features predictive of the adult outcome of children with ADHD. In the longest prospective follow-up to date of children with ADHD, predictors of multiple functional domains were examined: social, occupational, and overall adjustment and educational and occupational attainment.

Method: White boys (6ΓÇô12 years, mean age 8 years) with ADHD (N = 135), selected to be free of conduct disorder, were assessed longitudinally through adulthood (mean age 41) by clinicians blinded to all previous characteristics. Predictors had been recorded in childhood and adolescence (mean age 18).

Results: Childhood IQ was positively associated with several outcomes: educational attainment, occupational rank, and social and occupational adjustment. Despite their low severity, conduct problems in childhood were negatively related to overall function, educational attainment, and occupational functioning. Two other childhood features that had positive associations with adult adjustment were socioeconomic status and reading ability, which predicted educational attainment. Of multiple adolescent characteristics, 4 were significant predictors: antisocial behaviors predicted poorer educational attainment; educational goals were related to better overall function; early job functioning had a positive relation with social functioning; and early social functioning was positively related to occupational functioning.

Conclusion: Other than childhood IQ, which predicted better outcomes in several domains, there were no consistent prognosticators of adult function among children with ADHD. Providing additional supports to children with relatively lower IQ might improve the adult functional outcome of children with ADHD. However, predicting the course of children with ADHD remains a challenge

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J Am Acad Child Adolesc Psychiatry. 2018;57:544-46.

BUILDING THE EVIDENCE TO TREAT PRESCHOOLERS WITH ADHD IN REAL-LIFE SETTINGS.

Polanczyk GV.

Abundant evidence indicates that attention-deficit/hyperactivity disorder (ADHD) has its roots in the early stages of development. Genetic risk plays a major influence and interacts with a variety of environmental exposures in complex dynamic ways, leading to heterogeneous neurobiological processes that eventually emerge clinically.1 The heterogeneity of etiological mechanisms is reflected by a heterogeneous clinical constellation and trajectories of symptoms and associated disorders. One common developmental trajectory of ADHD is the onset during the preschool age, with stability of approximately 90% to school age in clinical samples.2

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J Voice. 2018.

VOCAL CHARACTERISTICS OF SCHOOL-AGED CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Moodley D-T, Swanepoel C, van LK, et al.

Objectives: The aim of this study was to describe the laryngeal anatomy, perceptual, acoustic, and aerodynamic vocal characteristics of school-aged children with and without Attention Deficit Hyperactivity Disorder (ADHD). The predisposition that children with ADHD have for laryngeal injuries are recurrent in nature and are more often than not overlooked as laryngitis. Previous studies have reported varied results on the prevalence rates of pediatric vocal fold nodules within the school-aged ADHD population. Study

Design: A static, two-group comparison was used in the study to investigate the clinical, perceptual, acoustic, and aerodynamic vocal characteristics of children between 7 and 9 years old with and without ADHD.

Methods: The study replicated the protocol as executed by Barona-Lleo and Fernandez (2016) with additions. The Multidimensional Voice Program and the Voice Range Profile as additions to the assessment of vocal parameters were used with which comparable dysphonia severity index scores were calculated. Once-off clinical, perceptual, acoustic, and aerodynamic voice assessments were conducted on 20 age-gender matched participants (Control group mean age [months] = 98.80, standard deviation = 10.379; ADHD group mean age [months] = 108.00, standard deviation = 10.873). It was hypothesized that children with ADHD would have more hyperfunctional vocal characteristics; leading to laryngeal injuries, than their control group peers.

Results: Forty-five percent (n = 9) of the total sample population (both groups combined) had laryngeal pathology. Similar parent reported etiological voice symptoms and vocal habits were seen across both groups. Both groups performed similarly across both perceptual and aerodynamic voice assessments. Acoustically, the control group achieved significantly higher producible pitches than the ADHD group (P = 0.028) and were found to have more dysphonic dysphonia severity index scores than their ADHD group peers (P = 0.034).

Conclusion: Prepubertal, school-aged children with or without ADHD may have similar vocal characteristics than previously thought. This is in support of the null hypothesis. The authors of the current study recommend that vocal screening in all school-aged children be carried out as an effective measure to monitor voice disorders in the pediatric population. Future research into larger sample sizes with this population with a special focus on the effect that central nervous system stimulants may have on the voice is recommended

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Med Hypotheses. 2018 Jan;110:83-85.

ENVIRONMENTAL FACTORS INFLUENCING THE LINK BETWEEN CHILDHOOD ADHD AND RISK OF ADULT CORONARY ARTERY DISEASE.

Fluegge K, Fluegge K.

Yorbik et al. reported novel findings regarding a hypothesized relationship between childhood attention-deficit hyperactivity disorder (ADHD) and later risk for coronary heart disease in adulthood. The authors found that mean platelet volume (MPV), a marker of platelet reactivity and a presumable biomarker in patients with

cardiovascular disease, was significantly elevated in children with ADHD compared to healthy controls. The mechanistic importance of this novel discovery remains unknown and warrants clarification. We have made the novel proposition that environmental exposure to the agricultural and combustion air pollutant, nitrous oxide (N2O), may be an etiological contributor to neurodevelopmental disorders. Clinical studies suggest that N2O may enhance platelet hyperaggregation, possibly via its biphasic role as an MAO inhibitor especially at trace levels of exposure or via the generation of oxidative stress. Therefore, this correspondence briefly details the hypothesis that altered biochemical profiles in neurodevelopmental disorders, derived from chronic environmental exposure to the agricultural and combustion air pollutant, N2O, may promote coronary artery disease in adulthood

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Med Monatsschr Pharm. 2017 Mar;40:130.
IN PROCESS.
Schoppmeyer M.

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Neural Regen Res. 2017;12:1640-47.
AGE-RELATED CONNECTIVITY DIFFERENCES BETWEEN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER PATIENTS AND TYPICALLY DEVELOPING SUBJECTS: A RESTING-STATE FUNCTIONAL MRI STUDY.
Hong J, Park B-Y, Cho H-H, et al.
Attention deficit and hyperactivity disorder (ADHD) is a disorder characterized by behavioral symptoms including hyperactivity/impulsivity among children, adolescents, and adults. These ADHD related symptoms are influenced by the complex interaction of brain networks which were under explored. We explored age-related brain network differences between ADHD patients and typically developing (TD) subjects using resting state fMRI (rs-fMRI) for three age groups of children, adolescents, and adults. We collected rs-fMRI data from 184 individuals (27 ADHD children and 31 TD children; 32 ADHD adolescents and 32 TD adolescents; and 31 ADHD adults and 31 TD adults). The Brainnetome Atlas was used to define nodes in the network analysis. We compared three age groups of ADHD and TD subjects to identify the distinct regions that could explain age-related brain network differences based on degree centrality, a well-known measure of nodal centrality. The left middle temporal gyrus showed significant interaction effects between disease status (i.e., ADHD or TD) and age (i.e., child, adolescent, or adult) ($P < 0.001$). Additional regions were identified at a relaxed threshold ($P < 0.05$). Many of the identified regions (the left inferior frontal gyrus, the left middle temporal gyrus, and the left insular gyrus) were related to cognitive function. The results of our study suggest that aberrant development in cognitive brain regions might be associated with age-related brain network changes in ADHD patients. These findings contribute to better understand how brain function influences the symptoms of ADHD

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NeuroMol Med. 2018.
DRD3 GENE AND ADHD: A PHARMACO-BEHAVIOURAL GENETIC STUDY.
Fageera W, Sengupta SM, Labbe A, et al.
Results of candidate gene investigations in ADHD have been difficult to replicate. The complexity of the phenotypes and their underlying determinants, and the relatively small effect sizes of genetic variants may, in part, be contributing to these inconsistencies. The objective of this study is to conduct an exploratory analysis using a comprehensive approach to investigate the role of candidate genes. This approach combines a dimensional behavioural approach akin to Research Domain Criteria (RDoC), a pharmaco-dynamic evaluation of behaviours relevant to ADHD, together with association and linkage testing in a large sample of children with ADHD. Parents, teachers, and research staff evaluated children with ADHD under three experimental conditions (EC): 1-áweek of baseline observation, followed by 1-áweek of methylphenidate (MPH) and 1-áweek of placebo, administered in a double-blind crossover order. Several

quantitative behavioural and cognitive dimensions relevant for ADHD were also assessed. We combined family-based (FBAT) and quantitative trait genetic analyses (n = 575 probands with members of their nuclear families) to investigate the role of DRD3 (Ser-9-Gly) in ADHD and its relevant behavioural dimensions. Comparing the behaviours of children with different genotypes under the three EC showed a nominal association between the T allele and poorer behavioural scores during the MPH week (as assessed by teachers), particularly in boys. With the family-based analysis, the T allele showed a nominal association with increased risk for ADHD, response to placebo and MPH as assessed by research staff, and the modulation of other behavioural and cognitive dimensions. These results provide convergent, albeit preliminary evidence for the implication of the DRD3 (Ser-9-Gly) polymorphism in the aetiology of ADHD and the modulation of its various behavioural dimensions, including RDoC cognitive constructs and response to pharmacological probes. This illustrative example suggests that this research paradigm might help to reliably uncover the role of other candidate genes in ADHD

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Neurosci Lett. 2018;685:30-34.

DIAGNOSTIC MODEL FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER BASED ON INTERREGIONAL MORPHOLOGICAL CONNECTIVITY.

Wang X-H, Jiao Y, Li L.

Previous brain morphology-related diagnostic models for attention-deficit hyperactivity disorder (ADHD) were based on regional features. However, building a model of individual interregional morphological connectivity is a challenging task. This study aimed to identify children with ADHD utilizing a novel interregional morphological connectivity model and discover the discriminative patterns in patients. Therefore, novel interregional morphological patterns rather than regional patterns were extracted via surface-based analysis. The interregional morphological features were trained and tested using a hybrid machine learning method, which was implemented using the leave-one-out cross-validation (LOOCV) method to produce the optimized discriminative model and discriminative patterns. The inclusion of interregional morphological connectivity significantly improved the performance of the diagnostic models compared to the performance of the model constructed using regional features. The optimized discriminative model exhibited a total accuracy of 74.65%, a sensitivity of 75% and a specificity of 74.29%. The brain regions displaying altered morphological connectivity included the insula, the caudal anterior cingulate cortex, the frontal pole, and the postcentral cortex, among others. In addition, the altered connections correlated with the clinical symptoms. In summary, patients with ADHD exhibited altered morphological connectivity, which might be a potential biomarker for the classification of ADHD. The discriminative features will potentially benefit studies investigating the brain network mechanisms of ADHD

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Nihon Eiseigaku Zasshi. 2018;73:225-34.

RELIABILITY AND VALIDITY OF THE BEHAVIORAL CHECK LIST FOR PRESCHOOL CHILDREN TO MEASURE ATTENTION DEFICIT HYPERACTIVITY BEHAVIORS.

Tsuno K, Yoshimasu K, Hayashi T, et al.

OBJECTIVES: Nowadays, attention deficit hyperactivity (ADH) problems are observed commonly among school-age children. However, questionnaires specific to ADH behaviors among preschool children are very few. The aim of this study was to investigate the reliability and validity of the 25-item Behavioral Check List (BCL), which was developed from interviews of parents with children who were diagnosed as having Attention-deficit/hyperactivity disorder (ADHD) and measures ADH behaviors in preschool age.

METHODS: We recruited 22 teachers from 10 nurseries/kindergartens in Miyagi Prefecture, Japan. A total of 138 preschool children were assessed using the BCL. To investigate inter-rater reliability, two teachers from each facility assess seven to twenty children in their class, and intraclass correlation coefficients (ICCs) were calculated. The teachers additionally answered questions in the 1/5-5 Caregiver-Teacher Report Form (C-TRF) to investigate the criterion validity of the BCL. To investigate structural validity, exploratory factor analysis with promax rotation and confirmatory factor analysis were performed.

RESULTS: The internal consistency reliability of the BCL was good (alpha = 0.92) and correlation analyses also confirmed its excellent criterion validity. Although exploratory factor analysis for the BCL yielded a five-factor model that consisted of a factor structure different from that of the original one, the results were similar to the original six factors. The ICCs of the BCL were 0.38-0.99 and it was not high enough for inter-rater reliability in some facilities. However, there is a possibility to improve it by giving raters adequate explanations when using BCL.
CONCLUSIONS: The present study showed acceptable levels of reliability and validity of the BCL among Japanese preschool children

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Nihon Eiseigaku Zasshi. 2018;73:164-77.

IMPORTANCE OF TWO BIRTH COHORTS (N=20,926 AND N=514): 15 YEARS' EXPERIENCE OF THE HOKKAIDO STUDY ON ENVIRONMENT AND CHILDREN'S HEALTH: MALFORMATION, DEVELOPMENT AND ALLERGY.

Kishi R, Araki A, Miyashita C, et al.

Since "Our Stolen Future" by Theo Colborn was published in 1996, global interest on the impact of chemical substances, such as the endocrine-disrupting action of chemicals, has increased. In Japan, "The Hokkaido Study on Environment and Children's Health: Malformation, Development and Allergy" was launched in 2001. It was a model of Japan Environment and Children's Study of the Ministry of the Environment. In a large-scale, Hokkaido cohort, we obtained the consent of 20,926 mothers at the organogenesis stage with the cooperation of 37 obstetrics clinics in Hokkaido. We tracked the effects of endocrine disruptors on developmental disorders. In a small-scale Sapporo cohort, we observed in detail the neuropsychiatric development of children with the consent of 514 mothers in their late pregnancy. We examined how prenatal exposure to low concentrations of environmental chemicals affect the development of organs and the postnatal development of children. Maternal exposure to POPs, such as PCB/dioxins and perfluorinated alkyl substances, has affected not only children's birth size, thyroid functions, and sex hormone levels, but also postnatal neurodevelopment, infection, and allergy among others. The associations of short-half-life substances, such as DEHP and BPA, with obesity, ASD, and ADHD have been investigated. Gene-environment interactions have been found for smoking, caffeine, folic acid, and PCB/dioxin. In 2015, our center was officially designated as the WHO Collaborating Centre for Environmental Health and Prevention of Chemical Hazards, and we continue to the contribute to the global perspectives of child health

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No To Hattatsu. 2016 Jul;48:259-64.

FACTORS ASSOCIATED WITH ANTISOCIAL BEHAVIOR IN PATIENTS WITH DEVELOPMENTAL DISORDER.

Nakamura Y, Shimazaki M, Komatsu Y, et al.

Objective: This study investigated the factors associated with antisocial behavior (AB) in children with developmental disorder and effective treatments.
Methods: Participants were 110 schoolchildren with developmental disorder and with or without accompanying AB who visited our hospital between October 2009 and October 2012. Among the children with AB, those who exhibited one or more symptoms of conduct disorder (CD) were assigned to the CD subgroup. We examined the background characteristics, past history, type of antisocial behavior, and symptom improvement after treatment in the children with AB and compared the relevant factors with children with developmental disorder without AB.
Results: Of the 110 participants, 72 (65.5%) did not exhibit AB and 38 (34.5%) did, 7 (5.5%) of whom fulfilled the criteria for CD. Compared to the children without AB, the children with AB showed a significantly higher occurrence of attention deficit/hyperactivity disorder (AD/HD), maltreatment, institutionalization due to maltreatment, parental mental/psychological problems, and family instability. After medical treatment combined with social-skills training and parental education, 22 of the 38 children with AB showed improved behavior. In the CD subgroup, 4 children were diagnosed with AD/HD and 3 with pervasive developmental disorder, and none of the 7 improved with treatment.

Conclusion: AB was associated with AD/HD, maltreatment, institutionalization, parental mental/psychological problems, and family instability. The most effective therapy was parental education. Children with AB need early intervention given that those who already exhibited symptoms of CD showed little improvement with treatment

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Pediatr Int. 2018 Jun;60:523-28.

PATTERN OF VIDEO GAME USE IN CHILDREN WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER AND TYPICAL DEVELOPMENT.

Kietglaiwansiri T, Chonchaiya W.

BACKGROUND: Video game playing is a favorite leisure activity among children worldwide. Individuals with attention-deficit-hyperactivity disorder (ADHD) often lack self-control, making them at risk for substance abuse and game addiction. There are conflicting results, however, between studies on the pattern of video gaming and game addiction between those with ADHD and healthy controls. We therefore compared the pattern of video game use and game addiction between Thai children with ADHD and healthy controls.
METHODS: A total of 80 participants with ADHD (median age, 9.5 years) and 102 controls (median age, 10 years) were recruited in this study. ADHD was diagnosed by a developmental pediatrician. Each control subject's teacher completed the ADHD questionnaire to ensure that they did not have the diagnosis of ADHD. Pattern of video game use and Game Addiction Screening Test (GAST) were completed by participants' parents.
RESULTS: More than half of the children with and without ADHD spent >2 h/day playing video games rather than engaging in other age-appropriate leisure activities, particularly on weekends. Participants with ADHD, however, had a higher rate of compulsive video game use than controls (37.5% vs 11.8%, P < 0.001).
CONCLUSIONS: Although video game playing was relatively prevalent in children regardless of ADHD status, those with ADHD had a higher rate of problematic video game use than controls. The pattern of leisure activities including video game use should be assessed during health supervision visits. As such, those at risk for game addiction could be identified early, resulting in appropriate intervention

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Pediatr Int. 2018 Jun;60:529-34.

INTERNET ADDICTION AND ATTENTION-DEFICIT-HYPERACTIVITY DISORDER: EFFECTS OF ANXIETY, DEPRESSION AND SELF-ESTEEM.

Kahraman O, Demirci EO.

BACKGROUND: Attention-deficit-hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. Behavioral disinhibition, poor neurocognitive skills and immediate reward preference in children with ADHD have been suggested as risk factors for Internet addiction (IA). The aim of the present study was therefore to investigate the relationship between IA and depression, anxiety, and self-esteem in adolescents with ADHD, and to identify the features of Internet use that predict IA.
METHODS: We studied 111 patients with ADHD aged 12-18 years, and 108 healthy controls. The ADHD patients and controls were asked to complete a sociodemographic data form, the Internet Addiction Scale (IAS), Children's Depression Inventory, Childhood Screening Scale for Anxiety in Children, and the Rosenberg Self-Esteem Scale.
RESULTS: IAS total score in the adolescents with ADHD was significantly higher than in the control group. Compared with the control group, the ADHD group depression scale score was significantly higher, and self-esteem score significantly lower (P < 0.05 for both). There was no difference between the groups in anxiety score. IAS score had a positive correlation with depression and anxiety scores, and a negative correlation with self-esteem score.
CONCLUSION: The relationship between IA scale score and depression, anxiety and self-esteem scale scores were similar in the ADHD and the control group. In addition, IAS subscale and total scores were significantly higher in the ADHD group than the control group, even after controlling for the effects of self-

esteem, depression and anxiety scores. Thus, ADHD is thought to be an independent risk factor for depression, anxiety and self-esteem, and, hence, for IA

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Pediatr Int. 2018 Mar;60:247-53.

ALEXITHYMIA, DEPRESSION AND ANXIETY IN PARENTS OF CHILDREN WITH NEURODEVELOPMENTAL DISORDER: COMPARATIVE STUDY OF AUTISTIC DISORDER, PERVASIVE DEVELOPMENTAL DISORDER NOT OTHERWISE SPECIFIED AND ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Durukan I, Kara K, Almbaideen M, et al.

BACKGROUND: Recent studies have shown that individuals with neurodevelopmental disorders and their relatives have problems expressing and recognizing emotions, but there is a lack of studies on alexithymia, and the relationship between parental alexithymia and depression-anxiety symptoms in these groups. The aim of this study was therefore to measure alexithymia, depression, and anxiety levels in parents of children with pervasive developmental disorders and attention deficit-hyperactivity disorder (ADHD), and determine whether there is a positive correlation between the child's neurodevelopmental problem severity and parent scores.

METHODS: Parents of 29 autistic disorder (AD), 28 pervasive developmental disorder not otherwise specified (PDD-NOS) and 29 ADHD children were recruited into the study, and completed a demographic information form, as well as the Toronto Alexithymia Scale (TAS-20), Beck Depression Inventory, and State-Trait Anxiety Inventory.

RESULTS: Alexithymia symptoms were higher in parents of children with AD than in others but unexpectedly, also these symptoms were higher in ADHD parents than in PDD-NOS groups. In addition, there were unexpected differences according to alexithymia subtype, while only the difference in maternal TAS-1 scores (difficulty in describing feelings) were statistically significant. Parental depression and state anxiety scores were increased as the child's symptom severity increased, but trait anxiety symptoms were higher in the AD and ADHD group than in the PDD-NOS group. In all groups, maternal depression and anxiety scores were higher than paternal scores, and differences were significant for depression and anxiety types in AD, and for only anxiety types in ADHD parents. The AD group had the strongest correlation between parental depression-anxiety and alexithymia.

CONCLUSION: The possibility of alexithymia, depression and anxiety should be kept in mind when working with parents of children with neurodevelopmental disorders

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Pediatr Pulmonol. 2018.

NEUROCOGNITIVE DISORDERS AND SLEEP IN CHILDREN WITH PRIMARY CILIARY DYSKINESIA.

Sismanlar Eyüboglu T, Aslan AT, Ceylan A, et al.

Background: Primary ciliary dyskinesia (PCD) patients have higher incidence of sleep disordered breathing which lead neurocognitive impairments such as attention-deficit/hyperactivity disorder (ADHD). It may effect academic performance of children and may cause impairment in emotional relationships. This study aim to evaluate hyperactivity and attention deficiency in PCD patients and investigate the relationship between sleep and hyperactivity and attention deficiency in PCD patients.

Method: Fifteen PCD patients aged 8-18 years and 31 age-matched healthy controls were compared. Ear, nose, and throat examination and home sleep testing were performed in PCD patients. Pediatric sleep questionnaire, Conners' Parents and Teacher scale and Stroop test were applied in both groups in order to investigate the relation between sleep disordered breathing and ADHD in PCD children.

Results: PCD patients had chronic rhinosinusitis (100%), tonsillar hypertrophy (80%) and adenoidal hypertrophy (60%). FEF25-75 was low in pulmonary function test. Sixty percent of the PCD patients had mild obstructive sleep apnea syndrome in home sleep testing. Mean AHI was 1.54-¦0.27. Compared with the controls PCD patients had higher PSQ scores. Hyperactivity scores on Conners' Parents scale and inattention findings in Stroop test were higher in PCD patients than the healthy controls (P<0.05).

Conclusion: Most of PCD children had mild obstructive sleep apnea syndrome. Hyperactivity and inattention findings were higher in PCD patients. Sleep disordered breathing assessment should be a routine part of PCD patients management and these patients should be carefully monitored in terms of hyperactivity and inattention

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Phys Occup Ther Pediatr. 2018 Aug;38:243-54.

SENSORY PROCESSING PATTERNS IN AUTISM, ATTENTION DEFICIT HYPERACTIVITY DISORDER, AND TYPICAL DEVELOPMENT.

Little LM, Dean E, Tomchek S, et al.

AIMS: The purpose of this study was to examine sensory processing in children ages 3-14 years with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and typical development (TD) using the Sensory Profile 2nd Edition (Dunn, 2014).

METHODS: Participants included 239 children (ASD = 77; ADHD = 78; TD = 84) matched on age and gender. Multivariate analysis of covariance was used to compare the extent to which the three grsoups differed on sensory processing patterns (i.e., sensitivity, avoiding, registration, seeking) and sensory systems (i.e., auditory, visual, touch, movement, body position, oral, conduct, attention, social). We also examined the effect of chronological age.

RESULTS: Children with ASD and ADHD did not differ in sensory processing patterns which were elevated as compared to a TD group. Children with ASD showed the highest rate of oral processing differences, followed by ADHD and TD. Children with ADHD had higher visual processing scores than children with ASD and TD. Older children had lower scores for seeking, auditory, visual, movement, touch, and conduct than younger children, regardless of diagnosis.

CONCLUSIONS: Findings suggest that sensory features may be an area of overlap of behaviors in ASD and ADHD, which may have implications for intervention approaches for children with these conditions

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PLoS ONE. 2018;13:e0193681.

A SERIOUS GAME FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: WHO BENEFITS THE MOST?

Bul KCM, Doove LL, Franken IHA, et al.

OBJECTIVE: The aim of the current study was to identify which subgroups of children with Attention Deficit Hyperactivity Disorder (ADHD) benefitted the most from playing a Serious Game (SG) intervention shown in a randomized trial to improve behavioral outcomes.

METHOD: Pre-intervention characteristics [i.e., gender, age, intellectual level of functioning, medication use, computer experience, ADHD subtype, severity of inattention problems, severity of hyperactivity/impulsivity problems, comorbid Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) symptoms] were explored as potential moderators in a Virtual Twins (VT) analysis to identify subgroups for whom the SG intervention was most effective. Primary outcome measures were parent-reported time management, planning/organizing and cooperation skills.

RESULTS: Two subgroups were identified. Girls (n = 26) were identified as the subgroup that was most likely to show greater improvements in planning/organizing skills as compared to the estimated treatment effect of the total group of participants. Furthermore, among the boys, those (n = 47) with lower baseline levels of hyperactivity and higher levels of CD symptoms showed more improvements in their planning/organizing skills when they played the SG intervention as compared to the estimated treatment effect of the total group of participants.

CONCLUSION: Using a VT analysis two subgroups of children with ADHD, girls, and boys with both higher levels of CD and lower levels of hyperactivity, were identified. These subgroups mostly benefit from playing the SG intervention developed to improve ADHD related behavioral problems. Our results imply that these subgroups have a higher chance of treatment success

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PLoS ONE. 2018;13.

REDUCED MICROBIOME ALPHA DIVERSITY IN YOUNG PATIENTS WITH ADHD.

Prehn-Kristensen A, Zimmermann A, Tittmann L, et al.

ADHD is a psychiatric disorder which is characterized by hyperactivity, impulsivity and attention problems. Due to recent findings of microbial involvement in other psychiatric disorders like autism and depression, a role of the gut microbiota in ADHD pathogenesis is assumed but has not yet been investigated. In this study, the gut microbiota of 14 male ADHD patients (mean age: 11.9 yrs.) and 17 male controls (mean age: 13.1 yrs.) was examined via next generation sequencing of 16S rDNA and analyzed for diversity and biomarkers. We found that the microbial diversity (alpha diversity) was significantly decreased in ADHD patients compared to controls (pShannon = 0.036) and that the composition (beta diversity) differed significantly between patients and controls (pANOSIM = 0.033, pADONIS = 0.006, pbetadisper = 0.002). In detail, the bacterial family Prevotellacae was associated with controls, while patients with ADHD showed elevated levels of Bacteroidaceae, and both Neisseriaceae and Neisseria spec. were found as possible biomarkers for juvenile ADHD. Our results point to a possible link of certain microbiota with ADHD, with Neisseria spec. being a very promising ADHD-associated candidate. This finding provides the basis for a systematic, longitudinal assessment of the role of the gut microbiome in ADHD, yielding promising potential for both prevention and therapeutic intervention

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PLoS ONE. 2018;13:e0194856.

A GENERAL PREDICTION MODEL FOR THE DETECTION OF ADHD AND AUTISM USING STRUCTURAL AND FUNCTIONAL MRI.

Sen B, Borle NC, Greiner R, et al.

This work presents a novel method for learning a model that can diagnose Attention Deficit Hyperactivity Disorder (ADHD), as well as Autism, using structural texture and functional connectivity features obtained from 3-dimensional structural magnetic resonance imaging (MRI) and 4-dimensional resting-state functional magnetic resonance imaging (fMRI) scans of subjects. We explore a series of three learners: (1) The LeFMS learner first extracts features from the structural MRI images using the texture-based filters produced by a sparse autoencoder. These filters are then convolved with the original MRI image using an unsupervised convolutional network. The resulting features are used as input to a linear support vector machine (SVM) classifier. (2) The LeFMF learner produces a diagnostic model by first computing spatial non-stationary independent components of the fMRI scans, which it uses to decompose each subject's fMRI scan into the time courses of these common spatial components. These features can then be used with a learner by themselves or in combination with other features to produce the model. Regardless of which approach is used, the final set of features are input to a linear support vector machine (SVM) classifier. (3) Finally, the overall LeFMSF learner uses the combined features obtained from the two feature extraction processes in (1) and (2) above as input to an SVM classifier, achieving an accuracy of 0.673 on the ADHD-200 holdout data and 0.643 on the ABIDE holdout data. Both of these results, obtained with the same LeFMSF framework, are the best known, over all hold-out accuracies on these datasets when only using imaging data-exceeding previously-published results by 0.012 for ADHD and 0.042 for Autism. Our results show that combining multi-modal features can yield good classification accuracy for diagnosis of ADHD and Autism, which is an important step towards computer-aided diagnosis of these psychiatric diseases and perhaps others as well

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Postgrad Med. 2018 Jun;130:481-93.

A RANDOMIZED, DOUBLE-BLIND STUDY OF SHP465 MIXED AMPHETAMINE SALTS EXTENDED-RELEASE IN ADULTS WITH ADHD USING A SIMULATED ADULT WORKPLACE DESIGN.

Wigal T, Brams M, Frick G, et al.

OBJECTIVES: The objective of this paper was to evaluate the efficacy, duration of effect, and tolerability of SHP465 mixed amphetamine salts (MAS) extended-release versus placebo and immediate-release MAS (MAS IR) in adults with attention-deficit/hyperactivity disorder (ADHD).

METHODS: Adults with ADHD Rating Scale, Version IV (ADHD-RS-IV) scores >/=24 were randomized to SHP465 MAS (50 or 75 mg), placebo, or 25 mg MAS IR in a double-blind, three-period, crossover study using a simulated adult workplace environment. On the final day of each 7-day treatment period, efficacy was assessed for 16 h postdose. Primary efficacy analyses for Permanent Product Measure of Performance (PERMP) total score averaged across all postdose assessments and each postdose time point were conducted in the intent-to-treat population using a mixed linear model. Secondary end-points included PERMP problems attempted and answered correctly and ADHD-RS-IV scores based on clinician ratings of counselor observations using the Time Segment Rating System and participant self-report. Tolerability assessments included treatment-emergent adverse events (TEAEs) and vital signs.
RESULTS: Least squares mean (95% CI) treatment differences (combined 50/75 mg SHP465 MAS-placebo) significantly favored SHP465 MAS over placebo for PERMP total score averaged across all postdose assessments (18.38 [11.28, 25.47]; P < .0001) and at each postdose assessment (all P < .02). Nominal superiority of MAS IR over placebo for PERMP total score averaged across all postdose assessments was observed (nominal P = .0001); treatment differences between SHP465 MAS and MAS IR were not significant (nominal P = .2443). The two most frequently reported TEAEs associated with SHP465 MAS were insomnia (36.5%) and anorexia (21.2%). Mean increases in pulse and blood pressure with SHP465 MAS exceeded those of placebo.
CONCLUSIONS: SHP465 MAS (combined 50/75 mg) significantly improved PERMP total score versus placebo, with superiority observed from 2 to 16 h postdose. The tolerability profile of SHP465 MAS was similar to previous reports of SHP465 MAS in adults with ADHD. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT00928148 identifier is NCT00928148

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2019;88:215-21.

ALTERED METHYLTETRAHYDROFOLATE REDUCTASE GENE POLYMORPHISM IN MOTHERS OF CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER .

Baykal S, Batar B, Nalbanto-ƒlu A, et al.

Attention Deficit and Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood and causes significant functional impairments in children. Behavioral genetic and molecular genetic studies have provided significant evidence in terms of highlighting the etiology of ADHD. Folate deficiency during pregnancy is an established risk factor for ADHD. Polymorphisms in the Methyltetrahydrofolate Reductase (MTHFR) encoding gene, such as A1298C and C667T, are associated with the decreased bioavailability of folate, and this condition can act like folate deficiency. In the literature, no study has investigated MTHFR polymorphisms in mothers of children with ADHD. Sixty-four children diagnosed with ADHD and their mothers as well as 40 healthy children and their mothers participated in this study. MTHFR polymorphisms were investigated in all participants. Comparison of the C677C and A1298C MTHFR polymorphisms in children with and without ADHD revealed no significant differences. We found that the maternal C677C_CT genotype counts, both observed and expected values, were significantly different from those based on Hardy-Weinberg Principle Analysis in the ADHD group. The most important result of this study was that maternal C677C MTHFR gene polymorphisms are significant risk factors in for ADHD, and we argue that children with ADHD are exposed to folate deficiency, even if their mothers received a sufficient amount of folate during pregnancy. This result also highlights one of the genetic factors of ADHD. Further studies should be performed to confirm this finding

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Psychiatry and Clinical Psychopharmacology. 2018.

THE ASSESSMENT OF SERUM OMENTIN LEVELS OF CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yürümez E, Çağatay Uğur M.

Objectives: We aimed to investigate plasma omentin concentrations in non-obese, drug-free patients with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in comparison with healthy volunteers.

Methods: Sixty children with ASD, 60 children with ADHD, and 60 control subjects were recruited. Plasma omentin levels were determined by the enzyme-linked immunosorbent assay.

Results: Plasma levels of omentin (479.0 ng/ml) were found to be significantly higher in patients with ASD (median = 422.6, min/max; 220-800) than in controls (382.5 ng/ml) (median = 322.0, min/max 184-800). No significant difference was found between ADHD and control groups with respect to plasma omentin levels. There was no significant correlation between omentin levels and age of children, ABCL, AbBC, CARS, CPRS, and CTRS scores.

Conclusions: To our knowledge, this is the first study that demonstrated the association between omentin and ASD and ADHD. The present results suggest that plasma omentin levels are increased in non-obese and drug-free patients with ASD when compared with in ADHD and healthy children. The omentin levels in ADHD and ASD need further refinement with larger samples and long-term follow-up periods

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Psychiatry and Clinical Psychopharmacology. 2018.

SUCCESSFUL TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ACCOMPANYING TO ALKAPTONURIA WITH METHYLPHENIDATE AND RISPERIDONE.

Arici A, Altun H.

Alkaptonuria (AKU) is a rare metabolic disorder resulting from deficiency of homogentisic acid (HGA) oxidase involved in the metabolism of tyrosine. Dark discolouration of urine, ochronosis at cartilage and connective tissues, arthritis at the third of fourth decade of life, cardiac valve deficits, renal stone disease, spontaneous tendon rupture, and liver involvement may be seen in alkaptonuria. It was reported that HGA oxidase gene was expressed in human cerebral tissue and neuronal cells in AKU with multi-systemic organ involvement. HGA accumulation has been implied and neurological problems and brain damage. To the best of our knowledge, there is no study or case report about psychiatric comorbidities in patients with AKU, although comorbid psychiatric disorders such as mental retardation, attention-deficit/hyperactivity disorder (ADHD), impulse control disorder or conduct disorder can be seen in some metabolic diseases such as mucopolysaccharidosis, WilsonΓÇÖs disease, or phenylketonuria. Here, we presented a paediatric AKU patient with comorbid ADHD, oppositional defiant/conduct disorder (ODD/CD), and borderline intellectual functioning who was successfully treated with extended-release methylphenidate (OROS-MPH) and risperidone. It was observed that these agents caused no worsening in AKU and that they were well-tolerated without adverse effects. However, there is a need for further studies investigating the safe use of OROS-MPH and risperidone in patients with AKU

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Psychiatry and Clinical Psychopharmacology. 2018.

THE RELATIONSHIP BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND REELIN GENE POLYMORPHISMS IN TURKISH POPULATION.

Kara B, Sahin N, Kara M, et al.

PURPOSE: Although attention deficit hyperactivity disorder (ADHD) is one of the most frequently seen psychiatric disorders in childhood, its etiology and pathophysiology are not fully elucidated. The aim of the present study was to investigate the association between ADHD and RELN gene in Turkish children.

METHOD: DNA samples were harvested from 102 patients with ADHD and 94 healthy controls. Three single-nucleotide polymorphisms of reelin gene (rs1270519, rs362691, and rs734147) were genotyped using real-time polymerase chain reaction.

RESULTS: A significant difference was detected between ADHD and control groups regarding rs1270519 polymorphism while no significant difference was detected between the groups regarding reelin rs362691 and rs734147 polymorphisms.
CONCLUSION: It was found that reelin rs12705169 gene polymorphism could play a role in ADHD etiology, indicating the need for further studies to investigate the relationship between ADHD and reelin gene polymorphism

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Psychiatry and Clinical Psychopharmacology. 2018.
A QUALITATIVE STUDY ON CORPORAL PUNISHMENT AND EMOTIONALLY ABUSIVE DISCIPLINARY PRACTICES AMONG MOTHERS OF CHILDREN WITH ADHD.
Evinç ŞG, et al.
OBJECTIVES: The present study aimed to investigate actual disciplinary behaviours of Turkish mothers in the context of relational environment and to investigate ADHD as a risk factor on abusive disciplinary practices.
METHODS: Totally 120 children (children with ADHD; study group and healthy controls; control group) and their mothers were interviewed with this aim. The interviews were qualitatively coded and analysed. T-test and Odds ratio were used for descriptive statistics with the aim of supporting the qualitative results.
RESULTS: According to the results of the study, emotionally abusive disciplinary behaviours (81% of all mothers 58% of all children) and corporal punishment (76% of all mothers and 65% of all children) were commonly used as a disciplinary method. Nevertheless, children with ADHD was shown to be at higher risk for both abusive disciplinary practices. The present study has also shown that children with ADHD and their mothers shared less positive activities compared to the control group. In addition to this, emotionally abusive disciplinary practices were found to be at least as hurtful as corporal punishment.
CONCLUSIONS: To our knowledge, the present study was the first one investigating Turkish mothers actual abusive disciplinary acts together with the relational environment between them and their children (including their relationship, positive sharing, problematic issues) by gathering information from both mothers and children of both study and control groups and then comparing these groups in terms of all these aspects. Qualitative nature of the study gave the opportunity of determining the actual disciplinary methods and the actual relational risk factors rather than attitudes and questionnaire scores about mother child relationship. Therefore, it can be suggested that the results of the study provide important information about the abusive disciplinary behaviours of Turkish mothers and also provide the opportunity of predicting risk factors keeping cultural context in mind of these behaviours

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Psychiatry and Clinical Psychopharmacology. 2018.
VITAMIN B12 AND HAEMOGLOBIN LEVELS MAY BE RELATED WITH ADHD SYMPTOMS: A STUDY IN TURKISH CHILDREN WITH ADHD.
Unal D, et al.
OBJECTIVE: In this study, we evaluated vitamin B12 and iron parameters in Turkish children with ADHD in order to examine the relationship between ADHD symptoms and these parameters.
METHODS: Drug-naive 100 ADHD patients, aged between 6 and 12 years old, were included in the study. None of them had acute or chronic diseases. All patients were assessed by using the Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version (K-SADS-PL). Conners Parent Rating Scale (CPRS) was used for screening ADHD symptoms and symptom severity. Blood samples were evaluated for ferritin, haemoglobin, MCV, RDW, and vitamin B12 parameters.
RESULTS: We indicated an inverse relationship between haemoglobin levels and learning, anxiety subscale scores of CPRS. Also, vitamin B12 and psychosomatic subscale scores were found negatively related whereas the relationship was in the opposite direction for ferritin. Vitamin B12 level was negatively correlated with learning problems and psychosomatic subscales of CTRS in the combined subtype of ADHD.

CONCLUSION: Vitamin B12 and iron support may be useful in treatment of childhood ADHD, especially for learning problems, besides medication

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Psychiatr Invest. 2018;15:649-54.

EFFECTS OF ATOMOXETINE ON HEIGHT AND WEIGHT IN KOREAN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RETROSPECTIVE CHART REVIEW.

Kweon K, Yoon JS, Park KJ, et al.

Objective We aimed to investigate the long-term effects of atomoxetine on growth in Korean children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Methods The medical records of 82 subjects (mean age, 9.0-¦2.0 years; 64 boys) with ADHD treated with atomoxetine for at least 1 year at the Department of Psychiatry at Asan Medical Center were retrospectively reviewed. Height and weight data were prospectively obtained and retrospectively gathered and converted to age-and gender-corrected z scores using norms from Korean youths. Growth changes were analyzed using random coefficients models with changes in height or weight z scores as the dependent variables.

Results Height z scores significantly decreased during the treatment period (+¦=-0.054, p=0.024). Height z scores decreased during the 1st year of treatment (+¦=-0.086, p=0.003), but did not change after the 1st year. Weight z scores did not change significantly during treatment (+¦=0.004, p=0.925).

Conclusion Our results suggest that long-term atomoxetine treatment may be associated with deficits in height growth in Korean youths, although this effect was minor and tended to be attenuated over the first year. Because of the limitations of this study such as retro-spective design and selection bias, further prospective studies are needed

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Psychiatry Res. 2018;269:79-85.

COGNITIVE WORKING MEMORY TRAINING (CWMT) IN ADOLESCENTS SUFFERING FROM ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A CONTROLLED TRIAL TAKING INTO ACCOUNT CONCOMITANT MEDICATION EFFECTS.

Ackermann S, Halfon O, Fornari E, et al.

Although, cognitive working memory training (CWMT) has been reported to enhance working memory functioning in youths with attention-deficit/ hyperactivity disorder (ADHD), few studies take into account the concomitant effects of medication. Sixty adolescents aged from 11 to 15 years were randomly assigned to CWMT treatment, whereas medication was either continued or not introduced (no randomization performed). Results revealed beneficial effects of CWMT on the different components of working memory (WM), namely the phonological loop, the visuospatial sketchpad and the central executive. In particular, CWMT allowed participants to obtain a level of performance similar to the typically-developing adolescents for the phonological loop (i.e., forward digit span) as well as for the visuospatial sketchpad (i.e., board span). For the central executive (i.e., backward digit span) the concomitant effects of CWMT and medication allows participants to obtain the performance level of the typically-developing adolescents. Although, no transfers were observed with respect to other cognitive functions, in medicated patients with ADHD, CWMT reduced hyperactivity / impulsivity symptoms at 2-month follow-up. The present study gives evidence of the efficacy of CWMT to enhance WM performance, as well as, to reduce symptoms. The overall results highlight the usefulness of multimodal interventions

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Quality of Life Research. 2015;24:100-01.

QUALITY OF LIFE IN CHILDREN WITH ADHD.

Hernandez-Martinez M, Pastor-Hernandez N, Pastor-Duran X, et al.

AIMS: The Attention Deficit and Hyperactivity Disorder (ADHD) has a direct impact in the patients with such condition and all those who surround them with repercussion in the cognitive, emotional and social scope of

the affected children, their family, schoolfellows and friends. The concept of Quality of Life (QoL) refers to the perceived patients' health status as well as the degree of wellness or satisfaction with their condition. BiblioPro offers objective tools to measure this subjective feeling by the patients by themselves of by third persons (family, friend, etc.) The objective of this study is to evaluate the impact of ADHD on the QoL of children having this disorder in comparison with an equivalent control group without ADHD.
METHODS: This is a cross prospective case-control study. An information sheet about the study was explained by the pediatricians to them and their parents. 58 children or both sexes with ages between 8 and 16 years-old were entered at the study after the signature of the informed consent. Inclusion criteria for the ADHD group were 28 children recently diagnosed without beginning any treatment. In the 30 children of the control group ADHD. The KINDL questionnaire was used to know the self-perceived QoL by all the children. Kid template was used for 8-12 years-old. Kiddo-« was the template for 13-16 years-old. This questionnaire evaluates 6 dimensions: 1-Physical wellness; 2-Emotional wellness; 3-Self esteem; 4-Friends; 5-Family; 6-School. Statistical data analysis has been done with IBM SPSS v. 22 using specific algorithms provided by BiblioPro to compute and normalize the dimensional scores.
RESULTS: Each of the six dimensions as well as the global score analyzed with the Student's t test showed highly significant differences ($p<0.02$) between the two groups. In all the scores, the best (highest value) fell onto the control group (without ADHD). Detailed results, normalized to 100 points, can be seen on the Table 1.
CONCLUSIONS: Self-perceived QoL is worse in children with ADHD An early diagnosis, intervention and follow-up can be done at Primary Care

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Res Dev Disabil. 2018;83:69-76.
ASSOCIATION BETWEEN SENSORY MODULATION AND DAILY ACTIVITY FUNCTION OF CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND CHILDREN WITH TYPICAL DEVELOPMENT.
Mimouni-Bloch A, Offek H, Rosenblum S, et al.
Background: The severity of the functional difficulties of children with attention-deficit/hyperactivity disorder (ADHD) is heterogeneous and may be affected by measurable factors.
Aims: To characterize subgroups of children with ADHD with or without sensory modulation difficulties (SMD) and the association between sensory modulation and daily activity function in children with ADHD and children with typical development.
Methods: 38 children with ADHD and 39 controls (ages 8-11) were recruited and assessed, using the Conner's Parent Rating Scale Revised: Short Form, the Short Sensory Profile (SSP) and the Children Activity Scale for Parents (ChAS-P).
Results: The total SSP score of the ADHD group was lower (142.13 vs. 180.08; $t=8.23$, $p < 0.001$) with a higher proportion of SMD (65.8% vs. 2.6%, ¤ç2 = 34.46, $p < 0.001$). The daily function of children with ADHD was lower than controls (mean ChAS-P: 3.95 vs. 4.78, $p < 0.001$). The difference was significant for children with ADHD and SMD (3.70 versus 4.81, $p < 0.001$), but not significant for children with ADHD and typical SSP (4.42 versus 4.81, $p=0.35$).
Conclusion: In this pilot study, we found that SMD, in children with ADHD is correlated with daily activity consequences. Hence, it should be evaluated in children with ADHD and addressed in their treatment plan

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Revue Neurologique. 2018.
THE NEUROPSYCHIATRY OF GILLES DE LA TOURETTE SYNDROME: THE ÉTAT DE L'ART.
Cavanna AE.
Gilles de la Tourette syndrome (GTS) is a chronic tic disorder characterised by the presence of multiple motor and vocal tics with onset during development. Tics are the most common hyperkinetic symptoms in childhood and co-morbid behavioural conditions (especially obsessive-compulsive disorder, attention-deficit and hyperactivity disorder, affective symptoms, and impulsivity) are present in the majority of patients. Although GTS is no longer considered a rare medical curiosity, its exact pathophysiology remains elusive. Recent

research on the brain correlates of the subjective urge to tic has highlighted the role of extra-motor pathways within the brain mechanisms of tic generation. Advances in our understanding of the pathophysiology of GTS can pave the way to the implementation of more effective treatment strategies for this heterogeneous neurobehavioral condition. Finally, the development of GTS-specific instruments for the assessment of health-related quality of life has allowed more standardised assessments across the lifespan, capturing the impact of both tics and behavioural co-morbidities

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Schizophr Res. 2018.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AS ANTECEDENTS OF LATER PSYCHOTIC OUTCOMES IN 22Q11.2 DELETION SYNDROME.

Niarchou M, Chawner SJRA, Fiksinski A, et al.

Individuals with 22q11.2 Deletion Syndrome (22q11.2DS) are at substantially heightened risk for psychosis. Thus, prevention and early intervention strategies that target the antecedents of psychosis in this high-risk group are a clinical priority. Attention Deficit Hyperactivity Disorder (ADHD) is one the most prevalent psychiatric disorders in children with 22q11.2DS, particularly the inattentive subtype. The aim of this study was to test the hypothesis that ADHD inattention symptoms predict later psychotic symptoms and/or psychotic disorder in those with 22q11.2DS. 250 children and adolescents with 22q11.2DS without psychotic symptoms at baseline took part in a longitudinal study. Assessments were performed using well-validated structured diagnostic instruments at two time points (T1 (mean age = 11.2, SD = 3.1) and T2 (mean age = 14.3, SD = 3.6)). Inattention symptoms at T1 were associated with development of psychotic symptoms at T2 (OR:1.2, p = 0.01) but weak associations were found with development of psychotic disorder (OR:1.2, p = 0.15). ADHD diagnosis at T1 was strongly associated with development of psychotic symptoms at T2 (OR:4.5, p < 0.001) and psychotic disorder (OR:5.9, p = 0.02). Our findings that inattention symptoms and the diagnosis of ADHD are associated with subsequent psychotic outcomes in 22q11.2DS have important clinical implications. Future studies examining the effects of stimulant and other ADHD treatments on individuals with 22q11.2DS are warranted

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Sch Psychol Int. 2018 Jun;39:234-50.

PARENTAL INVOLVEMENT IN THE LEARNING OF ADOLESCENTS WITH AND WITHOUT ADHD.

Musabelliu G, Wiener J, Rogers M.

This study examined parental involvement in adolescents' learning of parents of 108 adolescents 13- to 18-years of age (54 mothers of adolescents with ADHD, 44 mothers of adolescents without ADHD; 42 fathers of adolescents with ADHD and 35 fathers of adolescents without ADHD). Compared to mothers and fathers of adolescents without ADHD, both mothers and fathers of adolescents with ADHD reported lower self-efficacy in their ability to help their teens on the Parent Involvement Project Questionnaire-Modified (PIPQ-M). On the Parental Support for Learning Scale (PSLS), mothers of adolescents with ADHD perceived themselves as being less supportive and having fewer aspirations regarding their adolescents' future, compared with mothers of adolescents without ADHD. There were no differences between parents of adolescents with and without ADHD in any other aspects of involvement beliefs, experiences, and behaviors according to parent and adolescent report. Implications for school psychology practice are discussed

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Top Spinal Cord Inj Rehabil. 2016;22:253-59.

ADHD AND ATTENTION PROBLEMS IN CHILDREN WITH AND WITHOUT SPINA BIFIDA.

Wasserman RM, Stoner AM, Stern A, et al.

Objectives: To identify differences in the diagnosis and treatment of attention deficit/hyperactivity disorder (ADHD) between typically developing children and children with spina bifida.

Method: Sixty-eight children with spina bifida and 68 demographically matched, typically developing children participated in a larger, longitudinal study. Rates of maternal, paternal, and teacher reports of attention problems, as well as rates of maternal reports of ADHD diagnosis, diagnosing provider, pharmaceutical treatment, mental health treatment, and academic accommodations were obtained at 5 time points over a period of 8 years and were compared across groups.
Results: Children with spina bifida were more likely to have an ADHD diagnosis and attention problems. Attention problems and ADHD diagnoses were first reported at earlier time points for children with spina bifida than typically developing children. Among children with ADHD or attention problems, children with spina bifida were more likely to be treated with medication, but they were just as likely to use mental health services and receive resource services at school.
Conclusions: Children with spina bifida were diagnosed with ADHD and identified as having attention problems more frequently and at an earlier age. This finding could be due to earlier symptom development, greater parental awareness, or more contact with providers. Among those with ADHD or attention problems, stimulant medication was more likely to be prescribed to children with spina bifida, despite research that suggests it may not be as beneficial for them. Further research on the effectiveness of ADHD pharmacological treatment for children with spina bifida is recommended

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Transl Psychiatry. 2018;8.

SHARED ENDO-PHENOTYPES OF DEFAULT MODE DSFUNCTION IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Kernbach JM, Satterthwaite TD, Bassett DS, et al.

Categorical diagnoses from the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) manuals are increasingly found to be incongruent with emerging neuroscientific evidence that points towards shared neurobiological dysfunction underlying attention deficit/hyperactivity disorder and autism spectrum disorder. Using resting-state functional magnetic resonance imaging data, functional connectivity of the default mode network, the dorsal attention and salience network was studied in 1305 typically developing and diagnosed participants. A transdiagnostic hierarchical Bayesian modeling framework combining Indian Buffet Processes and Latent Dirichlet Allocation was proposed to address the urgent need for objective brain-derived measures that can acknowledge shared brain network dysfunction in both disorders. We identified three main variation factors characterized by distinct coupling patterns of the temporoparietal cortices in the default mode network with the dorsal attention and salience network. The brain-derived factors were demonstrated to effectively capture the underlying neural dysfunction shared in both disorders more accurately, and to enable more reliable diagnoses of neurobiological dysfunction. The brain-derived phenotypes alone allowed for a classification accuracy reflecting an underlying neuropathology of 67.33% (+/-3.07) in new individuals, which significantly outperformed the 46.73% (+/-3.97) accuracy of categorical diagnoses. Our results provide initial evidence that shared neural dysfunction in ADHD and ASD can be derived from conventional brain recordings in a data-led fashion. Our work is encouraging to pursue a translational endeavor to find and further study brain-derived phenotypes, which could potentially be used to improve clinical decision-making and optimize treatment in the future

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Transl Psychiatry. 2018;8.

BRAIN-COMPUTER-INTERFACE-BASED INTERVENTION RE-NORMALIZES BRAIN FUNCTIONAL NETWORK TOPOLOGY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Qian X, Loo BRY, Castellanos FX, et al.

A brain-computer-interface (BCI)-based attention training game system has shown promise for treating attention deficit/hyperactivity disorder (ADHD) children with inattentive symptoms. However, little is known about brain network organizational changes underlying behavior improvement following BCI-based training. To cover this gap, we aimed to examine the topological alterations of large-scale brain functional networks

induced by the 8-week BCI-based attention intervention in ADHD boys using resting-state functional magnetic resonance imaging method. Compared to the non-intervention (ADHD-NI) group, the intervention group (ADHD-I) showed greater reduction of inattention symptoms accompanied with differential brain network reorganizations after training. Specifically, the ADHD-NI group had increased functional connectivity (FC) within the salience/ventral attention network (SVN) and increased FC between task-positive networks (including the SVN, dorsal attention (DAN), somatomotor, and executive control network) and subcortical regions; in contrast ADHD-I group did not have this pattern. In parallel, ADHD-I group had reduced degree centrality and clustering coefficient as well as increased closeness in task-positive and the default mode networks (prefrontal regions) after the training. More importantly, these reduced local functional processing mainly in the SVN were associated with less inattentive/internalizing problems after 8-week BCI-based intervention across ADHD patients. Our findings suggest that the BCI-based attention training facilitates behavioral improvement in ADHD children by reorganizing brain functional network from more regular to more random configurations, particularly renormalizing salience network processing. Future long-term longitudinal neuroimaging studies are needed to develop the BCI-based intervention approach to promote brain maturation in ADHD

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Value Health. 2018;21:S126.

A CROSS SECTIONAL STUDY OF THE FACTORS THAT AFFECT THERAPY ADHERENCE IN CHILDREN WITH ATTENTION DEFICIT DISORDER/ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Saeed NS, Cleary SD, Maneno M.

Objectives: To examine the psychosocial factors that may impact therapy adherence as defined by parental-reported history of medication use among children with ADD/ADHD.

Methods: A cross-sectional study with data drawn from the 2011-2012 National Survey of Children's Health (NSCH) was conducted. Inclusion criteria for the study were U.S. children or adolescents, age 2-17 years, and a parental-reported history of ADD/ADHD.

Results: Of the 95,677 participants, 29.3% were females, about 75.6%, 13.6%, and 10.8% were White, Black, and Other race, respectively. The mean age of participants was 8.60-¦0.04 years. Significant predictors of ADD/ ADHD therapy adherence were Black race (OR= 0.51, 95% CI: 0.36 - 0.73), Other race (OR= 0.57, 95% CI: 0.40 - 0.81), always had received provider communication (OR= 2.26, 95% CI: 1.40 - 3.64) or usually had received provider communication (OR= 1.92, 95% CI: 1.15 - 3.20), income between 100-199% FPL (OR= 1.53, 95% CI: 1.06 - 2.22), income 400% or more FPL (OR= 1.90, 95% CI: 1.19-3.02), and having public insurance (OR= 2.04, 95% CI: 1.12 -3.71).

Conclusions: Findings suggest that more efforts are needed to address adherence among children of Black and Other race. Also, it shows the positive impact healthcare providers' communication has on improving ADD/ADHD therapy adherence

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ORIGINAL ARTICLE

WILEY Experimental Dermatology

X-linked ichthyosis: Clinical and molecular findings in 35 Italian patients

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Abstract

Recessive X-linked ichthyosis (XLI), the second most common ichthyosis, is caused by mutations in the *STS* gene encoding the steroid sulfatase enzyme. A complete deletion of the STS gene is found in 85%-90% of cases. Rarely, larger deletions involving contiguous genes are detected in syndromic patients. We report the clinical and molecular genetic findings in a series of 35 consecutive Italian male patients. All patients underwent molecular testing by MLPA or aCGH, followed, in case of negative results, by next-generation sequencing analysis. Neuropsychiatric, ophthalmological and paediatric evaluations were also performed. Our survey showed a frequent presence of disease manifestations at birth (42.8%). Fold and palmoplantar surfaces were involved in 18 (51%) and 7 (20%) patients, respectively. Fourteen patients (42%) presented neuropsychiatric symptoms, including attention-deficit hyperactivity disorder and motor disabilities. In addition, two patients with mental retardation were shown to be affected by a contiguous gene syndrome. Twenty-seven patients had a complete *STS* deletion, one a partial deletion and 7 carried missense mutations, two of which previously unreported. In addition, a de novo *STS* deletion was identified in a sporadic case. The frequent presence of palmoplantar and fold involvement in XLI should be taken into account when considering the differential diagnosis with ichthyosis vulgaris. Our findings also underline the relevance of involving the neuropsychiatrist in the multidisciplinary management of XLI. Finally, we report for the first time a de novo mutation which shows that *STS* deletion can also occur in oogenesis.

KEYWORDS

attention-deficit hyperactivity disorder, contiguous gene syndrome, deletion, point mutation, *STS* gene

1 | INTRODUCTION

X-linked ichthyosis (XLI) was first described by Lundborg in 1927[1] as a form of ichthyosis vulgaris characterized by recessive X-linked inheritance. However, the clinical and histological features of the disease were clearly recognized only in 1965 by Wells and Kerr,[2] who also linked it to other markers on X chromosome. Recessive XLI (OMIM #308100) manifests almost exclusively in men and represents the second most common form of ichthyosis with an estimated prevalence ranging from 1:1500 to 1:6000 men worldwide.[3–5]

The disease is caused by mutations in the *STS* gene encoding for the steroid sulfatase (STS) enzyme, a membrane-bound protein expressed at high levels in placenta, but also present in most organs and tissues including the skin, reproductive tract, breast, blood, liver and brain.[6,7] The *STS* gene (10 exons) spans ~135 kb of genomic DNA and is located on chromosome Xp22.31, 7 Mb from the

Diociaiuti and Angioni equally contributed to this study.

p-telomere. In 85%-90% of patients, the defect is a deletion comprising the entire *STS* gene and flanking sequences, while point mutations or partial deletions account for about 10% of cases. In addition, larger deletions involving contiguous genes may result in syndromic conditions, for example X-linked recessive chondrodysplasia punctata (OMIM #302950) (*ARSE*), Kallmann syndrome (OMIM #308700) (*KAL1*), ocular albinism type I (OMIM #300500) (*GPR143*) and short stature (OMIM #300582) (*SHOX*).[7]

X-linked ichthyosis manifests more frequently few weeks after birth, but congenital presentation is possible.[8] At first scales appear large, thin and translucent in a generalized distribution; over time, they are replaced by the typical polygonal dark firmly adherent lesions more prominent on the extremities, trunk and neck. Body folds may be involved, while palms and soles are usually reported as normal. Extracutaneous findings comprise cryptorchidism, corneal opacities and neuropsychiatric findings ranging from attention-deficit hyperactivity disorder to mental retardation.[9] In addition, patient mothers can present delayed or prolonged labour due to insufficient cervical dilation, in turn related to STS placental deficiency.

We report the clinical and molecular findings in a series of 35 consecutive XLI patients including two cases presenting with a contiguous gene syndrome. Four point mutations, two of which previously unreported, 1 single exon deletion and an exceptional case of de novo mutation in the *STS* gene were identified.

2 | PATIENTS AND METHODS

2.1 | Patient recruitment and characterization

Patients with a diagnosis of XLI seen in our Unit from November 2013 to December 2016 were included. The study was approved by the Ethical Committee of Bambino Gesù Children's Hospital and was conducted in accordance with the Helsinki Declaration.

All patients underwent complete clinical examination, and collection of family and personal history based on a specific questionnaire (Table 1). In all cases, the diagnosis was confirmed by molecular testing. Following diagnosis confirmation, patients performed neuropsychiatric and ophthalmologic examinations, and a paediatric evaluation based on clinical findings.

2.2 | Genetic investigations

After obtaining informed consent for genetic analyses, blood samples were drawn from the patients and mothers. Genetic studies were performed on genomic DNA extracted from circulating leucocytes. Molecular findings of eleven patients have been previously reported.[10]

2.2.1 | Multiple ligation-dependent probe amplification (MLPA) analysis

The *STS* gene deletion/duplication analysis was performed using the P160-C1 STS MLPA kit (MRC-Holland, Amsterdam, the Netherlands) containing probes for each exon of the *STS* gene, with the exception of exon 3, as well as two flanking probes targeting the *PUDP* gene. Deletions of a probe recognition sequence on the X chromosome

TABLE 1 History and clinical features in 35 patients affected with recessive X-linked ichthyosis

Feature	Number
Family history	
Y	20
N	15
Age of onset	
Birth	15
<1 month	9
1-6 months	8
>6 months	3
Scale size (legs)	
Small	12
Medium	17
Large	6[a]
Scale colour (legs)	
Light brown	10
Brown	14
Dark brown	8
White	3[a]
Fold involvement	
Y	18
N	17
Palmoplantar involvement	
None	28
Hyperlinearity	5[b]
Mild keratoderma	3[b]
Rapid improvement after sun-exposure[c]	
Y	29
N	1
Hypohidrosis[d]	
Y	12
N	17
Cryptorchidism	
Y	4
N	27
Neuropsychiatric findings[e]	
None	18
ADHD	9
Mental retardation	2
Motor disabilities	5

ADHD, attention-deficit hyperactivity disorder.
[a]Three patients observed in the neonatal period.
[b]One patient presenting both keratoderma and hyperlinearity.
[c]Information available in 30 patients.
[d]Information available in 29 patients.
[e]Information available in 33 patients, 2 patients presented with multiple neuropsychiatric findings.

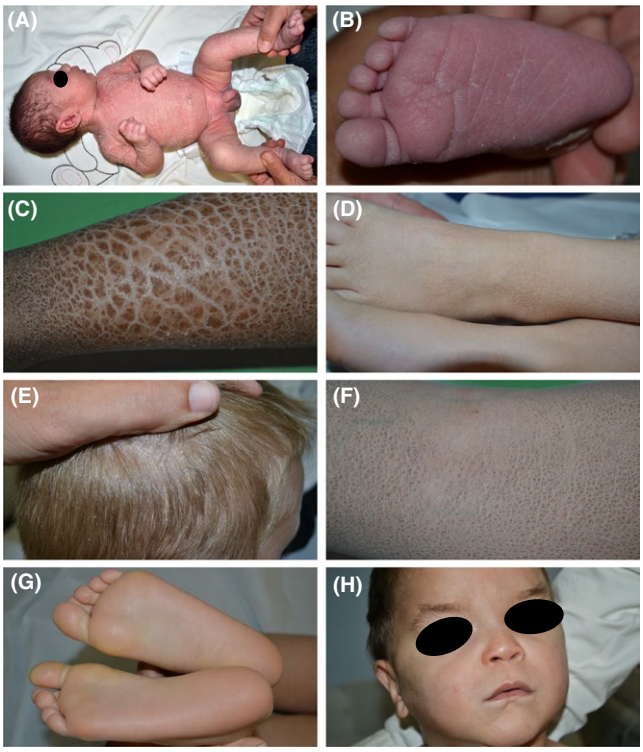

FIGURE 1 Clinical manifestations of recessive X-linked ichthyosis. A, Generalized whitish thin lamellar desquamation in a newborn. B, Plantar hyperkeratosis in the same patient. C, Polygonal, large, dark brown scales on the leg of a 10-year-old boy. D, In contrast, the pretibial scales are small and light brown in this 3-year-old child. E, Confluent, yellowish small scales of the scalp in a 6-year-old child. F, Partial popliteal fold involvement in an 11-year-old boy. G, Mild plantar keratoderma in a 6-year-old boy. H, Strabismus and facial dysmorphism in a patient affected by contiguous gene syndrome (case 2 of Figure 2): microretrognathia, flattened nasal bridge and asymmetric facial appearance

lead to a complete absence of the corresponding amplification product in men, whereas female heterozygotes are recognizable by a 35%-50% reduction in relative peak height. Analyses were performed by electrophoretic run on a 3130*xl* automatic sequencer and analysed with GeneMapper v 5.0 software (Applied Biosystems, Foster City, CA, USA). Data were processed with Coffalyser v 140721.1958 software (MRC-Holland).

2.2.2 | Comparative genomic hybridization array (aCGH)

aCGH test was performed by means of 4 × 180 oligo-array, according to the manufacturer's instruction (Agilent Technologies, Santa Clara, CA, USA). Briefly, DNA from patients and controls was labelled in different fluorescence and each sample-reference couple was competitively hybridized on a microarray surface. Scanned images were extracted and analysed by CytoGenomics v4.0, and results were confirmed by FISH (Fluorescence In Situ Hybridization) analysis on metaphases from peripheral blood culture, using a locus-specific *SHOX* probe (CytoCell, NY, USA).

2.2.3 | Next-generation sequencing analysis

Patients negative to MLPA analysis were screened with next-generation sequencing (NGS) to detect point mutations in the *STS* gene. The gene is included in a customized NGS panel for autosomal recessive congenital ichthyoses, XLI and syndromic ichthyoses.[10] The sequences of the probands were enriched using the Nextera Sequencing Panel according to the manufacturer's protocol (Illumina, Inc., San Diego, CA, USA), and sequenced on the Illumina MiSeq or NextSeq550 platform. The BaseSpace pipeline (Illumina, https://basespace.illumina.com/) and the VariantStudio software (Illumina, http://variantstudio.software.illumina.com/) were used for variant calling and annotating variants, respectively. Sequencing data were aligned to the hg19 human reference genome. The variants were analysed in silico using Scale-Invariant Feature Transform (SIFT), Polymorphism Phenotyping v2 (PolyPhen-2) for the prediction of deleterious non-synonymous SNVs for human diseases. Based on the guidelines of the American College of Medical Genetics and Genomics (5-1), a minimum mean depth coverage of 20× was considered suitable for analysis. Variants were examined for coverage and Qscore (minimum threshold of 30), and visualized by the Integrative Genome Viewer. Variants identified as pathogenic were confirmed by Sanger sequencing in the proband and his mother, following a standard protocol (BigDye Terminator v3.1 Cycle Sequencing Kit, Applied Biosystems by Life Technologies).

3 | RESULTS

We enrolled 35 consecutive male patients affected by XLI confirmed by molecular diagnosis. Most patients were children (n. 31 < 13-years-old), and the mean age at the time of observation was 7.8 ± 20.2 years (age range: 10 days-58 years).

Fifteen patients (42.8%) had a positive family history with one or more maternal relatives affected (Table 1). In addition, the mother of an XLI patient showed minimal greyish to light brown scaling on ankles, calves, popliteal folds, and very small scales in a linear arrangement along Blaschko lines on the posterior aspect of the tights (Figure S1).

3.1 | Skin findings

In fifteen cases (42.8%), the disease was present at birth (Table 1). Three patients, who were observed in the neonatal period, presented with large whitish loosely adherent thin generalized scales also affecting the scalp, and mild palmoplantar keratoderma (Figure 1A,B). One of them showed a translucent membrane resembling collodion at birth.[10] In all cases, scales detached during the first month of life, leaving a xerotic skin, followed by the appearance of small brownish scales. In the remaining patients, the disease was noticed by the parents in the first month of life in 9 cases, between the second and the sixth month in 8, and later in 3 (Table 1).

Starting from childhood, scales were light to dark brown in colour (Figure 2C,D, Table 1), more evident and larger on lower legs followed by arms and flanks. In almost all patients, the abdomen was more severely affected than the back. Scales were confluent and lighter on the scalp, which was involved in all cases (Figure 1E). Preauricular small scales were observed in the vast majority of patients seen during childhood. Partial or complete fold involvement consisting of scaling or hyperkeratosis was present in 18 of 35 patients (51%) (Figure 1F, Table 1). Palmoplantar manifestations were observed in 7 patients (20%), who presented palmoplantar hyperlinearity (4 cases) or mild keratoderma (2 cases) or both (1 case) (Figure 1G, Table 1).

Almost all patients reported a dramatic improvement of their skin condition within the first days of sun-exposure (Table 1). Twelve of 29 patients also reported hypohidrosis and occasionally reduced heat tolerance (Table 1).

3.2 | Extracutaneous findings

Four of 31 patients (12.9%) presented cryptorchidism or testicular maldescent (Table 1). Fourteen of 33 patients (42.4%) presented neuropsychiatric findings (Table 1). Specifically, manifestations of attention-deficit hyperactivity disorder (ADHD) spectrum were observed in 9 patients, comprising inattention deficits or isolated hyperactivity signs or oppositional behaviour or combined findings. Five of nine patients had already a diagnosis of ADHD when they came to our observation and, in the remaining four cases, behavioural abnormalities had been noticed by teachers. In two patients who had mental retardation molecular genetic studies disclosed a contiguous gene syndrome. Finally, 5 patients presented motor disabilities, including one of the two cases with a contiguous gene syndrome and a patient with ADHD manifestations. No corneal opacities were detected in our population.

One patient with a contiguous gene syndrome due to a microdeletion in Xp22.33p22.31 region (case 1, Figure 2A) showed, in addition to mild intellectual disability, short stature, a dysmorphic facies with flattened nasal bridge, hypertelorism and full lips, and shortness of terminal phalanges. The second patient presenting with a contiguous gene syndrome due to a Xp22.33p22.2 deletion (case 2, Figure 2A) showed, in addition to psychomotor delay and autistic symptoms, cryptorchidism, small penis, short stature (height below 3°), asymmetric shortening of legs, scoliosis, dysplasia of hip joints, delayed ossification, left choanal stenosis, dysmorphic facies, strabismus and nystagmus (Figure 1H).

3.3 | Molecular findings

All patients underwent molecular genetics testing. Due to the high incidence of genomic rearrangements, we investigated patients firstly with MLPA or aCGH and, in case of normal results, using a NGS-targeted approach including the *STS* gene. Twenty-seven patients showed a complete deletion of the *STS* gene, whereas one patient had a partial deletion consisting in loss of exon 7. All but one case of rare de novo deletion were inherited from the mother. Seven patients displayed a classic microdeletion ranging from 1.35 Mb to 1.6 Mb; two patients revealed extensive deletions, responsible of the consequent contiguous gene syndrome, of 8.2 and 9.7 Mb, respectively. Both deletions were from maternal segregation. The first was due to a complex chromosome rearrangement described by FISH as: ish. der(X)t(X;Y)(p22.31;q11.22)(Shox-,DYZ1 +)mat (case 1, Figure 2A). The second, which includes a DNA segment from the *SHOX* gene to the *GPR143* gene, was characterized as: arr[hg19] Xp 22.33p22.2(61 115-9 739 638)×0 mat (case 2, Figure 2A). Seven patients (20%), three couples of brothers and a child, had four germline missense mutations, c.323C>T (p.S108L) (Figure 2B), c.452C>G (p.P151R), c.1030G>A (p.G344R) (Figure 2C) and c.1075G>A (p.G359R) involving exons 4, 5 and 7. The complete list of all point mutations described in the literature is reported in Table 2.

4 | DISCUSSION

The presence of at least one affected maternal male relative in the pedigree was recorded in a significant proportion of our patients (42.8%) confirming the importance of collecting an accurate family history as a diagnostic hint in XLI. Interestingly, we observed minimal clinical signs of the disease in the mother of an affected child, in agreement with previous reports[11] and with the concept that *STS* only partially escapes X inactivation.[6] In addition, the lesions on the tights showed an intriguing linear and blaschkoid distribution which may be suggestive of wild-type *STS* inactivation at an early developmental stage.

We observed three newborns with congenital disease. A thin translucent membrane was present at birth over the entire body including palms and soles and rapidly started to peel off with whitish lamellar desquamation. This parchment-like membrane may simulate a collodion baby and its resolving course may suggest a self-healing form.[12,13] In addition, in 12 patients, the parents reported the presence of a fine whitish scaling in the first days of life, confirming that XLI manifests around birth in a significant proportion of cases.[14,15] However, whitish scales which represent the first disease symptom rapidly disappear and can thus be overlooked, while classical manifestations with dark polygonal scaling appear from late infancy to early childhood and usually lead to dermatological consultation. Our findings on lesion appearance and distribution in XLI are in keeping with the literature data.[6,14] Scalp was affected in all children and also in the few adults included in our study. The presence of fold involvement in about half of the patients limits its usefulness in differentiating XLI from ichthyosis vulgaris where folds are regularly spared. Of note, palmoplantar involvement, mainly presenting as hyperlinearity, was detected in a significant percentage of patients (20%), in contrast with the common notion that palmoplantar surfaces are not affected in XLI. Quite recently, Süßmuth et al[16] examined 51 XLI patients for common mutations in the *FLG* gene and showed a significant association between palmoplantar hyperlinearity and *FLG* mutations. On the other hand, palmar hyperlinearity has

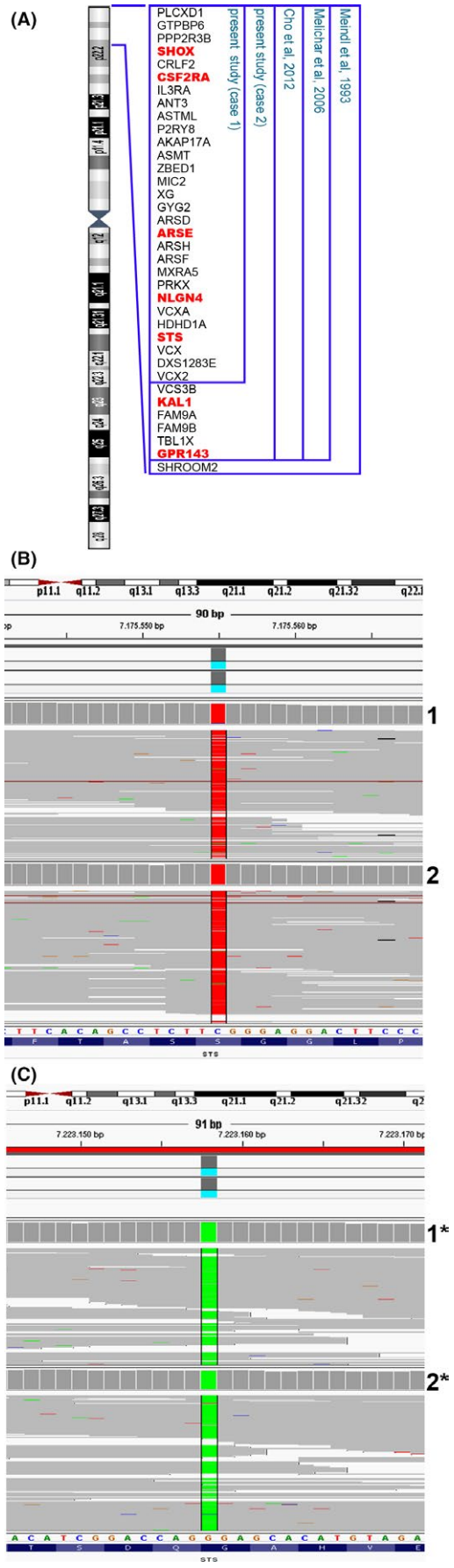

FIGURE 2 Molecular genetic findings in selected patients. A, Chromosome X ideogram depicting the gene content of the deletions detected in our two patients affected with contiguous gene syndrome and in previously described cases with the largest deletions. All involved OMIM genes (https://www.omim.org/) are listed (OMIM disease-causing genes are shown in red). NGS representation of two novel missense mutations found in the *STS* gene (NM_000351.4): B, the green column shows the transversion G>A (c.1030G>A, p.G344R) in two brothers (1, 2); C, the red column shows the transversion C>T (c.323C>T, p.S108L) in two heterozygous twins (1*, 2*)

been described in XLI also in the absence of *FLG* mutations.[17] The *FLG* gene is not comprised in our NGS panel for ichthyoses; thus, we could not determine whether XLI patients with palmoplantar manifestations carry *FLG* mutations. Nevertheless, our findings underline that involvement of palmoplantar surfaces does not exclude the diagnosis of XLI. Clinical improvement during summer time is a common feature in ichthyosis patients. However, XLI is characterized by an almost complete disease resolution following few days of sun-exposure. This feature is scarcely outlined in the literature and can make the diagnosis challenging during summer, in particular in Southern European countries. It also points to the possibility of treating adult patients with severe disease manifestations with short courses of phototherapy as an alternative to systemic retinoids. The presence of hypohidrosis in almost half of the patients is in keeping with the involvement of sweat glands attested by the histopathological finding of keratotic plugs filling in sweat glands orifices.[14]

The percentage of cryptorchidism in our patients (12.9%) is in line with the literature findings in XLI, while the absence of corneal opacities can be explained by their young age. Indeed, the detection of corneal opacities is quite rare before puberty.[18,19] Nine of 33 patients (27%) presented manifestations of ADHD, confirming recent literature findings on the increased prevalence of these behavioural phenotypes in XLI.[9,20] Indeed, the worldwide-pooled prevalence of ADHD is estimated at around 5% in school-age children,[21] and a population-based study in a sample of Italian children and adolescents indicated a prevalence of 3%, with a higher percentage of affected males (5.1%).[22] ADHD is reported in XLI patients due to both *STS* deletions and point mutations, suggesting that STS deficiency plays a direct role in the pathogenesis of inattentive/hyperactivity symptoms. STS converts dehydroepiandrosterone sulphate (DHEAS) in dehydroepiandrosterone (DHEA), both steroids being implicated in neurological processes related to ADHD symptoms in humans.[23] Moreover, blood levels of DHEA and DHEAS are increased by methylphenidate used for ADHD treatment.[24] Finally, mouse disease models support the involvement of STS in neurodevelopment and brain function,[25] in keeping with the high expression of STS in developing brain areas, such as cerebellar neuroepithelium, basal ganglia and thalamus, which have been associated with visual attention and impulsivity.[26] On the other hand, mental delay present in the two patients with contiguous gene syndrome is most likely related to the deletion of specific genes.

TABLE 2 Point mutations in the *STS* gene reported to date in the literature

Patient	Sequence change	Amino acid change	Exon	Reference
1	c261C>G	p.Y87X	3	del Refugio Rivera Vega et al[45]
2	c.268C>T	p.R90X	3	Winge et al[46]
3	c.323C>T	p.S108L	4	This study
4	c.452C>G	p.P151R	5	Diociaiuti et al[10]
5	c.494C>T	p.T165I	5	Liao et al[47]
6	c.529_532del4insAG	p.V177Sfs81*	5	Takeichi et al[12]
7	c.1022C>T	p.S341L	7	Basler et al[38]
8	c.1030G>A	p.G344R	7	This study
9	c.1032C>T	p.G344X	7	Morita et al[44]
10	1046_1048delAAG	p.E349del	7	Valdes-Flores et al[48]
11	c.1049T>G	p.V350G	7	Oyama et al[37]
12	c.1075G>A	p.G359R	7	Diociaiuti et al[10]/ Oyama et al[37]
13	c.1099G>A	p.G367R	8	Wei et al[49]
14	c.1114T>A	p.W372R	8	Basler et al[38]
15	c.1115G>C	p.W372S	8	Alperin et al[39]
16	c.1138G>C	p.G380R	8	Oyama et al[50]
17	c.1165C>T	p.Q389X	8	Oyama et al[50]
18	c.1213_1214insTC	p.P405Lfs408*	8	Murtaza[51]
19	IVS8 ds+1G-T	p.R419Sfs427*	8	Alperin et al[39]
20	c.1331A>G	p.H444R	9	Alperin et al[39]
21	c.1337G>A	p.C446Y	9	Basler et al[38]
22	c.1360C>T	p.R454C	9	Gonzalez-Huerta et al[41]
23	c.1361G>A	p.R454H	9	Valdes-Flores et al[40]
24	c.1679A>C	p.Q560P	10	Sugawara et al[42]
25	c.1679A>G	p.Q560R	10	Goodwin et al[43]

Most individuals (85%-90%) with XLI have extensive deletions of the *STS* gene and the percentage of gene defects due to deletions of *STS* is one of the highest among all genetic diseases. The most frequent picture is the loss of a genomic region encompassing about 1.6 Mb including, other than *STS*, also various genes such as *VCX3A*, *HDHD1*, *VCX*, *PNPLA4* and *VCX2* which may be responsible for additional symptoms. The *STS* deletion is usually complete, but partial *STS* gene deletions may be an occasional finding. In our series, we identified a patient with intragenic loss of exon 7 and classical features of XLI. Two isolated partial deletions, involving exons 2-10 and exons 1-5, respectively, have been described by Valdes-Flores and co-workers in patients with XLI.[27,28] A small intragenic deletion of 37 kb involving exons 2-6 of *STS* has been described in a 4-year-old boy with dry skin and eczema.[29] One more case of partial deletion of *STS* spanning exons 7-10 has been recently reported in a boy with primary microcephaly due to co-occurrence of mutations in the *ASPM* gene.[30] Different from these occasional observations, an exceptional rate of 25% has been reported in a series of Spanish patients.[31] The authors suggested that this uncommon finding should be explained by the high incidence of consanguineous patients and by a founder effect.[31]

Among the patients with complete *STS* deletion, we found a male newborn showing a de novo rearrangement. A first segregation study reported the paternal origin of the X chromosome transmitted to a daughter with a de novo deletion of *STS*.[32] A more recent study on seven unrelated sporadic cases of XLI demonstrated, by means of short tandem repeats, the paternal transmission to the mother of the proband in 5 out 7 cases (two cases were uninformative), suggesting that the *STS* deletion occurred in the male meiosis.[33] In contrast, in our case, the mother of the patient was negative to MLPA analysis indicating that the genomic rearrangement arose in the maternal meiosis. Thus, *STS* deletion seems to occur much more frequently in male gonads, in keeping with the high number of cell divisions in spermatogenesis. However, our case shows that it can also arise in oogenesis.

Two patients showed large deletions responsible for the appearance of a contiguous gene syndrome. In the first patient, two maternally inherited imbalances were detected as follows: a microdeletion in Xp22.33p22.31 region (8.2 Mb), including 5 OMIM disease-causing genes (*SHOX*: OMIM #300582, *CSF2RA*: OMIM #300770, *ARSE*: OMIM #302950, *NLGN4*: OMIM #300495, *STS*: OMIM #308100) and the microduplication of the long arm of chromosome Y (Yq11.221q12, 43 Mb in size). FISH analysis using a fluorescent-labelled-specific probe for the *SHOX* region on the patient and his mother allowed associating the result to the presence of a derivative X chromosome, originated by an imbalanced X;Y translocation. In this case, the clinical picture can be addressed only to the Xp deletion, being the duplication of the Yq chromosome asymptomatic. Facial dysmorphism, short stature, shortness of terminal phalanges, mild intellectual disability and ichthyosis were the main clinical features, in keeping with the extension of the genomic deletion, while the mother only showed short stature. The second patient presented with an Xp22.33p22.2 deletion, 9.7 Mb in size, encompassing 7 OMIM disease-causing genes (*SHOX*, *CSF2RA*, *ARSE*, *NLGN4*, *STS*, *KAL1*: OMIM #308700, and *GPR143*: OMIM #300500). FISH analysis confirmed the deletion in both the patient and his mother. Several reports described terminal deletions of Xp of variable extent in men; however, deletions involving also the genes of Kallmann syndrome and Ocular Albinism (OA1) are rather uncommon. We were able to find only three cases of large deletions including the OA1 locus.[34–36] Our case is the fourth patient with an interstitial deletion of Xp including all the genes previously reported. Actually, he is a 4-year-old child presenting retarded growth, facial dysmorphism, small penis and cryptorchidism, psychomotor delay, ichthyosis, strabismus and nystagmus, and stenosis of the left choana. The presence in our case series of two patients affected with the rare contiguous gene syndrome is likely related to our hospital role of tertiary care centre.

Within the patients found negative to MLPA and aCGH investigations, we identified four point mutations carried from three couples of siblings and one unrelated child. Mutation p.G359R, located in the distal part of exon 7, was described at the same time by our

group[10] and by Oyama and co-workers.[37] Along with p.G359R, we previously reported also the missense mutation p.P151R on exon 5 in a child with ichthyosis onset at birth.[10] Mutation p.S108L is a novel missense sequence variation located in exon 4, carried from a couple of heterozygous twins with disease onset at three weeks of age. p.S108L is the first mutation described to involve exon 4. Mutation p.G344R is a novel mutation in exon 7 found in a couple of siblings who presented ichthyosis at birth. Overall, no correlation between disease severity and the presence of deletions vs point mutations could be detected. Data from the literature seem to indicate that some *STS* codons are more frequently mutated. In fact, different missense mutations involve codons 372,[38,39] 454[40,41] and 560,[42,43] and a nonsense mutation has been reported at codon 344.[44] As shown in Table 2, 25 point mutations, including those reported in this study, have been identified to date. Most of the mutations are missense and, except for exon 1, 2 and 6, all the coding regions are involved, even if the large majority of mutations fall within exon 7 through 9. Moreover, in silico studies and clinical data suggest that these sequence variations may disrupt, depending on the position, both the N-terminal catalytic site and the C-terminal substrate-binding site compromising the function of the *STS* gene.

In conclusion, our findings underline once more that, in the absence of an informative family history, the differential diagnosis between ichthyosis vulgaris and XLI may not be trivial because of overlapping phenotypic spectrum.

They also show the relevance of a multidisciplinary approach in the management of XLI. Among the specialists involved, the neurologist and the neuropsychiatrist are fundamental to assess the presence of neuropsychiatric signs of the disease. Otherwise, molecular investigations currently represent an important tool to make sure and affordable the correct recognition of the disease, leading to the characterization of the genetic defect to provide a more accurate and effective counselling.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTIONS

AD, AA, MEH designed the research study; AD, AA, GZ, EP, VA, MEH performed the research; AD, AA, GZ, AN analysed the data; AD, AA, GZ, AN, MEH wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Clinical findings in the mother of a patient affected with recessive X-linked ichthyosis. Very small greyish to light brown scales on the ankle and heel (A). Similar small scales are visible in a linear arrangement on the posterior aspect of the right tight (B), the inset shows a detail of the linear lesions.

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RESEARCH Open Access

ADHD prevalence estimates in Italian children and adolescents: a methodological issue

Laura Reale and Maurizio Bonati*

Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is recognized as the most common, and most studied, developmental age disorder. Basic information, such as the most appropriate case definition and the best way to evaluate the disorder's prevalence rate, however, remains an open issue.

Methods: A comprehensive meta-analysis on the epidemiology of ADHD in Italy, which was lacking from the literature, was therefore performed to attempt to estimate the actual prevalence rate of ADHD, highlighting conceptual and quantitative differences between clinical-diagnosis and survey-based symptoms studies. The Medline, Embase, and PsycINFO databases, and the grey literature, were searched up to January 2018. The review was laid out in three main sections: an overall prevalence estimate, an epidemiological profile of ADHD symptoms, and an attempt to define the actual rate of ADHD diagnosis, as emerged from Italian studies.

Results: A total of 15 unique studies were included. These contributed to estimating the prevalence of ADHD in 67,838 subjects aged 5–17, representing 9 of the 20 regions (45%) of Italy. Overall, the pooled prevalence of ADHD was 2.9% (range: 1.1–16.7%). When distinguishing studies based on case definition, however, we found an average prevalence estimate, based on symptoms criteria, of 5.9% (range: 1.4 to 16.7%) and a best-estimate prevalence rate of 1.4% (range: 1.1 to 3.1%).

Conclusions: Following the case definition for epidemiological studies of ADHD, counting only subjects with an ADHD diagnosis performed and confirmed by clinical assessment would reduce the wide variability in prevalence estimates, and, above all, would both describe the real rate of subjects suffering from ADHD disorder and avoid misdiagnosis.

Keywords: Attention deficit/hyperactivity disorder, Prevalence, Methodology, Italy

Background

The exact time of onset for individual cases in psychiatry is often not known, and prevalence estimates on a given period are used as a substitute for identifying the proportion of cases of a particular disorder in a defined population [1].

Several factors can influence observed prevalence rates as the diagnostic criteria, the setting, the population studied, the type and severity of the disorder, and the comorbidities. Since measures of prevalence are also helpful in assessing health care needs and in planning health care services [2], estimates should be as accurate as possible. This is an issue especially in mental health care, where the risk of misdiagnosis and of false positives is a significant problem affecting appropriate and effective interventions, increasing the risk of medicalization and overuse of drug treatments, and creating stigma and discrimination [3, 4], as the worldwide debate also on attention deficit hyperactivity disorder (ADHD) confirms [5].

To date, ADHD is considered the most common, and most studied, developmental age disorder, even though basic information, such as the most appropriate case definition for estimating its prevalence rate, remains an open issue and leaves room for significant, debates in scientific literature [6, 7]. The reported range in prevalence is very wide (from 0.2 to 34.5%), and heterogeneity in the methodological approaches used contributes to these differences [8–12]. This is similar to the situation

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described for all child and mental health problems worldwide [13], supporting difficulties, greater in psychiatry than physical medicine, in discriminating disordered and non-disordered conditions [14, 15]. The 5% increase in children diagnosed as having ADHD reported in the US in recent years also suggests the need for valid tools to support diagnosis in practice [16].

ADHD is recognized as a difficult diagnosis to make accurately, not only because of the many comorbid conditions, but also for the low specificity of the core symptoms: the list of disorders or conditions that can make a child appear restless or distractible is almost endless. Making a proper diagnosis thus requires a detailed evaluation of development, educational demands, and what is expected of the child in a given circumstance and at a given time, as well as symptomatology, impairment, and risk [17, 18].

Although it is widely recognized that several ADHD symptoms, as investigated by symptom surveys or interviews, may occur as manifestations of other medical (i.e. hypoglycemia or sensory processing disorders) and psychiatric (i.e. mood, anxiety or autism spectrum disorders) disorders, few published studies have directly examined the rate and type of psychiatric and medical disorders in those previously identified as ADHD positive by teacher or parent ratings [19]. All psychiatric diagnoses are mainly clinical-based, and both subjectivity and cultural factors affect the evaluation of symptom severity (significant distress) and impairment (in social, academic or occupational functioning) in the disorder [20, 21]. Furthermore, subjects defined as having ADHD according to symptom survey-based evaluations may not truly be suffering from ADHD because they may meet only one of the five DSM-IV-TR criteria (criteria A) needed to reach a diagnosis of ADHD, and a clinical evaluation is necessary to assess the other four criteria [22]. The risk of "misdiagnosing normality" in psychiatry is high, in particular when symptom-based criteria for disorders, as in the DSM, are applied using symptom checklists, in particular in population settings and by non-medical-health professionals [14].

In such a context the goal of this study was to evaluate certain factors that can affect the prevalence of ADHD in reported studies and, consequently, the observed variability, in particular in overall pooled estimates. We analyzed the methodological approach used, and the implications in practice, of Italian ADHD studies.

Methods

The research was approved by the Institutional Review Board of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

Search strategy and selection criteria

We searched the Medline, Embase, and PsycINFO databases for articles written in English and published before January 2018 using the following Medical Subject Headings and free text terms: "ADHD", "ADD", "attention deficit", "attention deficit hyperactivity disorder", "hyperkinetic disorder", "epidemiology", "prevalence", "survey", "child*", and "adolesc*". Studies with an Italian affiliation and point prevalence estimates of ADHD in Italy were extracted. Non indexed journals were searched for in the Google Scholar search engine by using keywords to identify potentially eligible studies. Articles written in Italian were also considered. Additionally, the reference lists of all eligible articles were scanned, as well as key Italian journals and websites, to identify additional, potentially relevant papers. Studies considered eligible were those that used the diagnostic criteria or survey instruments based on DSM-III, DSM-III-R, DSM-IV, DSM-5, or ICD-10, with samples from community, school, or clinically referred populations. We included studies with participants aged < 18 years.

Data extraction and quality assessment

After removing duplicates, the two authors screened the titles and abstracts for adherence to eligibility criteria. In cases of uncertainty concerning eligibility, the records were discussed until a consensus was achieved. For studies deemed suitable, we obtained the full text for data extraction. References of suitable studies were searched to recover any relevant articles.

Data were extracted by the authors and involved general publication information, demographic variables of the population sample, year of sampling, setting, frame procedure, region and city, screening and diagnostic instruments used to define a case as ADHD, informant, and whether a clinical impairment evaluation was performed. The authors independently assessed each Italian study for methodological quality. The included articles were assessed by using a modified tool developed by Hoy et al. [23] for assessing risk of bias in prevalence studies that includes eight questions. These were: 1) was the study's target population a close representation of the national population in relation to relevant variables?; 2) was the sampling frame a true or close representation of the target population?; 3) was some form of random selection used to select the sample?; 4) was the likelihood of non response bias minimal?; 5) were data collected directly from the subjects?; 6) was the study instrument that measured the parameter of interest shown to have validity and reliability?; 7) was the same mode of data collection used for all subjects?; 8) were the numerator(s) and denominator(s) for the parameter of interest appropriate? A study was considered to have a high overall risk of bias if ≤3 criteria were met, moderate risk of bias if 4 or 5 criteria were met, and low risk of bias if 6 to 8 criteria were met.

Statistical analysis

For each retrieved study an assessment of inclusion, exclusion, and quality was performed independently by the two authors, and the inter-reviewer reliability was measured using Cohen's Kappa statistics. Study data were analysed using Stata version 11.1 (Stata Corp, College Station, TX). Because of the differences in study sample sizes, SEs of the prevalence estimates from each study were calculated based on the exact binomial likelihood. Summary effect estimates of prevalence were calculated by using a random effects meta-regression model because there was a clear heterogeneity between the studies tested using the I^2 statistic [24]. The study factors that might be related to prevalence estimate were first tested individually in a univariate analysis and then simultaneously in a multiple meta-regression model via likelihood ratio test conducted with R, using the 'metafor' package [25]. Study factors included: sample size, sampling frame, informant, quality of the study, geographical location, and diagnostic criteria. Studies were grouped according to considered factors, and the estimates were then pooled. We used the z test of 2 proportions to examine differences in prevalence estimates of studies by factors considered. Five studies reported prevalence estimates from different types of informants. These studies were included in univariate and multiple meta-regression analyses and in the overall pooled results for each prevalence estimate.

Results

Our search yielded 199 citations, 5 of which were duplicates (Fig. 1). After removal of unsuitable and ineligible studies, and the addition of 9 papers retrieved from the bibliographies of identified studies or grey literature, we had a total of 15 unique Italian studies for quality assessment and meta-analysis [26–40]. Included studies contributed 22 estimates of prevalence in 67,838 subjects, 5–17 years old, over a 30-year period (Table 1). Male sample was reported in 12 studies and lay within the range 45–55%. Both reviewers fully agreed on the choice of the pertinent studies (weighted K = 1). Studies meeting inclusion criteria were conducted in 9 of 20 Italian regions (45%) that cover 53% of the Italian 5–17 year old population. However, 7 studies (47%) were conducted in the North of the country. Among the 9 studies (60%) reporting the year of sampling the time period between the data collection and the publication ranged from 1 to 11 years (average 4). A majority of the studies was conducted in school populations ($n = 12$), while the rest were performed in clinical settings (2 in child and adolescent neuropsychiatric services and 1 in family paediatrician practices), using a whole population approach. Three of the school-based studies also involved child and adolescent neuropsychiatric services in the clinical confirmation of suspect ADHD. Overall, the methods used in the studies were rating scales, questionnaires, interviews, or other clinical tools based mainly on DSM-IV criteria (11 studies), while the remaining were conducted according to DSM-III-R (2 studies), DSM-III (1 study) and ICD-10 (1 study) criteria. The informants in the studies were teachers in 11 cases, patients in 1, and parents in 3; 2 studies included both teachers and parents.

A good agreement between reviewers on the evaluation of the quality of the studies was found (weighted K = 0.61). No studies met all 8 criteria, although 93% had a low, or moderate, risk of bias. The majority of studies rated poorly for the representativeness of sample (87%).

The overall, pooled prevalence of ADHD, including all reported prevalence estimates ($n = 22$), was 4.3% (95% confidence interval [CI]:3.1 to 5.7), with a wide inter-study range of 1.1 to 16.7% (Table 1). The prevalence estimate of ADHD was, on average, 0.5% lower including, in the overall pooled analysis, only the lowest estimate of each study (3.8%, CI 2.6–5.1). In only one study of low quality the prevalence estimate of ADHD was lower for males than female [38], while in all other studies the rate for boys was 1.2–7.6 higher than for girls.

The included studies used different algorithms to estimate the number of children and adolescents with ADHD. To examine the impact of these different assessment procedures, separate prevalence estimates were calculated for each specific algorithm used. The majority of studies defined ADHD based on symptom ratings by teachers alone (8 studies). Only 2 studies required an individual to meet symptom criteria based on both parent and teacher ratings, using the "AND rule" algorithm that codes as positive only if both rates agree. Finally, 6 of 15 studies (40%) used a best estimate diagnostic algorithm in which a clinical evaluation was performed at the end of the assessment to obtain an ADHD diagnosis based on standard classification criteria (4 based on DSM-IV, 1 on DSM-III-R, 1 on ICD-10, and no study on DSM-5). Four of these 6 studies assessed a population sample and 2 a population of clinically referred subjects.

Within the univariate models, prevalence estimates for ADHD were, on average, 1.7% lower when DSM-IV criteria were used than when other criteria were used (Table 2). One study was conducted in the North, Centre, and South of Italy and prevalence estimates for ADHD were, on average, 2.2% lower compared to the North, and close to those of other geographical locations. On average, similar ADHD prevalence estimates were obtained when the informant was the clinician or both the parent and teacher (AND rule), whereas estimates were 5.1% higher when based on teacher ratings, 1% higher when based on parental reports, and 15% higher when based on child interviews. There was a significant increase in prevalence estimates when the

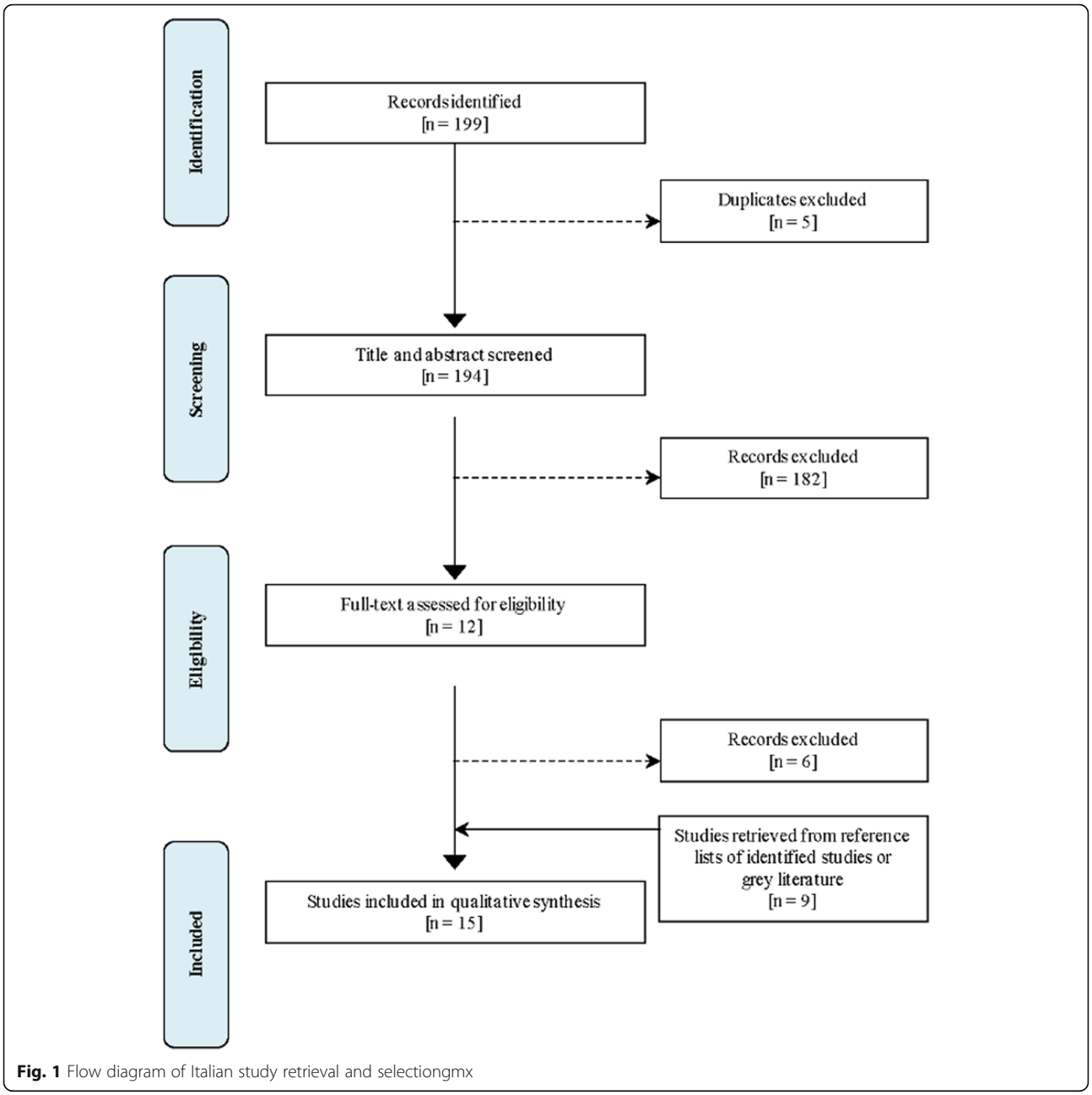

Fig. 1 Flow diagram of Italian study retrieval and selectiongmx

school setting was compared with that of the population (at school estimates were, on average 3.9% higher). Prevalence estimates were, on average, 2.8% lower when study sample sizes were > 1000 participants, and 1.5% higher when the quality of the study was low or moderate (RoB score ≤ 5). Prevalence estimates were, on average, slightly lower in studies published before 2006.

According to both the clinical and methodological diversity of the retrieved studies, all univariate analyses revealed that all considered covariates were significantly associated with heterogeneity of prevalence estimates.

After entering all study factors into a multivariate meta-regression, only teacher and child case definition remained significant (Table 2).

Discussion

Performing a clinical assessment to make a diagnosis in mental health care is necessary to define whether a subject suffers from a psychiatric disorder or not. In our opinion, therefore, selecting an appropriate case definition that is supported by a clinician-based diagnosis is a critical step to estimating the real prevalence rate of ADHD.

Table 1 Characteristics of Italian Studies evaluated for prevalence of ADHD

First author (year of publication)	Year of data collection	Frame	Age range or mean (yrs)	Sample size	Males in the study (%)	Criteria	RoB Score	Studies using symptom-based questionnaires					Studies with clinical-based diagnosis			
								Evaluation instrument	Evaluation informant	ADHD prevalence (%)	CI 95% (binomial exact)	Males/ Females ratio	Impairment evaluation	ADHD prevalence (%)	CI 95% (binomial exact)	Males/ Females ratio
O'Leary (1985) [26]	NR	School	6–8	344	54.1	DSM-III	5	CTRS	T	12.2	8.9–16.1	6.7				
Gallucci (1993) [27]	1991	School	8–10	232	46.1	DSM-III-R	6	SQ	T	3.9	1.8–7.2	7.2				
Camerini (1996) [28]	1995	School	6–12	2557	NR	DSM-IV	2	CTRS, SQ	T	5.0	4.2–6.0	7.6				
Marzocchi (2000) [29]	1995–1996	School	7–10	973	52.0	DSM-IV	5	CTRS, SDAI, DBD	T	8.3	6.7–10.2	4.1				
Corbo (2003) [30]	1999	FP	mean: 9.5	794	52.2	DSM-IV	4	CTRS, SQ	P	2.4	1.5–3.7	NR	NR	1.5	0.8–2.6	4.8
Ciotti (2003) [31]	2003	CANPS	7–14	Population 11,980	NR	ICD-10	5						NR	1.1	0.9–1.3	3.1
Madeddu (2006) [32]	2001–2002	School	11–13	570	46.8	DSM-III-R	4	DICA-R	C	16.7	13.7–20.0	0.9	Yes	1.2	0.5–2.5	1.5
Mugnaini (2006) [33]	NR	School	6.6–7.4	1891	50.5	DSM-IV	7	Modified VADTRS	T	7.1	6.0–8.4	2.7				1.6
Zuddas (2006) [34]	NR	School	6–12	T: 1085	53.0	DSM-IV	5	DBD test	T, P	T: 8.6	7.0–10.4	1.8				
				P: 1575	55.0					P: 2.5	1.8–3.4	1.4				
										AR: 1.4	0.8–2.3	NR				
Faravelli (2009) [35]	NR	School	6–11	999	50.6	DSM-IV	5	SQ	T	5.6	4.3–7.2	2.3				
Maschietto (2012) [36]	2007–2010	CANPS	6–17	Population 24,028	NR	DSM-IV	7						Yes	1.2	1.1–1.4	1.2
Bianchini (2013) [37]	2010–2011	School	5–14	6183	51.4	DSM-IV	6	SDAI	T	7.3	6.7–8.0	3.5	Yes	3.1	2.7–3.5	5.7
Gritti (2014) [38]	NR	School	8–9	1390	45.0	DSM-IV	4	CTRS	T	2.8	2.0–3.8	0.5				
Donfrancesco (2015) [39]	2002–2003	School	7–13	1887	49.0	DSM-IV	7	SDAG, SDAI	T, P	T: 4.6	3.6–5.5	7.2	Yes	1.3	0.9–2.0	9.7
										AR: 2.2	1.6–2.3	6.3				
Zucchetti (2015) [40]	NR	School	8–10	334	48.2	DSM-IV	5	SDAI	T	10.8	7.7–14.6	1.5				

Note. *AR* "and rule" algorithm, *C* child, *CANPS* child and adolescent neuropsychiatric service, *CTRS* Conners' Teacher Rating Scale, *DBD* Disruptive Behavior Disorder rating scale, *DICA-R* Diagnostic Interview for Child and Adolescent, *FP* family paediatrician, *NR* not reported, *P* parent, *SDAG* Attention and Hyperactivity Parent rating scale, *SDAI* Attention and Hyperactivity Teacher rating scale, *SQ* ad hoc study questionnaire, *T* teacher, *VADTRS* Vanderbilt Diagnostic Adhd Teacher Rating Scale

Table 2 Association between study factors and ADHD estimates

Study factors	Univariate analyses				Multivariate analyses			
	Estimated prevalence difference %	95% CI		*P*	Estimated prevalence difference %	95% CI		*P*
		Min	Max			Min	Max	
Diagnostic criteria (DSM-IV as reference)								
Other criteria	1.65	1.23	2.07	< 0.0001	1.21	-11.53	9.11	0.7944
Geographical location (North, Center and South as reference)								
Northern Italy	2.17	1.53	2.81	< 0.0001	−1.39	-14.42	11.65	0.8123
Central Italy	−0.46	−1.15	0.23	0.1772	−8.91	-21.66	3.83	0.1454
Southern Italy	0.58	−0.11	1.27	0.1134	−5.92	-18.35	6.52	0.3045
Case definition (clinician as reference)								
AND rule	−0.12	−0.56	0.32	0.6161	−0.64	-12.21	10.93	0.9013
Parent	0.96	0.32	1.60	0.0003	2.09	−9.81	14.00	0.6957
Teacher	5.05	4.67	5.43	< 0.0001	12.88	4.28	21.48	0.0087
Child	15.14	12.08	18.20	< 0.0001	26.01	9.96	42.07	0.0057
Origin of sample (population as reference)								
School	3.87	3.60	4.14	< 0.0001	4.41	−8.59	17.41	0.4569
Family Pediatrician Practice	0.76	0.07	1.45	0.0051	7.75	-17.67	33.16	0.5022
Quality (RoB score ≥ 6 as reference)								
RoB score ≤ 5	1.45	1.14	1.76	< 0.0001	−5.34	-14.25	3.56	0.2038
Sample size (> 1000 participants as reference)								
≤ 1000 participants	2.77	2.13	3.41	< 0.0001	4.21	−5.63	14.05	0.3528
Year of study publication (≥ 2006 as reference)								
< 2006	−0.03	−0.37	0.31	0.8688	−0.04	−9.62	9.55	0.9932
				Intercept	15.44	−0.89	31.77	0.0609

This opinion is not entirely new: 20 years ago, Swanson et al. [6] clearly wrote that an ADHD diagnosis should be based on clinical history since this allows one to define "the combination of inattentive, hyperactive, and impulsive behaviour as a disorder when these behaviours are severe, developmentally inappropriate, and impair function at home and school". They continued on to say that "rating scales, with the specific ADHD symptoms, have been developed and provide a systematic approach for documenting clinical history, but these are commonly compromised by rater-specific effects and thus should be confirmed by interview". This may be the main factor explaining the wide variation in prevalence estimates reported by the numerous individual studies and meta-analyses. Although documented, this study limitation is often ignored and thus increases the controversy over whether ADHD is overdiagnosed or underdiagnosed and the true prevalence rate of the disorder. The appraisal we performed of the meta-analyses confirms the weakness of the reported overall ADHD prevalence rates. Once again, also in our sample, the observed overlap of studies analysed in the meta-analyses seems unnecessary and may reflect a waste of efforts and an inefficiency in the process of summarizing evidence [41].

We performed a systematic evaluation of the rate of ADHD children and adolescents in Italy with the overall aim to distinguish studies estimating ADHD prevalence based only on symptom-surveys from studies providing a clinically comprehensive evaluation. We also aimed to provide an overall ADHD estimate, as done in previous reviews. The first rate we computed was the overall Italian prevalence of ADHD, found considering all types of samples with different case definition methodologies. As expected, considering Italy's ADHD history – characterized by a predominantly psychodynamic-psychoanalytic approach [42] – the overall prevalence rate of 2.9%, ranging from 1.1 to 16.7% is lower than the worldwide estimate of 5.29% [43]. Our rate and/or range are similar to those that emerged from older review studies [44–47], while they differ more from those of the most recent studies [8, 9, 11, 12, 43, 48, 49]. These data lead to significant concern that there is inconsistent, wide variability, not only between the rates found in the original studies, but also between the findings of the reviews, suggesting the need to consider which frame, diagnosis

criteria, and instruments the estimated and reported ADHD prevalence rates refer. According to other authors [6, 50], the prevalence of ADHD symptoms and the prevalence of ADHD diagnosis are rates that should be carefully differentiated from each other because they reflect two different subject populations, and they are also populations with different health care needs.

The first population (ADHD symptom rate) is the number of subjects presenting ADHD symptoms who could have an ADHD disorder or another psychiatric or medical disorder with similar clinical manifestations. This population is often recognized through symptom surveys compiled by parents or teachers, and needs a clinical evaluation to confirm whether ADHD is actually present. This population therefore represents the number of children and adolescents with behavioral symptoms of ADHD who need a specific evaluation by a specialist service/clinician.

From our findings, this population in Italy, calculated from studies with data rates based on only symptom-surveys, consists of about 439,000 subjects (5.9%, range: 1.4–16.7) among children and adolescents aged 5 to 17 years of the Italian paediatric population. This is, from a health care point of view, the population of subjects who need a psychiatric evaluation. This rate, based on symptom-surveys, differs from that found with the same methodological approach in Thomas and colleagues' review (5.9 vs. 13%) [12], as well as from those based on parent (2.5%, range: 2.4–2.5%) and teacher ratings (6.7%, range: 4.5–10.8%), which are both lower compared to similar, previous analyses on the literature [8, 9, 47, 49]. This result could also be expected, however, taking into consideration that cultural factors, such as higher symptom tolerance, may modulate the interpretation of the child's behaviours in parent and teacher evaluations [42, 51].

The second rate, the prevalence of ADHD diagnosis, is, according to us, the real rate of ADHD prevalence and refers to the number of patients presenting ADHD symptoms who have an ADHD diagnosis confirmed by a clinical evaluation. This population, similarly to the previous one, can be recognized through symptom surveys compiled by parents or teachers, but has an ADHD diagnosis and evaluation that confirm the presence of ADHD. This second population represents the number of children and adolescents with an ADHD diagnosis who need a specific treatment for ADHD.

From our findings, in Italy this population (ADHD diagnosis), calculated from studies including only patients with an ADHD diagnosis confirmed by clinical evaluation, consists of about 105,000 subjects (1.4%, range: 1.1–3.1) among the Italian paediatric population aged 5 to 17 years. From a health care point of view, this is the population of patients who need treatment. In line with previous comments, only a few review studies calculated the prevalence of ADHD diagnosis separately from the overall rate. It is even more important to keep in mind the distinction between diagnostic procedures if we consider that our findings (1.4%, range: 1.1–3.1) differ from those of Willcutt [9] (5.9%, range: 4.6–7.5) even when the better estimate diagnostic procedure is employed.

Finally, although we found similar rates between the overall ADHD prevalence (2.9%; range: 1.1–16.7) and the ADHD diagnosis prevalence (1.4%, range: 1.1–3.1), when diagnostic case definition based on clinical evaluation is used, comparisons of the range rates suggest that the differences between these homogenous types of studies are small, and, thus, in our opinion, more accurate.

Results should be interpreted in the context of two main limitations. First, the number of studies included is small and the methodological approach is heterogeneous so the findings that emerged may not be similar to those of other contexts or countries. Second, although this is the first study analyzing the overall ADHD prevalence in Italy, all data originate from a single country. This may affect the comparability of the reported findings and the generalization of the results to a worldwide scenario would therefore be inappropriate.

Conclusions

Epidemiological studies concerning ADHD need more efforts to identify the cases, to assess the prevalence, and to use administrative databases as provided by the American Agency for Healthcare Research and Quality (AHRQ) [52]. In our opinion, considering only subjects with an ADHD diagnosis performed and confirmed by full clinical assessment (according to European and international guidelines) as a case definition for epidemiological ADHD studies would reduce the wide variability in ADHD estimates previously described. Above all, it would represent the real rate of subjects suffering from ADHD disorder and would avoid misdiagnosis.

Mental health is certainly a public health issue, and many disorders arise in childhood. To support the promotion of mental wellbeing and the primary prevention of psychiatric condition [53] knowledge of the true dimension of the problem – in this case the ADHD prevalence – is fundamental for planning and achieving appropriate treatments and interventions.

Abbreviations

ADHD: Attention deficit hyperactivity disorder; AHRQ: American Agency for Healthcare Research and Quality; AR: "and rule" algorithm; CANPS: Child and Adolescent Neuropsychiatric Service; CI: Confidence interval; CTRS: Conners' Teacher Rating Scale; DBD: Disruptive Behavior Disorder rating scale; DICA-R: Diagnostic Interview for Child and Adolescent; DSM: Statistical Manual of Mental Disorders; DSM-III: Statistical Manual of Mental Disorders. Third edition; DSM-III-R: Statistical Manual of Mental Disorders. Third edition. Revised; DSM-IV: Diagnostic and Statistical Manual of Mental disorders. Fourth edition.; DSM-IV-TR: Diagnostic and Statistical Manual of Mental disorders. Fourth edition. Text revision; FP: Family Pediatrician; ICD-10: International Statistical Classification of Diseases and Related Health

Problems *10th* Revision; NR: Not reported; RoB score: Risk of Bias Assessment tool; SDAG: Attention and Hyperactivity Parent rating scale; SDAI: Attention and Hyperactivity Teacher rating scale; SEs: Standard error; SQ: Study questionnaire; VADTRS: Vanderbilt Diagnostic ADHD Teacher Rating Scale

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
MB designed the study. Both authors contributed to the literature search, data collection, data analysis, data interpretation, and manuscript writing.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts or competing of interest.

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Centro per l'Età Evolutiva

Convegno Scientifico

LE FUNZIONI ESECUTIVE IN ETA' EVOLUTIVA: DALLA VALUTAZIONE ALL'INTERVENTO

Edificio U6 Aula Martini - Università di Milano Bicocca

26 ottobre 2018 - La Valutazione

08.15 Registrazione dei partecipanti

09.30 Le FE come indicatori di adattamento funzionale
Gian Marco Marzocchi - Università di Milano Bicocca

10.15 Lo sviluppo delle FE e l'impatto sul successo scolastico
Paola Viterbori - Università di Genova

11.00 La valutazione clinica delle FE nei Disturbi del Neurosviluppo: analisi di profili specifici
Stefano Vicari, Deny Menghini & Floriana Costanzo - Ospedale Bambin Gesù di Roma

12.30 Brunch offerto

14.00 Le FE nell'ADHD e nei problemi di comportamento esternalizzati
Claudio Vio (UOC NPI di San Donà di Piave)

14.45 Le FE nei Disturbi dello Spettro Autistico: dalla valutazione all'impostazione della terapia
Paolo Stievano (ASL Roma 2), Giovanni Valeri & Barbara Trimarco (Ospedale Bambin Gesù di Roma)

15.30 I bambini con Disturbo Specifico di Linguaggio: valutare le FE per un migliore inquadramento clinico
Luigi Marotta (Ospedale Bambin Gesù di Roma)

16.15 Compilazione questionario ECM

27 novembre 2018 - L'Intervento

08.15 Registrazione dei partecipanti

09.30 Quali training per le FE sono più efficaci?
Gian Marco Marzocchi - Università di Milano Bicocca

10.00 I programmi per potenziare le FE in età prescolare
Maria Carmen Usai – Università di Genova

11.00 L'attività motorio-sportiva per stimolare le FE in età evolutiva
Marianna Alesi – Università di Palermo

11.45 La Robotica Educativa e la Tele-Riabilitazione
Chiara Pecini – IRCCS Stella Maris di Pisa

13.00 Brunch offerto

14.30 Un programma cognitivo integrato per l'attenzione esecutiva nella clinica, nella scuola e nello sport
Francesco Benso - Università di Genova

15.15 Applicazioni cliniche di trattamento delle FE nei Disturbi dello Spettro Autistico
Giovanni Valeri - Ospedale Bambin Gesù di Roma

16.00 Game training: come potenziare i network delle FE stimolando la motivazione e il divertimento dei bambini
Gianluca Daffi - Università Cattolica di Milano

16.45 Compilazione questionario ECM

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016 e N. 1077 del 02/02/2017) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia" "*Percorsi diagnostico-terapeutici per l'ADHD*".

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