

NEWSLETTER



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BIBLIOGRAFIA ADHD AGOSTO 2019

Acad Pediatr. 2019.

STIMULANT DIVERSION RISK AMONG COLLEGE STUDENTS TREATED FOR ADHD: PRIMARY CARE PROVIDER PREVENTION TRAINING.

Molina BSG, Kipp HL, Joseph HM, et al.

Objective: To address increasing rates of stimulant misuse in college students, this study developed an evidence-based, brief clinical practice intervention for primary care providers (PCPs) to reduce stimulant medication diversion among young adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: College students (N=114; 18-25 years; 68% attending universities; 24% attending community college) treated for ADHD with a stimulant and their PCPs across six practices participated in this initial, uncontrolled study of pre- to post-intervention change. An educational workshop providing strategies aimed at reducing stimulant diversion was developed and delivered to providers and staff across all practices (50% pediatric; 50% family medicine). Patients and providers completed baseline and post intervention surveys.

Results: Diversion was relatively infrequent, 16.7% at baseline and 14.9% post-intervention, respectively. Statistically significant decreases from baseline to post-intervention were found for three diversion risk factors: (1) number of times approached to divert, (2) intent to share, sell, or trade stimulants, and (3) disclosure of stimulant use. Providers and staff reported mostly high satisfaction with the training.

Conclusions: This study provides initial evidence for a PCP-delivered intervention to reduce stimulant diversion. Research is needed on the efficacy of targeting college students directly, working with pharmacies and student health centers, and preventing misuse among teenagers

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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.

Actas Esp Psiquiatr. 2019 Jan;47:16-22.

UPDATE THE MULTIMODAL TREATMENT OF ADHD (MTA): TWENTY YEARS OF LESSONS.

Martinez-Nunez B, Quintero J.

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder¹ and consists in a persistent pattern of inattention and / or hyperactivity - impulsivity that interferes with the functioning or development of the person who suffers from it. Because it is a disorder that is present since childhood, the treatment of these patients should be multimodal, and it should include doctors, therapists, teachers and parents². The choice of a pharmacological treatment adjusted to the specific needs of the patient optimizes the results of the intervention programs. In 1997, the National Institute of Mental Health (NIMH) started the study of multimodal treatment of attention deficit hyperactivity disorder (MTA), and this constitutes a landmark in the history of treatment research in child psychopathology. MTA is the largest study of its kind ever undertaken. In the present article we intend to review the existing clinical evidence about the results of the MTA from the nineties to the current date

Am J Occup Ther. 2019 May;73:7303345030p1-p8.

GAZE CONTROL DURING SIMULATOR DRIVING IN ADOLESCENTS WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yuval-Greenberg S, Keren A, Hilo R, et al.

IMPORTANCE: Attention deficit hyperactivity disorder (ADHD) is associated with driving deficits. Visual standards for driving define minimum qualifications for safe driving, including acuity and field of vision, but they do not consider the ability to explore the environment efficiently by shifting the gaze, which is a critical element of safe driving.

OBJECTIVE: To examine visual exploration during simulated driving in adolescents with and without ADHD.

DESIGN: Adolescents with and without ADHD drove a driving simulator for approximately 10 min while their gaze was monitored. They then completed a battery of questionnaires.

SETTING: University lab.

PARTICIPANTS: Participants with (n = 16) and without (n = 15) ADHD were included. Participants had a history of neurological disorders other than ADHD and normal or corrected-to-normal vision. Control participants reported not having a diagnosis of ADHD. Participants with ADHD had been previously diagnosed by a qualified professional.

OUTCOMES AND MEASURES: We compared the following measures between ADHD and non-ADHD groups: dashboard dwell times, fixation variance, entropy, and fixation duration.

RESULTS: Findings showed that participants with ADHD were more restricted in their patterns of exploration than control group participants. They spent considerably more time gazing at the dashboard and had longer periods of fixation with lower variability and randomness.

CONCLUSIONS AND RELEVANCE: The results support the hypothesis that adolescents with ADHD engage in less active exploration during simulated driving.

WHAT THIS ARTICLE ADDS: This study raises concerns regarding the driving competence of people with ADHD and opens up new directions for potential training programs that focus on exploratory gaze control

Am J Psychiatry. 2019;176:531-42.

BRAIN IMAGING OF THE CORTEX IN ADHD: A COORDINATED ANALYSIS OF LARGE-SCALE CLINICAL AND POPULATION-BASED SAMPLES.

Hoogman M, Muetzel R, Guimaraes JP, et al.

Objective: Neuroimaging studies show structural alterations of various brain regions in children and adults with attention deficit hyperactivity disorder (ADHD), although nonreplications are frequent. The authors sought to identify cortical characteristics related to ADHD using large-scale studies.

Methods: Cortical thickness and surface area (based on the Desikan-Killiany atlas) were compared between case subjects with ADHD (N=2,246) and control subjects (N=1,934) for children, adolescents, and adults

separately in ENIGMA-ADHD, a consortium of 36 centers. To assess familial effects on cortical measures, case subjects, unaffected siblings, and control subjects in the NeuroIMAGE study (N=506) were compared. Associations of the attention scale from the Child Behavior Checklist with cortical measures were determined in a pediatric population sample (Generation-R, N=2,707).

Results: In the ENIGMA-ADHD sample, lower surface area values were found in children with ADHD, mainly in frontal, cingulate, and temporal regions; the largest significant effect was for total surface area (Cohen's $d=0.21$). Fusiform gyrus and temporal pole cortical thickness was also lower in children with ADHD. Neither surface area nor thickness differences were found in the adolescent or adult groups. Familial effects were seen for surface area in several regions. In an overlapping set of regions, surface area, but not thickness, was associated with attention problems in the Generation-R sample.

Conclusions: Subtle differences in cortical surface area are widespread in children but not adolescents and adults with ADHD, confirming involvement of the frontal cortex and highlighting regions deserving further attention. Notably, the alterations behave like endophenotypes in families and are linked to ADHD symptoms in the population, extending evidence that ADHD behaves as a continuous trait in the population. Future longitudinal studies should clarify individual lifespan trajectories that lead to nonsignificant findings in adolescent and adult groups despite the presence of an ADHD diagnosis

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Anadolu Psikiyatr Derg. 2019;20:313-20.

IS ADHD AN INFLAMMATION-RELATED DISORDER?

Cevher BN, Kutlu A.

Objective: The current study investigated whether attention deficit hyperactivity disorder (ADHD) was associated with increased inflammatory response by assessing neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratios (PLR) which are new biomarkers of systemic inflammation in children with ADHD compared to healthy controls.

Methods: In this study, 65 children in the ages of 6-11 years who were diagnosed with newly ADHD according to DSM-IV diagnostic criteria were included in the case group, whereas 65 healthy children without any psychiatric or physical disorder in the similar age and gender were included as the control group. The study group included 130 children with normal mental capacity, without known acute or chronic medical and/or inflammatory disease, and no concurrent drug use. Complete blood count analyses were made in the morning after 12 hour fasting, NLR and PLR were calculated using the absolute cell counts.

Results: There was statistically significant difference in NLR, PLR and other complete blood count parameters between ADHD and healthy control groups. Higher MPV values detected in the case group were normalized after adjusting for comorbidity and body mass index values.

Conclusion: Similar NLR and PLR values in the ADHD and healthy control groups do not support the hypothesis of increased inflammatory response involvement in the etiology of the disease. However, considering the heterogeneity about ADHD's clinical presentation and etiopathogenesis, it is clear that wide systematic follow up studies are needed in this area

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Arch Clin Neuropsychol. 2019 Jul;34:700-05.

EFFECTS OF CANNABIS USE AND SUBCLINICAL ADHD SYMPTOMOLOGY ON ATTENTION BASED TASKS IN ADOLESCENTS AND YOUNG ADULTS.

Wallace AL, Wade NE, Hatcher KF, et al.

Objective: Research has demonstrated comorbidity between Attention-Deficit Hyperactivity Disorder (ADHD) and cannabis use, and some have proposed that subclinical ADHD symptoms may explain attentional deficits in cannabis users. Here we investigated whether subclinical ADHD symptoms and cannabis use independently or interactively predict performance on attention tasks in adolescents and young adults.

Method: Seventy-two participants (cannabis users (MJ) = 34, Controls = 38) completed neuropsychological tasks of inhibition and attention. Parent report on the Child Behaviors Checklist reflected current ADHD

symptoms. Multiple regression analyses examined whether ADHD symptoms and cannabis use independently or interactively predicted cognitive outcomes.

Results: Cannabis use was significantly associated with slower CPT hit rate response. Subclinical ADHD symptoms did not independently predict or moderate cannabis effects.

Conclusions: Cannabis users demonstrated slower response rate during an attentional task. Subclinical ADHD symptoms did not predict any deficits. As such, attention deficits seen in cannabis users are more related to substance use than ADHD symptomatology

Arch Dis Child. 2019;104:A225-A226.

A STUDY OF IRISH TRAINEE DOCTORS PRESCRIBING KNOWLEDGE FOR THE DIFFERENT MEDICATION OPTIONS FOR ADHD.

Irvine K, McNicholas F.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a common treatable childhood mental illness, with a prevalence of 7% in under 18 year olds. Functional impairment affects all environments and includes inattention impeding memory and learning, hyperactivity resulting in increased restlessness and movement, and impulsivity leading to poor judgement and risk taking behaviour. These impairments affect children's social inclusion and ability to integrate and enjoy life, but also their ability to fulfil important educational goals. Children and adolescents with ADHD are more likely to have co-morbid medical conditions, which in turn likely impacts on engagement and recovery within medical treatment plans. Stimulants (e.g. methylphenidate) are first line licensed medications for ADHD, and selective norepinephine reuptake inhibitors (e.g. atomoxetine) and alpha-2A adrenergic receptor agonists (e.g. guanfacine) are second line. At least 85% of children respond to stimulants, and only require alternative medications due to poor tolerance profiles. European Union member states classify narcotics according to United Nation conventions, and stimulant medications are classified as controlled drugs. This means that they have strict prescribing rules, which if not adhered to results in delayed dispensing, continued impairment, and increased demands on already stretched clinical resources. In Ireland ADHD is treated by tertiary mental health services, however in many European countries, paediatricians take a lead role in ADHD treatment.

Aim: This study examines the knowledge of trainee doctors in Ireland of the prescribing restrictions of stimulant medications, and the alternative non controlled medications used to treat ADHD.

Method: A questionnaire was designed to capture the current knowledge and prescribing habits of Irish trainee doctors on the 4 commonly used ADHD medications i.e. methylphenidate based, amphetamine based, atomoxetine and guanfacine. The percentage of correct answers were calculated, and Chi squared testing used.

Results: 47 questionnaires were completed and returned with a response rate of 57.5%. The majority of doctors knew that stimulants were controlled and how to prescribe these, however only one third of doctors distinguished correctly that the other 2 drug classes were not controlled, and similarly did not know how to prescribe them.

Conclusion: There is a knowledge gap amongst trainee doctors around prescribing for ADHD. Mainly for the non-controlled medication options, but also on specific points around prescribing the controlled stimulant medications. We hope that this identified gap in knowledge can be filled with targeted teaching; supporting doctors to become informed, competent and comfortable in prescribing for this common childhood illness

Arch Neurocienc. 2019;24:43-58.

SOCIAL COGNITION IN CHILDREN WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER: A LITERATURE REVIEW.

Yanez-Tellez MG, Hernandez-Torres D.

Children with attention deficit hyperactivity disorder(ADHD) present difficulties in social interaction, which can be attributed to deficiencies in social cognition (SC), however, this function has been little studied In this population. To conduct a review of the literature of the last 18 years about CS in children with ADHD, in the

subdomains of theory of mind, recognition of emotions in faces, pragmatic language and affective prosody. A search was made in PubMed and Scopus databases, combining the next keywords: "ADHD", "social cognition", "theory of mind", "emotion recognition", "pragmatic language" and "affective prosody". Articles were selected from 2000 to 2018. Facial emotion recognition is the most reported SC deficit in ADHD children, being the specific failures in the comprehension of gestures like fear, sadness, happiness and anger, although not in a consistent way. Moreover, deficits are also reported in theory of mind, especially in the social reference, basic emotions comprehension, metarepresentations, second-order inferences and in making complex social judgements

Asian J Psychiatr. 2019 Feb;40:9-14.

PSYCHIATRIC DISORDERS IN CHILDREN AND ADOLESCENTS: PREVALENCE AND SOCIODEMOGRAPHIC CORRELATES IN SEMNAN PROVINCE IN IRAN.

Talepasand S, Mohammadi MR, Alavi SS, et al.

AIM: The aim of this study was to estimate the prevalence of psychiatric disorders and sociodemographic correlates in children and adolescents ages 6-18 years in semnan province.

METHOD: Participants were 1037 children and adolescents ages 6 to 18 years in Semnan. This study was a survey study and its data have been taken from the National survey of Iranian Children and Adolescents' Psychiatric Disorders in 2017. A sample of children and adolescents from Semnan was selected by multistage cluster sampling method. Participants completed the K- SADS- PL interview.

RESULTS: Findings showed the general prevalence of psychiatric disorders in Semnan was 24.8 (CI95%: 22.2-27.5) with a proportion of female to male 1.1:1. As the age increased, the prevalence rate of psychiatric disorders decreased. In mothers with undergraduate education, the rate of prevalence of psychiatric disorders in children and adolescents was significantly lower than that of illiterate mothers (OR adjust = 0.309, $p = .01$). Among anxiety disorders, the highest rate of prevalence was related to Separation Anxiety Disorder (6.4%; CI95%: 5.03-8.01). Oppositional Defiant Disorder (4%; CI95%: 2.9-5.3) and Attention Deficit Hyperactivity Disorder (3.4%; CI95%: 2.4-4.7) had the highest rate of prevalence among behavioral disorders. Sex, Locus of life, socioeconomic status had no effect on the prevalence rate.

CONCLUSION: The disorders prevalence was higher than the previous prevalence that reported in Iran. Anxiety disorders are the most common disorders. The results showed that psychiatric disorders of the children and adolescents were not different in terms of sociodemographic factors in Semnan

Atten Defic Hyperact Disord. 2019 Mar;11:113-22.

SOCIAL-COMMUNICATIVE AND ATTENTION PROBLEMS IN INFANCY AND TODDLERHOOD AS PRECURSORS OF PRESCHOOL AUTISTIC TRAITS.

Moricke E, Greven CU, Visser JC, et al.

This longitudinal study focused on early behavioural problems and autistic traits. In a stratified, population-derived sample of 119 children, mothers reported through questionnaires on externalizing, internalizing, and social-communicative characteristics of their child in infancy (14 months) and toddlerhood (37 months), and on autistic traits at preschool age (4-5 years). Children with consistently normal behaviour from infancy to toddlerhood showed lower autistic traits at preschool age than children with deviant behaviour on one or both time points. High autistic traits at preschool age were predominantly preceded by problems in interaction, communication, language, play, and affect in infancy and/or toddlerhood, but also by inattention in toddlerhood. Adequate support and specific interventions in these domains are needed in an attempt to diminish further derailment of the child's behaviour and development, and to prevent the full manifestation of ASD or related disorders such as ADHD

Atten Defic Hyperact Disord. 2019 Mar;11:83-89.

ADHD: A HIDDEN COMORBIDITY IN ADULT PSYCHIATRIC PATIENTS.

Bitter I, Mohr P, Balogh L, et al.

Adult attention-deficit/hyperactivity disorder (aADHD) has recently been better recognized and treated in many European countries. In spite of this development, aADHD still features as a "hidden" comorbidity, often not diagnosed even in patients under psychiatric treatment for other psychiatric disorders. The aim of this study was to establish the prevalence rates of unrecognized aADHD in academic centers providing regular psychiatric services in the Czech Republic and Hungary. In a population of psychiatric in- and outpatients, Adult ADHD Self-Report Scale was administered. All positively and about half of the negatively screened subjects were clinically interviewed and the DSM diagnosis of ADHD was determined based on the symptom list and Conners' Adult ADHD Rating Scale. The estimated point prevalence rate of unrecognized comorbid aADHD among psychiatric in- and out patients was 6.99% (95% lower CI: 5.11, 95% upper CI 8.86) according to the DSM-IV-TR criteria and 9.27% (95% lower CI: 7.13, 95% upper CI 11.40) according to the DSM-5 criteria. Current suicide risk was significantly associated with the presence of undiagnosed aADHD; however, life time suicide attempts, depression, dysthymia, alcohol and substance dependence, anxiety and stress related disorders were not. Further educational efforts are needed to improve the recognition and treatment of aADHD in adults

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Atten Defic Hyperact Disord. 2019 Mar;11:21-29.

PARENT-CLINICIAN AGREEMENT IN RATING THE PRESENCE AND SEVERITY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.

Nobel E, Brunnekreef JA, Schachar RJ, et al.

We determined the validity of a parent-report questionnaire as a research tool for rating attention-deficit/hyperactivity disorder (ADHD) symptoms in children. Using Cohen's kappa and Pearson correlation, we examined the agreement between parent reports of ADHD symptoms (using the Swanson, Nolan and Pelham Questionnaire-IV; SNAP-IV) and clinical judgment (using a semi-structured parent interview). Also, we explored factors that may be associated with the level of agreement, using regression analyses. We found moderate levels of agreement for severity of overall ADHD ($r = 0.43$) and for hyperactive-impulsive symptoms ($r = 0.54$), but no significant agreement for inattentive symptoms. On individual symptom level (range kappa = - 0.05-0.22) and for the presence/absence of ADHD (kappa = 0.14), agreement was poor. Therefore, we conclude that parent-report questionnaires may be acceptable to rate the overall severity of ADHD symptoms in treatment effect studies, but not to detect the presence of ADHD in epidemiological studies

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Atten Defic Hyperact Disord. 2019 Mar;11:73-81.

APPARENT LACK OF PRACTICE EFFECTS IN THE TEST OF VARIABLES OF ATTENTION (TOVA) IN ADULT ADHD.

Rotem A, Danieli Y, Ben-Sheetrit J, et al.

The test of variables of attention (TOVA) is a continuous performance test commonly used as an aid for diagnosis of ADHD and assessment of treatment response. It has been studied and standardized in both children and adults. As a repetitive measurement of treatment efficacy, used both in research and in the clinic, it's important to disprove a practice effect. A retrospective cohort analysis was done, using only the placebo-arm participants from two different randomized, multicenter, double-blind clinical trials on the efficacy of a non-stimulant (metadoxine-XR). In order to reveal the practice effects, only the participants that showed no placebo effect (< 25% improvement), in the Conners' Adult ADHD Rating Scale-investigator rated (CAARS-Inv), the gold standard, were included. Demographic data, CAARS-Inv baseline and TOVA results during each visit were recorded and analyzed. Ninety-one participants from two studies were pooled (2014 $n = 24$, 2016 $n = 67$). They did not differ significantly in any demographic parameter, most side effect frequencies, and CAARS-Inv baseline scores. The baseline TOVA performances demonstrated similarity in the degree of inattention, variability, impulsivity, and response time. The TOVA scores were not altered

significantly between visits, as assessed by repeated-measures analysis of variance. No significant differences were detected between the TOVA baseline-to-endpoint scores as assessed by paired t test. No practice effects were detected, in both clinical trials, suggesting that the results of the TOVA are likely to represent genuine changes in attentional performance. Further studies are needed to replicate these findings

Behav Ther. 2019.

THE VALIDITY OF A FRUSTRATION PARADIGM TO ASSESS THE EFFECT OF FRUSTRATION ON COGNITIVE CONTROL IN SCHOOL-AGE CHILDREN.

Seymour KE, Rosch KS, Tiedemann A, et al.

Irritability refers to a proneness for anger, and is a symptom of internalizing and externalizing psychopathology. Since irritability is associated with significant cross-sectional and longitudinal impairments, research on the behavioral and neural correlates of pediatric irritability in populations at risk for significant irritability is of paramount importance. Irritability can be assessed in the laboratory using behavioral paradigms that elicit frustration. Few behavioral frustration paradigms have been designed to measure the effects of frustration on cognitive control. Therefore, the goal of the present study was to validate a behavioral frustration paradigm for use in school-age children which addressed some of the limitations of prior research. Participants included children, ages 8-12 years, who were either typically developing (TD; n = 38) or diagnosed with attention-deficit/hyperactivity disorder (ADHD; n = 67), which provided a sample of children with a range of baseline irritability. All participants completed the Frustration Go/No-Go (GNG) task, and self-reported irritability was assessed using the Affective Reactivity Index. Results showed that across participants, self-reported frustration, commission error rate, and tau all increased with the addition of frustration, with similar effect sizes in ADHD and TD groups. Further, self-reported irritability, more so than ADHD symptoms, predicted changes in self-reported frustration during the task. Together, these results support the construct validity of the Frustration GNG task as a means of assessing the effect of frustration on cognitive control. Clinical applications and future directions are discussed

Biomed J. 2018 Dec;41:337-39.

BASAL-BOLUS OR PREMIXED? SHEDDING LIGHT ON OPTIMAL INSULIN REGIME FOR TYPE 1 DIABETES.

Louise WE.

In this issue of the Biomedical Journal, we highlight original research that will help to guide the choice of insulin administration regimes for children with type 1 diabetes. We also investigate whether a common medication for attention deficit/hyperactivity disorder worsens sleep problems among these children, and discover a new approach to maximize the lifetime of a fragile piece of surgical equipment

Birth Defects Research. 2019;111:797-811.

DIFFERENTIAL NEUROIMAGING INDICES IN PREFRONTAL WHITE MATTER IN PRENATAL ALCOHOL-ASSOCIATED ADHD VERSUS IDIOPATHIC ADHD.

O'Neill J, O'Connor MJ, Yee V, et al.

Background: Attention deficit-hyperactivity disorder (ADHD) is common in fetal alcohol spectrum disorders (FASD) but also in patients without prenatal alcohol exposure (PAE). Many patients diagnosed with idiopathic ADHD may actually have ADHD and covert PAE, a treatment-relevant distinction.

Methods: We compared proton magnetic resonance spectroscopic imaging (MRSI; N = 44) and diffusion tensor imaging (DTI; N = 46) of the anterior corona radiata (ACR)—a key fiber tract in models of ADHD—at 1.5 T in children with ADHD with PAE (ADHD+PAE), children with ADHD without PAE (ADHD-PAE), children without ADHD with PAE (non-ADHD+PAE), and children with neither ADHD nor PAE (non-ADHD-PAE, i.e., typically developing controls). Levels of choline-compounds (Cho) were the main MRSI endpoint, given

interest in dietary choline for FASD; the main DTI endpoint was fractional anisotropy (FA), as ACR FA may reflect ADHD-relevant executive control functions.

Results: For ACR Cho, there was an ADHD-by-PAE interaction ($p = 0.038$) whereby ACR Cho was 26.7% lower in ADHD+PAE than in ADHD–PAE children ($p < 0.0005$), but there was no significant ACR Cho difference between non-ADHD+PAE and non-ADHD–PAE children. Voxelwise false-discovery rate (FDR)-corrected analysis of DTI revealed significantly ($q \leq 0.0101$ – 0.05) lower FA in ACR for subjects with PAE (ADHD+PAE or non-ADHD+PAE) than for subjects without PAE (ADHD–PAE or non-ADHD–PAE). There was no significant effect of ADHD on FA. Thus, in overlapping samples, effects of PAE on Cho and FA were observed in the same white-matter tract.

Conclusions: These findings point to tract focal, white-matter pathology possibly specific for ADHD+PAE subjects. Low Cho may derive from abnormal choline metabolism; low FA suggests suboptimal white-matter integrity in PAE. More advanced MRSI and DTI—and neurocognitive assessments—may better distinguish ADHD+PAE from ADHD–PAE, helping identify covert cases of FASD

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BMC Psychiatry. 2019;19.

ASSOCIATION BETWEEN PHARMACOTHERAPY FOR ADHD IN OFFSPRING AND DEPRESSION-RELATED SPECIALTY CARE VISITS BY PARENTS WITH A HISTORY OF DEPRESSION.

Chen Q, Larsson H, Almqvist C, et al.

Background: Pharmacotherapy is effective in reducing the core symptoms of attention-deficit/hyperactivity disorder (ADHD). We aimed to investigate the concurrent association between pharmacotherapy for ADHD in offspring and depression-related specialty care visits by the parents with a history of depression.

Methods: Using data from a variety of Swedish national registers, we conducted a cohort study with 8-year follow-up of 5605 parents (3872 mothers and 1733 fathers) who had a history of depression and an offspring diagnosed with ADHD. The hazard rate for parental depression-related specialty care visits during exposed periods when the offspring was on medication for treatment of ADHD was compared with the hazard rate during unexposed periods when the offspring was off medication. Within-individual comparisons were employed to control for time-constant confounding factors.

Results: Among mothers, the crude rates of depression-related specialty care visits during exposed and unexposed periods were 61.33 and 63.95 per 100 person-years, respectively. The corresponding rates among fathers were 49.23 and 54.65 per 100 person-years. When the same parent was compared with him or herself, fathers showed a decreased hazard rate for depression-related visits during exposed periods when the offspring was on medication for treatment of ADHD as compared to unexposed periods (hazard ratio, 0.79 [95% confidence interval, 0.70 to 0.90]). No statistically significant associations were observed in mothers.

Conclusions: Among parents with a history of depression, pharmacotherapy for ADHD in offspring is concurrently associated with a decreased rate of depression-related specialty care visits in fathers but not in mothers. Future research with refined measures of parental depression and other time-varying familial factors is needed to better understand the mechanisms underlying the association

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BMJ Evidence-Based Medicine. 2019;24:155-61.

DETERMINANTS OF INTER-PRACTICE VARIATION IN ADHD DIAGNOSIS AND STIMULANT PRESCRIBING: CROSS-SECTIONAL DATABASE STUDY OF A NATIONAL SURVEILLANCE NETWORK.

Hoang U, James AC, Liyanage H, et al.

Early recognition, identification and treatment of children with attention deficit hyperactivity disorder (ADHD) can reduce detrimental outcomes and redirect their developmental trajectory. We aimed to describe variations in age of ADHD diagnosis and stimulant prescribing among general practitioner practices in a nationwide network and identify child, parental, household and general practice factors that might account for these variations. Cross-sectional study of children aged under 19 years registered within a general

practice in the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network in 2016, RCGP RSC has a household key allowing parent and child details to be linked. Data from 158 general practices and 353 774 children under 19 were included. The mean age of first ADHD diagnosis was 10.5 years (95% CI 10.1 to 10.9, median 10, IQR 9.0-11.9) and the mean percentage of children with ADHD prescribed stimulant medications among RCGP RSC practices was 41.2% (95% CI 38.7 to 43.6). There was wide inter-practice variation in the prevalence of diagnosis of ADHD, the age of diagnosis and stimulant prescribing. ADHD diagnosis is more likely to be made later in households with a greater number of children and with a larger age difference between adults and children. Stimulant prescribing for children with ADHD was higher in less deprived practices. Older parents and families with more children fail to recognise ADHD and may need more support. Practices in areas of higher socio-economic status are associated with greater prescribing of stimulants for children with ADHD

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Brain Inj. 2019;33:1402-07.

CASE REPORT: NEUROIMAGING ANALYSIS OF PEDIATRIC ADHD-RELATED SYMPTOMS SECONDARY TO HYPOXIC BRAIN INJURY.

Tran K, Wu J.

A 2-year-old male pediatric patient experienced a partial occlusion of the internal carotid and subsequent asphyxiation resulting in hypoxic brain injury that was later misdiagnosed as primary attention deficient hyperactivity disorder (ADHD). Imaging analyses using diffusion tensor imaging (DTI), positron emission tomography (PET), and magnetic resonance imaging (MRI) quantitative volumetrics (QV) were used nine years following the incident to identify whether his development of ADHD is of a primary heritability or secondary hypoxic brain injury sequelae. The patient's DTI analysis generated decreases in fractional anisotropy (FA) values in the anterior corpus callosum, bilateral internal capsule, and hippocampus. Decreases in FA are seen in ADHD patients, but the degree of FA decrease in the patient under study is several orders of magnitude greater than in ADHD patients. Also, not normally observed in ADHD patients were decreases in the metabolism of the orbitofrontal cortex, anterior cingulate, left anterior insular cortex, and left striatum. Additionally, QV showed enlargements of various regions of the brain including the amygdala which is often cited in the literature to be reduced in ADHD patients. The diagnosis of this patient despite having non-characteristic neuroimaging data suggests a unique specificity of the hypoxic injury to the development of a secondary hypoxic brain injury caused ADHD

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Can Bull Med Hist. 2019;36:51-79.

"SNIPS AND SNAILS AND PUPPY DOG TAILS": BOYS AND BEHAVIOUR IN THE USA.

Smith M.

In The Adventures of Tom Sawyer and Huckleberry Finn, Mark Twain introduced two of the most iconic boys in American literature. Tom and Huck become heroic figures, despite their penchant for bad behaviour. Indeed, it is their propensity to be impulsive, break rules and defy authority that win them the day. Today, however, Tom Sawyer and Huck Finn have become the posterboys for a psychiatric disorder, Attention Deficit Hyperactivity Disorder, or ADHD. I trace how and why attitudes about pathological boys' behaviour reversed during the twentieth century, from a focus on shy, introverted, and physically passive boys to the very opposite - boys like Tom and Huck. I argue that, rather than imposing limits on childhood behaviour, we should be more accepting and encouraging of all types of children

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Child Neuropsychol. 2019.

PRENATAL SOCIOECONOMIC STATUS AND SOCIAL SUPPORT ARE ASSOCIATED WITH NEONATAL BRAIN MORPHOLOGY, TODDLER LANGUAGE AND PSYCHIATRIC SYMPTOMS.

Spann MN, Bansal R, Hao X, et al.

Few studies have assessed the association of parental socioeconomic status (SES) with brain measures in neonates, at a time when exposure to the postnatal environment is minimal. Social support may buffer the adverse consequences of SES, and has been associated with better cognitive and emotional development in children. We studied the association of prenatal SES and social support with neonatal brain structure, and toddler cognition, and psychiatric symptoms. In a sample of 37 healthy neonates, we correlated a measure of SES and marital/partner status (an index of social support) with morphological features of the cerebral surface measured on high-resolution MRI scans between the 1st and 6th weeks of postnatal life. We then assessed how SES relates to cognitive and behavioral outcomes at age 24-months. We found that neonates born to mothers with lower SES had greater local volumes at the surface of the right occipital lobe, left temporal pole, and left inferior frontal and anterior cingulate regions. Partner status moderated the associations of SES on neonatal brain morphology. Lower SES was associated with poorer language scores and less severe ADHD and ODD symptoms. In summary, SES was associated with neonatal brain structure and language and behavioral outcomes at toddler age. Future studies with a greater sample size and longitudinal MRI scans will help to determine whether prenatal SES continues to relate to early brain development in the same or different brain regions

Child Neuropsychol. 2019.

PSYCHOMETRIC ANALYSES OF THE TOWER OF LONDON PLANNING TASK REVEAL HIGH RELIABILITY AND FEASIBILITY IN TYPICALLY DEVELOPING CHILDREN AND CHILD PATIENTS WITH ASD AND ADHD.

Unterrainer JM, Rahm B, Loosli SV, et al.

The Tower of London (TOL) is probably the most often used assessment tool for planning ability in healthy and clinical samples. Various versions, including our proposed standard problem set, have proven to be feasible and reliable in adults. In contrast, reliability information for typically developing (TD) children and neurodevelopmental disorders during childhood are largely missing. Also, it would be highly desirable to attain a problem set that can be used across the whole lifespan. Therefore, here we examine reliability of our proposed standard problem set using a computerized TOL version in 178 TD children (two different samples), 49 children with high-functioning autism spectrum disorder (ASD) and 56 children with attention-deficit/hyperactivity disorder (ADHD) (age ranges of each group 6 to 13 years), and 130 young adults (age range 18 to 32 years). Greatest lower bound estimates of reliability were adequate to high in the two samples of TD children (.76 and .80) and high to very high in patients (ASD: .90; ADHD: .83). In young adults, all reliability indices were adequate to high. Moreover, a subset of four- and five-move problems exhibited sufficient performance variability and high part-whole correlations with the complete problem set in all samples. These findings demonstrate the reliability of the presented TOL problem set in both clinical and non-clinical child samples. A clinically feasible subset of four- and five-move problems is reflective of overall planning performance at all ages, hence enabling comparisons of planning ability within and between developmental samples across almost the whole lifespan

Clin EEG Neurosci. 2019;50:339-47.

A NEW METHOD OF DIAGNOSING ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN MALE PATIENTS BY QUANTITATIVE EEG ANALYSIS.

Chang M-Y, Ouyang C-S, Chiang C-T, et al.

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood. Diagnosis of ADHD is based on core symptoms and checklists. However, these are both subjective, which can lead to the problems of overdiagnosis and underdiagnosis. Elevated theta/beta ratio

(TBR) of EEG band has been approved by the US Food and Drug Administration as a tool to assist in the diagnosis of ADHD. However, several recent studies have demonstrated that there are no significant differences in TBR between people with and without ADHD. In this study, we attempted to develop a new method for differentiating between male with and without ADHD by analyzing EEG features. Thirty boys with ADHD combined type (aged 8 years 5 months - 1 year 11 months) and 30 age-matched controls (aged 8 years 5 months - 1 year 8 months) were enrolled in this study. A classification analysis-based approach comprising training and classification phases was developed for classifying each subject's EEG features as ADHD or non-ADHD. Eight crucial feature descriptors were selected and ranked based on the t test. Compared with TBR in our study, the developed method had a higher area under the curve (87.78%), sensitivity (80.0%), and specificity (80.0%). Our method is more precise than using TBR in the diagnosis of ADHD. This newly developed method is a useful tool in identifying patients with ADHD and might reduce the possibility of overdiagnosis and underdiagnosis

Clin EEG Neurosci. 2019;50:332-38.

PREDICTIVE VALUE OF SLOW AND FAST EEG OSCILLATIONS FOR METHYLPHENIDATE RESPONSE IN ADHD.

Sari GE, Tulay EE, Beser B, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder and is characterized by symptoms of inattention and/or hyperactivity and impulsivity. In the current study, we obtained quantitative EEG (QEEG) recordings of 51 children aged between 6 and 12 years before the initiation of methylphenidate treatment. The relationship between changes in the scores of ADHD symptoms and initial QEEG features (power/power ratios values) were assessed. In addition, the children were classified as responder and nonresponder according to the ratio of their response to the medication (>25% improvement after medication). Logistic regression analyses were performed to analyze the accuracy of QEEG features for predicting responders. The findings indicate that patients with increased delta power at F8, theta power at Fz, F4, C3, Cz, T5, and gamma power at T6 and decreased beta powers at F8 and P3 showed more improvement in ADHD hyperactivity symptoms. In addition, increased delta/beta power ratio at F8 and theta/beta power ratio at F8, F3, Fz, F4, C3, Cz, P3, and T5 showed negative correlations with Conners' score difference of hyperactivity as well. This means, those with greater theta/beta and delta/beta powers showed more improvement in hyperactivity following medication. Theta power at Cz and T5 and theta/beta power ratios at C3, Cz, and T5 have significantly classified responders and nonresponders according to the logistic binary regression analysis. The results show that slow and fast oscillations may have predictive value for treatment response in ADHD. Future studies should seek for more sensitive biomarkers

CNS Spectr. 2019;24:191-92.

EARLY-ONSET EFFICACY AND SAFETY PILOT STUDY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Pardo A, King TR, et al.

OBJECTIVE: To determine whether amphetamine extended-release oral suspension (AMPH EROS) has an onset of effect at 30 minutes postdose in children with ADHD.

METHODS: This randomized, double-blind, 2-treatment, 2-sequence, placebo-controlled crossover pilot study enrolled subjects aged 6 to 12 years with attention deficit/hyperactivity disorder (ADHD) and ADHD Rating Scale-5 scores of \geq 90th percentile for sex and age. A dose of 5 to 20 mg/day of AMPH EROS was determined during a 1-week open-label phase based on medication history, symptom control, and tolerability. Subjects completed a practice laboratory classroom then received one day of double-blind active drug or placebo each in random sequence during 2 double-blind laboratory classroom days. Subjects completed the first double-blind laboratory classroom session, returned to open label drug for 5 days then crossed over on day 6 during a second double-blind laboratory classroom session. DB dose was fixed at

AMPH EROS 15, 17.5, or 20 mg . The primary endpoint was change from predose in the Swanson, Kotkin, Agler, M-Flynn, Pelham rating scale combined score (SKAMP-C) at 30 minutes postdose on two DB days. The key secondary endpoint was change from predose in the SKAMP-C score at 3 hours postdose for AMPH EROS compared with placebo. Safety assessments included vital signs and adverse events.

RESULTS: Eighteen subjects were enrolled in the study (14 males and 4 females) with a mean age of 9 years. At both 30 minutes and 3 hours postdose, changes from baseline in SKAMP-C for AMPH EROS vs. placebo were statistically significant ($p < 0.01$ and $p = 0.0002$, respectively) with corresponding effect sizes of 0.96 and 1.57. Adverse events (>10%) during the open-label phase included upper respiratory tract infection, fatigue, upper abdominal pain, headache, decreased appetite, and affect lability.

CONCLUSIONS: AMPH EROS was effective in reducing ADHD symptoms at 30 minutes postdose. AEs were mild or moderate and consistent with those of other extended-release amphetamines

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CNS Spectr. 2019;24:219-20.

THE EFFICACY AND SAFETY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kando JC, King T, Pardo A, et al.

OBJECTIVES: To determine the efficacy and safety of amphetamine extended-release oral suspension (AMPH EROS) in the treatment of attention deficit/ hyperactivity disorder (ADHD) compared with placebo in a dose-optimized, randomized, double-blind study.

METHODS: The efficacy of AMPH EROS was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6-12 years) with ADHD. The study began with an open-label dose optimization (5 weeks) with an initial AMPH EROS dose of 2.5 or 5mg once daily in the morning. The dose could be titrated every 4-7 days in increments of 2.5-10 mg until an optimal dose or the maximum dose of 20 mg/day was reached. Subjects were required to tolerate a minimal dose of 10 mg/day. Subjects then entered a 1-week randomized, double-blind treatment phase with the individually optimized dose or placebo. At the end of the week, raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP-C) rating scale. SKAMP-C is a 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. The primary efficacy endpoint was change from pre-dose in the SKAMP-C score at 4 hours post dose. The key secondary endpoint efficacy parameters were onset and duration of clinical effect. The change scores from predose SKAMP-C scores at post dose time points (1, 2, 6, 8, 10, 12 and 13 hours) were used to evaluate the key secondary efficacy endpoints.

RESULTS: More boys (68.7%) than girls participated in the study. The study population was 55.6% white, most patients had inattentive or combined type ADHD presentations. The primary efficacy endpoint, the change from pre-dose SKAMP-C score at 4 hours post dose was statistically significantly improved ($p < 0.0001$) compared with placebo. Each of the secondary efficacy endpoints were also significantly improved ($p < 0.0001$ at each time point) compared with placebo. Adverse events reported (frequency >5%) reported during the dose optimization phase were decreased appetite, insomnia, affect lability, upper abdominal pain, mood swings, and headache.

CONCLUSIONS: AMPH EROS was effective in reducing symptoms of ADHD from 1 to 13 hours after dosing. Adverse events reported were consistent with those of other amphetamine products

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CNS Spectr. 2019;24:218-19.

EFFICACY MEASURES IN AN OPEN-LABEL DOSE-OPTIMIZATION OF AN AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Cutler A, Pardo A, King TR, et al.

Objectives: Report the efficacy of open-label amphetamine extended-release oral suspension (AMPH EROS) for the treatment of children with ADHD. AMPH EROS has a 1-hr onset of effect and a duration of

action of 13 hours and was approved by FDA for treatment of ADHD in children aged 6-17 years based on a doubleblind, placebo-controlled efficacy and safety study in children aged 6-12 years with ADHD. A significant treatment difference in change from pre-dose SKAMPcombined score was observed at the primary endpoint of 4 hours post-dose ($p < 0.0001$) and each post-dose time point assessed (1, 2, 4, 6, 8, 10, 12, 13 hours). Data reported here are from the 5-week, open-label dose optimization period. These efficacy data support the primary endpoint result.

METHODS: Males and females aged 6 to 12 years with ADHD enrolled and began open-label treatment with 2.5mg or 5 mg/day of AMPH EROS titrated in 2.5-10 mg/day increments until optimal dose (maximum 20 mg/day). Doses could be decreased for tolerability. Subjects took morning AMPH EROS for 5 weeks. Other efficacy outcomes during the open-label dose optimization phase: ADHD-RS (ADHD-Rating Scale), CGI-S (Clinical Global Impression of Severity), CGI-I (CGI-of Improvement) and CPRS (Conners' Parent Rating Scale). All subjects were assessed for safety.

RESULTS: For the ITT population ($n = 99$): treatment with AMPH EROS was associated with a mean change in ADHD-RS-IV (baseline to end of the open-label dose optimization; week 6) of 28.2 (-19.03) (Baseline score = 41.3-17.95). 90.9% of subjects had a change from baseline to open-label week 6 of 50% in the ADHDRS-IV total score and were defined as responders. The CGI-S scores decreased continuously from baseline, with a high 4.8 at baseline to a low of 2.0 at open-label week 6. The percentage of subjects classified as moderately ill or greater correspondingly decreased from 97% at Baseline to 1% at open-label week 6. The decrease in the CGI-I over the study was similar to the change in CGI-S scores. CPRS for most categories decreased continuously from Baseline to open-label week 6. Mean change from baseline to open-label week 6 on the CPRS inattention T-score subscale was -25.3 (-114.38) and -24.4 (-113.87). Adverse events (>5%) reported during dose optimization were decreased appetite, insomnia, affect lability, upper abdominal pain, mood swings and headache.

CONCLUSION: AMPH EROS was effective in reducing symptoms of ADHD in this open-label dose optimization. The AE profile of AMPH EROS was consistent with those of other amphetamine products

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CNS Spectr. 2019;24:177-78.

PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES EVALUATING EFFICACY AND SAFETY OF EXTENDED-RELEASE VILOXAZINE FOR PEDIATRIC ADHD.

Nasser A, Johnson JK, Adewole T, et al.

Study Objectives: Although stimulants are commonly used for attention-deficit/hyperactivity disorder (ADHD), 10-30% of patients have an inadequate response, adverse events, or comorbidities preventing use. Thus, there is a need for safe, effective nonstimulant options. Extended-release viloxazine (SPN-812), a nonstimulant, is currently in development for the treatment of ADHD in children and adolescents. SPN-812 is a structurally distinct, bicyclic norepinephrine reuptake inhibitor with selective serotonergic activity. Results of the Phase 2 program demonstrated efficacy (improved mean ADHD Rating Scale-IV total score) and safety of SPN-812 in children (6-12 years), as well as an onset of action within 1-2 weeks.

METHOD: Four ongoing Phase 3 randomized, doubleblind, placebo-controlled, outpatient, US studies are investigating the efficacy and safety of once-daily SPN- 812 for ADHD in children (ages 6-11; 100-400 mg) and adolescents (ages 12-17; 200-600 mg). Two studies are enrolling children and two are enrolling adolescents. Eligible subjects are required to have minimum baseline scores of ≥ 28 for ADHD-RS-5 and ≥ 4 for Clinical Global Impression-Severity scale (CGI-S). These studies will randomize ~1200 subjects, with ~800 subjects receiving SPN-812 over a 1-3-week titration and 5-week maintenance period. The primary endpoint in all studies is mean change from baseline to end of study (EOS) in ADHD-RS-5 total score for SPN-812 vs. placebo. Secondary endpoints include change from baseline to EOS in 30% responder rate (% change: ADHD RS 5); Hyperactivity/Impulsivity and Inattention ADHD-RS-5 subscale scores; Conners 3 Rating Scale (parent and selfreport); CGI-S/CGI-I (Improvement); Weiss Functional Impairment Rating Scale (parent report); Parenting Stress Index (children); and Stress Index for Parents of Adolescents (adolescents) after 6-8 weeks of treatment. Safety is assessed via adverse events, clinical laboratory tests, vital signs, electrocardiograms, physical examinations, and the Columbia-Suicide Severity Rating Scale. Phase 3 completers are offered the option of enrolling in an open-label extension study (OLE; up to 3 years) with a

starting dose of 100/200 mg (children/adolescents). Data will be summarized with descriptive statistics and analyzed using appropriate statistical methods.

RESULTS: As of August 2018, enrollment in 1 child study is complete, and the other 3 trials are at ~89%; rollover into the OLE is ~90%.

CONCLUSIONS: There is an unmet need for nonstimulant ADHD treatment for children and adolescents that is effective, long-acting, and well tolerated. SPN-812 is being investigated in four Phase 3 randomized, placebocontrolled studies for the treatment of children and adolescents with ADHD, based on demonstrated efficacy and safety in the Phase 2 program. This study is an encore of a poster presentation at the 2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP)

Current Pediatric Research. 2018;22:277-84.

A CONTRIBUTION OF METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) GENE POLYMORPHISMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Abdelshakoor KI, El-Gebaly HH, Kamal TM, et al.

Background: Attention Deficit Hyper-Activity Disorder (ADHD) is a neuro-behavioral, complex disorder influenced by many genes. The MTHFR gene C677T and A1298C polymorphisms affect both nucleotide synthesis and DNA methylation. This study aimed to assess the relationship between Methylene tetrahydrofolate Reductase (MTHFR) gene polymorphisms and ADHD in a sample of Egyptian children.

Methods: MTHFR gene polymorphisms were evaluated in 60 participants, 30 ADHD patients and 30 controls of healthy children with normal developmental and psychiatric evaluation with comparable age and sex. The patients were recruited from Psychiatric clinic, Faculty of Postgraduate Studies for Childhood-Ain Shams University, Cairo, Egypt during the period from January to August 2015 with age ranged from 6 to 12 years. MTHFR C677T and A1298C alleles distribution was investigated via polymerase chain reaction (PCR) and reverse hybridization.

Results: The recorded genetic results showed heterozygous advantage (Heterosis) regarding studied C677T allele genotype with statistically significant association reported in controls compared to ADHD cases ($p=0.0159$). Genotype distributions of A1298C allele showed statistically high significant association with ADHD cases compared to controls ($p=0.0002$). A significant association was found between males of ADHD cases and hetero- homozygous A1298C allele compared to controls ($p=0.0079$). Meanwhile, ADHD females showed statistically significant higher distribution of the hetero- homozygous genotypes compared to controls ($p=0.0072$).

Conclusions: There was an evident association between ADHD phenotype and MTHFR A1298C gene polymorphism, and there was a heterozygous advantage (Heterosis) regarding C677T allele genotype and ADHD cases leading to absence of association between MTHFR C677T gene polymorphism and ADHD

Current Pediatric Research. 2019;23:9-16.

A STUDY OF DOPAMINE D2 RECEPTOR TAQ1 A ALLELES IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Moro MM, El-Gebaly HH, Zaky EA, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder influenced by many genes. The Dopamine receptor D2 (DRD2) Taq1A polymorphism affects the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP). This study aimed to assess the relationship between Taq1 A polymorphism and ADHD in a sample of Egyptian children.

Methodology: DRD2-Taq1A gene polymorphism was evaluated in 100 participants, 50 ADHD patients and 50 controls of healthy children with normal developmental and psychiatric evaluation with comparable age and sex. The patients were recruited from Psychiatric clinic, Faculty of Postgraduate Studies for Childhood-Ain Shams University, Cairo, Egypt with age ranged from 6 to 12 years. RD2-Taq1A allele distribution was investigated via polymerase chain reaction (PCR).

Results: Phenotype distributions of A1 allele showed statistically significant association with ADHD cases compared to controls ($p=0.037$). A significant association was found between ADHD cases and heterozygous A1A2 genotype ($p=0.047$). Meanwhile, ADHD cases showed statistically significant lower distribution of the homozygous A2A2 genotype ($p=0.027$).

Conclusion: There was an evident association between ADHD phenotype and (DRD2) Taq1A gene polymorphism, and there was a heterozygous advantage regarding A1A2 allele genotype and ADHD cases

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Depress Anxiety. 2019 May;36:423-32.

CLINICAL RISK FACTORS AMONG YOUTH AT HIGH RISK FOR SUICIDE IN SOUTH AFRICA AND GUYANA.

Thornton VJ, Asanbe CB, Denton ED.

INTRODUCTION: Suicide is the second leading cause of death among youth worldwide, but low- and middle-income countries (LMICs) account for 78% of all suicides. The LMICs South Africa and Guyana rank high in the global suicide rates. To better understand and prevent suicide among the youth, the present study targets youths at high risk for suicide, in an LMIC, to contextually and representatively identify clinical risk factors for suicide.

METHODS: One hundred-ninety youths, aged 11-21, separated from biological parents at the time of assessment, in South Africa and Guyana, were administered the Child Behavior Checklist and Behavior Assessment System for Children to assess clinical symptoms. The youths were asked about current suicide ideation and previous attempt(s). Self-report responses to clinical items yielded scale scores for depression, social stress, atypicality, somatization, anxiety, and ADHD. Using an integrative data analytic technique, clinical scale scores were standardized and used to predict suicidal behaviors in a binary logistic regression analysis.

RESULTS: Approximately 22% of Black South African youths and 60% of Guyanese youths endorsed suicide ideation and attempt or suicide attempt only. In fully adjusted analyses, the odds of atypicality and somatization were 1.96 and 1.67 times greater among the youths who endorsed suicidal ideation when compared with those who did not ($p < .04$). Youth social stress was significantly associated with the suicide attempt, controlling for model covariates (odds ratio [OR], 1.88, $p = .05$). Gender moderated the effect of somatization on youth suicide.

CONCLUSION: Our results contextualize how social stress, atypicality, and somatization relate to LMIC youth suicide. Further study on high-risk samples will contribute to generalizable suicide-prevention models

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Dev Neuropsychol. 2019 Jul;44:368-84.

LONGITUDINAL ACADEMIC OUTCOMES OF CHILDREN WITH SECONDARY ATTENTION DEFICIT/HYPERACTIVITY DISORDER FOLLOWING PEDIATRIC STROKE.

Roberts SD, McDonald KP, Danguedan A, et al.

The current longitudinal study examined academic outcomes of children diagnosed with secondary attention deficit-hyperactivity disorder (S-ADHD) following stroke in comparison to children with stroke-only and children with developmental ADHD (D-ADHD), and explored potential predictors of progress in these groups. We followed 55 children ($n = 17$ S-ADHD, $n = 18$ stroke-only, and $n = 20$ D-ADHD) over approximately four years. Children with S-ADHD and D-ADHD were more likely to have a comorbid learning disability, but children with S-ADHD were more likely to have declines in their reading scores over time. No individual or neurological factors accounted for declines. Math scores were equally likely to decline across all youth

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Drug Invention Today. 2018;10:2152-55.

AWARENESS ABOUT ATTENTION-DEFICIT HYPERACTIVITY DISORDER AMONG TEENAGERS.

Revathi B, Jothi PA, Devi G.

Aim: The aim of this study is to create awareness and impart knowledge about attention-deficit hyperactivity disorder (ADHD) among teenagers and its prevalence in our society.

Materials and Methods: It is the questionnaire-based online survey which was taken by 150 participants using the link SurveyPlanet. Participants were mostly teenagers who are under the age group of 12-19.

Result: Through this survey, it is proved that nearly 50% of the participants were not able to focus well in their daily activities. They were under great pressure and impairment due to this disorder. Healthy mind and good lifestyle changes might help them to get rid of ADHD.

Conclusion: In common, people with good mental fitness are recognized and given appreciation. However, the proper way to analyze this disorder is lacking. It has been analyzed that parents whose children were affected with ADHD are not aware of their child's condition. Only about 56% use medications to prevent this disorder and the rest are not even trying to avoid it since they cannot analyze the problem or defect within their mental world. If they feel confident, they can improve their skills gradually, return back to their normal situations, and lead a happier life

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Emot Behav Difficulties. 2019;24:219-23.

DIAGNOSES AND THEIR INSTRUCTIONAL IMPLICATIONS-CHILDREN'S AGENCY AND PARTICIPATION IN SCHOOL ACTIVITIES.

Hjorne E, Saljo R.

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Environ Int. 2019;131.

ORGANOPHOSPHATE PESTICIDE METABOLITE CONCENTRATIONS IN URINE DURING PREGNANCY AND OFFSPRING ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND AUTISTIC TRAITS.

van den Dries MA, Guxens M, Pronk A, et al.

Background: Prenatal exposure to organophosphate (OP) pesticides has been associated with altered neuronal cell development and behavioral changes in animal offspring. However, the few studies investigating the association between prenatal OP pesticide exposure and neurodevelopmental outcomes such as Attention-Deficit Hyperactivity Disorder (ADHD) and autistic traits in children produced mixed findings.

Objective: The objective of the present study was to examine whether maternal urinary concentrations of OP pesticide metabolites are associated with ADHD and autistic traits in children participating in the Generation R Study, a population-based birth cohort from Rotterdam, the Netherlands.

Method: Maternal concentrations of 6 dialkylphosphates (DAPs) were measured using gas chromatography coupled with tandem mass spectrometry in urine samples collected at <18 weeks, 18-25 weeks, and > 25 weeks of gestation in 784 mother-child pairs. DAP metabolite concentrations were expressed as molar concentrations divided by creatinine levels and log₁₀ transformed. ADHD traits were measured at ages 3, 6, and 10 years using the Child Behavior Checklist (CBCL) (n = 781) and autistic traits were measured at age 6 years using the Social Responsiveness Scale (SRS) (n = 622). First, regression models were fit for the averaged prenatal exposure across pregnancy. Second, we investigated associations for each collection phase separately, and applied a mutually adjusted model in which the effect of prenatal DAP concentrations from each time period on ADHD and autistic traits were jointly estimated. All associations were adjusted for relevant confounders.

Results: Median DAP metabolite concentration was 309 nmol/g creatinine at <18 weeks, 316 nmol/g creatinine at 18-25 weeks, and 308 nmol/g creatinine at >25 weeks of gestation. Overall, DAP metabolite concentrations were not associated with ADHD traits. For instance, a log₁₀ increase in averaged total DAP

concentrations across gestation was not associated with a lower ADHD score (-0.03 per SD 95 CI: 0.28 to 0.23). Similarly, no associations between maternal DAP concentrations and autistic traits were detected.

Conclusions: In this study of maternal urinary DAP metabolite concentrations during pregnancy, we did not observe associations with ADHD and autistic traits in children. These are important null observations because of the relatively high background DAP concentrations across pregnancy, the relatively large sample size, and the 10-year follow-up of the offspring. Given the measurement error inherent in our OP pesticide exposure biomarkers, future studies using more urine samples are needed to accurately measure OP pesticide exposure over pregnancy in relation to ADHD and autistic traits

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Eur Arch Psychiatry Clin Neurosci. 2019;269:689-99.

A GENE VARIATIONS CONTRIBUTE TO THE SUSCEPTIBILITY OF CHILDREN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CASE-CONTROL ASSOCIATION STUDY.

Wang M, Gu X, Huang X, et al.

It was presumed syntaxin-1A (STX1A) might relate to the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), but the results were inconsistent. The present study aims to confirm whether the STX1A gene is involved in the susceptibility of children ADHD. We genotyped three single nucleotide polymorphisms (SNPs) of STX1A gene using Sequenom MassARRAY technology. A case-control study was performed among Chinese Han population including 754 cases and 772 controls from two different provinces. The Conners Parent Symptom Questionnaire and Integrated Visual and Auditory Continuous Performance Test were used to assess ADHD clinical symptoms. We found for the first time that rs3793243 GG genotype carriers had a lower risk of ADHD compared with AA genotype (OR 0.564, 95% confidence interval (CI) 0.406-0.692, $P = 0.001$), and rs875342 was also associated with children ADHD (OR 1.806, 95% CI 1.349-2.591, $P = 0.001$). In addition, the two positive SNPs were also significantly associated with the clinical characteristics of ADHD. Expression quantitative trait loci analysis indicated that rs3793243 might mediate STX1A gene expression. Using a case-control study to explore the association between STX1A gene and children ADHD in Chinese Han population, our results suggest STX1A genetic variants might contribute to the susceptibility of children ADHD

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Eur Arch Psychiatry Clin Neurosci. 2019;269:645-55.

VISUAL AND AUDITORY STEADY-STATE RESPONSES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Khaleghi A, Zarafshan H, Mohammadi MR.

We designed a study to investigate the patterns of the steady-state visual evoked potential (SSVEP) and auditory steady-state response (ASSR) in adolescents with attention-deficit/hyperactivity disorder (ADHD) when performing a motor response inhibition task. Thirty 12- to 18-year-old adolescents with ADHD and 30 healthy control adolescents underwent an electroencephalogram (EEG) examination during steady-state stimuli when performing a stop-signal task. Then, we calculated the amplitude and phase of the steady-state responses in both visual and auditory modalities. Results showed that adolescents with ADHD had a significantly poorer performance in the stop-signal task during both visual and auditory stimuli. The SSVEP amplitude of the ADHD group was larger than that of the healthy control group in most regions of the brain, whereas the ASSR amplitude of the ADHD group was smaller than that of the healthy control group in some brain regions (e.g., right hemisphere). In conclusion, poorer task performance (especially inattention) and neurophysiological results in ADHD demonstrate a possible impairment in the interconnection of the association cortices in the parietal and temporal lobes and the prefrontal cortex. Also, the motor control problems in ADHD may arise from neural deficits in the frontoparietal and occipitoparietal systems and other brain structures such as cerebellum

Eur Arch Psychiatry Clin Neurosci. 2019.

FAMILY AND DEVELOPMENTAL HISTORY OF ADHD PATIENTS: A STRUCTURED CLINICAL ROUTINE INTERVIEW IDENTIFIES A SIGNIFICANT PROFILE.

Waltereit J, Haas F, Ehrlich S, et al.

Similar to other neurodevelopmental disorders, the diagnosis of attention-deficit hyperactivity disorder (ADHD) is based on clinical and psychosocial assessment. This assessment is performed in clinical practice using the clinical routine interview technique. Domains of the clinical routine interview are, among others, present symptoms, history of present illness and family and developmental history. Family and developmental history are important parts in the diagnostic process of ADHD. In contrast to the domains of present symptoms and history of present illness, there are currently no structured interviews or rating scales available to thoroughly assess family and developmental history in ADHD. The aim of the study was to assess the profile of operationalized data from a structured clinical routine interview addressing family and developmental history from ADHD patients and control participants. A structured interview to assess family and developmental history was derived from the guidelines used at different university hospitals for Child and Adolescent Psychiatry as well as from the descriptions in leading textbooks. Based on these guidelines and descriptions, the interview was an optimization of possible questions. Clinical data were obtained from parents of male patients who had the diagnosis of ADHD between the ages of 12-17 years ($n = 44$), and of healthy controls ($n = 41$). Non-metric data were operationalized into three categories, 0 normal behavior, 1 minor pathological behavior, 2 major pathological behavior. ADHD patients express a profile that significantly differs from control participants. Comparison of significant items with the empirical ADHD literature indicates strong agreement. Our findings support the importance and feasibility of the clinical routine interview in family and developmental history in the context of diagnosing ADHD

Eur Child Adolesc Psychiatry. 2019.

METACOGNITIVE AND MOTIVATION DEFICITS, EXPOSURE TO TRAUMA, AND HIGH PARENTAL DEMANDS CHARACTERIZE ADOLESCENTS WITH LATE-ONSET ADHD.

Sibley MH, Ortiz M, Graziano P, et al.

The objective of this study is to evaluate support for three hypotheses about the etiology of adolescent-onset ADHD symptoms: (1) a cool cognitive load hypothesis, (2) a hot rewards processing hypothesis, and (3) a trauma exposure hypothesis. Participants ($N = 50$) were drawn from two public high schools in a culturally diverse metropolitan area. A detailed procedure for identifying and confirming late-onset ADHD cases is described. Adolescents with late-onset ADHD ($n = 15$) were identified and compared to childhood-onset ($n = 17$) and non-ADHD classmates ($n = 18$). Adolescents and parents completed measures of neurocognition, rewards processing, clinical profile, and environmental demands. Late-onset cases were clinically and neurocognitively indistinguishable from childhood-onset cases; however, they experienced higher demands from parents ($d = 1.09$). Compared to the non-ADHD group, late-onset cases showed significant deficits in metacognition ($d = 1.25$) and academic motivation ($d = 0.80$), as well as a pronounced history of multiple trauma exposure (OR 11.82). At 1-year follow-up, ADHD persisted in 67.7% of late-onset cases. Late-onset cases (26.7%) were more likely than childhood-onset cases (0.0%) to transfer to alternative schools by 1-year follow-up. Multiple factors may contribute to adolescent-onset ADHD. Adolescents with metacognition and motivation deficits may be at greatest risk for the late-onset ADHD phenotype, particularly in highly demanding environments. Exposure to traumatic stress may play a key role in the exacerbation of existing deficits or onset of new symptoms. Late-onset ADHD was persistent in most cases and associated with higher risk for school disengagement than childhood-onset ADHD. Further work is needed to better understand the etiologies of late-onset ADHD symptoms

Eur Child Adolesc Psychiatry. 2019.

AGGRESSIVE SYMPTOMS IN CHILDREN WITH TIC DISORDERS.

Benaroya-Milshtein N, Shmuel-Baruch S, Apter A, et al.

Episodes of explosive anger and aggression are reported in patients with tic disorders and probably contribute to psychosocial stress and low quality of life. The source of these symptoms is controversial. The objective of the study was to study the relationship between tic disorders, their associated comorbidities, and aggressive behavior. The cohort included 47 children and adolescents (age 7-17 years) with Tourette syndrome or other chronic tic disorders attending a tertiary pediatric Tourette clinic. Associated psychopathology was assessed with the Yale Global Tic Severity Scale, Yale Brown Obsessive Compulsive Scale, Conners ADHD Rating Scale, Screen for Child Anxiety-Related Emotional Disorders, and Child Depression Inventory. Aggression was assessed with the Overt Aggression Scale and scores were compared with a group of 32 healthy age- and sex-matched children. There were no significant differences in aggression scores between the children with tic disorders and controls. Verbal aggression was the most prevalent type of aggression, found in 70% of the patients with tic disorders. The level of aggression was not correlated to tic severity. Comorbid attention-deficit hyperactivity disorder and obsessive-compulsive disorder increased the probability of aggressive behavior in patients with tic disorders. On regression analysis, the only significant predictor of aggression was the severity of attention-deficit hyperactivity disorder. This study suggests that there is no difference in aggressive behavior between children with tics without comorbidities and healthy children. It is possible that aggressive behavior in children with tic disorders is predominantly associated with comorbid attention-deficit hyperactivity disorder

Eur J Clin Pharmacol. 2019;75:S53.

CONCOMITANT USE OF PSYCHOTROPIC DRUGS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Javaloyes GL, Sancho-Lopez A, et al.

Introduction: There is a perception that there is an increment in the number of paediatric patients who are receiving treatment with psychotropic drugs, particularly in ADHD patients

Objectives: Describe the profile of current drug therapy use in paediatric patients diagnosed of ADHD in specialized care setting and its evolution from 2011 to 2017. Analyse concomitant medicines associated with stimulants for the treatment of ADHD with/without psychiatric comorbidity

Methods: Retrospective, longitudinal drug utilization study. We included all patients with electronic medical records and a diagnosis of ADHD (ICD10:F90.0-F90.9) seen at the Paediatric Northwest Mental Health Area in Madrid between 2011-2017

Results: Of the 7,078 patients seen in this period, 3,416 patients diagnosed of ADHD were included. Of these, 44% had associated psychiatric-comorbidities. The longitudinal analysis showed a progressive increase in the percentage of patients diagnosed over the last years, from 28.4% in 2011 to 59.6% in 2017. The percentage of ADHD with psychiatric comorbidity remained stable. The overall percentage of treated patients increased from 74% in 2011 to 87% in 2017. There were no significant differences in relation to patients who had associated comorbidity (2017:86.2% vs.86.9%). The frequency of prescription for each pharmacological group is shown in Table 1. Stimulants were the most prescribed drugs. The prescription of other therapeutic groups was significantly higher in the group with psychiatric comorbidity ($p < 0.05$)

Summary / Conclusions: ADHD diagnosis has increased over time between 2011-2017. Almost half of ADHD children have associated comorbidities. The percentage of patients with pharmacological treatment remained stable. It is remarkable that up to 10% of ADHD patients without psychiatric comorbidities were also treated with other psychotropic medicines, which appears poorly justified

Eur J Neurol. 2019;26:210.

ATTENTION DEFICIT HYPERACTIVITY DISORDERS (ADHD) IN WOMEN WITH TURNER SYNDROME.

Lugo S, Pagan M, Rivera DM, et al.

Background and aims: Girls with Turner syndrome (TS) often demonstrate behavioral problems related to anxiety, hyperactivity, impulsivity and inattention. We hypothesize that patients with TS have higher prevalence of attention deficit hyperactivity disorders (ADHD) when compared to general population based on our clinical observation.

Methods: A retrospective chart review of diagnosis codes of TS or Gonadal Dysgenesis between 2005 and 2015. 94 patients (Age 5 - 50 years) were evaluated based on documented karyotype as well as the presence of short stature, ovarian failure, hearing or visual impairment, and hypothyroidism. Diagnoses were determined by ICD 10 code, neuro-psychology evaluation, self-reported history or medications associated with psychiatric conditions. Patients with hearing loss were excluded.

Results: 94 patients had a diagnosis Codes of Turner Syndrome or Gonadal Dysgenesis; of those 82 patients met the inclusion criteria. Of the 82 patients 29 were positive for Neuropsychiatric Disorder (35%). ADHD was most prevalent condition with 11 patients (13%) having a documented ADHD diagnosis. Of those with ADHD 91% had ovarian failure.

Conclusion: Patients with Turner Syndrome have higher prevalence for ADHD when compare to general population. Prevalence of ADHD in general population is about 5% with higher prevalence in males. In our study we find a prevalence of 13% in women with TS. ADHD screening, early diagnosis and management should be an essential part of managing women with TS. It is also important to screen for other comorbidities of TS such as hearing loss and thyroid disorders which may affect attention span

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Eur J Neurol. 2019;26:596.

MOTOR SEQUENCING TRAINING HAS POSITIVE EFFECT ON EXECUTIVE AND MOTOR ABILITIES IN CHILDREN WITH ADHD.

Kiseleva N, Kiselev S.

Background and aims: It is known that children with ADHD have deficit in executive and motor abilities. It is of great significance to receive the evidence for efficiency of different training programmes that are aimed to help children with ADHD. The goal of this study was to assess the impact of 12 weeks of motor sequencing training on the executive and motor abilities in children with ADHD.

Methods: The participants were 24 children aged 5-6 years (mean age=5.1) with ADHD. Children were randomly assigned to the intervention and comparison group. Children from intervention group participated in 12 weeks of motor sequencing training. This programme trains the child to plan, sequence and process information more effectively through repetition of goal-directed movements. This programme is built on the conceptual framework derived from the work of Luria's theory of restoration of neurocognitive functions (Luria, 1963, 1974). The Luria's child neuropsychological assessment battery was administered before and after the intervention period.

Results: Analysis of covariance tested the effect of motor training programme on four scales of the Luria's child neuropsychological assessment battery: Executive scale; Motor scale; Visuo-spatial scale; Memory scale. Group differences ($p < .05$) were found for the Executive scale and Motor scale. Post-test mean for the intervention group were significantly ($p < .05$) greater than the control group.

Conclusion: Motor sequencing training in children with ADHD benefits both motor abilities and executive functions

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Europ J Spec Needs Educ. 2019.

WHAT'S IN A NAME: THE EFFECT OF CATEGORY LABELS ON TEACHERS' ÇÖ BELIEFS.

Gibbs S, Beckmann JF, Elliott J, et al.

In this paper, we report an investigation of the possible influence on teachers' essentialist thinking and efficacy beliefs of category labels used to describe children's educational difficulties. A 2x2x2

counterbalanced design was employed in which primary school teachers in Finland and the UK were exposed to vignettes that portrayed a child exhibiting difficulties in one of two domains: either behaviour or reading. Vignettes were presented in two versions. In one, the child was labelled as having either ADHD or Dyslexia; in the alternate condition, no such label was ascribed, descriptions were identical in all other respects. Participating teachers were presented with two vignettes, one from each domain and in each condition. Responses to measures of Efficacy and Essentialist beliefs were solicited. Overall responses indicated that category labels evoked stronger essentialist beliefs but did not influence teachers efficacy beliefs. Finnish teachers reported stronger essentialist and lower efficacy beliefs than their counterparts in the UK

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Eur Neuropsychopharmacol. 2019;29:S1268-S1269.

RECONCEPTUALIZING PSYCHOPATHOLOGY FOR GENETIC STUDIES USING HIERARCHICAL DIMENSIONAL STRUCTURAL MODELS: THE EXAMPLE OF EXTERNALIZING AND AVPR1A.

Waldman I.

Background: Recent trends in the psychopathology literature have reconceptualized psychopathology in terms of transdiagnostic or hierarchical dimensional perspectives. Despite these trends, the modal phenotypes used in psychiatric genetic studies (e.g., in GWASs of psychiatric disorders conducted through the Psychiatric Genetics Consortium) are single, specific psychiatric diagnoses. In this paper, I explore different conceptualizations of a higher-order Externalizing symptom dimension in children, as well as different analytic methods used to characterize this dimension, in its association with the Arginine Vasopressin 1a receptor gene (AVPR1a), a gene that was genome-wide significantly associated in a GWAS of aggression.

Methods: In phenotypic analyses, data were available on parent ratings of DSM-IV symptoms of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) from $n=2800$ children whereas in genetic analyses data were available from $n=600$ children, all aged 6-16 years old. These three disorders were divided into their constituent symptom dimensions. These included Inattention, Impulsivity, and Hyperactivity for ADHD, Negative Affect and Behavioral Dyscontrol for ODD, and Aggressive and Rule Breaking dimensions of Conduct Disorder. In analyses of genetic association six SNPs in AVPR1a were used to characterize the gene in a series of gene-based tests.

Results: I contrasted different models for characterizing the Externalizing symptom dimension with each other, as well as with models of its constituent diagnoses and symptom dimensions. Comparisons of these phenotypic models used the percentage of variance explained and the relative fit of the alternative models to adjudicate among them. In phenotypic analyses, the best-fitting model contained a higher-order Externalizing factor on which the 7 symptom dimensions loaded, as well as residual correlations among the ADHD dimensions, the ODD dimensions, and the CD dimensions. This model fit better than a bifactor model in which a General Externalizing factor influenced all of the ADHD, ODD, and CD symptoms directly, as well as a model in which the 7 constituent symptom dimensions were correlated with each other. In gene-based analyses of AVPR1a the higher-order Externalizing higher-order factor was more strongly associated with AVPR1a than the 7 lower-order symptom dimensions, Conduct Disorder symptom scale composites, and the Conduct Disorder diagnosis.

Discussion: Results of these analyses highlight the benefits of conceptualizing and operationalizing psychopathology in terms of hierarchical dimensional models, as well as which conceptualizations of the externalizing spectrum and analytic methods for genetic associations are optimal.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1188-S1189.

USING GENETIC INSTRUMENTS TO ASSESS CAUSAL PATHWAYS TO EDUCATIONAL ATTAINMENT IN ADHD AND AUTISM: EVIDENCE FROM A TWO SAMPLE MENDELIAN RANDOMISATION STUDY.

Dardani C, Leppert B, Riglin L, et al.

Background: Attention Deficit/ Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) show genetic and phenotypic overlap (Satterstrom et al., 2018; Stergiakouli et al., 2017). ADHD and ASD recently have been found to have genetic links to one of the strongest predictors of social and economic outcomes; educational attainment (Demontis et al., 2017; Grove et al., 2017). Observational evidence indicates that children with ADHD or ASD, are at increased risk of poor school performance (Crump et al., 2013). However, it is currently unknown whether the two conditions have causal effects on educational attainment or whether these associations are a result of unmeasured or residual confounding. We examined the causal effect of liability for ADHD and ASD on educational attainment in a two- sample Mendelian Randomisation (MR) framework.

Methods: We performed two MR analyses to test the causal effect of each exposure (ADHD and ASD) on years of schooling. We considered as instrumental variables for ADHD, 12 genome-wide significant SNPs, identified in the most recent GWAS meta-analysis on ADHD (Demontis et al., 2017). Instruments for ASD were defined based on the latest GWAS meta-analysis of ASD (Grove et al., 2017). To increase the power of the ASD analysis, in addition to the 5 genome-wide significant SNPs, we utilized the 15 top SNPs identified in the ASD GWAS, with p- values ranging from $7 \cdot 10^{-7}$ to $1 \cdot 10^{-7}$. For each of the main analyses, SNP-outcome coefficients were extracted from the latest published GWAS on educational attainment (Okbay et al., 2016). SNP- exposure and SNP- outcome coefficients were combined using an Inverse Variance Weighted approach. We performed sensitivity analyses to test the robustness of our findings and detect and account for pleiotropy. We also performed replication analyses using the largest forthcoming GWAS of educational attainment (Lee et al., to be published).

Results: There was evidence consistent with a causal effect of liability to ADHD on 0.27 fewer years of schooling (95% CI: -0.43 to -0.12, $p= 0.0003$). The direction and magnitude of the causal effect estimate was consistent in sensitivity analyses assessing pleiotropy, as well as in the replication analysis with the most recent and largest educational attainment GWAS. On the contrary, limited evidence was found in favor of a causal effect of liability to ASD on years of schooling ($b= 0.03$, 95% CI: -0.053 to 0.125, $p= 0.432$). The result was confirmed in the replication analysis, although sensitivity analyses indicated strong evidence of heterogeneity among the genetic variants used as instruments.

Discussion: Our findings provide evidence for distinct causal pathways for ADHD and ASD towards educational outcomes. Using two-sample MR, we found results were consistent with liability to ADHD being a causal risk factor for poorer educational outcomes. This finding can provide support towards improving current treatment approaches or support infrastructure for children with ADHD, in order to enhance academic outcomes. On the contrary, there was lack of evidence suggesting a causal effect of ASD on education. This could be attributed to a number of factors, including the small effect size genetic variants, contributing to the broad and heterogeneous expression of the ASD phenotype. Larger studies as well gender and phenotype stratified datasets are needed in order to disentangle the associations among ASD and educational attainment.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1113.

GENETICS OF TREATMENT RESPONSE FOR ATOMOXETINE IN ADHD.

Kim H-W, Zayats T, Park K, et al.

Background: Atomoxetine is one of the widely-used non-stimulant agents for treatment of attention-deficit/hyperactivity disorder (ADHD). It is known to be effective for reducing core ADHD symptoms and improving psychosocial functioning, but responses to atomoxetine vary among individuals with ADHD. The role of genetic factors in this variability is not well-known. Thus, we investigated the genetic influence on treatment response by examining its association with the known ADHD genes.

Methods: Our sample consisted of 57 children (mean age: 7.8-11.4 years; 86% boys) treated with atomoxetine, 30 of whom responded to it. The association was tested between the 25 genes in 12 genome-

wide significant ADHD loci, using MAGMA software. To examine gene regulatory regions, windows of 5kilobases (kb) upstream and 1,5 kb downstream of each gene were included in the analyses. False discovery rate (FDR) was applied to correct for multiple testing. Q value of 0.05 was considered statistically significant.

Results: Two genes ΓÇô POC1B and MIR3666 - revealed signs of association with treatment response to atomoxetine. After FDR, only POC1B (POC1 centriolar protein) gene revealed border/line significant association (FDR $q=0.050$).

Discussion: Our results indicate that biological processes underlying ADHD and those underlying treatment responses may be different.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1279.

GEOGRAPHICAL VARIATION IN GENETIC AND ENVIRONMENTAL INFLUENCES ON AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SWEDEN AND THE UNITED KINGDOM USING BOTH TWIN ANALYSES AND POLYGENIC RISK SCORES.

Reed Z, Larsson H, Plomin R, et al.

Background: Our previous work has shown that geographical location affects the balance of genetic and environmental influences on many developmental disorders and traits. For example, we may find greater heritability for a disorder in a city Centre, suggesting that the urban environment draws out genetic influences. In this study we applied our spACE approach using twin data to estimate genetic and environmental influences on autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) at locations across Sweden and the UK. We also explored how polygenic risk for these traits varies across a single city region using data from Bristol in the UK.

Methods: We first used twin data from Sweden's Child and Adolescent Twin Study to estimate spatial patterns of genetic, shared environmental and non-shared environmental influences on symptoms of ASD and ADHD measured using the Autism-Tics, A/HD and other Comorbidities inventory at ages 9 and 12. We fitted spACE structural equation models at thousands of locations across the country, with each twin pair's contribution weighted by their inverse Euclidean distance from each location. We compared the resulting maps to our previous analyses in the UK's Twins Early Development Study using the Childhood Asperger Syndrome Test and the Conner's Parent Rating Scale at age 12. For our single-city-region polygenic risk score analyses we used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in weighted linear regression models to determine the association of published polygenic risk scores with symptoms of ASD and ADHD at multiple locations. Phenotype data in ALSPAC were collected at age 7 using the Skuse social score for ASD and the Strengths and Difficulties Questionnaire hyperactivity scale for ADHD.

Results: We found geographical variation in genetic and non-shared environmental influences for both ASD and ADHD in Sweden, paralleling our previous results from the UK. In our analysis of polygenic risk scores, we also found evidence of geographical variation on a local scale in the city of Bristol and surrounding areas.

Discussion: Our twin analysis results show different patterns of geographical variation in genetic and non-shared environmental influences on symptoms of ASD and ADHD. This indicates that where we grow up effects the aetiology of these traits. For example, it appears that more densely populated areas show greater heritability for ASD in both the UK and Sweden, while patterns for ADHD appear more complex. We also found geographic variation in polygenic risk score associations across the Bristol area, providing complementary evidence that where we live moderates the effect of known polygenic risk on these outcomes.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1188.

THE POLYGENIC INFLUENCE ON ADHD DEPENDS ON AGE AND CLINICAL TRAJECTORY.

Sprooten E, Mota NR, Bralten J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a variable developmental course of symptomatology. Polygenic common variation accounts for a significant portion of ADHD heritability. Twin studies suggest that the genetic risk factors for ADHD depend on the age of onset and the degree of persistence of the disorder. We investigated whether differential genetic effects are also discernable in polygenic risk scores (PRS) derived from genotype data.

Methods: Genotype and clinical data were available for 951 individuals from the longitudinal NeuroIMAGE cohort of individuals aged 4 to 30 years. The diagnostic status of ADHD changed between any two measurements in 14% of the sample. Illumina PsychArray-24-v1.1A genotypes were processed and imputed using Ricopili. PRS were based on European GWAS from the PGC-ADHD working group. We investigated the age-by-PRS interaction on ADHD-status in a generalized mixed-model with individual and family as nested random effects. We also tested for associations of ADHD-status with PRS within four age-quantiles.

Results: The generalized mixed-model showed an age-by-PRS interaction on ADHD-status ($P=0.007$). A polynomial fit to the residuals suggested that PRS predicted ADHD status best at age <13.2 years, and with increasing age the prediction diverged increasingly from the observed diagnosis. PRS explained the most variance in ADHD-status in the first 3 age-quantiles from 4 to 18 years ($0.18 < r^2 < 0.29$; all $P < 10^{-8}$), and less from 18 to 30 years ($r^2=0.04$; $P=0.04$).

Discussion: Polygenic influences on ADHD change over time. Age-stratified and longitudinal studies are necessary to understand the age- and trajectory-dependent genetic architecture underlying ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1218-S1219.

INTERFERENCE CONTROL AND SOCIAL AWARENESS AS A CANDIDATE INTERMEDIATE PHENOTYPE FOR ADHD.

Shon S-H, Kim H-W, Park K .

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder. Because ADHD has a heterogeneous clinical manifestation with a complex syndromic clinical definition, it has been suggested that quantitative phenotypes, that is, intermediate phenotypes, could be useful for dissecting the genetic basis of ADHD. The aim of the current study is to identify the intermediate phenotype by comparing clinical and neuropsychological profiles of children who presumed to have different genetic predisposition.

Methods: We compared the following three groups; children with ADHD ($n=307$), their unaffected sibling ($n=63$), and typically developing children ($n=112$). The children completed the Continuous Performance (CPT), Stroop, Children's Trail Making, and Rey-Kim Memory tests. The parents of these subjects underwent the Attention-Deficit/Hyperactivity Disorder Rating Scale (ARS), 10-item Parent General Behavior Inventory (P-GBI), and the Social Responsiveness Scale (SRS).

Results: The Social Awareness scale of the SRS was highest in typically developing children, followed by unaffected siblings, and ADHD children (Bonferroni adjusted $p < 0.001$). ADHD and their unaffected sibling showed significantly lower scores on Color-Word scores of the Stroop test than typically developing children (Bonferroni adjusted $p < 0.001$).

Discussion: Our results suggest that interference control, measured by the Stroop test, and social awareness of the SRS could be a potential intermediate phenotype of ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1189-S1190.

STRUCTURAL BRAIN ALTERATIONS AND THEIR ASSOCIATION WITH COGNITIVE FUNCTION AND SYMPTOMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FAMILIES.

Jiang W, Duan K, Chen J, et al.

Background: Attention-deficit/Hyperactivity Disorder (ADHD) is a heritable neurodevelopmental disorder characterized by inattention along with hyperactivity and impulsivity. Smaller whole brain volume, and gray matter abnormality in basal ganglia, fronto-striatal-parietal pathways, and the cerebellum are the most consistent findings in ADHD. We investigated 336 families from the Dutch NeuroIMAGE projects (von Rhein et al., 2015) in a multivariate analysis, to examine brain structure alterations and their association with symptoms and cognition among ADHD subjects, their unaffected siblings, subthreshold cases, and controls.

Methods: 508 participants (aged from 7 to 18 years) from 336 families from the NeuroIMAGE project were included in this study, with structural brain scans collected on two scanners. ADHD subjects were diagnosed according to DSM-IV or DSM-IV-TR, and inattention and hyperactivity/impulsivity symptom severity were assessed for all subjects. Subjects were grouped into those with ADHD (N=210), their unaffected siblings (N=108), subthreshold cases (N=49), and non-ADHD controls (with no ADHD siblings, N=141), according to previous designations. The WAIS Digit Span score, the Stop Signal Reaction time, the ratio of the Reaction Time Variability to its mean, and total Errors from a go/no-go task were included. All T1-weighted MRI images were segmented using SPM12 with a children-specific template (Wilke, Holland, Altaye, & Gaser, 2008). The segmented, normalized, modulated, smoothed (6 mm FWHM), and gender- and site-corrected gray matter images were decomposed into 20 components and their loading coefficients using the Group ICA toolbox (GIFT). Age and age² effects were tested for effects on all components and included, when significant. To determine case/control effects, linear mixed models with family as random factors, diagnosis as a fixed factor, and relevant covariates were used. Similar models including age, gender, IQ, and medication status were used to test association with cognition and symptoms only in components that showed case/control effects.

Results: Two components showed significant case/control effects with p-values corrected for False Discovery Rates (FDR), consistently showing lower loading coefficients in cases than controls. Component 1 included a maximum cluster in bilateral insula, and unaffected siblings showed significantly reduced loadings relative to controls, similar to cases; subthreshold cases did not. No relationship was found with cognitive or symptom scores. Component 2 (Crus II) only showed a case/control difference; subthreshold cases were intermediate between cases and unaffected siblings, who were similar to controls. After correcting for IQ and medication status, component 2 showed a negative correlation with inattention symptoms across the entire group (corrected p = 0.011, beta = -0.43, VE = 1.4%).

Discussion: In a multivariate approach to gray matter network differences in ADHD, we identified two components showing significant gray matter reduction in ADHD, including primarily insula and Crus II. The insula component showed a similar reduction in unaffected siblings, but no relationship to symptom severity or cognition. The cerebellar component, in contrast, showed a relationship to inattention regardless of clinical status, but the unaffected siblings were similar to controls. This approach suggests that areas reflecting genetic liability within ADHD can be partly separated from areas modulating symptom severity.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1098-S1099.

EXPRESSION QUANTITATIVE TRAIT LOCI IN THE DEVELOPING HUMAN BRAIN AND THEIR ENRICHMENT IN NEUROPSYCHIATRIC DISORDERS.

O'Brien H, Hannon E, Hill M, et al.

Background: Genetic influences on gene expression in the human fetal brain plausibly impact upon a variety of postnatal brain-related traits, including susceptibility to neuropsychiatric disorders. However, to date, there have been no studies that have mapped genome-wide expression quantitative trait loci (eQTL) specifically in the human prenatal brain.

Methods: We performed strand-specific, whole transcriptome sequencing of total RNA derived from brain tissue from 120 human fetuses aged 12-19 post-conception weeks, deriving expression measures for 144,448 Ensembl transcripts, annotated to 28,875 genes. Genomic DNA from each sample was genotyped for approximately 710,000 single nucleotide polymorphisms (SNPs), followed by genotype imputation using

the Haplotype Reference Consortium r1.1 panel. Cis-eQTL were identified by linear regression of allele dosage against gene expression measures, adjusted for PEER factors and other covariates, using FastQTL. **Results:** We identified high confidence cis-eQTL for >1300 genes and >3000 individual transcripts (FDR < 0.05). Fetal brain eQTL were found to be enriched among risk variants for attention deficit hyperactivity disorder, schizophrenia and bipolar disorder. We further identified changes in gene expression within the prenatal brain that potentially mediate risk for neuropsychiatric traits, including increased expression of C4A in association with genetic risk for schizophrenia, increased expression of LRRC57 in association with genetic risk for bipolar disorder and altered expression of multiple genes within the chromosome 17q21 inversion in association with variants influencing the personality trait of neuroticism.

Discussion: We have mapped eQTL operating in the human fetal brain, providing evidence that these confer risk to certain neuropsychiatric disorders, and identifying gene expression changes in the prenatal brain that could mediate susceptibility to these conditions.

Disclosure: Nothing to disclose

Eur Neuropsychopharmacol. 2019;29:S1110-S1111.

ELUCIDATING THE GENETIC AND BIOLOGICAL FACTORS UNDERLYING THE RELATIONSHIP BETWEEN ADHD AND BMI VARIATION.

Mota NR, Klein M, Poelmans G, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is frequently associated with other psychiatric and somatic conditions. One of the most important non-psychiatric comorbidities of ADHD, in terms of public health, is obesity. Clinical overlap between ADHD and obesity is well documented, with studies showing an increased prevalence of obesity in ADHD patients and higher rates of ADHD in obese individuals. The latest ADHD GWAS meta-analysis showed significant genetic correlations between ADHD and all classes of obesity ($r_g=0.29-0.34$) and obesity-related traits, such as body-mass-index (BMI; $r_g=0.26$) (Demontis et al, BioRxiv 2017). However, the biological mechanisms driving this association are largely unknown. Some candidate systems have been suggested, e.g., disturbances in the circadian rhythm (CIRCA) and dopaminergic neurotransmission (DOPA) systems.

Methods: We examined the association of ADHD polygenic risk scores (PRS) with obesity risk and BMI variation in the general population, as well as the association of BMI-PRS and ADHD-related measures. We used the results from the latest ADHD GWAS (see above; N(Euro)=19,099 cases and 34,194 controls) and BMI GWAS (N=681,275; Yengo et al, BioRxiv 2018) as discovery samples. Our target sample was a Dutch population cohort ascertained by the Nijmegen Biomedical Study (N=13,200 adults). We also tested the association of CIRCA and DOPA gene-sets with the ADHD and BMI GWAS results mentioned above. Lastly, in order to identify common biological mechanisms through a genome-wide approach, we performed a gene-based cross-disorder meta-analysis of these GWASs, followed by canonical pathway and network enrichment analyses using Ingenuity.

Results: ADHD-PRS were significantly associated with obesity risk ($R^2=1.0\%$; $P=5.1E-4$) and BMI variation ($R^2=0.66\%$; $P=2.4E-6$). Regarding BMI-PRS, a significant association with the presence of ADHD symptoms during childhood was observed ($R^2=0.75\%$; $P=1.1E-4$). When current inattention (IA) and hyperactivity/impulsivity (HI) scores were analysed separately, a significant association of BMI-PRS and HI scores ($R^2=0.35\%$; $P=9.4E-4$) was seen, suggesting that this symptom domain has a more prominent role in the ADHD-obesity(-BMI) relationship. Gene-set association analyses showed that the CIRCA gene-set was only associated with BMI, while the DOPA gene-set was associated with both ADHD and BMI. In our genome-wide approach, a total of 206 genome-wide significant genes showed increased significance compared to both original GWASs. Enrichment analyses with these genes revealed one significant canonical pathway, namely CREB Signalling in Neurons (PBH=0.035), containing 9 genes. The top enriched network contained 28 genes and was centred around the NF-KB complex.

Discussion: In conclusion, in terms of a shared biology underlying the relationship between ADHD and obesity (represented by BMI), our results so far support the involvement of the dopaminergic neurotransmission system through a candidate gene-set approach. Furthermore, they indicate that neuroplasticity, a common feature of both neuronal CREB signalling and NF-KB signalling, could play a key

role in this relationship. Given the great impact both ADHD and obesity have on society, it is important to further unravel the biological mechanisms that are disturbed in both conditions.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1147.

NEONATAL EPIGENOME-WIDE ASSOCIATION STUDY USING GUTHRIE-CARDS OF LATER DIAGNOSED ASD AND ADHD CASES.

Staubstrup N, Starnawska A, Hansen C, et al.

Background: Autism Spectrum Disorder and Attention Deficiency/Hyperactive Disorder are multifactorial and prevalent disorders associated with epigenetic variation in peripheral tissue. However, due to the plasticity of epigenetic marks determining cause and causality is challenging. The epigenetic patterns are especially sensitive during fetal development and environmental exposures risk such as maternal stress has shown to leave lasting variations in the DNA methylation profile of the offspring associated with an increased risk of mental disorders later in life. With the intend to identify DNA methylation variants predicting the onset of ASD or ADHD later in life, we interrogate the genotype and DNA methylation profile of 700 ADHD cases, 700 ASD cases and 700 controls using Guthrie-cards from the Danish Neonatal Screening Biobank adding background information from Danish registers.

Methods: From the iPSYCH cohort of individuals born between 1981 and 2012 with a diagnosis of ADHD or ASD entered in the Danish Psychiatric Register between 2005 and 2012 a total of 1400 unrelated individuals were included along with a random control group of 700 from the same cohort. DNA extracted from the Guthrie-cards of the 2100 included individuals was used for DNA methylation measurement and genotyping using the EPIC DNA methylation or the PsychChip SNP array (Illumina), respectively. All data processing steps are performed on a secure cluster using R.

Results: Data is of high quality with >99% of samples passing our rigorous QC. Data analysis is currently ongoing, and a status hereof will be presented.

Discussion: We expect that epigenetic variants will be able to explain a part of the susceptibility to ASD and ADHD, and that epigenetic modifications will have applicability in the development of novel biomarkers and as targets for pharmaceutical intervention. We believe that this study will provide valuable information to this end.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1085.

EXPLORING THE DEVELOPMENTAL GENETIC ARCHITECTURE OF SOCIAL BEHAVIOUR: EVIDENCE FOR GENETIC OVERLAP WITH ASD AND ADHD.

Schlag F, Buitelaar J, Grove J, et al.

Background: The acquisition of social skills represents an important developmental milestone that most children master effortlessly, while developmental delays and deviations in social behaviour often have long-reaching effects on later mental health and wellbeing. The spectrum of social abilities is phenotypically complex. For example, prosocial behaviours capture positive interactions, while socially disruptive behaviours may lead to problematic peer relations. The developmental genetic architecture of social behaviour and its genetic overlap with psychiatric disorders is, however, largely unknown. Here, we investigate age-, trait- and reporter-specific changes in genetic factors underlying social skills in the general population and study shared genetic influences with Autism Spectrum Disorders (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: Two social traits capturing low prosociality (LPS) and peer problems (PP) were repeatedly assessed in participants of a UK birth cohort (ALSPAC; N=6174, 4 to 17 years), using either mother- and/or teacher-report. Single Nucleotide Polymorphism (SNP)-heritability (SNP-h²) for social traits was estimated with linkage disequilibrium score (LDSC) regression, based on genome-wide quasi Poisson regression analyses modelling right skewed data. Genome-wide summary statistics for ASD and ADHD were

obtained through the PGC/IPSYCH consortium. The association between polygenic risk for disorder and social traits was assessed with polygenic scoring (PGS, p -threshold <0.1), also using a quasi Poisson regression framework. Estimates were combined with random-effects meta-regression.

Results: We identified opposite developmental trends in LDSC-h² estimates for mother-reported LPS and PP respectively (trait x age interaction, $p=0.0002$). While LPS SNP-h² decreased with progressing age, with the highest estimate at age 4 years (SNP-h²=0.18(SE=0.08)), PP SNP-h² increased, with the highest estimate at age of 17 years (SNP-h²=0.43(SE= 0.12)). Teacher-rated LDSC-h² was strongest at 11 years, both for LPS (0.21(SE=0.09)) and PP (0.15(SE=0.10)), although the data was too sparse to model developmental patterns. Using a meta-regression framework, we identified a positive association between ASD polygenic risk and PP, irrespective of age and rater (beta-PGS = 0.05 (SE=0.01), $p=0.0002$), but not for LPS. Similarly, we observed evidence for a developmentally stable positive genetic overlap between ADHD polygenic risk and social behaviour. This was observed for mother-rated (beta-PGS = 0.05 (SE=0.01), $p<10^{-4}$) and teacher-rated (beta-PGS = 0.11(SE=0.02) $p<10^{-4}$) PP, as well as teacher-rated LPS (beta-PGS = 0.07 (SE=0.02), $p<10^{-4}$), but not mother-rated LPS.

Discussion: Social traits have complex genetic architectures that follow trait-specific developmental patterns, but show genetic overlap with both ASD and ADHD that is developmentally stable. However, the strength of genetic links with psychiatric disorder can differ by rater and/or type of social behaviour.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1043.

ASSOCIATIONS OF POLYGENIC RISKS FOR CHILDHOOD NEUROPSYCHIATRIC DISORDERS WITH SOMATIC HEALTH PROBLEMS ACROSS THE LIFESPAN.

Brikell I, Yi L, Martin J, et al.

Quantitative-genetics have been instrumental in demonstrating that genetic factors in part explain why childhood neuropsychiatric disorders co-occurs. Emerging evidence suggest that one important explanation to the frequently observed genetic correlations is that one general genetic psychopathology-factor influences a broad spectrum of neuropsychiatric conditions. There is only a limited literature on how the genetic factors of childhood neuropsychiatric disorders contribute to somatic health problems across the lifespan, including indicators of metabolic syndrome (e.g., obesity, hypertension and type-2 diabetes), inflammation (e.g., eczema, asthma) and vascular disease (e.g., migraine, cardiovascular disease). This study utilize data from a record-linkage between the Swedish twin registry, which contain information about the main childhood neuropsychiatric polygenic risk scores from more than 30 000, and the Swedish national registers, which contain outcome information about neuropsychiatric and somatic health problems across the life-span. We use published GWAS summary statistics of childhood neuropsychiatric disorders and somatic health problems to derive polygenic risk scores. We use regression analyses to estimate the associations of the derived polygenic risk scores with our primary outcomes. Results suggest that the genetic liability of ADHD are associated with indicators of metabolic syndrome, inflammation and vascular disease. Implications for future etiologic models are discussed. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1244.

GENETIC AND CLINICAL ANALYSES OF PSYCHOSIS SPECTRUM IN A LARGE MULTI-ETHNIC YOUTH COHORT (N>8,000) REVEAL SIGNIFICANT LINK WITH ADHD.

Loehuis LO, Mennigen E, Bearden C, et al.

Background: Psychosis spectrum (PS) symptoms are heritable, and children with PS have an increased risk of conversion to a psychotic disorder and other psychiatric disorders later in life. However, the precise role of genetic risk for PS and its interplay with other psychiatric symptoms across development remains poorly understood.

Methods: The Philadelphia Neurodevelopmental Cohort (PNC) is a genotyped population-based sample of >8,000 youths who received a structured psychiatric evaluation and a computerized neurocognitive battery.

The cohort is multi-ethnic, with the majority of participants of European ($\Gamma\hat{+}65\%$) and African ($\Gamma\hat{+}25\%$) ancestry. In this sample, $\Gamma\hat{+}20\%$ of youth were categorized as PS based on elevations in positive or negative/disorganized symptoms. Using a LASSO regression model, we aimed to predict PS using polygenic risk scores (PRS) based on GWAS from heritable neuropsychiatric traits. We also performed individual trait PRS associations, evaluated ancestry- and age-specific effects. Odds ratios (ORs) reported are comparing first and fifth quintile of PRS scores. Finally, we further investigated the phenotypic dimensions on which genetic risk is acting.

Results: We observed that genetic risk for ADHD was the most significant predictor of PS in the multi-trait regression model as well as the individual trait analyses ($\beta = 0.03$, $P = 2.41e-05$). This effect was driven by the children of European ancestry ($\beta = 0.05$, $5.61e-07$, OR 1.85), and not observed in the African ancestry group ($P = 0.93$). None of the other neuropsychiatric traits, including schizophrenia PRS, were associated with PS in children. While evidence for shared genetic risk for adult-onset SCZ and ADHD is only nominally significant (genetic correlation is 0.23, $P = 0.009$, LDhub), attentional deficits are a known precursor of psychotic symptoms. Indeed, across ancestries, we observe a strong phenotypic overlap between PS and ADHD - 4% of the sample meets DSM criteria, of which about half fall into the PS group $P < 2e-16$ - as well as a wide range of ADHD-related symptoms, with OR ranging between 3 and 4 and $P < 2e-16$. However, the observed genetic association is not driven by symptom overlap: even in the subset of children that do not endorse even the mildest ADHD symptoms (concentration problems at school, 60%), the association between ADHD PRS and PS risk remains. We observe a significant interaction with PRS and age (in EA, $P = 7.1e-06$), with a stronger association for younger children (< 12 years). This interaction is recapitulated at the phenotype level. Finally, whilst ADHD and psychosis phenotypic overlap is hypothesized to be partly mediated by substance use, substance use did not drive the phenotypic nor the genotypic correlations in our sample.

Discussion: Surprisingly, we observed that ADHD (and not schizophrenia) genetic risk is associated with PS in youth. Children with high genetic risk for ADHD had an almost two-fold increased risk for PS compared to those with low risk. This association holds even in the absence of ADHD symptoms, is strongest in young children, and diminishes closer to age of onset of schizophrenia. While preliminary, these findings shed light on how genetic risk can be investigated across early disease trajectories to improve our understanding of disease risk factors and psychiatric comorbidities. It also highlights the need for increasing ethnic diversity in GWA studies.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1269-S1270.

DESCRIBING THE GENETIC ARCHITECTURE OF ADHD USING LINKED-READ SEQUENCING: A CASE-CONTROL STUDY FROM THE ISOLATED POPULATION OF THE FAROE ISLANDS.

Wang AG, Gregersen NO, Mortensen +, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a mental disorder characterised by an ongoing pattern of inattention and/or hyperactivity-impulsivity. ADHD is highly heritable and genetic studies show substantia contribution of common variants to disorder susceptibility. Moreover, a reason meta-analysis show genome-wide significance of 12 independent loci comprising evolutionarily constrained genomic regions and loss-of-function intolerant genes. In this study the potential enrichment of ADHD risk variants will be explored based on whole-exome data from linked-read sequencing of individuals from the isolated population of the Faroe Islands. The demographic history of the Faroese population may have induced enrichment of variants rarely seen in outbred European populations, including enrichment of risk variants for ADHD.

Methods: Cases in this study comprises 56 patients with ADHD, recruited to the ADHD outpatient clinic at the Department of Psychiatry, General Hospital in Tórshavn, Faroe Islands. Diagnosis have been verified by a psychiatrist/child and youth psychiatrist, a psychologist and a ADHD specialized nurse. Further, the diagnostics were verified with the diagnostic tools: ADHD-RS (Attention Deficit/Hyperactive Disorder-Rating Scale), TOVA (Test Variables of Attention), BRIEF (Behavioural Rating Inventory of Executive Function) and in some cases DIVA (Diagnostic Interview for ADHD in adults) and QbTest (Quantified Behaviour Test Plus). Cases have been reviewed by experienced psychiatrists and the diagnostic most solid/robust cases have

been selected for genetic analyses. Healthy controls in this study comprises 200 individuals voluntarily recruited to the FarGen infrastructure, at the Genetic Biobank of the Faroe Islands. Self-reported healthy status was confirmed by the diagnostic registry at the National Hospital of the Faroe Islands. High-molecular weight (HMW) DNA extracted from peripheral blood was barcoded by a gel-bead emulsion (GEM) process in the Chromium™ controller. The 256 exomes were captured using the SureSelectXT Human All Exon kit and sequenced on the NextSeq 500. The linked-reads were aligned to the reference genome (GRCh37/hg19) and variants were called using GATK.

Results: The exomes were sequenced with an average coverage of 56, >98% of the reads were aligned to the reference genome. Due to the barcodes introduced to the DNA fragments in the GEM process we were able to perform molecular phasing, which assign >85% of the genes under 100 kb to a haplotype and phased >75% of the SNPs. Moreover, we will present results from single variant and gene-based association analyses, as well as possible structural variants will be presented.

Discussion: To our knowledge this is the first study to use linked-read sequencing to identify susceptibility variants/genes for ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1315-S1316.

INVESTIGATING THE GENETIC ARCHITECTURE OF PSYCHIATRIC DISORDERS AND THEIR MEDICAL COMORBIDITY FROM A DEVELOPMENTAL PERSPECTIVE.

Merikangas A, Kember R, Calkins M, et al.

Background: Mental disorders are a leading cause of disability worldwide. One of the major sources of disability is comorbidity between mental and physical conditions, which has been documented in both clinical and community samples of both adults and youth. Previous work on the Children's Hospital of Philadelphia (CHOP)/University of Pennsylvania Philadelphia Neurodevelopmental Cohort (PNC) has demonstrated pervasive comorbidity between physical and mental disorders in youth. Shared genetic etiology between some seemingly disparate mental and physical disorders has been identified. Establishing the loci underlying this comorbidity across development may provide insight into etiology and identify key pathways for treatment of both disorders.

Methods: The sample included 9498 youth ages 8 to 21 years from the PNC identified through pediatric clinics in the CHOP health care network (mean age=14.2; female= 51.7%; European American=55.8%; African American=32.9%; Other Ancestry=11.4%). Measures were as follows: physical condition based on electronic medical records and interview data on 42 physical conditions of 14 organ systems/specialties, mental disorders were assessed with an abbreviated version of the structured Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) psychiatric diagnostic interview, alcohol and other substance use were assessed with the Minnesota Twin and Family Study computerized substance use assessment or the K-SADS substance screener, and participants were genotyped and standard quality control measures employed. Patterns of medical/psychiatric comorbidity across development were established with traditional regression techniques, and empirically based phenotype groups were calculated using latent variable analysis. SNP-based heritabilities were calculated to estimate the degree of influence of common genetic variation on the established subtypes, and polygenic risk scores were calculated for disorders to establish if SNPs associated with medical conditions predict psychiatric phenotypes, and vice versa.

Results: Models adjusted for sociodemographic correlates, other physical and mental disorders, and false discovery revealed broad patterns of associations between neurodevelopmental disorders with behavior disorders and attention deficit/ hyperactivity disorder (ADHD); neurologic/central nervous system conditions with mood disorders and ADHD; and autoimmune/ inflammatory conditions with mood disorders.

Discussion: To our knowledge, our study is the first to examine the genetic architecture underlying comorbid medical/mental conditions in a large diverse sample of children. Our findings show strong overlap between physical and mental conditions and the specific patterns of comorbidity have important implications for etiology. Prospective tracking of cross-disorder morbidity will be important to establish more effective mechanisms for prevention and intervention since the order of onset cannot be determined from these data.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1106-S1107.

ASSOCIATION OF AGGRESSION AND ADHD SUBSCALES IN CHILDREN AND ADULTS.

Boomsma D, Dolan C, Bartels M, et al.

Background: Based on Bayesian machine learning analysis performed in the MATRICS (Multidisciplinary Approaches to Translational Research In Conduct Syndromes) consortium, in clinical adolescent ADHD and population cohorts, differential associations between aggression and hyperactivity and between aggression and inattention were suggested.

Methods: We aimed to replicate these findings in the ACTION (Aggression in Children: Unraveling gene-environment interplay to inform Treatment and InterventiON strategies) consortium, using the database from the large population-based Netherlands Twin Register. Analyses were done for data obtained during in childhood (age 7-16 years) and adulthood, employing both cross-sectional and longitudinal regression analyses. In children and in adults, outcome and predictor variables were assessed by comparable instruments. Aggression was assessed by the Achenbach System of Empirically Based Assessment (ASEBA) age-appropriate inventories, namely the Child behavior Check List (CBCL), and the Youth or the Adult Self Report (YSR / ASR). Hyperactivity and inattention were assessed by the Conners Parent Rating Scale-Revised: Short version (CPRS-R:S) and the Conners Adult ADHD Rating Scales (CAARS). The data were analyzed in children and adult by linear regression and multivariate genetic structural equation modeling.

Results: Based on linear regression analyses in which hyperactivity and inattention predicted aggression, we observed different results in children and in adults. In children, hyperactivity was a stronger predictor of aggression than inattention. However, in adults, inattention which tends to show stronger persistence into adulthood than hyperactivity, was the stronger predictor. Multivariate genetic structural equation modeling in twin families confirmed that in children hyperactivity was the stronger predictor for aggression, with the predictive power mainly due to the genetic associations. In adults, predictive power of Inattention also was mainly due to genetic associations.

Discussion: We obtained empirical evidence in independent samples for differential associations between aggression and hyperactivity and between aggression and inattention.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1271.

HYPERACTIVITY SYMPTOM IS PREDICTED BY AGE-OF-MENARCHE POLYGENIC RISK SCORE IN ADHD CHILDREN.

Kim H-W, Zayats T, Park K, et al.

Background: Early puberty has been reported to be associated with a number of attention-deficit/hyperactivity disorder (ADHD) symptoms and severity of its impairment, including inattention, difficulties in emotion regulation and risky behaviour. In addition, age at menarche was also reported to be inversely correlated with performance IQ. However, little is known about the contribution of genetics to the association between puberty onset and ADHD. We investigated the possibility of such genetic effect by examining the influence of the polygenic risk score (PRS) of age-at-menarche on diagnosis of ADHD and its two main symptoms, inattention and hyperactivity.

Methods: The PRS of age-at-menarche was calculated in 324 Korean children (208 cases and 116 controls) utilizing the PRSice software and summary statistics from a large-scale (N=370,000) genome-wide

association study on age at menarche. ADHD was diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and confirmed with the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL). Hyperactivity and inattention scores were derived from the K-SADS-PL ADHD supplement (clinician-rated) and ADHD Rating Scale (parent-rated). ADHD symptoms were examined in cases and controls separately. As genetics of age at menarche in women highly correlate with those of voice breaking in men, males and females were analysed together. Permutation was applied to correct for multiple testing. Empirical p-value (pemp) of 0.05 was considered statistically significant. **Results:** The age-at-menarche PRS was not associated with ADHD diagnosis (pemp= 0.495). Among ADHD symptoms, parent-rated hyperactivity symptom score showed significant association with the examined PRS in ADHD cases (pemp= 0.047), but not in controls (pemp= 0.968). Clinician-rated hyperactivity symptom was not associated with the examined PRS both in cases (pemp=0.184) and controls (pemp= 0.157).

Discussion: These results suggest that genetics of puberty onset may play an important role in the development of symptoms of hyperactivity in children with ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1270.

CHARACTERIZING THE GENETICS OF ADHD TRAITS WITH COGNITIVE DEFICITS USING A MULTIVARIATE APPROACH.

Corfield E, Burton C, Strug L, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common, impairing and persistent disorder of children and youth. Genetic studies usually focus on univariate methodologies in clinical cohorts. However, simultaneously investigating correlated phenotypes using a multivariate approach could accelerate gene discovery by reducing phenotypic and genetic heterogeneity. Response inhibition (the ability to stop a speeded motor response) is a heritable and stable cognitive deficit that is correlated and co-heritable with ADHD. Therefore, this study aims to investigate the genetic architecture of ADHD by using a multivariate genome-wide association (GWA) approach in a pediatric community sample with a quantitative measure of ADHD traits and a cognitive deficit.

Methods: The Spit for Science community sample includes 4,815 Caucasian children and youth (aged 6-17) with genotyping data and measured ADHD traits and response inhibition, which were used in all analyses. ADHD traits were measured by The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale, while response inhibition was measured by the stop-signal reaction time in the Stop-Signal task. A multivariate GWA analysis of 8,786,567 SNPs ADHD traits and response inhibition was conducted with the relevant covariates (age, sex, respondent, batch effects, and population stratification) using the MultiPhen approach. This approach uses a reverse proportional odds linear regression with the genotype regressed on each phenotype. The likelihood ratio test is then used to assess if the joint combination of effects is significant. Results from the multivariate GWA analysis were used to identify specific genes associated with ADHD traits and response inhibition by conducting a gene-based association analysis in MAGMA. The biological relevance of the results was assessed by functional mapping and annotation using FUMA. Polygenic risk score analysis will be conducted to determine if the multivariate GWA results predict clinical ADHD.

Results: No genome-wide significant risk loci or genes were identified, however, two variants and six genes reached suggestive p-value thresholds. The top risk loci from the joint analysis of ADHD traits and response inhibition were common intron variants rs12497498 in SSUH2 ($p = 5.76 \times 10^{-7}$) and rs56373513 in GLIS3 ($p = 8.13 \times 10^{-7}$). If two separate univariate GWA analyses were conducted only rs12497498 would have been identified as a risk variant of interest for ADHD traits. The top genes (with $p < 0.0001$) from the gene-set analysis were RNF148, RNF133, ZMIZ1, FAM163A, PDZRN4, and FGF22.

Discussion: Although no genome-wide significant risk variants were identified the regions of interest identified from this study warrant further investigation as they will increase our understanding of the biological mechanisms of with ADHD with cognitive deficits. Furthermore, it is hoped that the use of multiple phenotypes in GWA analyses increases the variance explained in clinical ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1206.

ADHD POLYGENIC RISK SCORES IN ROMANIAN AND UK BIPOLAR PATIENTS WITH CHILDHOOD ADHD.

Grigoriu-Serbanescu M, Giaroli G, Thygesen J, et al.

Background: The comorbidity between bipolar disorder (BP) and ADHD has been observed in family studies which suggests a shared genetic basis for the disorders. Faraone et al (2012) reported in a meta-analysis an ADHD prevalence of 27% in the offspring of BP-I parents and 16.5% in BP-I parents compared to 5.29% in the general population aged ≤ 18 years (Polanczyk et al, 2007) and 2.5% in adults (Simon et al, 2009). A meta-analysis of PGC ADHD GWAS data (Neale et al, 2010) and PGC BP GWAS data (Sklar et al, 2011) identified two genome-wide significant common loci for BP and ADHD and an additional locus for early onset BP (≤ 21 y) and ADHD (Van Hulzen et al, 2017). The objective of our study was to investigate the shared genetic basis of childhood onset ADHD (cADHD) and BP using polygenic risk scores (PRS) derived from the latest GWAS of ADHD (Demontis et al, bioRxiv, 2017) for predicting the presence of cADHD in BP patients and their association with BP age-of-onset (AO) and proband sex in our target samples.

Methods: cADHD was retrospectively rated using the Wender Utah Rating Scale (Ward M et al, 1993) with a cut-off of 46 for diagnosing cADHD in 470 BP-I Romanian (RO) patients and 472 BP UK patients. GWAS genotype data were generated using the Omni Express array for the RO sample and from the PsychChip for the UK samples. GWAS data was available for all patients and 329 RO and 1287 UK controls. Ten ADHD-PRS P-thresholds (PT) ranging from PT_0.01 to PT_0.5 were computed in the RO and UK samples. The statistical analysis was performed with R. All reported P-values are nominal with no correction for multiple testing.

Results: 1. ADHD-PRS significantly discriminated between cases and controls in the RO sample. The best discrimination was found for PT-0.1 to PT-0.5 (P-values = 0.034 to 0.028; $R^2 = 0.8\%$). However, ADHD-PT did not differentiate the UK BP cases from controls. 2. Both in the total RO and UK BP samples ADHD-PRS PT significantly predicted the linear Wender score with P-values from 0.042 to 0.008 ($R^2 = 0.9\%$ to 1.5%). 3. In the RO sample the ADHD-PRS differentiated the BP cases with cADHD (N= 203) from controls at all PT with best P-values for PT-0.1 to 0.5 (P = 0.007, $R^2 = 2\%$). No ADHD-PT differentiated the cases with cADHD (N = 162) from controls in the UK sample, although a trend (P = 0.06) was observed for PT_0.4 and PT_0.5. 4. No ADHD-PRS PT differentiated between cases with cADHD (N= 203) and cases with no cADHD (N = 267) in the RO sample, but in the UK sample four PRS-PT distinguished between cases with cADHD (N = 162) and cases with no cADHD (N = 310) (best P Pt_0.01= 0.015; $R^2 = 1.8\%$). 5. Both in the RO and the UK BP sample all ADHD-PRS PT significantly predicted the Wender score when sex was used as a covariate (P = 0.01 to 0.004). 6. There was a strong influence of the covariate AO on ADHD-PRS loading in the total BP RO and UK samples (PAO < 0.000) with a negative correlation between BP-AO and ADHD-PRS loading. Comparing the early onset (EO) cases (AO ≤ 21) with the late onset cases (AO > 22) the ADHD-PRS predicted the linear Wender score only in EO cases in both samples, although at different PT.

Discussion: We are the first investigators to use polygenic risk score analysis to investigate ADHD as a trait in bipolar disorder. The results demonstrated increased ADHD PRS in bipolar subjects with ADHD symptomatology in childhood and these findings were influenced by the age of onset of BP and by gender. These results extend the findings of overlapping genetic aetiology between BP and ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1155.

COMMON POLYGENIC VARIATIONS FOR PSYCHIATRIC DISORDERS AND COGNITION IN RELATION TO BRAIN MORPHOLOGY IN THE GENERAL PEDIATRIC POPULATION.

Alemanly S, Jansen P, Muetzel R, et al.

Background: Brain structure, psychiatric disorders, and cognition are genetically influenced traits. However, the extent to which genetic factors underlying psychopathology and cognition relate to brain structure remains unclear. We sought to address this by examining the relationship between polygenic scores (PGS) for five major psychiatric disorders and two cognitive traits with brain morphology in a large population-based sample of children.

Methods: The participants included 1,139 children from the Generation R Study assessed at 10 years-of-age with genotype and neuroimaging data available. Polygenic scores (PGS) were calculated for schizophrenia, bipolar disorder, major depression disorder, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), educational attainment (EA) and intelligence, using results from the latest genome-wide association studies (GWAS). Image processing was performed using FreeSurfer to extract cortical and subcortical brain volumes.

Results: Higher genetic susceptibility for ADHD was associated with smaller total brain volume (TBV), whereas higher susceptibility for ASD, EA and intelligence showed positive associations with TBV. Only associations for ADHD, EA and intelligence remained significant after correcting for multiple testing. Although no associations with specific brain regions surpassed multiple testing correction, nominally significant associations were found between higher genetic load for ADHD and smaller caudate nucleus volume and higher genetic load for EA and larger thalamus volume.

Discussion: Mostly common genetic variants related to cognition and ADHD, among the other psychiatric disorders, were associated with TBV in children. Whole-brain and caudate volumetric reductions have been consistently reported in individuals affected by ADHD. Our findings suggest that genetic variants associated with risk for ADHD may, at least partially, account for these reductions. Overall, these findings indicate that the neurobiological manifestation of polygenic susceptibility for ADHD, EA and intelligence involves early differences in global brain morphology.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1268.

ANDROGEN RECEPTOR SIGNALING PATHWAYS INFLUENCE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kappel D, da SB, Cupertino RB, et al.

Background: The differential sex-based prevalence of ADHD has long been subject to scrutiny. The role of sex-hormones, especially androgens during the neurodevelopmental period has been extensively demonstrated. Androgens regulate and interact with neurotransmitters and neuromodulators influencing developmental processes. Since androgenic disruptors modify these processes it has been suggested that its exposure during development was related to ADHD susceptibility. Also, it has been shown that women suffering from the androgenizing polycystic ovary syndrome, have higher rates of ADHD, and so are their children. We hypothesize that one way by how exposure to androgens and its response network might affect susceptibility to ADHD is through the activation of androgen receptor (AR) function as a nuclear transcription factor.

Methods: 407 adults with ADHD (53.1% males, mean age of 33.6 years) and 463 unrelated controls (47.9% males, mean age of 29.4 years) were genotyped with PsychChip array for >5M SNPs. Annotation from human genome build 37 (hg19) with a 2kb upstream and 1kb downstream region was considered for each gene. Gene-set analysis was conducted using MAGMA, with a principal components regression model for gene-based analyses. Sex, age, the 10 first and otherwise associated principal components were included as covariates in this step. We retrieved a Hallmark Androgen response gene-set from MSigDB to be tested in a case-control association study. This gene-set contains 98 curated genes involved in the response to androgen receptor signaling. Also, a list of 534 annotated genes with at least one occurrence of potential transcription factor binding sites (TFBS) for AR was created to investigate potential gene targets related to ADHD susceptibility.

Results: No genome-wide association was observed at the SNPs or gene level. In the gene-set analysis, we found evidence that the Hallmark Androgen response gene-set was significantly associated with ADHD susceptibility in our sample ($p=0.039$). We also observed that this gene-set seems to be associated with ADHD regardless of gender effects. When analyzed separately in both genders, the gene-set remained significantly associated, although with a larger effect in men ($p=0.024$; $p=0.009$, for women and men, respectively). In the secondary analyses, we observed that from the 534 genes expected to have a TFBS for AR, 14 have been associated with ADHD previously. Some are from the recent ADHD GWAS (FOXP2, TMEM161B), others are classical ADHD candidate genes as BDNF and SNAP25.

Discussion: Our results add to the current knowledge that factors related to the influence of sex-hormones might play a role in ADHD susceptibility. The perspective of the involvement of such factors is interesting due to its influence during fetal development and also due to sex-hormones effects during puberty. These associations could be representing and underlying mechanisms related to ADHD development and differential sex-based prevalence in children and adults.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019.

ADHD SYMPTOMS IN THE ADULT GENERAL POPULATION ARE ASSOCIATED WITH FACTORS LINKED TO ADHD IN ADULT PATIENTS.

Li T, Mota NR, Galesloot TE, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder in children and adults. It is characterized by inappropriate levels of inattention (IA) and/or hyperactivity and impulsivity (HI). The ADHD diagnosis is hypothesized to represent the extreme of a continuous distribution of ADHD symptoms in the general population. In this study, we investigated whether factors linked to adult ADHD as a disorder are associated with adult ADHD symptoms in the general population. Our population-based sample included 4987 adults (mean age 56.1 years; 53.8% female) recruited by the Nijmegen Biomedical Study (NBS). Participants completed the Dutch ADHD DSM-IV Rating Scale for current and childhood ADHD symptoms, the Symptom Check List-90-R (SCL-90-R) anxiety subscale, and the Eysenk Personality Questionnaire (EPQR-S). Partial Spearman correlation and Hurdle negative binomial regression analysis were used to assess how age, sex, childhood ADHD symptoms, anxiety symptoms, and personality traits (neuroticism, extraversion, and psychoticism) are associated with current IA and HI symptoms. Increasing age was associated with a lower proportion of participants reporting HI symptoms and with reduced levels of HI; IA levels remained fairly stable over the age-range, but the probability of reporting IA symptoms increased throughout middle/late adulthood. Females were more likely to report IA symptoms than males. Childhood ADHD symptoms, neuroticism, and psychoticism were positively associated with current IA and HI symptoms, while extraversion had an opposite association with these symptom domains. Anxiety symptoms affected HI symptoms in females. Our results indicate that factors associated with categorical ADHD are also correlated with ADHD symptoms in the adult population

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Eur Neuropsychopharmacol. 2019;29:S1086-S1087.

OPPOSITE GENETIC EFFECTS FOR POLYGENIC ASD RISK SHARED WITH AND INDEPENDENT OF ADHD: EVIDENCE FOR A CANCELLING-OUT HYPOTHESIS STUDYING GENETIC OVERLAP WITH LANGUAGE AND LITERACY.

Verhoef E, Grove J, Shapland CY, et al.

Background: Autism Spectrum Disorders (ASD) share genetic liability with complex cognitive skills, such as verbal intelligence quotient (IQ) scores, and thus genetic overlap with highly related literacy- and language-related abilities (LRAs) is expected. However, recent evidence suggests that such genetic overlap can differ by ASD subgroup. Especially ASD with comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms may genetically correlate more with impaired than enhanced cognitive performance. Moreover, multi-trait scores such as IQ may conceal association patterns for individual subskills. Here, we study genetic overlap

between ASD and a wide range of LRAs. Specifically, we disentangle polygenic links into ASD genetic effects shared with and independent of ADHD using methodologies robust to collider bias.

Methods: Thirteen LRAs capturing oral comprehension, reading, spelling, phonological awareness/memory and verbal IQ were studied in 7 to 13-year-old children from a UK birth cohort (ALSPAC; N=5,919; SNP- $h^2 > 0.25$). Genome-wide summary statistics for 1) ASD excluding individuals comorbid for ADHD (cases:10,321; controls: 22,664), and 2) ADHD (cases:14,584; controls:22,492) were obtained through the iPSYCH consortium. To disentangle polygenic relationships between ASD and LRAs, ASD genetic effects on LRAs were modelled as effects shared with and independent of ADHD using multivariable regressions (MVR), analogous to Mendelian Randomization (MR). ASD instruments were selected by applying conservative ($p < 5 \times 10^{-8}$), typical MR ($p < 0.0015$) and common polygenic-scoring (PGS, $p < 0.05$) thresholds.

Results: Studying PGS-comparable instruments and without implying causality, we identified positive genetic associations between ASD risk and all LRAs, conditional on ADHD, passing an experiment-wide multiple testing threshold ($p < 0.007$). In contrast, polygenic ASD risk shared with ADHD showed an inverse association, based on the same set of ASD instruments. This pattern was observed for standardised reading and spelling instruments, verbal IQ and oral comprehension, but not phonological memory, phonemic awareness and study-specific LRAs. The strongest effects were present for reading speed at age 9 with a 0.02 Z-score increase ($SE = 0.003$, $P = 6 \times 10^{-10}$) and a 0.038 decrease ($SE = 0.007$, $P = 2 \times 10^{-8}$) in performance per log odds in ASD and ADHD liability respectively (latter capturing shared ASD/ADHD effects). Using typical MR instruments, this genetic overlap was attenuated, but still present for several reading and spelling abilities, and completely abolished when analysed with conservative ASD instruments.

Discussion: Subthreshold genetic variants capturing ASD liability may show opposite polygenic effects on reading, spelling and reasoning for ASD with and without ADHD symptoms, although implicating the same genomic regions. Polygenic ASD risk was associated with increased reading, spelling and reasoning performance conditional on ADHD. However, the same genomic regions were also associated with lower reading, spelling and reasoning performance via ADHD, as shared ASD/ADHD effects. This has implications for the presence of null effects in ASD collections with large proportions of patients comorbid for ADHD and detectable genetic correlations between clinical ASD and ADHD.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1314.

THE VALUE OF POLYGENIC RISK SCORES IN PREDICTING THE TRANSITION FROM CHILDHOOD AND ADOLESCENT PSYCHIATRIC SYMPTOMS INTO CHRONIC ADULT PSYCHOPATHOLOGY.

Middeldorp CM, Akingbuwa O, Jarvelin M-R, et al.

Background: Adult psychiatric disorders can be preceded by a broad range of childhood psychiatric symptoms. Schizophrenia, for example, is associated to anxious, depressive, behavioural and ADHD symptoms in childhood. A critical need to be able to provide targeted treatment is the ability to identify the children at highest risk for this unfavorable trajectory. Earlier polygenic risk score analyses in the Netherlands Twin Register (NTR), the Avon Longitudinal Study of Parents and Children (ALSPAC) and Generation R have suggested that the association with schizophrenia is due to shared genetic risk factors. Fewer studies have investigated the association with Major Depressive Disorder and Bipolar disorder, as fewer genetic variants were identified for these disorders. For other adult traits associated with adult psychiatric disorders, such as wellbeing and neuroticism, genetic overlap with childhood psychopathology has not been analysed yet. Given the large increase in genetic variants associated with adult psychopathology and associated traits, together with the large increase in available genotypes in individuals with longitudinal data on psychiatric symptoms from birth or childhood, it is timely to test genetic associations, and, if present, to test whether these associations vary with age.

Methods: Polygenic risk scores (PRS) will be based on the most recent results from Genome-Wide Association Meta-Analyses for schizophrenia, depression, bipolar disorder, wellbeing, neuroticism, BMI, height, educational attainment and insomnia. The associations with internalizing, ADHD and social problems measured between age 7 and age 18 will be analyzed in the cohorts participating in the CAPICE consortium: ALSPAC, Child and Adolescent Twin Study in Sweden (CATSS), Generation R, NTR, Norwegian Mother and Child Cohort Study (MoBa), Northern Finland Birth Cohort (NFBC), Twins Early Development Study

(TEDS) and Twin Study of Child and Adolescent Development (TCHAD), total N = 40,000. Meta-regression analyses will show whether associations depend on age and type of psychiatric symptoms in the children.

Results: Preliminary analyses in the Netherlands Twin Register showed the strongest genetic associations in the expected directions with schizophrenia, MDD, neuroticism and wellbeing, although not always significant. Especially ADHD was negatively associated with the educational attainment PRS.

Discussion: The results show how childhood, adolescent and adult psychiatric symptoms are influenced by overlapping genetic factors explaining persistence of symptoms from childhood into adulthood. Adding polygenic risk scores to models predicting which children are at high risk for chronic symptoms may improve prediction. Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1107-S1108.

GENETIC INFLUENCES CONTRIBUTING TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ACROSS THE LIFESPAN: EVIDENCE FROM GENOME-WIDE ASSOCIATION STUDIES.

Rovira P, Artigas MS, Sanchez-Mora C, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder whose impairing symptoms persist into adulthood in around 65% of the diagnosed children. Being able to predict ADHD persistence in childhood based on genetic load could be a first step towards prevention of ADHD persistence, which is a key clinical concern. The aim of the present study was to compare the genetic background of children and adult ADHD patients and to elucidate whether a subset of children with ADHD exists which is more genetically similar to adult patients, as well as identifying new loci associated with ADHD.

Methods: Genomic data from the International Multi-centre persistent ADHD CollaboraTion (IMpACT) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) were used to conduct a genome-wide association (GWA) meta-analysis of 6,619 adult ADHD patients and 15,976 controls. A meta-analysis of all childhood ADHD GWAS data available at the time, within the Psychiatric Genomics Consortium (PGC) and iPSYCH, was also conducted. We estimated the genetic correlation between children and adult ADHD and also between adult ADHD and other traits using LD-score regression. Moreover, we examined whether a subgroup of children was more genetically similar to adult patients, who could therefore be hypothesized to be at risk of persistent ADHD, using the well-powered BUHMBOX method. In addition, we ran a combined children and adult meta-analysis of 17,236 patients and 32,513 controls.

Results: The top hits of the adult meta-analysis ($P < 2.92 \times 10^{-7}$) included genes previously associated with neuronal migration. We observed significant genetic correlation between adult ADHD and major depressive disorder ($P = 8.01 \times 10^{-5}$), neuroticism ($P = 5.73 \times 10^{-5}$), risk taking ($P = 2.57 \times 10^{-16}$), years of schooling ($P = 1.76 \times 10^{-26}$) and intelligence ($P = 6.91 \times 10^{-13}$), among others. A strong correlation between genetic variants contributing to adult and childhood ADHD ($r_g = 0.81$ (S.E. = 0.08); $P = 5.10 \times 10^{-21}$) was found and no evidence for genetically different subgroups of children with ADHD was detected. In the combined meta-analysis of adults and children, we identified three new genome-wide significant loci, present near genes related to neuronal migration and to monoamine and neurotrophin neurotransmission.

Discussion: The results support the hypothesis of a shared genetic background between children and adult ADHD and point to new genetic variants associated with the disorder. Prospective studies exploring the genetic background of children with ADHD will allow us to elucidate the genetic impact on the persistence and remittance of ADHD symptoms.

Disclosure: Nothing to disclose

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Eur Neuropsychopharmacol. 2019;29:S1105-S1106.

MULTIVARIATE GWA META-ANALYSIS IN OVER 500K OBSERVATIONS ON AGGRESSION AND ADHD SYMPTOMS.

Nivard M, Boomsma D.

Background: We present the results of a multivariate genome-wide association (GWA) study of the developmental genetic etiology of aggression (AGG) and attention-deficit/hyperactivity disorder (ADHD). The project involves a collaboration in over 20 international cohorts from Europe, Australia, New-Zealand and the USA. The cohorts are characterized by repeated measures of Aggression and ADHD symptoms at different ages and assessment by multiple informants and multiple instruments. In total, the meta-analysis included 526,000 observations from over 200 GWA studies.

Methods: First, a series of univariate GWA studies was performed for every available combination of age, informant and instrument within each cohort. This resulted in 1 to 36 analyses per cohort, with sample sizes ranging between 309 and 10,812. Next, results were pooled into age-by-rater combinations (e.g. mother-rated aged 3-5, teacher-rated 8-11, etc.) that resulted in an excess of 10,000 independent observations, and then meta-analyzed. Genetic correlations between the age-by-rater combinations, both within and across AGG and ADHD, were estimated with LD Score Regression. Finally, we performed a meta-regression analysis across all GWA studies, correcting for the fact that repeatedly measured subjects were included in the analyses. We then estimated the genetic correlation between our meta-analysis and several somatic and psychiatric traits.

Results: We obtained an average SNP-heritability of 6.3% and 8.3% for AGG and ADHD, respectively, across the age-by-rater meta-analyses. Within phenotype, the highest average genetic correlations were seen between maternal ratings and self-reports: 0.49 (AGG) and 0.85 (ADHD). Genetic correlations between mother and teacher ratings was 0.39 for AGG and 0.74 for ADHD. Interestingly, the genetic correlation between teacher ratings and self-report approached zero for both traits. Averaged across raters and age, the genetic correlation across AGG and ADHD was 0.75. We estimate several significant correlations between either AGG and/or ADHD and cognitive/psychiatric/health outcomes. Most notably were the genetic correlations with childhood IQ (-0.61), age at first birth (-0.58), depressive symptoms (0.51), smoking initiation (0.46) and parental age at death (-0.36), indicating the presence of a relation between AGG/ADHD and poor (health) outcomes. Follow up analysis subset the relation between childhood ADHD symptoms and poor health outcomes may be mediated by educational attainment and social economic status.

Discussion: The present work is, to our knowledge, the first repeated measures multi rater genome wide association study of psychiatric phenotype. Our works helps further the understanding of prodromal, and subclinical psychiatric symptoms during development. SAAGY (Study of Aggression and ADHD trait Genetics in Youth) includes multiple international cohorts (ALSPAC, CATSS, FinnTwin12, GenR, GINI/LISA, INMA, NFBC 1966/1986, NTR, QIMR, RAINE, TCHAD, TEDS, Dunedin, MOBA, MTF5, TRAILS, Young Finns Study, ABCD, MUSP, BREATHE, E-Risk, Add Health Michigan State University, Understanding Society).

Disclosure: Nothing to disclose

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Evidence-Based Practice in Child and Adolescent Mental Health. 2019.

THE CONTRIBUTION OF SENSORY SENSITIVITY TO EMOTIONAL LABILITY IN CHILDREN WITH ADHD SYMPTOMS.

DeSerisy M, Hirsch E, Roy AK.

Emotional lability and sensory sensitivity have been shown to contribute to the overall clinical picture in children with attention deficit hyperactivity disorder (ADHD). Further, both of these characteristics have been individually demonstrated to contribute to poorer quality of life, increased functional impairment, and poorer treatment response. However, to date, no study has evaluated the relationship among all three of these factors. The current study hypothesized that increased sensory sensitivity would moderate the relationship between hyperactive/impulsive symptoms of ADHD and emotional lability in youth. Results indicate that heightened sensory sensitivity strengthens the relationship between hyperactive/impulsive symptoms of ADHD and emotional lability in children with three or more clinically impairing ADHD symptoms. This dimensional approach was taken in accordance with growing evidence that even children with sub-threshold

ADHD experience significant functional impairment and high rates of sensory sensitivity. These findings suggest that clinicians treating children with ADHD symptoms and emotional lability should consider assessing for sensory sensitivity as integration of multi-sensory techniques or referral to concurrent occupational therapy may significantly improve treatment outcomes and quality of life for these children and their families

Genes Brain Behav. 2019 Apr;18:e12553.

EXPLORING THE BEHAVIORAL AND COGNITIVE PHENOTYPE OF KBG SYNDROME.

van Dongen LCM, Wingbermuhle E, van der Veld WM, et al.

KBG syndrome is a neurodevelopmental disorder, caused by dominant mutations in ANKRD11, that is characterized by developmental delay/intellectual disability, mild craniofacial dysmorphisms, and short stature. Behavior and cognition have hardly been studied, but anecdotal evidence suggests higher frequencies of ADHD-symptoms and social-emotional impairments. In this study, the behavioral and cognitive profile of KBG syndrome will be investigated in order to examine if and how cognitive deficits contribute to behavioral difficulties. A total of 18 patients with KBG syndrome and a control group consisting of 17 patients with other genetic disorders with comparable intelligence levels, completed neuropsychological assessment. Age-appropriate tasks were selected, covering overall intelligence, attention, memory, executive functioning, social cognition and visuoconstruction. Results were compared using Cohen's d effect sizes. As to behavior, fewer difficulties in social functioning and slightly more attentional problems, hyperactivity, oppositional defiant behavior and conduct problems were found in the KBG syndrome group. Regarding cognitive functioning, inspection of the observed differences shows that patients with KBG syndrome showed lower scores on sustained attention, cognitive flexibility, and visuoconstruction. In contrast, the KBG syndrome group demonstrated higher scores on visual memory, social cognition and emotion recognition. The cognitive profile of KBG syndrome in this sample indicates problems in attention and executive functioning that may underlie the behavior profile which primarily comprises impulsive behavior. Contrary to expectations based on previous (case) reports, no deficits were found in social cognitive functioning. These findings are important for counseling purposes, for tailored education planning, and for the development of personalized intervention

Genomics. 2019.

THE FIRST EVIDENCE OF AN ASSOCIATION BETWEEN A POLYMORPHISM IN THE ENDOCANNABINOID-DEGRADING ENZYME FAAH (FAAH RS2295633) WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ahmadalipour A, Mehdizadeh FL, Zeinalzadeh N, et al.

Several single nucleotide polymorphisms (SNPs) of the fatty acid amide hydrolase (FAAH), the degrading enzyme of the endocannabinoids, have been shown to be associated with many neuropsychiatric disorders. Here, FAAH rs2295633 was studied in ADHD and case-control healthy children. There was a significant difference in the allele frequency ($P = .04$) and genotype distribution ($P = .04$) of the FAAH rs2295633 between ADHD cases and controls. The ADHD children appeared to have less of TT genotype (OR 0.396, 95% CI 0.178–0.884, $p = .024$) and T allele (OR 0.658, 95% CI 0.440–0.982, $p = .04$). To our best knowledge, this is the first statistical significant association between FAAH rs2295633 genotype and ADHD disorder. Larger sample sizes and functional studies are warranted to explore the clinical utility of FAAH genotyping as a possible marker for increased ADHD risk in children

Guncel Pediatri. 2019;17:300-13.

ATTACHMENT AND PARENTING STYLES IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Uzun ME, Ucar HN, Vural AP.

INTRODUCTION: Children and adolescents with attention deficit hyperactivity disorder (ADHD) experience problems with adults, especially with their parents, due to self-regulation deficiencies involving impulse control, self-restraint and inhibition problems. It is also reported that problems in parental attitudes play an important role in increasing the severity of ADHD findings. Because of these two conditions, we thought that there may be a relationship between attachment patterns and parenting styles of adolescents with ADHD.

METHODS: 59 adolescents with ADHD and 66 adolescents without any psychopathology were included in the study. Socio-demographic data form and Adolescent Relationship Scales Questionnaire were applied to participants and Parental Attitude Research Instrument was applied to their parents.

RESULTS: There was no statistically significant difference in attachment styles between ADHD and control group. Parents of the ADHD group had significantly higher scores in the subscales of rejection of the homemaking role, marital conflict, and strict discipline than parents of the control group. Higher levels of dismissing attachment style were associated with higher strict discipline attitudes in the ADHD group.

DISCUSSION and CONCLUSION: Our study suggests that evaluation of attachment characteristics and parental attitudes in ADHD that is a neurodevelopmental disorder, may be necessary as an integrated approach

Hum Brain Mapp. 2019.

DISRUPTED BRAIN FUNCTIONAL NETWORKS IN DRUG-NAÏVE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER ASSESSED USING GRAPH THEORY ANALYSIS.

Chen Y, Huang X, Wu M, et al.

Neuroimaging studies have revealed functional brain network abnormalities in attention deficit hyperactivity disorder (ADHD), but the results have been inconsistent, potentially related to confounding medication effects. Furthermore, specific topological alterations in functional networks and their role in behavioral inhibition dysfunction remain to be established. Resting-state functional magnetic resonance imaging was performed on 51 drug-naïve children with ADHD and 55 age-matched healthy controls. Brain functional networks were constructed by thresholding the partial correlation matrices of 90 brain regions, and graph theory was used to analyze network topological properties. The Stroop test was used to assess cognitive inhibitory abilities. Nonparametric permutation tests were used to compare the topological architectures in the two groups. Compared with healthy subjects, brain networks in ADHD patients demonstrated altered topological characteristics, including lower global (FDR $q = 0.01$) and local efficiency ($p = 0.032$, uncorrected) and a longer path length (FDR $q = 0.01$). Lower nodal efficiencies were found in the left inferior frontal gyrus and anterior cingulate cortex in the ADHD group (FDR both $q < 0.05$). Altered global and nodal topological efficiencies were associated with the severity of inhibitory cognitive control deficits and hyperactivity symptoms in ADHD ($p < 0.05$). Alterations in network topologies in drug-naïve ADHD patients indicate weaker small-worldization with decreased segregation and integration of functional brain networks. Deficits in the cingulo-fronto-parietal attention network were associated with inhibitory control deficits

Int J Environ Res Public Health. 2019 Mar;16.

PARENTAL TYPE D PERSONALITY AND CHILDREN'S HYPERACTIVE BEHAVIORS: THE MEDIATING ROLE OF PARENT(-)CHILD INTERACTIVE ACTIVITIES.

He GH, Liu L, Strodl E, et al.

This study explored the associations between parental Type D personality (TDP), parent(-)child interactive activities, and children's hyperactive behaviors. Moreover, the study examined whether parent(-)child interactive activities mediated the associations between parental TDP and children's hyperactive behaviors. A cross-sectional survey was conducted among children from all kindergartens in a district of a southern city

in China. Data on parental TDP, the frequency of parent(-)child interactive activities, children's hyperactive behaviors, and socio-demographic characteristics were provided by 47,648 parent(-)child dyads. Multiple regression analysis was employed to assess the associations between parental TDP, parent(-)child interactive activities, and children's hyperactive behaviors. Mediation analysis was applied to explore the mediating role of parent(-)child interactive activities on the associations between parental TDP and children's hyperactive behaviors. Parental TDP was negatively associated with the frequency of parent(-)child interactive activities and positively associated with children's hyperactive behaviors. The frequencies of parent(-)child interactive activities were negatively associated with children's hyperactive behaviors. The frequency of parent(-)child interactive activities partially mediated the associations between parental TDP and children's hyperactive behaviors. Future research may consider parental TDP and parent(-)child interactive activities as potential important predictors of hyperactive behaviors in children. Such research will help identify further targets for intervention to reduce hyperactive behaviors in children

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Int J Environ Res Public Health. 2019 Jan;16.

THE ASSOCIATION BETWEEN LEAD AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Donzelli G, Carducci A, Llopis-Gonzalez A, et al.

The etiology of Attention-Deficit/Hyperactivity Disorder (ADHD) is complex and multifactorial. Although the development of ADHD symptoms remains to be elucidated, in recent years, epigenetic processes have emerged as candidate mechanisms. Lead is one of the most dangerous environmental pollutants, and it is suspected to be associated with ADHD. The aim of the present study was to review the epidemiological literature currently available on the relation between lead exposure and the diagnosis of ADHD. The PubMed and EMBASE databases were searched from 1 July 2018 up to 31 July 2018. The authors included observational studies (cohort, case(-)control and cross-sectional studies) published in English carried out on children within the last 5 years, measuring lead exposure and health outcomes related to ADHD. Seventeen studies met the inclusion criteria: 5 of these studies found no association between lead exposure and ADHD whereas the remaining 12 studies showed positive associations, even though not all of them were homogeneous in terms of exposure periods considered or ADHD diagnosis. To conclude, the evidence from the studies allowed us to establish that there is an association between lead and ADHD and that even low levels of lead raise the risk. However, there is still a lack of longitudinal studies about the relationship between lead exposure and the development of ADHD. Given the potential importance for public health, further research that includes the entire potential risk factors for ADHD in children must be encouraged

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Int J Environ Res Public Health. 2019 Mar;16.

DISABILITY-SPECIFIC ASSOCIATIONS WITH CHILD HEALTH AND FUNCTIONING .

Chan KL, Lo CKM, Ho FK, et al.

This study examined the health profile of children with different types of disabilities and explored the disability-specific associations with various types of health and functioning using a large nonclinical sample of children. A cross-sectional school survey was conducted during 2016 and 2017. A total of 4114 children (aged 6(-)18 years) receiving primary or secondary education, or their proxy, in Hong Kong participated in the study. Disabilities were categorized as (a) physical disabilities; (b) learning and developmental disabilities; (c) intellectual disabilities; (d) internalizing disorders or mental illness; and (e) autism spectrum disorder. Health-related quality of life (QoL), sleep-related QoL, activities of daily living (ADL), emotional functioning, and social functioning were assessed and compared between children with disabilities and those without. The results showed that children with disabilities showed poorer physical functioning, health-related QoL, and emotional and social functioning than their counterparts without disabilities. Disability-specific associations with health were found: (a) physical disabilities and intellectual disabilities were associated with greater difficulties in ADL; (b) language impairment and Attention deficit/ hyperactivity disorder (ADHD) were negatively associated with sleep-related QoL; (c) all types of disabilities but hearing impairment were

negatively associated with health-related QoL (HRQoL); and (d) language impairment, ADHD, internalizing disorder, as well as autism spectrum disorder were associated with greater abnormal behavioral difficulties. The findings warrant the development of tailor-made intervention programs and give insights to effective resource allocation for the children in need

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Int J Environ Res Public Health. 2019 Apr;16.

PERINATAL EXPOSURE TO ENVIRONMENTAL ENDOCRINE DISRUPTORS IN THE EMERGENCE OF NEURODEVELOPMENTAL PSYCHIATRIC DISEASES: A SYSTEMATIC REVIEW.

Rivollier F, Krebs MO, Kebir O.

Background: Exposure to endocrine disruptors is on the rise, with new compounds regularly incriminated. In animals and humans, this exposure during critical developmental windows has been associated with various developmental abnormalities, including the emergence of psychiatric disorders. We aimed to review the association between perinatal endocrine disruptor exposure and neurodevelopmental disorders in humans, focusing on cognitive and psychiatric disorders.

Methods: We performed a systematic review with key words referring to the fields of neurodevelopment and endocrine disruptors. We reviewed 896 titles, choosing studies on the basis of titles and abstracts. We searched through the methodology sections to find perinatal exposure and neurodevelopmental disorders, following the categories indicated in the Diagnostic and Statistic Manual of Mental Disorders (5th edition). References in some studies brought us to a total of 47 studies included here.

Results: Convergent studies report an association between exposure to endocrine disruptors and autism spectrum disorder, attention-deficit hyperactivity disorder, global developmental delay, intellectual disability, communication disorders and unspecified neurodevelopmental disorders.

Conclusion: Sufficient data exist to report that exposure to some endocrine disruptors is a risk factor for the emergence of neurodevelopmental disorders. Studying endocrine disruptor exposure in humans is still associated with some limits that are difficult to overcome

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Int J Qual Stud Health Well -being. 2019 Dec;14:1564520.

LIBERATING PARENTS FROM GUILT: A GROUNDED THEORY STUDY OF PARENTS' INTERNET COMMUNITIES FOR THE RECOGNITION OF ADHD.

Dauman N, Haza M, Erlandsson S.

PURPOSE: This study presents a qualitative analysis of information posted on the Internet by two communities of French parents promoting the recognition of ADHD in the context of current health and school practices.

METHOD: Grounded Theory (Strauss & Corbin's approach) was applied to the posted messages, with the aim to discover the main concern and common theme through a constant comparison analysis.

RESULTS: Liberating parents from feeling responsible for their child's misconduct was found to be the core category. From this perspective, we account for the commitment of the digital communities to formalize the child's conduct as a consequence of a neurodevelopmental disorder. This approach helps to account for the promotion of behavioural expertise and conditioning strategies (e.g., positive reinforcement) for handling the child's so-called disorder as appropriate parental responses. Giving evidence for parenting struggles was the third main concern of the communities, in the face of perceived skepticism from professionals towards ADHD as a medical condition.

CONCLUSIONS: By using examples from countries that are found to have a more pro-medical approach to ADHD, the communities aim at improving such medical practices in France. Issues surrounding the claim that ADHD would require a specific style of parenting are also discussed

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International Journal of Clinical Pharmacy. 2019;41:859-63.

CONSUMPTION OF METHYLPHENIDATE AND ATOMOXETINE IN THE PRIVATE HEALTHCARE SECTOR IN SOUTH AFRICA: A LONGITUDINAL STUDY.

Munasur-Naidoo AP, Truter I.

Background Globally Attention-Deficit/Hyperactivity Disorder (ADHD) has been in the spotlight. Despite some controversies, treatment of ADHD remains the cornerstone of patient care.

Objective To describe the consumption of methylphenidate and atomoxetine in the private healthcare sector in South Africa over a four-year period (2013-2016).

Method Data were extracted from the Intercontinental Marketing Service (IMS) database for the drug utilisation study. Consumption patterns were expressed as number of Defined Daily Doses (DDD)/1000 inhabitants/day and number of DDDs/1000 inhabitants/month.

Results Methylphenidate (95.85%) was the medication of choice when compared to atomoxetine (4.15%) in 2013. The corresponding figures for 2016 were 96.40% and 3.60%. Consumption of ADHD medication showed slight changes over the 4-year period. If only the private healthcare sector population is considered, consumption of methylphenidate was 6.010 DDDs/1000 inhabitants/day in 2013, and 7.827 DDDs/1000 inhabitants/day in 2016. A previous study (1994-1996) reported 0.12 DDDs/1000 inhabitants/day for methylphenidate. Consumption of atomoxetine was 0.044 DDDs/1000 inhabitants/day in 2013 and 0.050 DDDs/1000 inhabitants/day in 2016.

Conclusion Consumption showed an increase in use of methylphenidate in South Africa, with small changes observed over the study period. Further studies are required

Int J Environ Res Public Health. 2019;16.

A SYSTEMATIC REVIEW OF POLYVICTIMIZATION AMONG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY OR AUTISM SPECTRUM DISORDER.

Hellstram L.

Children with Autism Spectrum Disorder (ASD) or Attention Deficit Hyperactivity Disorder (ADHD) have shown an increased risk for violence and victimization. However, research on exposure to multiple forms of victimization in different contexts are scarce. Hence, the current aim is to review the evidence about polyvictimization among children with ASD or ADHD. PsycInfo, ERIC, Scopus, and PubMed databases were systematically searched until 12 March 2019 to identify empirical studies with reported prevalence rates of at least four forms of victimization among children with ASD or ADHD. A total of 6/1300 articles were included in the review, ranging in sample sizes from 92 to 4114. The reported prevalence rates for polyvictimization were 1.8% and 23.1% for children with ASD and 7.3% for children with ADHD. The results emphasize the high prevalence of violence and victimization, including polyvictimization, among children with ASD or ADHD. Polyvictimization among children with ASD or ADHD is a highly under researched area. Significant knowledge gaps and important methodological considerations that provide important implications for future research include lack of information on cyber bullying, frequency or intensity of victimization, and the failure to include children as informants and to report health outcomes associated with polyvictimization

Int J Pediatr Otorhinolaryngol. 2016;86:193-95.

EFFECT OF ADENOTONSILLECTOMY ON ATTENTION DEFICIT-HYPERACTIVITY DISORDER IN CHILDREN WITH ADENOTONSILLAR HYPERTROPHY: A PROSPECTIVE COHORT STUDY.

Ahmadi MS, Poorolajal J, Masoomi FS, et al .

Background: This study was conducted to explore the effect of adenotonsillectomy on the improvement of attention deficit hyperactivity disorder (ADHD) symptoms in children with adenotonsillar hypertrophy.

Methods: This prospective cohort study was conducted on 59 children aged 6-12 years with adenotonsillar hypertrophy and ADHD who were candidates for adenotonsillectomy at Besat Hospital, Hamadan University of Medical Sciences, in 2014. The status of ADHD was evaluated at baseline and one and three months after surgery using Conners' Rating Scales.

Results: Of 59 children with ADHD (35 boys and 24 girls), 41 improved one month after surgery and 51 after three months. Only 8 children had no improvement. The Conners' score decreased significantly from 71.37 at baseline to 61.31 ($P = 0.001$) and 49.14 ($P = 0.001$) one and three months after surgery, respectively. The score of attention deficit and hyperactivity decreased from 1.76 and 2.10 at baseline to 1.52 and 1.83 after one month ($P = 0.001$) and to 1.24 and 1.52 after three months ($P = 0.001$), respectively. The results were statistically significant for both boys and girls.

Conclusion: This study indicated that adenotonsillectomy can significantly improve ADHD in children with adenotonsillar hypertrophy and help them return to normal life

Int J Psychiatry Clin Pract. 2019.

MULLERIAN INHIBITING SUBSTANCE, SEX HORMONE BINDING GLOBULIN AND SEX HORMONE LEVELS IN STIMULANT-NAÏVE, FIRST-DIAGNOSED PREPUBERTAL BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: COMPARISON WITH MATCHED HEALTHY CONTROLS AS WELL AS BEFORE AND AFTER OROS-METHYLPENIDATE TREATMENT.

Gokcen C, Erbagci AB, Mutluer T, et al.

Objectives: Attention-Deficit/Hyperactivity Disorder (ADHD) is a complex neurodevelopmental disorder with strong male predominance. Since Müllerian Inhibiting Substance (MIS) produces sex-linked bias in animal studies, we aimed to investigate the role of MIS, Sex Hormone Binding Globulin (SHBG) and sex hormone levels in boys with ADHD.

Methods: We compared prepubertal, psychostimulant-naïve boys with ADHD with age-matched healthy control boys (HCs). Patients were re-evaluated after 30 days of methylphenidate treatment assessing ADHD severity, and serum MIS, testosterone, estradiol, and albumin concentrations.

Results: Compared to 30 HCs, with ADHD ($n = 49$, age = 6.9 ± 0.2 years) had lower SHBG ($p = .014$), and higher free testosterone ($p = 0.006$) and bioavailable testosterone ($p = .002$) percentages. Methylphenidate improved ADHD measures (all $p < .0001$) and abnormal baseline hormonal levels, increasing SHBG levels ($p = .024$), and lowering free ($p = .001$) and bioavailable testosterone ($p = .016$) percentages so that only free testosterone percentages remained higher versus HCs post-treatment ($p = .02$).

Conclusions: Compared to age- and sex-matched HCs, prepubertal, stimulant-naïve boys with ADHD had significantly lower SHBG and higher free and bioavailable testosterone percentages, suggesting a possible contribution of sex hormones to ADHD. Osmotic-release oral system methylphenidate treatment for 30 days significantly improved ADHD symptoms and abnormal sex hormone levels, normalizing SHBG and bioavailable testosterone percentages that were similar to HCs while free testosterone remained elevated versus HCs. Key points Compare to healthy matched controls prepubertal stimulant-naïve boys with ADHD had significantly lower SHBG and higher free and bioavailable testosterone percentages, suggesting a possible effect on sex hormones to ADHD. After 30-day methylphenidate treatment, ADHD symptoms significantly improved, and SHBG and bioavailable testosterone percentages normalized which were similar to HCs, while free testosterone remained elevated versus HCs. We found a negative relationship between MIS levels and hyperactivity scores in ADHD boys. This finding suggests that MIS may contribute to hyperactivity symptoms, either directly by affecting behavior or indirectly by affecting sex hormone levels

Ir J Med Sci. 2019.

ADCOM STUDY ADOLESCENT COMMUNICATION GROUP THERAPY FOR EXTERNALISING DISORDERS.

Sadiq F, Mulligan A.

Background: Communication difficulties are associated with oppositional symptoms in young people. We hypothesise that a communication group intervention will reduce oppositional symptoms in young people. Previous research on communication and social skills training in young people with externalising disorders is limited.

Aims: We aimed to (1) develop and describe a group communication intervention to promote social competence in adolescents with behaviour difficulties, for use in CAMHS with those with attention-deficit/hyperactivity disorder (ADHD)/externalising disorders, and (2) collect pilot data on the effectiveness of this intervention.

Methods: We developed and delivered a programme of eight sessions to eight adolescents aged 12 to 13-áyears. We describe the intervention and challenges running the programme. We present pilot study data on pre- and post-oppositional symptoms.

Results: Our programme was relatively well attended; pilot data indicated a small reduction in oppositional symptoms in all participants. Challenges in running the group were noted.

Conclusions: Our pilot study data suggest that further research is needed to study the effects of a communication group intervention on oppositional symptoms in a larger number of adolescents

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Italian Journal of Pediatrics. 2019;45.

RISK FACTORS ANALYSIS OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND ALLERGIC RHINITIS IN CHILDREN: A CROSS-SECTIONAL STUDY.

Chen K, Zheng X, Li Z, et al.

Background: To investigate relationship between symptom of attention-deficit/hyperactivity disorder (ADHD) and allergic rhinitis (AR) in AR children of different genders and ages.

Methods: Four hundred and sixty-five allergic rhinitis children aged 6-12 years old were recruited in this study. Skin-prick test, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Total Nasal Symptoms Score (TNSS) and Swanson, Nolan, and Pelham version IV scale (SNAP-IV) were recorded. Patients were divided into AR with ADHD and AR without ADHD, according to SNAP-IV scale results.

Results: Children with inattention/hyperactivity scale (IHS) > 1.25 accounted for 26.4% of all children with AR. TNSS with IHS > 1.25 group were significantly higher than IHS 1.25 group. Univariate analysis showed that age, gender, duration of AR symptoms, skin index, and PRQLQ subscales were associated with symptoms of hyperactivity and attention deficit (IHS > 1.25). After normalizing age and gender factors, duration of AR symptoms and skin index correlated with IHS > 1.25. After stratifying age and gender, correlation between IHS > 1.25 and skin index and PRQLQ subscales was mainly found in male children, and association between duration of AR symptoms and IHS > 1.25 was reflected in each group.

Conclusions: ADHD in children with AR is associated with severity, duration, and skin index of AR, and this association is more pronounced in male children

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J Autism Dev Disord. 2019 May;49:2101-15.

COURSE AND PREDICTORS OF SLEEP AND CO-OCCURRING PROBLEMS IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Mazurek MO, Dovgan K, Neumeyer AM, et al.

The chronicity of sleep disturbance and its relation to co-occurring symptoms in children with autism spectrum disorder (ASD) are not well understood. The current study examined longitudinal relations among sleep and co-occurring symptoms in a large well-characterized sample of 437 children with ASD assessed at baseline and follow-up (M = 3.8 years later). Twenty-three percent experienced worsening sleep problems over time, while 31.5% showed improvement. Path analysis indicated that sleep problems at baseline predicted later development of ADHD symptoms in younger children and somatic complaints in older children. For younger children, sensory over-responsivity predicted future sleep problems. Findings suggest that sensory over-reactivity may contribute to sleep problems in some children with ASD, and that sleep problems may result in poor daytime functioning

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J Clin Psychopharmacol. 2019 May;39:284-85.

IMMEDIATE-RELEASE METHYLPHENIDATE-ASSOCIATED RECURRENT NASAL BLEEDING IN SIBLINGS.

Chandradasa M, Rathnayake LC.

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J Craniofac Surg. 2019 Mar;30:497-502.

UNDERSTANDING THE LEARNING DISABILITIES LINKED TO SAGITTAL CRANIOSYNOSTOSIS.

Cabrejo R, Lacadie C, Brooks E, et al.

OBJECTIVE: The purpose of this study is to investigate further findings that corroborate similarities between corrected sagittal craniosynostosis and attention deficit hyperactivity disorder (ADHD). The aim is to further characterize the neurocognitive deficits seen in adolescents with corrected craniosynostosis by comparing it to established learning deficits such as ADHD.

METHODS: A total of 30 functional magnetic resonance imaging (fMRI) of 10 sagittal nonsyndromic craniosynostosis (sNSC), 10 ADHD-combined, and 10 control adolescents were studied. The fMRI scans were analyzed utilizing Statistical Parametric Mapping (University College London, UK) and analyzed with BiImageSuite (Yale University, New Haven, CT).

RESULTS: The ADHD has lower connectivity to Brodmann area (BA) 11 (Montreal Neurological Institution [MNI]: -12,26,-21), BA20 (MNI: 62,-24,-25), and BA21 (MNI: 62,-32,-23) compared to sNSC and controls ($P < 0.001$). The sNSC has a unique visuospatial defect, compared to ADHD, created by decreased connectivity to BA31 (MNI: -3,-68,37), BA7 (MNI: -4,-68,41), BA19 (MNI: 0,-83,31), visual association cortex (MNI: -4,-78,22), and primary visual cortex (MNI: 7,-74,21) ($P < 0.001$).

CONCLUSION: Patients born with sNSC have different neural connections than children born with ADHD. Patients born with sNSC have decreased connections in areas of visual processing and increased connections in areas of attention and auditory processing than patients with ADHD. Therefore, children with sagittal craniosynostosis may have learning difficulties that, similar, yet different from ADHD

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J Inj Violence Res. 2019 Jan;11:45-52.

EVALUATING THE RELATIONSHIP BETWEEN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND RIDING BEHAVIOR OF MOTORCYCLISTS.

Sadeghi-Bazargani H, Hasanzadeh K, Salarilak S, et al.

BACKGROUND: Motorcycling is one of the main causes of injury, and motorcyclists are vulnerable to road traffic injuries. Attention Deficit Hyperactivity Disorder (ADHD) in adults is presumably one of the determinants of road traffic injuries and motorcyclists' risky behavior. Despite the few studies on the relationship between motorcycle injuries and adult ADHD, their association has not been investigated using standardized instruments. This study aimed to analyze the relationship between motorcyclists' adult ADHD and risky riding behaviors.

METHODS: This community-based, cross-sectional study was performed on 340 motorcyclists in Bukan city, west Azerbaijan province, Iran in 2015 and 2016 using a cluster-random sampling in seven areas of the city. According to the city map used by Bukan's Health Centers, the city was divided into 14 clusters. Then, seven clusters (out of 14) were selected randomly. To reach the anticipated sample size, the data were collected from these seven clusters. In this study, the data collection instruments were: standard Motorcycle Rider Behavior Questionnaire (MRBQ), Conners' Adult ADHD Rating Scales (CAARS) questionnaire and a checklist designed by the researchers. The Stata 13 software package was used to analyze the collected data. Pearson correlation coefficient and multiple linear regression were performed to study the linear relationship between ADHD screening and MRBQ scores.

RESULTS: All 340 participants were male and the mean age was 30.2 years ($SD=9.1$). In addition, 22.1% of motorcyclists had a history of motorcycle crash. Bivariate analysis showed a significant association between risky riding behaviors and age, motorcycling records, and mean of riding hours per day (P -value less than

0.05). Multivariate analysis confirmed the correlation between ADHD and risky riding behaviors in all subscales (A, B, D) (p less than 0.05).

CONCLUSIONS: Those with a high ADHD screening score are more likely to have risky riding behaviors

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J Pediatr Endocrinol Metab. 2019 Feb;32:203-06.

CHALLENGING DIAGNOSIS OF THYROID HORMONE RESISTANCE INITIALLY AS HASHIMOTO'S THYROIDITIS.

Ch'ng TW, Chin VL.

Background Resistance to thyroid hormone (RTH) commonly presents with goiter, attention deficit hyperactivity disorder (ADHD), short stature and tachycardia. However, due to its variable presentation with subtle clinical features, a third of the cases are mistreated, typically as hyperthyroidism.

Case presentation A 15-year-old female with ADHD and oligomenorrhea was initially diagnosed as Hashimoto's thyroiditis but found to have a rare heterozygous mutation in c803 C>G (p Ala 268 Gly) in the THRbeta gene, confirming resistance to thyroid hormone.

Conclusions Fluctuating thyroid function tests in addition to thyroid peroxidase antibody (TPO Ab) positivity complicated the diagnosis of RTH, initially diagnosed as Hashimoto's thyroiditis. A high index of suspicion is needed to prevent misdiagnosis and mistreatment

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J Pediatr Endocrinol Metab. 2019 Apr;32:409-13.

MYT1L MUTATION IN A PATIENT CAUSES INTELLECTUAL DISABILITY AND EARLY ONSET OF OBESITY: A CASE REPORT AND REVIEW OF THE LITERATURE.

Al TA, Alfadhel M.

Background Obesity has become one of the greatest health risks worldwide. Recently, there was an explosion of information regarding the role of the central nervous system (CNS) in the development of monogenic and syndromic obesity.

Case presentation Over the last decade, terminal and interstitial submicroscopic deletions of copy number variants (CNVs) in 2p25.3 and single nucleotide variants (SNVs) in myelin transcription factor 1 like (MYT1L) were detected by genome-wide array analysis and whole exome sequencing (WES) in patients with a nonspecific clinical phenotype that commonly includes intellectual disability (ID), early onset of obesity and speech delay. Here, we report the first Saudi female patient with mild to moderate ID, early onset of obesity and speech delay associated with a de novo pathogenic SNV in the MYT1L gene (c. 1585G>A [Gly529Arg]), which causes an amino acid change from Gly to Arg at position 529 that leads to mental retardation, autosomal dominant 39

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JAMA Network Open. 2019;2.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND MORTALITY RISK IN TAIWAN.

Chen VCH, Chan H-L, Wu S-I, et al.

Importance: Few studies have investigated levels of mortality in patients with attention-deficit/hyperactivity disorder (ADHD), and findings have been inconsistent and lacking information on specific causes of deaths. Objective: To investigate the association between ADHD and causes of death in Taiwan.

Design, Setting, and Participants: A nationwide population-based cohort study was conducted using a cross-national Taiwanese registry. The ADHD group comprised 275980 individuals aged 4 to 44 years with a new diagnosis between January 1, 2000, and December 31, 2012. All individuals with ADHD were compared with 1931860 sex- and age-matched controls without ADHD.

Exposures: The association between ADHD and mortality was analyzed using a Cox regression model that controlled for sex, age, residence, insurance premium, outpatient visits, congenital anomaly, intellectual disability, depression disorder, autism, substance use disorder, conduct disorder, and oppositional defiant

disorder. The analysis of suicide, unintentional injury, homicide, and natural-cause mortality was performed by a competing risk adjusted Cox regression controlling for other causes of mortality and potential confounding factors.

Main Outcomes and Measures: Data on mortality from all causes, suicide, unintentional injury, homicide, and natural causes collected from a national mortality database.

Results: There were 275980 individuals with ADHD and 1931860 comparison individuals without ADHD in this study. Sex and age at index date were matched. The mean (SD) age was 9.61 (5.74) years for both groups. Most of the participants were male (209406 in the ADHD group; 1465842 in the non-ADHD group; 75.88% for both groups). A total of 4321 participants from both cohorts died during the follow-up period (15.1 million person-years), including 727 (0.26%) from the ADHD group and 3594 (0.19%) from the non-ADHD group. Of those who died, 546 (75.1%) in the ADHD group and 2852 (79.4%) in the non-ADHD group were male. After adjusting for potential confounders, compared with the non-ADHD group, patients with ADHD showed higher overall mortality (adjusted hazard ratio, 1.07; 95% CI, 1.00-1.17) and higher injury-cause mortality from suicide (adjusted hazard ratio, 2.09; 95% CI, 1.62-2.71), unintentional injury (adjusted hazard ratio, 1.30; 95% CI, 1.10-1.52), and homicide (adjusted hazard ratio, 2.00; 95% CI, 1.09-3.68). No increased risk of natural-cause mortality was observed after adjustment.

Conclusions and Relevance: In this study, ADHD was associated with higher injury-cause mortality, particularly that due to suicide, unintentional injury, and homicide. Although the risk of injury mortality was significantly higher in patients with ADHD than in the non-ADHD group, the absolute risk of mortality was low

JAMA Network Open. 2019;2.

ANTI PSYCHOTIC TREATMENT AMONG YOUTHS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sultan RS, Wang S, Crystal S, et al.

Importance: Significant concern exists over treating youths with attention-deficit/hyperactivity disorder (ADHD) with antipsychotic medications, yet little is known about the factors associated with antipsychotic treatment.

Objectives: To describe the percentage of youths who fill antipsychotic prescriptions in the year following a new diagnosis of ADHD and characterize the clinical and demographic factors associated with antipsychotic initiation.

Design, Setting, and Participants: A retrospective longitudinal cohort analysis of antipsychotic treatment was performed in 187563 youths, aged 3 to 24 years, with a new diagnosis of ADHD (without recent diagnosis of any US Food and Drug Administration [FDA]-indicated conditions for antipsychotic treatment). The sample was derived from the 2010 to 2015 MarketScan Commercial Database, with the analysis completed between November 1, 2018, and May 30, 2019.

Main Outcomes and Measures: The percentage of youths prescribed an antipsychotic in the first year following a new diagnosis of ADHD. Among those prescribed antipsychotic medications, the percentage who received a diagnosis of conduct disorder, oppositional defiant disorder, or a disorder for which 1 or more antipsychotic medication has received an indication for use in youths from the FDA (schizophrenia, bipolar disorder, and Tourette disorder) and the percentage that filled an antipsychotic prescription before filling a stimulant prescription (methylphenidate or amphetamine derivative).

Results: Of the 187563 youths included in the study, 114 305 (60.9%) were male with a mean (SD) age of 13.74 (5.61) years. In the year following a new ADHD diagnosis, 4869 youths (2.6%; 95% CI, 2.5%-2.7%) with ADHD were prescribed an antipsychotic. Youths treated with antipsychotics with ADHD were more likely than their peers who were not receiving an antipsychotic to have recently received diagnoses of self-harm and/or suicidal ideation (adjusted odds ratio [aOR], 7.5; 95% CI, 5.9-9.6), oppositional defiant disorder (aOR, 4.4; 95% CI, 3.9-4.9), and substance use disorder (aOR, 4.0; 95% CI, 3.6-4.5). The youths who received antipsychotics were also more likely to have received inpatient treatment (aOR, 7.9; 95% CI, 6.7-9.3). During the year following the new ADHD diagnosis, 52.7% (95% CI, 51.3%-54.1%) of youths treated with antipsychotics received a diagnosis for which antipsychotics have either an FDA or evidence-supported indication for their use. Among youths who initiated antipsychotic medications, 47.9% (95% CI, 46.5%-49.3%) did not receive a stimulant prescription between their ADHD diagnosis and antipsychotic initiation.

Antipsychotic prescribing was proportionally highest for preschool-aged children (4.3%) and associated with neurodevelopmental disorders (aOR, 3.9; 95% CI, 1.3-11.2) and recent inpatient mental health treatment (aOR, 8.9; 95% CI, 1.7-45.8).

Conclusions and Relevance: Approximately half of youths with a new ADHD diagnosis may have an evidence-supported indication for an antipsychotic medication. Less than half of these youths received a stimulant; the evidence-supported first line treatment for ADHD, before the antipsychotic was initiated. Use of antipsychotic prescribing appears to be associated with high levels of psychiatric comorbidity

JAMA Psychiatry. 2019.

ASSOCIATION OF GENETIC AND ENVIRONMENTAL RISKS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH HYPOMANIC SYMPTOMS IN YOUTHS.

Hosang GM, Lichtenstein P, Ronald A, et al.

Importance: Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder are highly comorbid, with significantly associated symptoms. The mechanisms that account for their co-occurrence are not known.

Objective: To examine the degree to which genetic and environmental risk factors for ADHD traits, across childhood and adolescence, are associated with adolescent hypomanic symptoms.

Design, Setting, and Participants: This study used data on 13532 twin pairs from the Child and Adolescent Twin Study in Sweden, a prospective, longitudinal twin study. Their parents provided ADHD data when children were 9 or 12 years of age. Of those who reached 15 years of age, 3784 participated. Of those who reached 18 years of age, 3013 participated. The study was performed from December 20, 2017, to December 5, 2018. Data analysis was performed at the Department of Medical Epidemiology & Biostatistics, Karolinska Institutet, Stockholm, Sweden, from March 1, 2018, to October 31, 2018.

Main Outcomes and Measures: Attention-deficit/hyperactivity disorder traits and hypomanic symptoms were assessed using parent-rated instruments. Associations between ADHD and adolescent hypomanic symptoms across childhood and adolescence were investigated using generalized estimating equations. Multivariate twin models were used to examine the extent to which genetic and environmental risk factors for ADHD were associated with hypomania.

Results: Among 3784 15-year-old twin pairs and 3013 18-year-old twin pairs, ADHD and hypomanic symptoms were significantly associated (age 15 years: $\beta = 0.30$; 95% CI, 0.24-0.34; $P < .001$; age 18 years: $\beta = 0.19$; 95% CI, 0.16-0.22; $P < .001$), especially for the hyperactivity-impulsivity ADHD symptom domain (age 15 years: $\beta = 0.53$; 95% CI, 0.46-0.60; $P < .001$; age 18 years: $\beta = 0.36$; 95% CI, 0.30-0.42; $P < .001$) compared with the inattention domain (age 15 years: $\beta = 0.40$; 95% CI, 0.34-0.47; $P < .001$; age 18 years: $\beta = 0.24$; 95% CI, 0.19-0.29; $P < .001$). Between 13% and 29% of the genetic risk factors for hypomania were also associated with ADHD, with higher estimates detected for symptoms of hyperactivity-impulsivity (10%-25%) compared with inattention (6%-16%). Environmental factors played a negligible role in the associations. Genetic factors unique to adolescent hypomania were associated with 25% to 42% of its variance, suggesting some etiologic distinction between these forms of psychopathology.

Conclusions and Relevance: More than a quarter of the genetic risk factors for adolescent hypomanic traits were also associated with ADHD symptoms in childhood and adolescence, with hypomania-specific genetic risk factors detected. These findings suggest that ADHD and hypomanic symptoms are associated with shared genetic factors, which should be the focus of further research

JAMA Psychiatry. 2019.

ASSOCIATION OF PSYCHIATRIC COMORBIDITY WITH THE RISK OF PREMATURE DEATH AMONG CHILDREN AND ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sun S, Kuja-Halkola R, Faraone SV, et al.

Importance: A previous register-based study reported elevated all-cause mortality in attention-deficit/hyperactivity disorder (ADHD), but cause-specific risks and the potential associations of psychiatric comorbidities remain unknown.

Objectives: To investigate the all-cause and cause-specific mortality risks in ADHD and to explore the potential role of psychiatric comorbidities.

Design, Setting, and Participants: This prospective cohort study used Swedish national registers to identify 2 675 615 individuals born in Sweden from January 1, 1983, through December 31, 2009, as the study population, among whom 86 670 individuals (3.2%) received a diagnosis of ADHD during follow-up. Follow-up was completed December 31, 2013, and data were analyzed from October 2018 through March 2019.

Exposures: Attention-deficit/hyperactivity disorder identified by first clinical diagnosis or first prescription of ADHD medications as recorded in Swedish registers. Clinical diagnosis of psychiatric comorbidity was available in the National Patient Register.

Main Outcomes and Measures: All-cause and cause-specific mortalities and hazard ratios (HRs) using Cox proportional hazards regression models.

Results: In the overall cohort of 2 675 615 individuals, 1 374 790 (51.4%) were male (57 919 with an ADHD diagnosis) and 1 300 825 (48.6%) were female (28 751 with an ADHD diagnosis). Mean (SD) age at study entry was 6.4 (5.6) years. During follow-up, 424 individuals with ADHD and 6231 without ADHD died, resulting in mortality rates of 11.57 and 2.16 per 10 000 person-years, respectively. The association was stronger in adulthood (HR, 4.64; 95% CI, 4.11-5.25) compared with childhood (HR, 1.41; 95% CI, 0.97-2.04) and increased substantially with the number of psychiatric comorbidities with ADHD (HR for individuals with only ADHD, 1.41 [95% CI, 1.01-1.97]; HR for those with 4 comorbidities, 25.22 [95% CI, 19.60-32.46]). In adulthood, when adjusting for early-onset psychiatric comorbidity, the association between ADHD and risk of death due to natural causes was attenuated substantially and was no longer statistically significant (HR, 1.32; 95% CI, 0.94-1.85). When adjusting for later-onset psychiatric disorders, the association was attenuated to statistical nonsignificance for death due to suicide (HR, 1.13; 95% CI, 0.88-1.45) but remained statistically significant for death caused by unintentional injury (HR, 2.14; 95% CI, 1.71-2.68) or other external causes (HR, 1.75; 95% CI, 1.23-2.48).

Conclusions and Relevance: Psychiatric comorbidity appears to play an important role in all-cause and cause-specific mortality risks in ADHD. In adulthood, early-onset psychiatric comorbidity contributed primarily to the association with death due to natural causes, whereas later-onset psychiatric comorbidity mainly influenced death due to unnatural causes, including suicide and unintentional injury. These findings suggest that health care professionals should closely monitor specific psychiatric comorbidities in individuals with ADHD to identify high-risk groups for prevention efforts

J Abnorm Child Psychol. 2019 Aug;47:1315-26.

EXPLORING THE VARIABILITY IN REACTION TIMES OF PRESCHOOLERS AT RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: AN EX-GAUSSIAN ANALYSIS.

Hwang-Gu SL, Chen YC, Liang SH-Y, et al.

Reaction times (RTs) are typically slower and more variable in individuals with attention-deficit/hyperactivity disorder (ADHD). Analysis of the ex-Gaussian RT distribution, which is described by mu, sigma (mean and standard deviation, respectively, of the normal distribution) and tau (that of exponential distribution), reveals that individuals with ADHD do not display overall slower RTs but have a high proportion of extremely slow RTs, represented by a high tau value. Although this is a vital component for describing ADHD-related RT variability in school-aged children, adolescents, and adults, it has not been thoroughly studied at the preschool age. We assessed 65 preschoolers at risk of ADHD and 98 typically developing preschoolers with the Conners' Kiddie Continuous Performance Test (K-CPT) and parental and teacher reports of ADHD symptoms. We found that preschoolers at risk of ADHD had greater values for RT standard deviation, sigma, and tau than typically developing preschoolers at long inter-stimulus intervals (ISIs) (3 s), but not at short ISIs (1.5 s). This suggests that attention problems in preschool children may only be apparent in the tasks with a relatively slow event rate. Our study demonstrates that the ex-Gaussian tau value is essential for describing the inattentive component of task performance in preschoolers with heightened ADHD symptoms.

Furthermore, the fact that the tau effect was modulated by ISI suggests that the longer duration (3 s vs. 1.5 s) is a non-optimal energetic state in preschoolers at risk of ADHD, and that this might account for the subtle attentional flaw in task performance

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J Abnorm Child Psychol. 2019 Aug;47:1327-38.

FAMILY BURDEN OF RAISING A CHILD WITH ADHD.

Zhao X, Page TF, Altszuler AR, et al.

The purpose of the study was to estimate the burden to families of raising a child with attention-deficit/hyperactivity disorder (ADHD). Data were drawn from a longitudinal sample recruited in western Pennsylvania. When participants were between 14 and 17 years old, parents completed a questionnaire assessing economic burden over the course of raising their children. Domains of economic burden to families included direct costs related to child's behaviors (excluding treatment expenses) and indirect costs related to caregiver strain. On average, participants with ADHD incurred a total economic burden over the course of child development that was more than five times greater compared to youths without ADHD (ADHD = \$15,036 per child, Control = \$2,848 per child), and this difference remained significant after controlling for intellectual functioning, oppositional defiant symptoms, or conduct problems. Parents of participants with ADHD were more likely to have changed their job responsibilities or been fired and reported lower work efficiency. The current evaluation of economic burden to individual families extends previous estimates of annual societal cost of illness (COI) of ADHD. Our rough annual estimate of COI for ADHD in children and adolescents is \$124.5 billion (2017 US Dollars). Findings underscore the need for interventions to reduce the costly dysfunctional outcomes in families of children with ADHD

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J Adolesc Health. 2019.

RESPONSIBILITY FOR ASTHMA MANAGEMENT AMONG ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wenderlich AM, Baldwin CD, Fagnano M, et al.

Purpose: Among diverse, low-income urban adolescents with persistent asthma, we examined whether attention-deficit/hyperactivity disorder (ADHD) comorbidity, compared with asthma alone, was associated with clinical outcomes, healthcare utilization, and responsibility for self-management.

Methods: We conducted a secondary analysis of data from a large school-based study of adolescents with asthma in Rochester, NY. Adolescents reported asthma symptoms over 2 weeks and primary care and hospital admissions over 1 year. We assessed shared responsibility for asthma management between caregivers and adolescents.

Results: ADHD comorbidity was common (28%) in this sample of 370 adolescents. Adolescents with ADHD had more primary care utilization and hospitalizations than those without, despite having similar asthma symptoms. Caregivers and adolescents with ADHD reported that adolescents had less shared responsibility for nine asthma management tasks.

Conclusions: Adolescents with ADHD share less responsibility for asthma self-management. These teens' increased healthcare use might provide opportunities for clinicians to provide extra self-management support

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J Autism Dev Disord. 2019.

THE 2-YEAR COURSE OF INTERNET ADDICTION AMONG A JAPANESE ADOLESCENT PSYCHIATRIC CLINIC SAMPLE WITH AUTISM SPECTRUM DISORDER AND/OR ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

So R, Makino K, Hirota T, et al.

Internet addiction (IA) has been reported as prevalent in adolescents with autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD). However, the course of IA in this population has not been

elucidated. The authors performed a 2-year follow-up study including 89 out of 132 adolescents with ASD and/or ADHD in a psychiatric clinical setting who participated in the original cross-sectional study assessing IA prevalence. Within this sample of participants from both the original and the follow-up study, results showed a 2-year IA remission and incidence rate of 60% and 5%, respectively. Our findings imply that the course of IA in psychiatric populations with ASD and/or ADHD might be similar to reports from previous studies with general adolescent populations

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J Child Adolesc Ment Health. 2019.

IRON DEFICIENCY IN SOUTH AFRICAN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Magula L, Moxley K, Lachman A.

Objective: Iron deficiency may play a role in the pathophysiology of attention deficit hyperactivity disorder (ADHD) by causing dopamine dysfunction, but there is conflicting evidence in the literature regarding this relationship. This study investigates the possible correlation between iron deficiency and ADHD in children and adolescents attending a South African child and adolescent psychiatry outpatient service.

Method: In this retrospective study, we gathered data from 245 outpatient children and adolescents who had their serum ferritin and/or iron levels tested between February 2011 and January 2016. Relevant statistical methods were used to test for correlations between ADHD and various demographic and clinical factors, including iron deficiency.

Results: Out of 245 patients, 88 (35.9%) had iron deficiency, 156 (63.7%) had ADHD and 55 (22.4%) had both iron deficiency and ADHD. Variables found to be significantly correlated with ADHD included gender, age, and methylphenidate treatment, but there was no significant correlation between ADHD and iron deficiency.

Conclusions: Our study emphasizes the great complexity involved in understanding ADHD. Comparisons between mentally-ill paediatric patients and matched healthy controls from the same communities are required to further explore the possible association between iron deficiency and ADHD

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J Child Adolesc Psychopharmacol. 2019;29:426-32.

METHYLPHENIDATE TREATMENT INITIATED DURING CHILDHOOD IS CONTINUED IN ADULTHOOD IN HALF OF THE STUDY POPULATION.

Cheung K, Verhamme KMC, Herings R, et al.

Objectives: To estimate the number of patients who started methylphenidate during childhood and continued treatment beyond the age of 18 years and to study the determinants that may be associated with continuing treatment.

Methods: Patients 17 years of age and younger who have received at least one prescription of methylphenidate were identified in the Integrated Primary Care Information database (1996-2017). Logistic regression analyses were performed to assess the association between potential determinants and continuation with methylphenidate treatment at the age of 18 years.

Results: Fifty-three percent of all methylphenidate users (n = 1020) continued their treatment after the age of 18 years. Patients were more likely to continue treatment with methylphenidate if they started treatment at the age of 15-17 years compared with patients of 11 years and younger (adjusted odds ratio [OR]: 5.74, 95% confidence interval [CI]: 1.48-22.31), if they had a medication possession ratio (MPR) between 0.80 and 1.00 compared with a low MPR (adjusted OR: 2.18, 95% CI: 1.23-3.85) and if they lived in an area with a medium level of urbanization (adjusted OR: 1.98, 95% CI: 1.06-3.69). Furthermore, a relatively high number of patients had a MPR >1.0 (24.8%), of whom 91.3% started their treatment when they were between 15 and 17 years of age.

Conclusions: Methylphenidate treatment initiated during childhood was continued in half of the study population when reaching the age of 18, where adolescents were more likely to continue treatment than

young children. We also found that 25% of our study population had a MPR >1, mainly patients 15-17 years of age, which may suggest misuse or abuse of methylphenidate

J Child Adolesc Psychopharmacol. 2019;29:433-38.

TESTICULAR FUNCTION AFTER LONG-TERM METHYLPHENIDATE TREATMENT IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang L-J, Lee S-Y, Chou W-J, et al.

Objective: Treating attention-deficit/hyperactivity disorder (ADHD) with methylphenidate (MPH) has become increasingly common, while both animal studies and case reports have previously suggested that MPH may exert adverse effects on the reproductive system or gonadal hormones. This study aims to investigate whether long-term MPH treatment of boys with ADHD can induce testicular dysfunction (TD).

Methods: A nationwide cohort that included 59,746 boys diagnosed with ADHD and 52,008 healthy subjects retrieved from the National Health Insurance database in Taiwan was also observed between 1999 and 2011. TD was defined by the International Classification of Diseases, 9th revision, Clinical Modifications codes (257.0, 257.1, 257.2, 257.8, or 257.9). Cumulative time of MPH use was categorized into nonuse, short-term use (1-365 days), and long-term use (>365 days). We compared the rate of TD diagnosis between ADHD patients and controls and analyzed the risk of developing a TD after MPH treatment.

Results: Compared with the control group (0.06%), the ADHD group had a higher comorbidity rate of TD (0.14%) (adjusted odds ratio [aOR] = 1.95, 95% confidence interval [95% CI]: 1.26-3.04, $p = 0.003$). However, MPH did not significantly influence the risk of developing TD (adjusted hazard ratio = 1.40, 95% CI: 0.77-2.54, $p = 0.272$). Compared with ADHD boys without MPH treatment, patients who were prescribed short-term MPH (aOR = 0.96, 95% CI: 0.51-1.82, $p = 0.900$) and long-term MPH (aOR = 1.40, 95% CI: 0.69-2.83, $p = 0.351$) showed no significance associated with an increased risk of developing TD.

Conclusions: Our nationwide cohort showed that long-term treatment with MPH has no harmful effect on the testosterone function of ADHD patients. However, due to the increased comorbidity rate of ADHD and TD, early recognition and detection of TD in ADHD children have the potential to change the trajectory of TD morbidity later in life

J Child Adolesc Psychopharmacol. 2019;29:419-25.

INFLUENCE OF PSYCHOPHARMACOTHERAPY ON THE QUALITY OF LIFE OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Temizsoy H, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) may have a lasting effect on the quality of life (QoL) of children and their parents. Children with ADHD as well as their parents report a lower QoL compared with healthy children and children with chronic diseases such as bronchial asthma. The primary objective of this study was to investigate the changes of QoL of children with ADHD and their parents' subjective well-being before and after starting pharmacotherapy. We used the appropriate KINDL questionnaire for assessing the children's QoL and the World Health Organization (WHO) Big Five Questionnaire for assessing parental well-being.

Methods: We assessed the QoL and the parental well-being in 60 children and adolescents with ADHD between the ages of 6 and 12 years [mean age 8.7 years, (standard deviation = 1.8)], treated at the Department of Child and Adolescent Psychiatry of the Medical University of Vienna. QoL was rated using the KINDL questionnaires, and parental well-being was assessed using the WHO Big Five Questionnaire (WHO-5) before and after starting pharmacotherapy. We used t-tests and three-way GLM-ANOVA (SPSS, version 22; IBM Corp.) for evaluating the statistical significance of pre-post differences.

Results: The QoL of the children with ADHD and the subjective well-being of the parents improved significantly after introducing pharmacotherapy.

Conclusions: Pharmacotherapy is recommended in children with clinically significant ADHD not only because it helps to improve the symptoms of ADHD, but also their QoL and the well-being of their parents

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J Child Psychol Psychiatry. 2019 Jul;60:762-72.

INVESTIGATION OF A DEVELOPMENTAL PATHWAY FROM INFANT ANGER REACTIVITY TO CHILDHOOD INHIBITORY CONTROL AND ADHD SYMPTOMS: INTERACTIVE EFFECTS OF EARLY MATERNAL CAREGIVING.

Miller NV, Hane AA, Degnan KA, et al.

Background: ADHD is a neurodevelopmental disorder with a complex pathogenesis. Individual differences in temperamental reactivity – in particular, anger reactivity—are predictive of ADHD. The goal of this study was to examine the moderating (maternal caregiving behaviors; MCB) and mediating (inhibitory control) variables of reactivity using a 9-year multimethod prospective longitudinal design.

Methods: Participants included 291 children (135 male; 156 female) who participated in a larger study of temperament and social-emotional development. Anger reactivity was assessed by observation of facial anger during an arm restraint task, and MCB were observed during a series of semi-structured mother–infant tasks, both at 9 months of age. Inhibitory control was assessed by performance on a go/no-go task at 5 years of age. ADHD symptoms were assessed by parent and teacher report questionnaires at 7 and 9 years, respectively.

Results: Anger reactivity and poor inhibitory control were predictive of later ADHD symptoms. Results supported a moderated mediation model, in which the indirect effects of anger reactivity on ADHD symptoms through inhibitory control were conditional on quality of early MCB. Inhibitory control mediated the effect of anger reactivity on ADHD symptoms, but only among children exposed to lower-quality MCB.

Conclusions: Infant anger reactivity exerts a direct effect on later ADHD from infancy, suggesting anger reactivity as a very early indicator of ADHD risk. Higher-quality caregiving did not buffer against the direct risk of anger reactivity on ADHD but did buffer against the indirect risk by reducing the negative effect of anger reactivity on inhibitory control. Thus, in the developmental pathway from anger reactivity to ADHD, more sensitive, less intrusive parenting supports the development of protective mechanisms (i.e. inhibitory control) to remediate ADHD risk

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J Clin Exp Neuropsychol. 2019 Aug;41:615-33.

TEMPERAMENT, EXECUTIVE FUNCTION, AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN ADOLESCENTS: THE MEDIATING ROLE OF EFFORTFUL CONTROL.

Krieger V, Amador-Campos JA, Gallardo-Pujol D.

Introduction: Temperament dimensions may be related to executive functions (EF) and may be involved in the expression and maintenance of symptoms of attention-deficit/hyperactivity disorder (ADHD). The current study aimed to assess whether effortful control (EC) mediates the relationship between EF and inattentive symptoms, and whether surgency (S) and negative affectivity (NA) mediate the relationships between EF and hyperactive–impulsive ADHD symptoms in adolescents.

Method: Working individually, participants aged between 12 and 16 years (N = 118; 75 with ADHD) performed tests of cognitive EF (working memory, planning, flexibility, and inhibition), and parents and teachers completed a multi-informant assessment focusing on measures of ADHD symptoms and temperament dimensions (EC, S, and NA).

Results: There were significant differences between ADHD and control participants in EF and temperament dimensions. ADHD participants had lower scores than controls in working memory, planning, and inhibition EF; they also had lower scores in EC and higher scores in S and NA. Structural equation modeling indicated differential associations between EC, S, and NA temperament dimensions, and working memory, planning and inhibition EF, and ADHD symptoms. Mediation analysis suggested that EF exerted indirect effects on the inattentive and hyperactive–impulsive symptoms, via EC; higher EF abilities were related to higher levels

of EC, which in turn were related to lower scores of inattentive and hyperactive–impulsive ADHD symptoms. S and NA did not mediate relations among EF and hyperactive–impulsive symptoms.

Conclusion: The findings expand on those of previous studies of the complex relationship between temperament dimensions and EF and confirm the differential association between impairments in some EF, low EC, and the expression of inattentive and hyperactive–impulsive symptoms in adolescents, which may account for the ADHD–control group differences

Journal of Clinical Medicine. 2019;8.

EFFECTS OF EXERCISE ON COGNITIVE PERFORMANCE IN CHILDREN AND ADOLESCENTS WITH ADHD: POTENTIAL MECHANISMS AND EVIDENCE-BASED RECOMMENDATIONS.

Christiansen L, Beck MM, Bilenberg N, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with a complex symptomatology, and core symptoms as well as functional impairment often persist into adulthood. Recent investigations estimate the worldwide prevalence of ADHD in children and adolescents to be ~7%, which is a substantial increase compared to a decade ago. Conventional treatment most often includes pharmacotherapy with central nervous stimulants, but the number of non-responders and adverse effects call for treatment alternatives. Exercise has been suggested as a safe and low-cost adjunctive therapy for ADHD and is reported to be accompanied by positive effects on several aspects of cognitive functions in the general child population. Here we review existing evidence that exercise affects cognitive functions in children with and without ADHD and present likely neurophysiological mechanisms of action. We find well-described associations between physical activity and ADHD, as well as causal evidence in the form of small to moderate beneficial effects following acute aerobic exercise on executive functions in children with ADHD. Despite large heterogeneity, meta-analyses find small positive effects of exercise in population-based control (PBC) children, and our extracted effect sizes from long-term interventions suggest consistent positive effects in children and adolescents with ADHD. Paucity of studies probing the effect of different exercise parameters impedes finite conclusions in this regard. Large-scale clinical trials with appropriately timed exercise are needed. In summary, the existing preliminary evidence suggests that exercise can improve cognitive performance intimately linked to ADHD presentations in children with and without an ADHD diagnosis. Based on the findings from both PBC and ADHD children, we cautiously provide recommendations for parameters of exercise

Journal of Clinical Medicine. 2019;8.

CHARACTERISTICS OF ADHD SYMPTOM RESPONSE/REMISSION IN A CLINICAL TRIAL OF METHYLPHENIDATE EXTENDED RELEASE.

Weiss M, Childress A, Nordbrock E, et al.

Clinical trials in attention-deficit/hyperactivity disorder (ADHD) have typically measured outcome using clinician ratings on the Attention-Deficit/Hyperactivity Disorder Rating Scale, Fourth Edition (ADHD-RS-IV) and the Clinical Global Impression-Improvement (CGI-I) scale. Remission has been defined as an endpoint score of less than or equal to 18 on the ADHD-RS-IV (or a mean score of 1). Responders have been defined as patients who achieve a CGI-I score of much or very much improved (1 or 2). There is a lack of agreement in the literature on what percent change in symptoms on the ADHD-RS-IV should be used to define improvement or remission. This study uses data from a clinical trial of a methylphenidate extended release (MPH-MLR; Aptensio XR-«) phase III clinical trial to attempt to determine the percent change of symptoms that best corresponds with improvement and remission. Symptom remission at endpoint (ADHD-RS-IV total score ≤ 18) was most closely aligned with a ~46% reduction in ADHD-RS-IV total score. Clinical improvement was most closely aligned with a ~40% reduction in ADHD-RS-IV total score.

The three different measures of outcome were strongly aligned during double blind and open label treatment, and were independent of subtype status. Our data suggest that at least 40% improvement in symptoms is needed to achieve a robust response at endpoint

J Gen Psychol. 2019 Jul;146:258-82.

WISC-III COGNITIVE PROFILES IN CHILDREN WITH ADHD: SPECIFIC COGNITIVE IMPAIRMENTS AND DIAGNOSTIC UTILITY.

Moura O, Costa P, Simões MR.

This study aimed to investigate the presence of specific cognitive impairments and the diagnostic utility of the WISC-III in children with ADHD. Ninety-eight children with ADHD and 81 children without ADHD matched by age and gender (control group), between the ages of 6 and 12 years, participated in the study. Children with ADHD revealed the most pronounced deficits in the subtests tapping working memory and processing speed. Freedom from Distractibility was the cognitive profile most impaired and that showed the highest diagnostic accuracy to discriminate children with ADHD. The optimal cutoff scores of the most common WISC-III cognitive profiles revealed greater diagnostic accuracy than the traditional approach of full or partial profiles. Taken together, these results suggested that in the context of a comprehensive psychological assessment, the WISC may provide knowledge about the specific cognitive strengths and weaknesses that characterize this disorder and may be useful in the decision-making process relative to ADHD diagnosis

J Intellect Disabil Res. 2019;63:691.

READING DIFFICULTIES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Rhodes S, Stewart T, Booth J, et al.

Introduction: While it is well recognised that many children with ADHD have a high rate of dyslexia, few studies have examined the specific profile of reading difficulties across reading components in children with the condition. Little research has examined the influence of co-occurring ASD symptoms on the reading profile of children with ADHD.

Methods: Twenty drug naive children with ADHD were recruited from the waiting lists of Child and Adolescent Mental Health Services (CAMHS). All completed tasks of word reading and reading comprehension from the Weschler Individual Achievement Test (WIATIII) as well as tests of verbal and non-verbal IQ (WASI-II and BPVS-III). Parents completed ADHD and ASD symptom measures. Diagnosis was confirmed by clinical interview including parent and teacher verification.

Results: Findings reveal a specific profile of reading difficulties in children with ADHD. Relationships observed between reading profile and co-occurring ASD symptoms will be highlighted.

Implications: Further research is required to understand the factors that influence the reading profile of children with ADHD

J Intellect Disabil Res. 2019;63:667-68.

THE WISC PROFILE AMONG THAI CHILDREN WITH ADHD AND ASD WITH AND WITHOUT ADHD.

Mungkhetklang C.

Introduction: Previous studies found different the Wechsler Intelligence Scale for Children (WISC) profile between children with Autistic Spectrum Disorder (ASD) and children with Attention Deficit/ Hyperactive Disorder (ADHD). This study aims to explore the different WISC profile between Thai children with ADHD and ASD and also those ASD who have co-morbid with ADHD (ASD + ADHD).

Methods: One-hundred-ninety-four children with ADHD, eightythree children with ASD without ADHD (ASD-no-ADHD) and thirty children with ASD + ADHD from Rajanukul Institute, Thailand were examined using the WICS-Forth edition (WISC-IV). The scaled and index score of these groups were explored.

Results: Verbal Comprehension Index was the lowest for all groups. The subtest for which had the lowest and highest scaled scores were the same: Similarities was the lowest and Block Design was the highest, only Matrix Reasoning was also equally highest for ADHD. Vocabulary and Comprehension were equally lowest with Similarities for all groups; Symbol Search was also the lowest together with those three subtests for ASD + ADHD.

Implications: Our finding suggesting that the main impairment for all groups is verbal domain whereas visual processing is the strength. Therefore educational programs should be directed at utilizing on tasks with less verbally but visually based which may be easier for them to learn

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J Neural Transm. 2019.

CHILDREN'S FRIENDSHIP TRAINING PROGRAM FOR ISRAELI ELEMENTARY SCHOOL AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ilan SD, Fishman Y, Kufert Y, et al.

The present study examined whether the effectiveness of the Children's Friendship Training (CFT) in children with ADHD is maintained following treatment endpoint and whether it is effective in a different culture outside the USA. Parent reports of social skills, behavioral problems, conflict, and children's social knowledge were collected at baseline, pre-treatment (week-12), post-treatment (week-24) and follow-up (week-36) (treatment group: N = 25, waitlist: N = 20). Relative to waitlist, children's social knowledge, social skills and conflict resolution were improved at post-treatment and improvement was maintained at follow-up

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J Neurodevelopmental Disord. 2019 Jul;11.

INFANT REGULATORY FUNCTION ACTS AS A PROTECTIVE FACTOR FOR LATER TRAITS OF AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER BUT NOT CALLOUS UNEMOTIONAL TRAITS.

Bedford R, Gliga T, Hendry A, et al.

Background: Reduced executive functions (EF) are commonly associated with developmental conditions (e.g., autism spectrum disorder, ASD; attention deficit/hyperactivity disorder, ADHD), although EF seems to be typical in children with callous unemotional (CU) traits. Regulatory function (RF) is a proposed infant precursor that maps on onto factors driving later EF. Here, we first test whether RF is specifically and negatively associated with ASD and ADHD traits, but not CU traits. Second, we test whether RF can act as a protective factor, by moderating the association between infant markers and subsequent ASD and ADHD traits.

Methods: Participants were 79 infants at high (N = 42) and low (N = 37) familial risk for ASD. Data come from the 14-month infant visit (Autism Observational Scale for Infants; AOSI; activity level and RF from the Infant Behavior Questionnaire; IBQ) and the 7-year visit (ASD traits: Social Responsiveness Scale, SRS; ADHD traits: Conners 3, CU traits: Inventory of Callous Unemotional Traits).

Results: Infant RF was negatively associated with later traits of ASD (B = - 0.5, p = 0.01) and ADHD inattention (B = - 0.24, p = 0.02) but not hyperactivity (B = - 0.25, p = 0.10) or CU traits (B = 0.02, p = 0.86). RF moderated the association between infant AOSI score and ASD traits, with a significant effect in those with low RF (B = 0.10, p = 0.006), not high RF (B = 0.01, p = 0.78). Similarly, for ADHD, infant activity level was associated with later ADHD inattention in those with low (B = 0.17, p = 0.04) but not high RF (B = 0.07, p = 0.48). For ADHD hyperactivity symptoms, activity level was predictive at both high and low levels of RF.

Conclusions: Strong RF may allow children to compensate for other atypicalities, thus attenuating the association between infant markers and later disorder traits. Whilst infant RF was associated with both ASD and ADHD inattention traits, there was no association with ADHD hyperactivity or CU traits. This suggests that any protective effect may not be universal and emphasises the need for a better understanding of the underlying moderating mechanisms

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Lancet Psychiatry. 2019 Aug;6:632-33.

ADHD MEDICATION TREATMENT AND RISK OF PSYCHOSIS.

Hechtman L.

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Minerva Psichiatrica. 2019;60:129-36.

THE EFFECT OF COMBINATION OF PRAMIPEXOLE AND METHYLPHENIDATE IN THE TREATMENT OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Tashakori A, Riahi F, Khozuey Z.

BACKGROUND: In this article we studied for three months the effect of combination of pramipexole and methylphenidate in the treatment of children with attention deficit hyperactivity disorder (ADHD).

METHODS: In this double-blind randomized clinical trial study, 30 children who suffered from ADHD have been selected among the patients referred to the psychiatric clinic of Ahvaz Golestan Hospital. The patients were randomly assigned in the case study group (methylphenidate and pramipexole) and control group (methylphenidate and, placebo), Participants were examined before the start of treatment, and after six, eight, ten, and twelve weeks from the start of the treatment by the parent's Conners questionnaire.

RESULTS: The mean age of patients were 8.47 ± 2.08 years. The mean of the final Conners Score for case and control group, respectively, in week 0 was 68.53 ± 16.10 vs. 62.73 ± 16.85 $p > 0.05$, and in week 12 was 19.69 ± 7.27 vs. 35.23 ± 10.22 ($P < 0.001$). In weeks 6, 8, 10 and 12 (all weeks of evaluation), subtests of conduct problems, social problems, psychological problems, and shy anxiety, and also the final Conners Score of the case group were significantly lower in than to the control group ($P < 0.05$), the mean of Clinical Global Impression (CGI) of the case group showed a significant statistical difference in comparison to the control group ($P < 0.05$). In weeks 0, 6, 8, 10 and 12 (all weeks of evaluation). But the mean of Children Global Assessment Scale (CGAS) of the case group was significantly lower than that of the control group just in week 10 and 12 ($P < 0.05$).

CONCLUSIONS: Combination of pramipexole and methylphenidate is probably more effective than methylphenidate alone in treating the ADHD disorder from first week of evaluation to week 6. But after six-week treatment, pramipexole just maintains the Conner Score in low scores and the more reduction is not significant

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Mitochondrion. 2019;49:83-88.

MITOCHONDRIAL-ASSOCIATED PROTEIN BIOMARKERS IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lee C-J, Wu C-C, Chou W-J, et al.

This study aimed to determine the role of mitochondria-associated proteins (HtrA2, + α -synuclein, and Park7) in attention deficit/hyperactivity disorder (ADHD). A total of 125 patients with ADHD (77.6% were males) and 66 healthy controls (66.7% were males) were recruited. We found that girls with ADHD demonstrated higher plasma HtrA2 level than control girls, and their HtrA2 levels were positively correlated with verbal comprehensive ability, and negatively correlated to behavior symptoms. Among boys, we observed no correlations between these mitochondrial proteins, neuropsychological findings, and clinical symptoms.

Our findings suggest that an underlying gender-specific mitochondria pathway may influence with the pathophysiology of ADHD

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Monatsschr Kinderheilkd. 2019.

HERBAL MEDICINES IN PEDIATRICS: WHAT IS EVIDENCE BASED?

Langler A, Zuzak TJ, Fricke O, et al.

Herbal medicines and plant extracts (often equated with phytotherapeutics) are often used in children, frequently without a medical prescription. Contrary to the popular belief that there are no evidence-based studies for herbal supplements, a look at the scientific literature shows that there are some well-controlled studies of children and adolescents for some clinically relevant symptoms. The best studied areas of indications include gastrointestinal complaints, respiratory tract infections and, to a lesser extent, psychiatric disorders. Some of the herbal medicines or plant extracts studied showed statistically significant and clinically relevant positive effects on symptom control compared to standard treatment and/or placebo. Severe adverse events were not observed in the cited studies in any treatment group. This review summarizes the results of published controlled studies relevant to everyday medical practice, including safety aspects of the indicated areas of indications and provides practical recommendations for implementation

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Neurosci Biobehav Rev. 2019 Aug;103:109-18.

ASSOCIATION BETWEEN SUICIDAL SPECTRUM BEHAVIORS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Septier M, Stordeur C, Zhang J, et al.

The relationship between ADHD and suicidal spectrum behaviors (SSBs) remains uncertain. We conducted the first meta-analysis on the association between ADHD and SSBs taking possible confounders into account. Based on a pre-registered protocol (PROSPERO-CRD42018093003), we searched Pubmed, Ovid and Web of Knowledge databases through April 6th, 2018, with no language/publication type restrictions, and contacted study authors for unpublished data/information. From a pool of 2798 references, we retained 57 studies. Random-effects models were performed. Study quality was rated using the Newcastle-Ottawa Scale. After pooling crude ORs, we found a significant association between ADHD and suicidal attempts (2.37, 95% CI = 1.64–3.43; $I^2 = 98.21$), suicidal ideations (3.53, 2.94–4.25; $I^2 = 73.73$), suicidal plans (4.54, 2.46–8.37; $I^2 = 0$), and completed suicide (6.69, 3.24–17.39; $I^2 = 87.53$). Results did not substantially change when pooling adjusted ORs. Findings were also in general robust to sensitivity analyses to assess possible moderators. Awareness of the association between ADHD and SSBs should contribute to more effectively prevent SSBs

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Nord J Psychiatry. 2019 Feb;73:118-24.

METHYLPHENIDATE EFFECTS ON PROCESSING SPEED IN A CLINICAL SAMPLE OF ADULTS WITH ADHD AND SUBSTANCE USE DISORDER: A PILOT STUDY.

Arvidsson M, Dahl ML, Franck J, et al.

BACKGROUND: Substance use disorders (SUDs) are common comorbidities of Attention Deficit Hyperactivity Disorder (ADHD). The most commonly prescribed medication for ADHD is methylphenidate. The clinical response to methylphenidate may be monitored against DSM-5 symptomatology, rating scales or interviews.

AIMS: To evaluate the use of perceptual and cognitive processing speed measures to monitor methylphenidate effects in adults with ADHD and SUD.

METHODS: A Quick Test of Cognitive Speed (AQT) monitored perceptual and cognitive processing speed in 28 adults with ADHD and SUD on treatment with methylphenidate before and after the morning dose.

RESULTS: Twenty-six patients responded on AQT after the morning dose of methylphenidate. One-way ANOVA indicated significant treatment effects for color, form, and color-form combination naming, but not for shift cost values. Before the morning dose of methylphenidate, 92% were identified by cutoff time criteria for longer-than-normal processing times. After the morning dose of methylphenidate, 65% obtained color and form measures in the normal range for age peers. Only 35% obtained color-form processing measures in the normal range. Inter-individual response variability before medication intake was considerably larger than previously reported in studies of adults with ADHD only.

CONCLUSION: Proportionally, fewer adults with ADHD and SUD exhibited normalization of processing speed than previously observed for adults with ADHD without SUD. A potential clinical implication of the present study is that the AQT test may be used as a tool for dose-adjustment of central stimulants in the treatment of adults with ADHD and SUD

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Nord J Psychiatry. 2019 Feb;73:111-17.

CONVERGENT AND DIVERGENT VALIDITY OF THE SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA FOR SCHOOL-AGE CHILDREN - PRESENT AND LIFETIME VERSION DIAGNOSES IN A SAMPLE OF CHILDREN AND ADOLESCENTS WITH OBSESSIVE-COMPULSIVE DISORDER.

Kragh K, Husby M, Melin K, et al.

The presence of comorbid conditions associated with paediatric obsessive-compulsive disorder (OCD) is reported to range from 50 to 80% and to have an impact on treatment outcome. Accurate identification of comorbid psychiatric disorders is necessary in order to provide personalised care. Reliable and valid diagnostic interviews are essential in the process of establishing the correct diagnoses. The objective of this study was to evaluate the convergent and divergent validity of four diagnose categories generated by the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL). The diagnose categories were: anxiety, depression, attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD). The K-SADS-PL was applied in a clinical sample of youth aged 7-17 years (N = 269), who were participants in the Nordic long-term OCD-treatment study (NordLOTS). Youth and parents completed measures to evaluate symptoms of anxiety, depression, ADHD, and ODD. Convergent and divergent validity of K-SADS-PL anxiety diagnosis was supported based on both anxiety self- and parent-reports. Similarly, support was found for convergent and divergent validity of ADHD and ODD diagnoses. For depressive disorder, support for convergent validity was found based on the depression self-report. Support for divergent validity of depression was found based on both the depression self- and parent-reports. Results of the present study suggest that the K-SADS-PL generates valid diagnoses of comorbid anxiety disorders, depression disorders, ODD, and ADHD in children and adolescents with OCD

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Nord J Psychiatry. 2019 May;73:244-47.

PREVALENCE AND CLINICAL CHARACTERISTICS OF BODY DYSMORPHIC DISORDER IN ADOLESCENT INPATIENT PSYCHIATRIC PATIENTS-A PILOT STUDY.

Jafferany M, Osuagwu FC, Khalid Z, et al.

Background: Body dysmorphic disorder (BDD) is preoccupation with perceived body defects leading to distress and impairment in social functioning. Most of adolescent BDD literature has been done on patients within the outpatient setting with prior versions of DSM with dearth of information about BDD and comorbid psychiatric conditions among adolescents within the inpatient setting.

Aims: This pilot study evaluated the prevalence rate, clinical characteristics in adolescent BDD compared to non-BDD adolescents in a psychiatric inpatient setting in addition to their comorbid issues like anxiety, OCD, ADHD and substance abuse.

Methods: Forty-five consecutively admitted adolescent patients participated with 17 meeting the DSM 5 criteria for BDD while 28 did not. Patients were asked four questions designed around the DSM-5 criteria for BDD after which they were asked to complete questionnaires like BDDQ child and adolescent version,

BDDM, Multiaxial Anxiety Scale for Children, Children's Depression Inventory, Y-BOCS and Vanderbilt ADHD rating scales.

Results: Seventeen participants had BDD. Mean age of BDD patients was 13.1 while non-BDD was 12.4. Male patients with BDD were seven (41%) while female BDD patients were 10 (58.8%). Anxiety, depression, OCD and substance use disorders were common comorbid diagnoses. Majority of patients in the BDD group classified their BDD as a severe problem with more BDD, patient's considering suicide because of their BDD.

Discussion: BDD is present in adolescents admitted in inpatient psychiatric hospital with more female patients endorsing BDD versus their male counterparts. Patients with BDD are more likely to endorse more comorbid psychiatric issues such as anxiety, OCD, ADHD and substance abuse

Paediatrics and Child Health (Canada). 2019;24:e30.

SLEEP BEHAVIOURS AND DISTURBANCES CHARACTERIZING ADOLESCENTS WITH ADHD SYMPTOMS.

Dimakos J, Somerville G, Finn C, et al.

BACKGROUND: Sleep disturbances are commonly reported in adolescents with Attention-deficit/hyperactivity disorder (ADHD). Little data currently exists identifying the sleep behaviours or the symptoms of sleep disorders among adolescents with ADHD.

OBJECTIVES: The aim of this study was to characterize sleep behaviours and disturbances of adolescents with ADHD symptoms. We hypothesized that adolescents with high levels of ADHD symptoms would present more symptoms of primary sleep disorders and poorer sleep hygiene as compared to typically developing adolescents.

DESIGN/METHODS: 82 adolescents (53 females and 29 males) aged between 13 and 18 years old (M=14.61 SD=1.27) participated in the study. ADHD symptoms were characterized by the ADHD subscale of the Youth Self Report, a widely used child-report measure that assesses problem behaviour. In addition, they completed the Adolescent Sleep Hygiene Scale and their parents completed the Sleep Disorders Inventory for Students.

RESULTS: Participants were divided into two groups based on their scores on the ADHD scale, with students above or below 60 representing the high and low symptom groups, respectively. Analyses of variance (ANOVAs) revealed that students in the high levels of symptoms group had significantly higher levels of symptoms of obstructive sleep apnea, excessive daytime sleepiness, narcolepsy, restless leg syndrome, and delayed sleep phase syndrome, as well as a poorer overall sleep hygiene as compared to typically developing adolescents.

CONCLUSION: Pediatricians and other health care providers should screen adolescents with ADHD for possible sleep disorders and advise them regarding healthy sleep practices

PLoS ONE. 2019;14.

NEUROPHYSIOLOGICAL AND BEHAVIORAL CORRELATES OF ALERTNESS IMPAIRMENT AND COMPENSATORY PROCESSES IN ADHD EVIDENCED BY THE ATTENTION NETWORK TEST.

Abramov DM, Cunha CQ, Galhanone PR, et al.

In Attention Deficit Hyperactivity disorder (ADHD), fMRI studies show asymmetric alterations: widespread hypoactivation in anterior cortical areas and hyperactivation in some posterior regions, and the latter is considered to be related to compensatory processes. In Posner's attentional networks, an important role is attributed to functional interhemispheric asymmetries. The psychophysiological Attention Network Test (ANT), which measures the efficiency of the alerting, orienting, and executive networks, seems particularly informative for ADHD. Potentials related to ANT stimuli (ANT-RPs) have revealed reduced cognitive potential P3 in ADHD. However, there are no studies associated with asymmetry of ANT-RPs. In the present study, conducted with 20 typically developing boys and 19 boys with ADHD, aged 11–13 years, the efficiency of the three Posner's networks regarding performance and amplitude asymmetries in ANT-RPs was evaluated according to the arithmetic difference of these parameters between different cue and target presentation

conditions. The results were correlated to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) scores. Regarding accuracy and intraindividual variation in reaction time, ADHD subjects showed lower efficiency of executive and alerting network, and this effect was correlated with DSM. Regarding alerting network, ANT-RPs in ADHD did not have the right-side amplitude prevalence in the temporal regions, which was observed in controls. In all ANT conditions, significantly higher asymmetries were observed in ADHD than in controls in the occipital regions 40–200 ms after target onset. Their amplitude in ADHD subjects was inversely proportional to DSM scores of inattentiveness and directly proportional to accuracy and efficiency of the executive network. The results suggest impaired alerting and executive networks in ADHD and compensatory occipital mechanisms

Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;96.

ACUTE BLOOD PRESSURE CHANGE WITH METHYLPHENIDATE IS ASSOCIATED WITH IMPROVEMENT IN ATTENTION PERFORMANCE IN CHILDREN WITH ADHD.

Traicu A, Grizenko N, Fortier M, et al.

This exploratory study aims to determine whether the change in systolic blood pressure (sBP) after acute methylphenidate (MPH) administration (Δ BPMPH) is associated with the neurocognitive response to MPH in the Conners Continuous Performance Test (CPT) in 513 children with ADHD (aged 6 to 12 years old). We noted that higher increases in sBP were associated with larger improvement in CPT performance with MPH. In the univariate regression model, the Δ BPMPH accounted for an additional 2% of the variance in the change in CPT-Overall Index (OI) after controlling for covariates ($p < .001$). Linear regression analysis also indicated that Δ BPMPH significantly contributed to predict a change in omission errors, reaction time, and reaction time variability ($p < .001$, $p < .01$, $p = .001$, respectively), but not in commission errors or detectability index (d'). Participants with a clinically meaningful sBP increase of at least 5 mmHg ($n = 191$) improved by 4.8 points on the CPT-OI score ($p < .001$), compared to an improvement of only 0.6 points for participants whose sBP declined by at least 5 mmHg ($n = 121$). In conclusion, larger sBP increases after MPH administration were associated with greater enhancement in CPT performance. These results could be useful in informing MPH dosing in clinical practice

Psychiatry Clin Neurosci. 2019.

EFFICACY AND SAFETY OF TIPEPIDINE AS ADJUNCTIVE THERAPY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL.

Dehbozorgi S, Bagheri S, Moradi K, et al.

Aim: This study evaluated the efficacy and safety of tipegidine as an add-on to methylphenidate in the drug treatment of attention-deficit/hyperactivity disorder (ADHD).

Methods: This study was an 8-week, randomized, parallel group, double-blind, placebo-controlled trial recruiting 53 ADHD-diagnosed children. Patients were randomly divided to receive methylphenidate + tipegidine or methylphenidate + placebo for 8 weeks. Participants were assessed using the parent version of ADHD Rating Scale-IV and the Clinical Global Impression scale at baseline, at week 4, and at the end of the trial. Moreover, the safety and tolerability of the treatment strategies were compared.

Results: On general linear model repeated measures analysis a significant effect was seen for time +ù treatment interaction on the total and hyperactivity/impulsivity subscales of the Parent ADHD Rating Scale-IV during the trial period (Greenhouse-Geisser corrected: $F = 3.45$, $d.f. = 1.52$, $P = 0.049$, and $F = 5.17$, $d.f. = 1.52$, $P = 0.014$, respectively). The effect for time +ù treatment interaction, however, was not significant on Clinical Global Impression-Severity scale (Greenhouse-Geisser corrected: $F = 1.79$, $d.f. = 1.43$, $P = 0.182$). The frequencies of adverse events were similar between the two groups.

Conclusion: Eight weeks of treatment with tipegidine, as a supplementary medication, resulted in satisfactory efficacy and safety of the adjuvant therapy in management of patients with ADHD. Rigorous

investigations, however, involving larger sample sizes, more extended treatment periods, and dose responses should be considered

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Psychiatr Invest. 2019;16:433-42.

TRANSITIONS IN PROBLEMATIC INTERNET USE: A ONE-YEAR LONGITUDINAL STUDY OF BOYS.

Choi BY, Huh S, Kim D-J, et al.

Objective Longitudinal studies may help elucidate the factors associated with Problematic Internet Use (PIU); however, little prospective research has been conducted on the subject. The aim of the current study was to prospectively examine PIU in children/adolescents and identify the possible risk factors associated with transitions in PIU severity.

Methods 650 middle-school boys were surveyed at two points one year apart and assessed for PIU using the Internet Addiction Proneness Scale for Youth (KS-II) and on other psychological characteristics.

Results We found that 15.3% at baseline and 12.4% at one year met the criteria for at-risk/high-risk PIU (ARHRPIU). Both the persistent- ARHRPIU and emerging-ARHRPIU groups revealed greater depressive, motor impulsive, and smart-phone-addiction tendencies than the remitting-ARHRPIU group or the persistent low-risk group. In addition, we found that individuals exhibiting higher hyperkinetic attention-deficit/hyperactivity disorder (ADHD) scores were less likely to remit from ARHRPIU, and that individuals exhibiting more ADHD-related cognitive dysfunction and reporting fewer Internet-game-free days were more likely to demonstrate an emergence of ARHRPIU.

Conclusion The present findings support previous studies in that specific negative-health features are linked to transitions in ARHRPIU. Furthermore, these findings suggest that intervention is needed and may be best targeted at specific groups of youths

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Psychiatr Invest. 2019;16:370-78.

PILOT STUDY: AN OCULAR BIOMARKER FOR DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Bae S, Kim JT, Han JM, et al.

Objective Biomarkers of attention deficit hyperactivity disorder (ADHD) are crucial for early diagnosis and intervention, in which the identification of biomarkers in other areas of the body that represent the immature brain of children with ADHD is necessary. The present study aimed to find biomarkers of ADHD in the retina and assessed the relationship between macular thickness of the retina and cortical thickness of the brain in children with ADHD.

Methods Twelve children with ADHD and 13 control children were recruited for the study. To find ocular markers of ADHD, we investigated the correlation between clinical symptoms of ADHD assessed with the Korean ADHD Rating Scale (K-ARS), cortical thickness of the brain, and macular thickness measured with the mean thickness from the Early Treatment Diabetic Retinopathy Study (ETDRS).

Results Children with ADHD showed increased macular thicknesses quantified as an ETDRS ring in both eyes, compared to control subjects. Moreover, the right inner ETDRS ring had a positive correlation with K-ARS scores. The ADHD group had an increased ratio of thickness of the right frontal lobe to that of the parietal cortex, compared with the control group. There were positive correlations between the means of the inner ETDRS ring (right) and the left paracentral/right isthmus cingulate thicknesses in the control group. However, there were negative correlations between the means of the inner ETDRS ring (right) and the left frontal pole/right pars triangularis thicknesses in the ADHD group. The results of both groups were at the uncorrected level.

Conclusion The different patterns of macular thickness might represent the immature cortical thickness of the brain in children with ADHD

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Psychiatry Res. 2019 Apr;274:228-34.

MAGNESIUM STATUS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A META-ANALYSIS.

Effatpanah M, Rezaei M, Effatpanah H, et al.

Current research suggests conflicting evidence surrounding the association between serum magnesium levels and the diagnosis of attention deficit hyperactivity disorder (ADHD). This systematic review and meta-analysis aims to explore, summarize and quantify the published literature addressing this topic. We conducted an exhaustive literature search on Scopus and PubMed for all the relevant observational studies published up to August 2018. A meta-analysis using a random-effects model was used to summarize the overall association between serum magnesium level and ADHD from the available data. We identified seven studies which reported the mean and standard deviation (SD) of magnesium concentration in both ADHD and control groups. The random-effects meta-analysis showed that subjects with ADHD had 0.105mmol/l (95% CI: -0.188, -0.022; $P < 0.013$) lower serum magnesium levels compared with to their healthy controls. Moreover, we observed striking and statistically significant heterogeneity among the included studies ($I(2)=96.2\%$, $P=0.0103$). The evidence from this meta-analysis supports the theory that an inverse relationship between serum magnesium deficiency and ADHD exists. High heterogeneity amongst the included studies suggests that there is a residual need for observational and community-based studies to further investigate this issue

Psychiatry Res. 2019 Apr;274:243-46.

IMPAIRMENT IN PLANNING TASKS OF CHILDREN AND ADOLESCENTS WITH ANXIETY DISORDERS.

Rodrigues CL, Rocca CCA, Serafim A, et al.

Anxiety disorders are associated with poor neuropsychological performance in attention and memory. However, little is known about the impact of these difficulties on other cognitive functions, such as planning. The ability to plan, including attention, working memory and set-shifting components, can be assessed by the Tower of Hanoi task (ToH). This study evaluated seventy-one participants, aged from 7-17 years. Thirty-seven subjects met DSM-IV diagnostic criteria for at least one anxiety disorder and 34 individuals comprised the controls. The neuropsychological tests used were: the ToH, a problem-solving task, involves planning ability and other executive functions (working memory, attentional control and cognitive flexibility); for the assessment of processing speed and problem-solving, the Vocabulary/Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence was used to measure for estimated-IQ in both groups. The groups were compared with a generalized linear model controlling for age, IQ and ADHD comorbidity. Compared with controls, anxiety disorders subjects made more errors and required more time to complete the ToH. Children and adolescents with anxiety disorders have poorer planning ability compared to subjects without anxiety disorders, and the difficulty in planning is affected by interference from other cognitive functions, such as attention, working memory, cognitive flexibility and problems-solutions

Psychiatry Res. 2019;279:370-71.

COMMENTARY ON “THE NEUROCOGNITIVE NATURE OF CHILDREN WITH ADHD COMORBID SLUGGISH COGNITIVE TEMPO: MIGHT SCT BE A DISORDER OF VIGILANCE?”.

Plourde V.

Psychol Assess. 2019 May;31:685-98.

THE ROLE OF NEUROCOGNITIVE TESTS IN THE ASSESSMENT OF ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Nikolas MA, Marshall P, Hoelzle JB.

Despite widespread recognition that attention-deficit/hyperactivity disorder (ADHD) is a lifelong neurodevelopmental disorder, optimal methods of diagnosis among adults remain elusive. Substantial overlap between ADHD symptoms and cognitive symptoms of other mental health conditions, such as depression and anxiety, and concerns about validity in symptom reporting have made the use of neuropsychological tests in ADHD diagnostic assessment appealing. However, past work exploring the potential diagnostic utility of neuropsychological tests among adults has often relied on a relatively small subset of tests, has failed to include symptom and performance validity measures, and often does not include comparison groups of participants with commonly comorbid disorders, such as depression. The current study examined the utility of an extensive neuropsychological measure battery for diagnosing ADHD among adults. Two hundred forty-six participants (109 ADHD, 52 depressed, 85 nondisordered controls) completed a multistage screening and assessment process, which included a clinical interview, self, and informant report on behavior rating scales, performance and symptom validity measures, and an extensive neuropsychological testing battery. Results indicated that measures of working memory, sustained attention, response speed, and variability best discriminated ADHD and non-ADHD participants. While single test measures provided performed poorly in identifying ADHD participants, analyses revealed that a combined approach using self and informant symptom ratings, positive family history of ADHD, and a reaction time (RT) variability measure correctly classified 87% of cases. Findings suggest that neuropsychological test measures used in conjunction with other clinical assessments may enhance prediction of adult ADHD diagnoses

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Psychol Assess. 2019 Jun;31:793-804.

ASSESSING ADHD IN COLLEGE STUDENTS: INTEGRATING MULTIPLE EVIDENCE SOURCES WITH SYMPTOM AND PERFORMANCE VALIDITY DATA.

Nelson JM, Lovett BJ.

Prior research supports the use of multiple types of evidence from multiple sources when assessing ADHD in adults. However, limited research has examined how to best integrate the resulting set of data into a well-supported diagnostic conclusion. Moreover, clients sometimes overreport symptoms or display low effort on performance tasks, further complicating the interpretation of assessment data. The present study examined self-ratings and observer (e.g., parent) ratings of symptoms as well as performance task data from 514 postsecondary students assessed for ADHD at a university-affiliated clinic. Observer ratings were more reliable than self-ratings and were more likely to be corroborated by other data. The 2 types of ratings showed moderate to large relationships with each other as continuous variables ($.32 < r < .52$) while agreement around categorical symptom cutoffs was slight or fair ($.12 < \text{kappa} < .32$). Both types of ratings showed only small relationships with a performance test designed to assess ADHD symptoms. Approximately half of the cases in the sample had at least 1 piece of potentially noncredible data (suggesting potential symptom overreporting, inconsistent responding, or inadequate effort). Requiring ratings from multiple informants (as opposed to a single informant) of clinically significant symptoms for a diagnosis substantially reduced the effect of noncredible data, while also reducing the number of diagnoses by approximately half. Implications of these and other findings for practice and future research are discussed

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Res Dev Disabil. 2019 May;88:22-29.

SUSTAINED ATTENTION IN SENSORY MODULATION DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Mazor-Karsenty T, Parush S, Shalev L.

BACKGROUND: There are high comorbidity rates between sensory modulation disorder (SMD) and attention deficit hyperactivity disorder (ADHD). Knowledge regarding the objective neuropsychological differentiation between them is scarce.

AIM: This study examines the effects of SMD and ADHD on a sustained attention task with and without aversive auditory conditions.

METHOD: Sixty six young adult females were tested on the Conjunctive - Continuous Performance Task-Visual (CCPT-V) measuring sustained attention, under two conditions: 1) aversive condition (with the three most aversive sounds chosen by the participant), and 2) non-aversive condition (without sounds).

RESULTS: Both the SMD and ADHD factors exhibited performance deficits in the sustained attention task. All study participants performed worse on both sustained attention and speed of processing when aversive sounds were present.

CONCLUSION: We conclude that impaired sustained attention cannot differentiate between SMD and ADHD. Hence, these results should be taken under consideration in the assessment process of ADHD vs. SMD

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Res Autism Spectr Disord. 2019 Aug;64:76-83.

ATYPICAL EATING BEHAVIORS IN CHILDREN AND ADOLESCENTS WITH AUTISM, ADHD, OTHER DISORDERS, AND TYPICAL DEVELOPMENT.

Mayes SD, Zickgraf H.

Background: Previous research has not yet examined the prevalence of atypical eating behaviors in children and adolescents with autism compared to those with ADHD, other disorders, and typical development.

Method: The sample comprised 2102 children: 1462 with autism, 327 with other disorders (e.g., ADHD, intellectual disability, language disorder, and learning disability), and 313 typical children, 1–18 years of age (mean 7.3). Atypical eating behaviors were assessed with the Checklist for Autism Spectrum Disorder based on a standardized parent interview conducted by licensed psychologists.

Results: Atypical eating behaviors were significantly more common in autism (70.4%) than in children with other disorders (13.1%) and typical children (4.8%). For children with autism who had atypical eating behaviors, the most common behavior was limited food preferences (88%), followed by hypersensitivity to food textures (46%), other peculiar patterns most often eating only one brand of food (27%), pocketing food without swallowing (19%), and pica (12%). Grain products and/or chicken (usually nuggets) were the preferred foods for 92% of children with autism who had limited food preferences. For children with autism who had atypical eating behaviors, 25% had three or more atypical eating behaviors (vs. 0% for children with other disorders or typical development). Only children with autism had pica or pocketed food.

Conclusions: The number and types of atypical eating behaviors found only in children with autism and not in children with other disorders or typical development should alert clinicians to the possibility of autism and the need to evaluate for autism in order to facilitate early identification and access to evidence-based treatment

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Rev Med Suisse. 2019 Mar;15:555-58.

A SENSORIMOTOR PRECURSOR OF THE HYPERACTIVITY SYNDROM. STUDY OF A SAMPLE OF SWISS FRENCH-SPEAKING CHILDREN.

Gaillard F, Quartier V, Roman P.

Psychological examination aims at objectifying the key symptoms of hyperactivity, namely the disorders of attention and of the executive functions (briefly, the activation-inhibition control). The records of 237 patients, aged 5 to 17 and attending our day clinics between 2004 and 2016, are analyzed retrospectively.

40 cases present an attention-deficit/hyperactivity disorder (ADHD), combined presentation, after DSM-5 criteria. These children and adolescents show not only a typical impulsivity on the computerized test of -attention, but also some deficit in learning to write, a precocious manifestation of their neurodevelopmental disorders. This comorbidity correctly classifies 82.4 % of the hyperactivity and control cases, a quite strong effect in the context of the hard to reach -diagnosis of the ADHD syndrom

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Revista de Logopedia, Foniatría y Audiología. 2019 Jul;39:105-14.

PRAGMATIC ABILITIES IN CHILDREN WITH ASD, ADHD, DOWN SYNDROME AND TYPICAL DEVELOPMENT THROUGH THE GALICIAN VERSION OF THE CCC-2.

de la Torre Carril A, Pérez-Pereira M.

Background: Pragmatics is an area of language that may be impaired in a wide variety of disorders. However, there is a dearth of instruments for the assessment of pragmatic abilities. The Children's Communication Checklist (CCC-2) is the most widespread test, although more adaptations of this instrument to other languages are necessary.

Aims: In this paper we (1) develop a pilot study to adapt the CCC-2 to the Galician language, (2) check the capacity of this version to assess communicative difficulties in Galician speakers from 4 to 16 years of age, and (3) we also check its capacity to discriminate the linguistic profiles of different disorders.

Method: The reference profile of the Galician CCC-2 was established with a sample of 48 schoolchildren. Comparisons of the scores obtained by children with ASD (n = 11), ADHD (n = 10), Down Syndrome (DS) (n = 9) and Typical Development (n = 10) were carried out.

Results: The Galician CCC-2 (1) accurately identified children with and without communicative impairments, (2) distinguished between profiles with predominance of pragmatic (ASD and ADHD) and structural disorders (DS), and (3) distinguished between different profiles with predominance of pragmatic impairment.

Conclusions: The Galician CCC-2 seems to be a useful instrument to assess pragmatic disorders and to differentiate among different clinical groups

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Seizure. 2019;71:233-39.

AUTISM, ADHD AND PARENT-REPORTED BEHAVIOURAL DIFFICULTIES IN YOUNG CHILDREN WITH EPILEPSY.

Reilly C, Atkinson P, Memon A, et al.

Purpose: To provide data on the prevalence of Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and parent reported behaviour difficulties in young children with epilepsy, and to compare results with children with neurodisability (neurodevelopmental/neurological difficulties) without epilepsy.

Method: Children with epilepsy (1-7 years, n = 48) and children with neurodisability (1-7 years, n = 48) matched for gender, chronological and developmental age underwent psychological assessment. Parents completed measures of behaviour including the Strengths and Difficulties Questionnaire (SDQ). DSM-5 diagnoses of ASD and ADHD were made at consensus case conferences. Factors associated with child behaviour were analysed using linear regression.

Results: Of the children with epilepsy, 18% met ASD criteria and 40% met ADHD criteria (corresponding figures in the non-epilepsy group were 41% and 27%). A large proportion (76%-78%) in both groups scored in the at-risk range on the SDQ and frequently had difficulties across multiple behavioural domains. Children with epilepsy had more concerns expressed regarding attention and mood. None of the epilepsy factors were significantly associated with scores on the behavioural measures.

Significance: Young children with epilepsy had a very high level of parent reported behavioural difficulties and a high risk for ADHD and ASD highlighting the need for comprehensive multidisciplinary assessment. Behavioural concerns were not greater than for other children with non-epilepsy related neurodisability with the exception of attention and mood. Epilepsy related factors were not associated with child behaviour, suggesting that seizures per se do not confer a unique risk for behavioural difficulties

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Soc Psychiatry Psychiatr Epidemiol. 2019 Jun;54:671-82.

EVIDENCE OF CONCURRENT AND PROSPECTIVE ASSOCIATIONS BETWEEN EARLY MALTREATMENT AND ADHD THROUGH CHILDHOOD AND ADOLESCENCE.

Gonzalez RA, Velez-Pastrana MC, McCrory E, et al.

PURPOSE: An emerging body of work suggests a link between childhood maltreatment and attention-deficit hyperactivity disorder (ADHD). However, research examining the role of maltreatment in the early course of the disorder lacks robust evidence from longitudinal studies. Our aim was to examine concurrent and prospective associations between maltreatment experiences and ADHD diagnosis and sex differences, and to estimate the association between repetitive maltreatment exposure and ADHD through childhood and adolescence.

METHODS: Data were obtained from the Boricua Youth Study, a longitudinal study of 2480 children and adolescents of Puerto Rican background. Neglect, physical, emotional and sexual abuse, and foster placement were regressed on ADHD diagnosis measured at each of three waves using the Diagnostic Interview Schedule for Children-IV. Multilevel regressions estimated the effects of exposure on ADHD, adjusted by age, sex, income, household education, parental psychopathology, comorbidity and ADHD medication status.

RESULTS: Emotional abuse and foster placement had robust associations with ADHD diagnosis. For girls, physical abuse had a threefold increase in the odds of having ADHD diagnosis; for boys, associations were observed only for emotional abuse. Prospective models examining the risk of ADHD following maltreatment provided initial evidence for the effects of physical abuse on ADHD, and a linear trend for repetitive exposure suggested increased probability for disorder persistence.

CONCLUSIONS: Associations between early maltreatment and ADHD were robust. Different categories of maltreatment increase the likelihood of ADHD for girls and boys. Increased exposure to maltreatment may predict symptom persistence. Interventions addressing ADHD must consider the effects of both sex and family environment

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Soc Psychiatry Psychiatr Epidemiol. 2019 Jun;54:683-91.

ADHD AND DEPRESSIVE SYMPTOMS IN ADOLESCENTS: THE ROLE OF COMMUNITY VIOLENCE EXPOSURE.

Stickley A, Kuposov R, Koyanagi A, et al.

PURPOSE: Comorbid depression is common in adolescents with attention-deficit/hyperactivity disorder (ADHD). As yet, however, little is known about the factors associated with co-occurring depression in this population. To address this research gap, the current study examined the role of community violence exposure in the association between ADHD symptoms and depression.

METHODS: Data came from 505 Russian adolescents [mean age 14.37 (SD = 0.96)] who had teacher-reported information on ADHD symptoms that was collected in conjunction with the Social and Health Assessment (SAHA). Adolescent self-reports of witnessing and being a victim of community violence were also obtained while depressive symptoms were self-assessed with an adapted version of the Center for Epidemiologic Studies-Depression Scale (CES-D). Logistic regression analyses were performed to examine associations.

RESULTS: In univariable analyses, both witnessing and being a victim of violence were associated with significantly increased odds for depressive symptoms in adolescents with ADHD symptoms compared to non-ADHD adolescents who had not experienced community violence. However, in the multivariable analysis

only being a victim of violence continued to be associated with significantly increased odds for depression [odds ratio (OR) 4.67, 95% confidence interval (CI) 1.33-16.35].

CONCLUSION: Exposure to community violence may be associated with depression in adolescents with ADHD symptoms. Clinicians should enquire about exposure to community violence in adolescents with ADHD/ADHD symptoms. Early therapeutic interventions to address the effects of violence exposure in adolescents with ADHD may be beneficial for preventing depression in this group

Stem Cell Res. 2019 Jan;34:101353.

GENERATION OF FOUR IPSC LINES FROM PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS) OF AN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) INDIVIDUAL AND A HEALTHY SIBLING IN AN AUSTRALIA-CAUCASIAN FAMILY.

Tong J, Lee KM, Liu X, et al.

Peripheral blood mononuclear cells were donated by a male teenager with clinically diagnosed attention deficit hyperactivity disorder (ADHD) under the Diagnostic and Statistical Manual of Mental Disorders IV criteria and his unaffected male sibling. Induced pluripotent stem cells were developed using integration-free Sendai Reprogramming factors containing OCT4, SOX2, KLF4, and c-MYC. All four iPSC lines displayed pluripotent cell morphology, pluripotency-associated factors at the DNA and protein level, alkaline phosphatase enzymatic activity and a male karyotype of 46, XY. All lines had capacity for in vitro differentiation into all the three germ layers. All were negative for Mycoplasma

Sultan Qaboos Univ Med J. 2018 Nov;18:e455-e460.

EFFECTS OF AN ADENOTONSILLECTOMY ON THE COGNITIVE AND BEHAVIOURAL FUNCTION OF CHILDREN WHO SNORE: A NATURALISTIC OBSERVATIONAL STUDY.

Al-Zaabi K, Al-Adawi S, Jaju S, et al.

Objectives: This study aimed to evaluate cognitive and behavioural changes among 9-14-year-old Omani children with obstructive sleep apnoea (OSA) after an adenotonsillectomy (AT).

Methods: This naturalistic observational study was conducted at the Sultan Qaboos University Hospital, Muscat, Oman, between January 2012 and December 2014. Omani children with adenotonsillar hypertrophy (ATH) underwent overnight polysomnography and those with confirmed OSA were scheduled for an AT. Cognitive and behavioural evaluations were performed using standardised instruments at baseline prior to the procedure and three months afterwards.

Results: A total of 37 children were included in the study, of which 24 (65%) were male and 13 (35%) were female. The mean age of the males was 11.4 +/- 1.9 years, while that of the females was 11.1 +/- 1.5 years. Following the AT, there was a significant reduction of 56% in mean apnoea-hypopnoea index (AHI) score (2.36 +/- 4.88 versus 5.37 +/- 7.17; P <0.01). There was also a significant positive reduction in OSA indices, including oxygen desaturation index (78%), number of desaturations (68%) and number of obstructive apnoea incidents (74%; P <0.01 each). Significant improvements were noted in neurocognitive function, including attention/concentration (42%), verbal fluency (92%), learning/recall (38%), executive function (52%) and general intellectual ability (33%; P <0.01 each). There was a significant decrease of 21% in both mean inattention and hyperactivity scores (P <0.01 each).

Conclusion: These results demonstrate the effectiveness of an AT in improving cognitive function and attention deficit hyperactivity disorder-like symptoms among children with ATH-caused OSA. Such changes can be observed as early as three months after the procedure

Swiss Med Wkly. 2019;149:28S.

DIAGNOSTICS AND TREATMENT OF ADHD IN SWITZERLAND: A PHYSICIAN PERSPECTIVE ON PRACTICE AND CHALLENGES.

Von RM, Albermann K, Dratva J, et al.

Background: Attention deficit/hyperactivity disorder (ADHD) is a major public health problem with numerous negative outcomes for the affected individuals and with a high burden to families and society. Although a multimodal therapeutic approach (i.e., pharmacological treatment as well as non-pharmaceutical treatment options) is considered the gold standard, the observed increasing methylphenidate (MPH) treatment could correspond to a reduced use of other treatments options. This study therefore aims to provide insights into the current practice of pediatricians as well as perceived challenges during the process of diagnosis and treatment.

Methods: An online survey on diagnostic and therapy procedures, personal attitudes, and perceived challenges regarding ADHD was sent to the members of the Swiss Society for Pediatrics (without reminder). With 151 questionnaires that were analyzed, response rate was low (9.3 %).

Results: Pediatricians reported the exchange with parents and children as well as the burden of the children to be central when selecting a therapy. On average they arrange three meetings with parents, of which two take place in presence of the child. They report including information from several sources before arriving at a diagnosis. Pharmacological therapy was most frequently prescribed, followed by psychotherapy, and occupational therapy. Challenges mentioned were: the subjective character of the diagnosis and frequent co-morbidities, limited resources for case management, limited availability of child and youth psychiatric and psychotherapeutic treatment, and unfavorable public attitudes toward medication.

Conclusions: Participating pediatricians considered a multimodal approach when treating ADHD and showed a high involvement of family and child in the choice of therapy. However, they highlight the potential of improving the cooperation with other specialists, such as teachers and school social workers, and of improving the availability of psychotherapy and information on ADHD.

Main messages: Pediatricians are in close exchange with parents and children and consider several (non-) pharmacological ADHD treatment options. Challenges comprise the interprofessional cooperation and coordination as well as the availability of psychotherapy and information on ADHD

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J Individ Psychol (1998). 2019;75:104-21.

SIBLING NICHES AND THE DIAGNOSIS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Rasmussen PR, Self JA, Few L, et al.

The diagnosis of attention-deficit hyperactivity disorder (ADHD) has been controversial. The current investigation was conducted to determine the extent to which ADHD diagnosis might reflect family constellation patterns and sibling niche adoption. While not ruling out important neurological factors, results did reveal a significant pattern of difference between siblings holding different positions in their family constellations. Most notable was the 1 in 4 probability of ADHD diagnosis for younger brothers with sisters in a two-sibling family. The results suggest that casual diagnosis of this condition, which fails to consider family constellation parameters, may lead to inappropriate and less-than-optimal treatments

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Transl Psychiatry. 2019 Feb;9:72.

STRUCTURAL NEUROIMAGING CORRELATES OF SOCIAL DEFICITS ARE SIMILAR IN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: ANALYSIS FROM THE POND NETWORK.

Baribeau DA, Dupuis A, Paton TA, et al.

Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) have been associated with difficulties recognizing and responding to social cues. Neuroimaging studies have begun to map the social brain; however, the specific neural substrates contributing to social deficits in neurodevelopmental disorders remain unclear. Three hundred and twelve

children underwent structural magnetic resonance imaging of the brain (controls = 32, OCD = 44, ADHD = 77, ASD = 159; mean age = 11). Their social deficits were quantified on the Social Communication Questionnaire (SCQ) and the Reading the Mind in the Eyes Test (RMET). Multivariable regression models were used to examine the structural neuroimaging correlates of social deficits, with both a region of interest and a whole-brain vertex-wise approach. For the region of interest analysis, social brain regions were grouped into three networks: (1) lateral mentalization (e.g., temporal-parietal junction), (2) frontal cognitive (e.g., orbitofrontal cortex), and (3) subcortical affective (e.g., limbic system) regions. Overall, social communication deficits on the SCQ were associated with thinner cortices in the left lateral regions and the right insula, and decreased volume in the ventral striatum, across diagnostic groups ($p = 0.006$ to <0.0001). Smaller subcortical volumes were associated with more severe social deficits on the SCQ in ASD and ADHD, and less severe deficits in OCD. On the RMET, larger amygdala/hippocampal volumes were associated with fewer deficits across groups. Overall, patterns of associations were similar in ASD and ADHD, supporting a common underlying biology and the blurring of the diagnostic boundaries between these disorders

Transl Psychiatry. 2019 Feb;9:77.

GENOME-WIDE ASSOCIATION SCAN IDENTIFIES NEW VARIANTS ASSOCIATED WITH A COGNITIVE PREDICTOR OF DYSLEXIA.

Gialluisi A, Andlauer TFM, Mirza-Schreiber N, et al.

Developmental dyslexia (DD) is one of the most prevalent learning disorders, with high impact on school and psychosocial development and high comorbidity with conditions like attention-deficit hyperactivity disorder (ADHD), depression, and anxiety. DD is characterized by deficits in different cognitive skills, including word reading, spelling, rapid naming, and phonology. To investigate the genetic basis of DD, we conducted a genome-wide association study (GWAS) of these skills within one of the largest studies available, including nine cohorts of reading-impaired and typically developing children of European ancestry ($N = 2562$ - 3468). We observed a genome-wide significant effect ($p < 1 \times 10^{-8}$) on rapid automatized naming of letters (RANlet) for variants on 18q12.2, within MIR924HG (micro-RNA 924 host gene; rs17663182 $p = 4.73 \times 10^{-9}$), and a suggestive association on 8q12.3 within NKAIN3 (encoding a cation transporter; rs16928927, $p = 2.25 \times 10^{-8}$). rs17663182 (18q12.2) also showed genome-wide significant multivariate associations with RAN measures ($p = 1.15 \times 10^{-8}$) and with all the cognitive traits tested ($p = 3.07 \times 10^{-8}$), suggesting (relational) pleiotropic effects of this variant. A polygenic risk score (PRS) analysis revealed significant genetic overlaps of some of the DD-related traits with educational attainment (EDUyears) and ADHD. Reading and spelling abilities were positively associated with EDUyears ($p \sim [10^{-5}$ - $10^{-7}]$) and negatively associated with ADHD PRS ($p \sim [10^{-8}$ - $10^{-17}]$). This corroborates a long-standing hypothesis on the partly shared genetic etiology of DD and ADHD, at the genome-wide level. Our findings suggest new candidate DD susceptibility genes and provide new insights into the genetics of dyslexia and its comorbidities

Transl Psychiatry. 2019 Jan;9:8.

PSYCHIATRIC DISORDERS IN CHILDREN WITH 16P11.2 DELETION AND DUPLICATION.

Niarchou M, Chawner SJRA, Doherty JL, et al.

Deletion and duplication of 16p11.2 (BP4-BP5) have been associated with an increased risk of intellectual disability and psychiatric disorder. This is the first study to compare the frequency of a broad spectrum of psychiatric disorders in children with 16p11.2 deletion and duplication. We aimed to evaluate (1) the nature and prevalence of psychopathology associated with copy number variation (CNV) in children with 16p11.2 by comparing deletion and duplication carriers with family controls; (2) whether deletion and duplication carriers differ in frequency of psychopathology. 217 deletion carriers, 77 deletion family controls, 114 duplication carriers, and 32 duplication family controls participated in the study. Measures included standardized research diagnostic instruments. Deletion carriers had a higher frequency of any psychiatric disorder (OR = 8.9, $p < 0.001$), attention deficit hyperactivity disorder (ADHD) (OR = 4.0, $p = 0.01$), and autism spectrum disorder (ASD) (OR = 39.9, $p = 0.01$) than controls. Duplication carriers had a higher

frequency of any psychiatric diagnosis (OR = 5.3, $p = 0.01$) and ADHD (OR = 7.0, $p = 0.02$) than controls. The prevalence of ASD in child carriers of deletions and duplications was similar (22% versus 26%). Comparison of the two CNV groups indicated a higher frequency of ADHD in children with the duplication than deletion (OR = 2.7, $p = 0.04$) as well as a higher frequency of overall psychiatric disorders (OR = 2.8, $p = 0.02$) and psychotic symptoms (OR = 4.7, $p = 0.02$). However, no differences between deletion and duplications carriers in the prevalence of ASD were found. Both deletion and duplication are associated with an increased risk of psychiatric disorder, supporting the importance of early recognition, diagnosis, and intervention in these groups

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SOCIAL FUNCTIONING IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SLUGGISH COGNITIVE TEMPO.

Ferretti NM, King SL, Hilton DC, et al.

The current review summarizes the research to date on social functioning for youth with attention-deficit/hyperactivity disorder (ADHD) with a focus on three key domains: peer rejection, friendship, and social information processing. The review extends past reviews by examining the research to date on how the presence of sluggish cognitive tempo (SCT) symptoms, a common correlate of ADHD, affects the social presentation of youth with ADHD. Overall, youth with ADHD show significant difficulty with peer rejection, forming and maintaining friendships, and abnormalities in how they process and respond to social information. Further, the presence of SCT symptoms results in great social withdrawal and isolation. Future studies are needed to better understand the social difficulties of youth with ADHD, particularly using experimental approaches that can manipulate and isolate mechanisms within the social information processing model. In addition, novel intervention approaches are needed to more effectively ameliorate the social difficulties of youth with ADHD and those with co-occurring SCT symptoms

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Review

The Association between Lead and Attention-Deficit/Hyperactivity Disorder: A Systematic Review

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Abstract: The etiology of Attention-Deficit/Hyperactivity Disorder (ADHD) is complex and multifactorial. Although the development of ADHD symptoms remains to be elucidated, in recent years, epigenetic processes have emerged as candidate mechanisms. Lead is one of the most dangerous environmental pollutants, and it is suspected to be associated with ADHD. The aim of the present study was to review the epidemiological literature currently available on the relation between lead exposure and the diagnosis of ADHD. The PubMed and EMBASE databases were searched from 1 July 2018 up to 31 July 2018. The authors included observational studies (cohort, case-control and cross-sectional studies) published in English carried out on children within the last 5 years, measuring lead exposure and health outcomes related to ADHD. Seventeen studies met the inclusion criteria: 5 of these studies found no association between lead exposure and ADHD whereas the remaining 12 studies showed positive associations, even though not all of them were homogeneous in terms of exposure periods considered or ADHD diagnosis. To conclude, the evidence from the studies allowed us to establish that there is an association between lead and ADHD and that even low levels of lead raise the risk. However, there is still a lack of longitudinal studies about the relationship between lead exposure and the development of ADHD. Given the potential importance for public health, further research that includes the entire potential risk factors for ADHD in children must be encouraged.

Keywords: Lead; Attention-Deficit/Hyperactivity Disorder; ADHD; environmental pollutants; observational studies analysis; systematic review

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental disorders affecting children [1]. ADHD also affects many adults [2]. Symptoms of ADHD are divided into two categories of inattention and hyperactivity and impulsivity that include behaviors like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, fidgeting, or an inability to remain seated in appropriate situations [3].

Three types of ADHD have been identified in the Diagnostic and Statistical Manual of Mental Disorders (DSM): Combined Type, Predominantly Inattentive Type and Predominantly Hyperactive-Impulsive Type [4]. Most individuals show symptoms of both inattention and hyperactivity-impulsivity. However, there are some individuals in whom either one or the other pattern/subtype is predominant. To make an accurate diagnosis of ADHD, it is important that the appropriate subtype is indicated on the basis of the predominant symptom pattern over the past 6 months.

In the last few decades, numerous studies attempted to determine the prevalence of ADHD. However, prevalence rates for children and adolescents differ significantly among different studies, from as low as nearly 1% to as high as nearly 20% [5]. A systematic review and meta-regression analysis including 102 studies comprising 171,756 subjects from all world regions reported an ADHD/Hyperkinetic Disorder (HD) worldwide-pooled prevalence of 5.29% [6]. Another meta-analytic review covering 86 studies found that the prevalence of DSM-IV ADHD varied from 5.9% to 7.1% in children and adolescents [7].

While it is well-accepted that ADHD/HD is a highly heritable disorder, not all of the risk is genetic. It is estimated that between 10% and 40% of the variance associated with ADHD is likely to be accounted for by environmental factors [8]. The proposed and mostly reviewed ADHD environmental risk factors include prenatal substance exposures, heavy metal and chemical exposures, nutritional factors and lifestyle/psychosocial factors [9].

The etiology of ADHD is complex and multifactorial. The importance of both environmental risk factors and genetic factors has been indicated in several epidemiological studies. The development of ADHD symptoms remains to be elucidated, but in recent years, epigenetic processes have emerged as candidate mechanisms [10]. Considering that the genetic factors are non-modifiable risk factors in the short run, in order to decrease the risk of ADHD, it is necessary to reduce the exposure to environmental risk factors.

As to the environmental risk factors, the authors focused on the pollution from lead. Lead is a naturally occurring bluish-gray metal present in small amounts in the earth's crust [11]. Its widespread use has resulted in extensive environmental contamination, human exposure and significant public health problems of global dimensions [12].

Lead is one of the most dangerous environmental pollutants. The WHO has identified lead as one of ten chemicals of major public health concern that require action by the Member States in order to protect the health of workers, children and women of reproductive age [13]. Lead exposure is responsible for 540,000 deaths and 13.9 million years lost to disability and death due to long-term effects on health. Developing regions are paying the highest price in terms of the burden of this disease [14]. In environmental exposure, the various polluting agents rarely exist in isolation so the combined exposure to lead and other pollutants or risk factors may result in more severe outcomes [15,16].

Patterns and sources of exposure to lead, prevalence rates of lead poisoning and the severity of outcomes vary greatly from country to country and from place to place within countries [17]. People are exposed to lead from different sources and through different pathways (such as air, food, water, dust and soil). Lead-based paint is the most widespread and dangerous high-dose source of lead exposure for young children [18]. Lead also occurs in drinking water through leaching from lead-containing pipes, faucets and solder frequently found in the plumbing of older buildings. Lead in lead-glazed food containers may contaminate water, food and beverage. Lead may also be found in and around workplaces; in some commercial products (e.g., imported jewelry and candies; children's toys; cosmetics; and folk, traditional or home remedies); in second- and third-hand tobacco smoke exposures (SHS and THS); and in soil, air and water near the sites of historic or ongoing mining operations or smelters [19].

Lead exposure produces a variety of adverse health effects in children. It may cause intellectual, behavioral or motor function deficits as well as hand-eye coordination and reaction time problems and a lowered performance on intelligence tests [20]. Long-term lead exposure can also damage the

kidneys and nervous system and increase the risk of high blood pressure in adults [21]. Furthermore, maternal exposure to high levels of lead during pregnancy may be associated with increased incidences of miscarriage, stillbirth, premature birth and low birth weight [22,23]. Currently, there is no safe threshold for lead exposure, but it is known that, as lead exposure increases, the range and severity of symptoms and effects also increases [24]. Scientific evidence has shown that even low levels of lead exposure, BLLs >5 ug/dL, may cause a decrease in intelligence and an increase of behavioral and learning difficulties in children [25].

Not disregarding the genetic factors, the authors focused only on the environmental pollution from lead. Therefore, the aim of this study has been to perform a systematic review in order to explore and analyze the existing literature for the potential relationships between lead exposure and ADHD so to have a deeper and up-to-date understanding of the effects of this pollutant on the mental health of children.

2. Methods

2.1. Study Identification and Eligibility Criteria

A preliminary search performed to assess the prevalence of other systematic reviews covering the possible association between lead and hyperactivity disorder yielded 2 relevant articles [26,27] which the findings of have been considered when discussing the conclusions. The databases on which the query was performed in order to identify the publications eligible for inclusion in the review were EMBASE and MEDLINE (accessed from PubMed). The literature searches were conducted using the keywords “environmental”, “pollution”, “lead” and “hyperactivity disorder” in the following query:

((“environmental” OR “pollution” OR “lead”) AND “hyperactivity disorder”).

Moreover, the authors have used the following research filters: articles published from 1 July 2013 to 30 June 2018, the exclusion of animal studies and publication in the English language. Figure 1 shows the search strategy followed for this review. A total of 829 articles were identified. An initial screening identified 82 candidate studies. The initial screening of the studies was performed using the information available in both the titles and the abstracts. These potentially relevant studies were retrieved in full text and assessed for eligibility according to the following criteria:

1. the inclusion of humans as study subjects without restriction on the demographic characteristics of the population;
2. the conduction of an exposure assessment to lead during pregnancy or early childhood; and
3. the inclusion of measures of hyperactivity disorder symptoms or diagnosis.

The publications were included in the analysis only if they met all the eligibility criteria. After a full assessment of the potentially relevant studies, 17 were proposed to be included in the present systematic review.

When writing this paper, the authors fully considered the methodological norms established for the publication of systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [28,29].

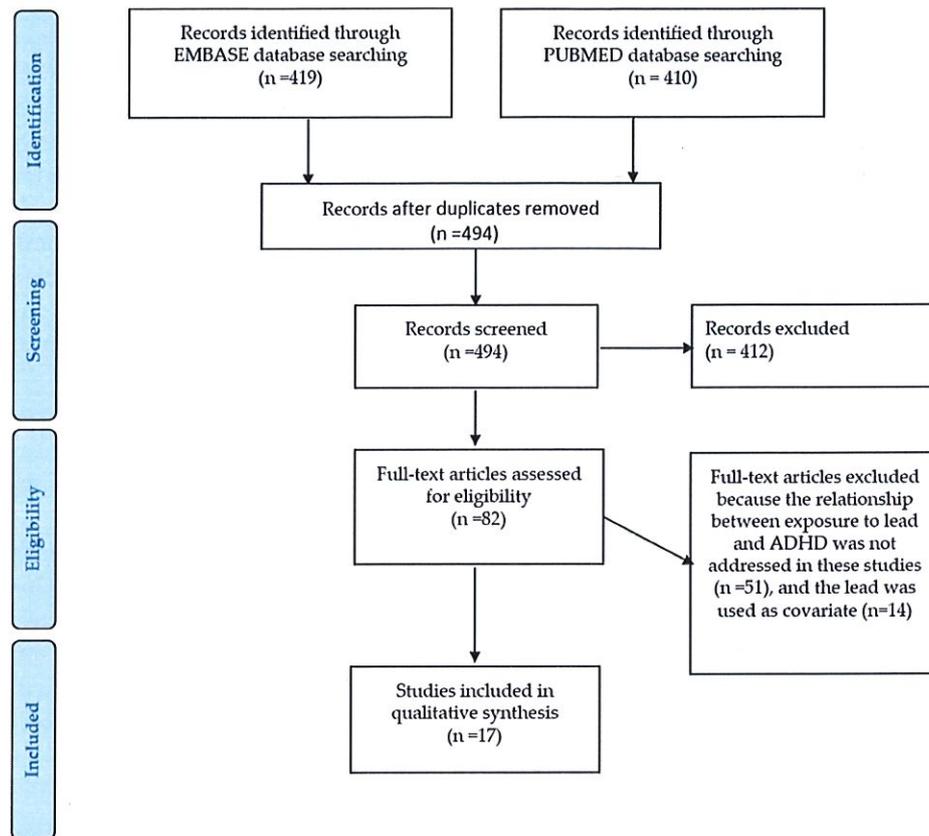


Figure 1. A PRISMA flow diagram for ADHD: Attention-Deficit/Hyperactivity Disorder.

2.2. Internal Validity

To further assess the chosen articles and guide the evaluation of the data included in them, the authors classified the publications using the scale proposed by the Scottish Intercollegiate Guidelines Network [30] for establishing the levels of evidence (Table 1) and grades of recommendation (Table 2). The aim of the Scottish Intercollegiate Guidelines Network (SIGN) system is to ensure that the grade of the internal and external validity of a study is robustly assessed and leads to the final grade for a recommendation. The methodology behind this system is based on a set of variables that recognize key factors, especially biasing and confounding factors, that can influence the quality of a study or its conclusions. The SIGN system emphasizes the aspects of study design (systematic reviews of Randomized Controlled Trials or RCTs and meta-analyses, RCTs, cohort studies, case-control studies, non-analytic studies and expert opinion) which can lead to biased results, and importantly, the SIGN system also identifies the direction of that bias. Though this methodology clearly gives the gold standard to RCTs, it is recognized that non-randomized studies can strengthen or put in doubt the results of RCTs [31]. The evidence is classified by its epistemological strength, and only the strongest evidence gives way to strong recommendations while the weaker evidences can only give rise to weak recommendations. The SIGN scale of the level of evidence proposes that the study design and the risk of bias are used to assess the level of evidence or the quality of the scientific evidence provided. In order to rate the study design, the numbers “1”, “2”, “3” and “4” are used, and while grading the criteria of “++”, “+” or “–” are used to represent the assessed risk of bias. Based on this assessment of the quality of the evidence in the articles, the strength of the associated recommendations is classified according to “A”, “B”, “C” and “D” grades in order from the best to the worst.

Table 1. The levels of evidence [30].

Levels of Evidence		
1	1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2	2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3		Non-analytic studies, e.g., case reports, case series
4		Expert opinion

Abbreviations: SIGN: Scottish Intercollegiate Guidelines Network (2008); LE: levels of evidence; RCT: randomized and controlled trials.

Table 2. The grades of recommendation [30].

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population
	A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating the overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating the overall consistency of results
	Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating the overall consistency of results
	Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4
	Extrapolated evidence from studies rated as 2+

Abbreviations: SIGN: Scottish Intercollegiate Guidelines Network (2008). GR: Grade of Recommendation; RCT: Randomized and Controlled Trials.

Such a graded scale has been derived from the principles of evidence-based medicine (EBM). EBM is an approach that assures the use of the most up-to-date, reliable and scientifically solid evidence available in making decisions about a particular situation being studied (Sackett, 1997) [32]. Ethical or other limitations can affect the quality or rating of the current best evidence available, taking into account the defined area of study. Some limitations are, at times, insurmountable; however, these must not be seen as detrimental to the study, as the example of the link between ADHD and lead exposure does not lend itself to randomized clinical trials. Ethical constraints, moreover, limit the current best available evidence to case-control or cohort-type studies. This proves to be a challenge when the authors try to establish an association between ADHD and lead since it means that any included study can at most receive a 2++B rating. From all this, the authors derive that the recommendations extracted from the studies that the authors present in this review can, at the most, be classified as moderately strong or 2++B. However, given that the principles of EBM have been followed correctly, the conclusions of this review are valid as they can be derived from the best currently available evidence.

All of the studies that the authors included in the present review are either case-control or cohort studies and, therefore, can only be scored as level 2. The assessed risk of bias and the degree of probability that the relationship is causally represented place most of the studies in the 2+ category given their results (as shown in Table 3). This prevalence limits the strength of the associated recommendations to grades C. This is true also if the authors consider the target population and the consistency of the results in each of the studies so that most of them end up categorized as having a grade of recommendation C.

Table 3. The studies on lead exposure and ADHD.

Citation	Location	Sample Size (Birth Years)	Study Design	ADHD Symptom Measured	Exposure Measurement	Results	LE	GR
Huang et al., 2016 [33]	Mexico	4126–13 years	Cross-sectional	Inattention Hyperactivity/Impulsivity Combined ADHD	BLLs	BLLs among children with low exposure (≤ 5 $\mu\text{g}/\text{dL}$) was positively associated with hyperactive/impulsive behaviors but not with inattentiveness.	2+	C
Zhang et al., 2015 [34]	China	2433–7 years	Cross-sectional	Inattention Hyperactivity/Impulsivity Combined ADHD	BLLs	The children with high BLLs (≥ 10 $\mu\text{g}/\text{dL}$) had a 2.4 times higher risk of ADHD than the children with low BLLs.	2+	C
Ji et al., 2018 [35]	Boston	1479 mother–infant pairs (299/1176)	Birth cohort 1998–2013	Combined ADHD	BLLs	Children with 5–10 $\mu\text{g}/\text{dL}$ lead levels had 66% increased odds of having an ADHD diagnosis as compared with children with less than 5 $\mu\text{g}/\text{dL}$ lead levels.	2+	C
Choi et al., 2016 [36]	South Korea	2195	Birth cohort 2005–2010	Combined ADHD	BLLs	Relative risk for ADHD symptoms was 1.552 in children with blood lead levels > 2.17 $\mu\text{g}/\text{dL}$ (highest quartile) compared with those with blood lead levels of ≤ 2.17 $\mu\text{g}/\text{dL}$.	2+	C
Neugebauer et al., 2014 [37]	Germany	117	Birth cohort 2000–2002	Inattention Hyperactivity/Impulsivity Combined ADHD	BLLs	Lead exposure was positively associated with ADHD.	2+	C
Forns et al., 2014 [38]	Spain	385	Birth cohort 2004–2006	Inattention Hyperactivity/Impulsivity Combined ADHD	Urine sample	Hyperactivity/Impulsivity and Combined ADHD significantly increased by 20% and 9% per each doubling of BLLs, respectively.	2+	C
Stoen et al., 2013 [39]	Belgium	270	Birth cohort 2002–2003	Combined ADHD	BLLs	No statistically significant associations between lead and ADHD.	2+	C
Yang et al., 2018 [40]	China	421/395 6–16 years	Case-control	Combined ADHD	BLLs	Doubling the prenatal lead exposure is associated with an odds ratio for hyperactivity of 3.43.	2+	C
Lee et al., 2016 [41]	Taiwan	76/46 < 10 years	Case-control	Inattention Hyperactivity/Impulsivity	Urine sample	No statistically significant associations between lead and ADHD.	2–	
Joo et al., 2017 [42]	South Korea	214/2146–10 years	Case-control	Inattention Hyperactivity/Impulsivity	BLLs	BLLs were positively correlated with inattention and hyperactivity/impulsivity symptoms ($p < 0.05$).	2+	C
Park et al., 2016 [43]	South Korea	114/114	Case-control	Inattention Hyperactivity/Impulsivity	BLLs	Exposure to low BLLs (geometric mean = 1.65 $\mu\text{g}/\text{dL}$) was associated with inattention symptoms but not with hyperactivity/impulsivity.	2+	C
Yu et al., 2016 (a) [44]	Taiwan	173/159	Case-control	Combined ADHD	BLLs	Children with a blood lead concentration > 2.30 $\mu\text{g}/\text{dL}$ had a 2.5 times higher risk of ADHD.	2+	C
Yu et al., 2016 (b) [45]	Taiwan	97/1104–15 years	Case-control	Combined ADHD	BLLs	No statistically significant associations between lead and ADHD.	2–	
Chan et al., 2015 [46]	USA	266 11–13 years	Case-control	Inattention Hyperactivity/Impulsivity Combined ADHD	Analysis of teeth	BLLs were significantly associated with increased incidents of Hyperactivity/Impulsivity and Inattention.	2+	C
Hong et al., 2015 [47]	South Korea	10018–11 years	Case-control	Inattention Hyperactivity/Impulsivity Combined ADHD	BLLs	BLLs were significantly associated with parent and teacher ratings for Hyperactivity/Impulsivity but not with Inattention.	2+	C
Kim et al., 2013 [48]	USA	71/58 3–7 years	Case-control	Combined ADHD	BLLs	High BLLs were associated with a higher risk of ADHD.	2+	C
Dikme et al., 2013 [49]	Turkey	59/591.6–16 years	Case-control	Combined ADHD	BLLs	No statistically significant associations between lead and ADHD.	2–	

Abbreviations: BLLs, Blood Lead Levels.

We also focused on the internal validity of the studies analyzed. The factors that influencing internal validity that were considered are:

1. a sufficiently large sample size;
2. the specification of the inclusion and assessment criteria;
3. an accurate diagnosis of ADHD and lead exposure assessment; and
4. an adjustment for the confounding variables.

The classification according to the SIGN scale and the assessment of the internal validity were performed mainly by one author with frequent consultations with a second author, and once a consensus among the two was reached, the classification was given to the other authors for revision and approval. No notable disagreements arose among the authors at this point.

2.3. Data Extraction

During the analysis of the results from the different studies, the authors noticed how these had been expressed either in a non-homogenous or in a non-standardized manner. Therefore, the authors standardized and presented the results in a single integrated scale in order to avoid any possible confusion. However, the available data and the methodologies utilized in the various studies restricted the standardization to a limited number of the studies (7 out of 17 articles).

3. Results

3.1. Characteristics of the Studies

The chosen studies were analyzed according to the following characteristics: location, sample size, birth years or range of age, study design, ADHD measurement criteria, exposure measurement, results, level of evidence and grade of recommendation. Table 3 summarizes the characteristics of the studies. Table 4 and Figure 2 show the Odd Ratios (ORs) standardized to 5 µg/dL for 7 out of the 17 articles included.

Table 4. A summary of the results.

Citation	N°	Adjusted ORs			Standardized ORs		
		OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Zhang et al., 2015 [34] —binary: cutoff 10 µg/dℓ All ADHD	1	2.4	1.1	5.2	1.55	1.05	2.28
Ji et al., 2018 [35] —binary: cutoff 5 µg/dL All ADHD	2	1.66	1.08	2.56	1.66	1.08	2.56
Choi et al., 2016 [36] —binary: cutoff 2.17 µg/dℓ All ADHD	3	1.552	1.002	2.403	2.753	1.005	7.539
Neugebauer et al., 2014 [37] —doubling of exposure concentrations All ADHD	4	1.09	1.01	1.17	1.12	1.01	1.22
Joo et al., 2017 [42] —binary: cutoff 1.90 µg/dℓ All ADHD	5	1.28	0.89	1.83	1.91	0.74	4.91
Park et al., 2016 [43] —categorical All ADHD (1.13–1.71 µg/dℓ)	6	1.26	0.56	2.84	2.78	0.08	101.35
All ADHD (1.72–2.29 µg/dℓ)	7	1.26	0.55	2.87	1.96	0.18	21.43
All ADHD (2.30–5.35 µg/dℓ)	8	2.54	1.09	5.94	7.59	1.21	48.10
Kim et al., 2013 [48] —categorical All ADHD (>2 µg/dℓ)	9	4.63	1.36	15.72	46.13	2.16	979.79
All ADHD (>3 µg/dℓ)	10	7.25	1.66	31.67	27.16	2.33	317.02

The column N° refers to Figure 2.

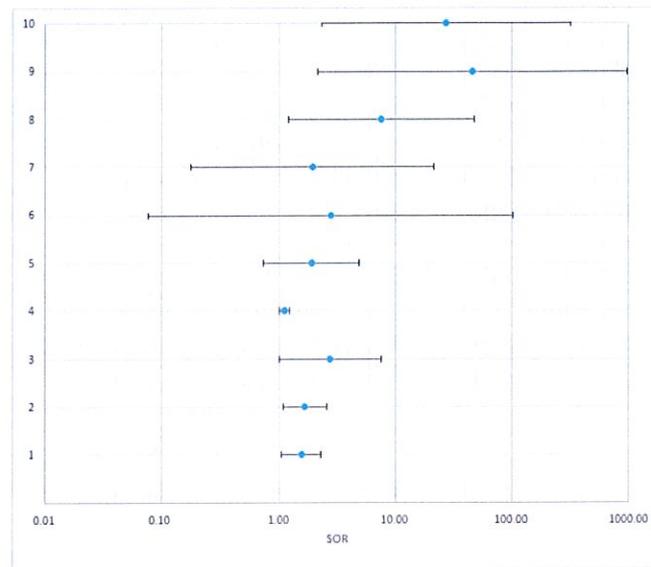


Figure 2. The standardized odds ratios (per 5 µg dL).

3.2. Study Design and Population

Two cross-sectional studies, 5 cohort studies and 10 case-control studies drawn from 9 different countries are included in this study. Sample sizes ranged from 117 [37] to 2195 [36] summing up to a total of 8940 participants.

Three studies used a Taiwanese population [41,44,45] and four South Korean populations [36,42,43,48]. Within the studies that used European populations, one used a German population [37], one a Spanish population [38] and one a Belgian population [39]. The other studies used an American population [35,46,48], a Chinese population [34,40], a Turkish population [49] and a Mexican population [33].

3.3. Measurement of Lead Exposure

Fourteen out of 17 studies have determined the levels of lead in blood (BLLs). Blood samples were obtained from each child via venipuncture in the arm. Two of these studies, References [35,39], also collected and analyzed the cord blood lead levels of the mothers. One each of the cohort [38] and case-control [41] studies collected urine samples and analyzed them by inductively coupled plasma mass spectrometry (ICP-MS). Another study [46] collected molar teeth and longitudinally sectioned them with a diamond blade on an Isomet low-speed saw (Buehler, Lake Bluff, IL, USA). Lead concentrations were determined through Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) with a sensitivity limit of 0.2 µg/L.

3.4. Cross-Sectional Studies

Huang and coauthors [33] have shown that blood lead levels among Mexican children with low exposure (≤ 5 µg/dL) were positively associated with hyperactive/impulsive behaviors but not with inattentiveness. Zhang and coauthors [34] investigated the ADHD status among preschool-aged children in Guiyu, an electronic waste (e-waste) recycling town in Guangdong, China. The study showed that children with high BLLs (≥ 10 µg/dL) had a 2.4 times higher risk of ADHD than those with low BLLs (< 10 µg/dL).

3.5. Cohort Studies

Ji and coauthors [35] analyzed the data from 1479 mother-infant pairs (299 ADHD and 1180 neurotypical) in the Boston Birth Cohort. Lead levels were analyzed both as a binary variable

and as 3 categories. In the first case, children with 5–10 µg/dL lead levels compared to those with less than 5 µg/dL had 66% increased odds of having an ADHD diagnosis. In the second case, children with 2–4 µg/dL and 5–10 µg/dL lead levels compared with those with less than 2 µg/dL had an OR of 1.08 (95% CI, 0.81–1.44) and 1.73 (95% CI, 1.09–2.73), respectively. Choi and coauthors [46] showed that, after an adjustment for potential confounders, ADHD developed more frequently in children with blood lead levels >2.17 µg/dL (highest quartile) compared with those with blood lead levels <2.17 µg/dL. Neugebauer and coauthors [37] showed that lead levels were positively correlated with ADHD. Impulsivity significantly increased by 20% with each doubling of blood lead concentrations (geometric mean ratio: 1.20; 95% CI: 1.08–1.33). On the Overall ADHD scale, the increase was approximately 9% per doubling of the lead concentration (geometric mean ratio: 1.09; 95% CI: 1.01–1.17). Forns and coauthors [38] analyzed the data from a population-based cohort established in the city of Sabadell (Barcelona, Catalonia, Spain). In this study, no association was found between ADHD symptomatology (inattention and hyperactivity) and lead levels. Sioen and coauthors [39] found that in all children, the prenatal lead exposure was significantly associated with hyperactivity at the ages of 7–8 years.

3.6. Case–Control Studies

Yang and coauthors [40] investigated the trace element status of lead in children with ADHD and compared them with normal controls. The analyses were performed according to different age groups: childhood (from 6 to 11 years of age) and adolescence (from 12 to 16 years of age). No significant relationship was indicated between lead and ADHD symptoms. Lee and coauthors [41] carried out a case–control study in order to investigate the possible differences in the urinary levels of lead between patients with different ADHD subtypes and the healthy controls. They found that lead levels were positively correlated with the inattention and hyperactivity/impulsivity symptoms. Joo and coauthors [42] found that BLLs were significantly associated with inattention when the model was adjusted for postnatal second-hand smoke exposure (OR = 1.63; 95% CI = 1.03–2.58). Park and coauthors [43] revealed that the children with blood lead concentrations above 2.30 µg/dL were at a 2.5-fold (95 % CI: 1.09–5.87, $p < 0.05$) greater risk of ADHD. Yu and coauthors [44] found no significant difference in BLLs between children with and without ADHD. Yu and coauthors [45] showed that there was no significant difference in BLLs between children with and without ADHD ($p = 0.15$). Chan and coauthors [46] found no significant association between ADHD symptoms and the concentration of lead in teeth. Hong and coauthors [47] found that the association of blood lead with higher impulsivity was robust to the adjustment for a variety of covariates. However, blood lead levels were not significantly associated with inattention in the adjusted models. Kim and coauthors [48] showed that blood lead concentration was not related to ADHD in the unadjusted analysis, but after considering the covariates, high lead concentrations were associated with a higher risk of ADHD. The pattern was similar using categorical blood lead (≥ 2 or ≥ 3 µg/dL). Dikme and coauthors [49] found no significant difference between the patients and control groups in terms of lead levels ($p = 0.575$).

4. Discussion

ADHD is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide [50]. ADHD heritability, estimated from 60% to 80%, highlights the considerable role of environmental factors in the disorder susceptibility [9]. It is accepted that both biological and environmental factors can contribute to the development of ADHD. Several studies showed that human exposures to environmental pollutants can represent a risk factor for ADHD. For example, the exposure to heavy metals; dietary factors [51]; and the environmental exposure to dangerous chemicals such as bisphenol A [52], polycyclic aromatic hydrocarbons [53] and pesticides [54] may contribute to ADHD.

Currently, no safe blood lead level in children has been identified. The Center for Disease Control Advisory Committee on Childhood Lead Poisoning Prevention recommended that blood lead levels at or above 5 µg/dL are sufficient to initiate public health actions [19]. However, a recent meta-analysis [27] has indicated that even blood lead levels <3 µg/dL may be associated with ADHD symptoms in children. These findings emphasize that there is no safe blood lead threshold and that if public actions focus only on the reduction of the exposure of children to high lead levels, they fail to protect children with lower levels that represent the larger group.

Another systematic review [26] has examined the literature on the role of lead exposure in children with ADHD symptoms. However, in this other review, there are included articles up to May 2014 and only studies in which lead exposure was examined using blood samples have been considered. The results highlighted that in 16 out of the 18 studies considered, there was a significant association between BLLs of less than 10µg/dL in children and at least one type of ADHD [26]. Our systematic review expands the body of knowledge about this subject because it includes more recent literature (articles published from 1 July 2013 to 30 June 2018) and studies which considered urine samples and teeth. In the same way, the majority of the studies the authors considered have revealed a significant association between environmental lead exposure and ADHD.

4.1. Summary of the Evidence

The results of the present study revealed that in 12 out of the 17 studies, a significant association was found between lead exposure and one of the types of ADHD. One thing that must be considered is that 4 of the 5 studies without any significant association were classified as 2- in the scale used to individually evaluate the levels of evidence and, owing to their high risk of bias, these should not be used in compiling recommendations. Furthermore, the remaining study which did not find any association considered the level of lead in urine samples. This fact can represent a bias due to an individual variation in concentration and since urinary lead levels are less sensitive in the lower range of exposure, for example, at blood lead concentrations lower than 10 µg/dL [55]. However, the current results must be interpreted with caution owing to the presence of a high heterogeneity.

4.2. Strengths and Limitations of the Current Review

The searches may have failed to retrieve all the relevant publications concerning the association between ADHD and lead owing to the fact that the field of analysis was restricted to studies published in English available through the Pub Med and EMBASE databases. This review, like any other review about observational data, may suffer biases related to the publicity of the studies since it is believed that studies with significant positive results are more widely distributed than those without significant results or with negative ones [56].

Conceptual Constraints

The authors have included the keywords “environmental” and “pollution” to collect also the studies where the keyword “lead” was not present in the title and abstract. However, in the publications retrieved, the keywords “environmental” and “pollution” carry a variety of meanings as there are no standardized definitions of these concepts. In this review, the authors only focused on environmental lead pollution and its impact on children's health. This represents a constraint to the research because it limits the number of studies included in this review.

4.3. Strengths and Limitations of the Studies Included in the Review

4.3.1. ADHD Diagnosis

The use of a medical diagnosis of ADHD by a physician based on the Diagnostic and Statistical Manual of Mental Disorders reduces the likelihood of a misdiagnosis. However, the majority of the reviewed studies reports data from parents' responses or teachers' responses to behavior checklists (e.g.,

SNAP-IV [57]) that vary from one study to another, and this fact may have produced misdiagnosis or biases. Furthermore, some studies did not consider the separation of ADHD inattention and hyperactivity-impulsivity symptoms.

4.3.2. Observation and Exposure Periods

The observation and exposure periods used in the studies reviewed are not homogenous. If the studies are performed at too early an age, the rate of detection or misdiagnosis can possibly be significant so to alter the results.

4.3.3. Lead Exposure Assessment

This review has also included studies in which lead exposure was examined using urine and teeth. However, the main limitation of using urine samples is the individual variation. In addition, urinary lead is less sensitive in the lower range of exposures (i.e., $<10 \mu\text{g}/\text{dL}$), and for this reason, the authors believe that the quantification of lead in blood is more appropriate. Regarding the use of teeth, the authors should take into consideration that there is presently no well-defined low, medium or high concentration levels for environmental risk factors such as lead. All concentrations measured can only be used in relation to other samples in the study when analyzing teeth.

4.3.4. Measures of Association

The association between the lead exposure and the risk of having ADHD was calculated following different approaches. Logistic regression models have been used in the majority of studies to obtain the adjusted odds ratios. However, lead levels were analyzed as continuous, binary and/or categorical variables on the basis of different cutoff points obtained from previous studies and the Centers for Disease Control and Prevention (CDC) guidelines. The remaining studies have used the Mann–Whitney U test or Spearman's correlation test to analyze the relationships between lead levels and ADHD diagnosis.

4.3.5. Cofounders

The existence of confounding variables in a study may make it difficult to establish a clear causal link between the exposure and outcome unless appropriate methods are used to adjust for the effect of the confounders [58]. Most of the studies examined in this review considered, indeed, the confounding variables such as maternal marital status, age, educational years, socioeconomic status, maternal smoking during pregnancy, child's age at behavioral testing, sex, birth weight, paternal educational years, etc. However, not all the reviewed studies considered the same potential confounding variables, and this could be a source of information bias in this review. Moreover, five of the articles included in this review and classified with the level 2- did not consider any confounding variables.

5. Conclusions

Based on the results of this review, additional data is needed to fully ascertain the nature of the relationship between lead exposure and ADHD. Future research should consider the influence of all potentially confounding variables and also use a standardized method of ADHD diagnosis. Future studies should be focused on lead exposure of the mothers during late pregnancy and the first years of life of the children. The combined exposure to multiple chemicals or risk factors should also be evaluated together with the influence of genetic factors.

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References

1. Polanczyk, G.; Willcutt, E.G.; Salum, A.G.; Kieling, C.; Rohde, L.A. ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *Int. J. Epidemiol.* **2014**, *43*, 434–442. [CrossRef] [PubMed]
2. Parekh, R. American Psychiatric Association. 2017. Available online: <https://www.psychiatry.org/patients-families/adhd/what-is-adhd> (accessed on 26 August 2018).
3. American Psychiatric Association. Attention Deficit/Hyperactivity Disorder. 2013. Available online: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM-5-ADHD.pdf (accessed on 9 November 2018).
4. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*; APA: Washington, DC, USA, 2000.
5. Liu, A.; Xu, Y.; Yan, Q.; Tong, L. The Prevalence of Attention Deficit/Hyperactivity Disorder among Chinese Children and Adolescents. *Sci. Rep.* **2018**, *8*, 11169. [CrossRef] [PubMed]
6. Polanczyk, G.; de Lima, M.; Horta, B.; Biederman, J.; Rhode, L. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *Am. J. Psychiatry* **2007**, *164*, 942–948. [CrossRef] [PubMed]
7. Willcutt, E. The Prevalence of DSM-IV Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. *Neurotherapeutics* **2012**, *9*, 490–499. [CrossRef] [PubMed]
8. Sciberras, E.; Mulraney, M.; Silva, D.; Coghill, D. Prenatal Risk Factors and the Etiology of ADHD—Review of Existing Evidence. *Curr. Psychiatry Rep.* **2017**, *19*. [CrossRef] [PubMed]
9. Froehlich, T.E.; Anixt, J.S.; Loe, I.M.; Chirdkiatgumchai, V.; Kuan, L.; Gilman, R.C. Update on Environmental Risk Factors for Attention-Deficit/Hyperactivity Disorder. *Curr. Psychiatry Rep.* **2011**, *13*, 333–344. [CrossRef] [PubMed]
10. Walton, E.; Pingault, J.B.; Cecil, C.A.; Gaunt, T.R.; Relton, C.L.; Mill, J.; Barker, E.D. Epigenetic profiling of ADHD symptoms trajectories: A prospective, methylome-wide study. *Mol. Psychiatry* **2017**, *22*, 250–256. [CrossRef] [PubMed]
11. Tchounwou, P.B.; Yedjou, C.G.; Patlolla, A.K.; Sutton, D.J. Heavy Metals Toxicity and the Environment. *Mol. Clin. Environ. Toxicol.* **2012**, *101*, 133–164.
12. Tong, S.; von Schirnding, Y.E.; Prapamontol, T. Environmental lead exposure: A public health problem of global dimensions. *Bull. World Health Org.* **2000**, *78*, 1068–1077.
13. World Health Organization. International Lead Poisoning Prevention Awareness Campaign. 2017. Available online: http://www.who.int/ipcs/lead_campaign/QandA_lead_2017_en.pdf (accessed on 11 November 2018).
14. Institute for Health Metrics and Evaluation. Lead Exposure. 2018. Available online: <https://vizhub.healthdata.org/gbd-compare/> (accessed on 11 November 2018).
15. Wildemann, T.M.; Weber, L.P.; Siciliano, S.D. Combined exposure to lead, inorganic mercury and methylmercury show deviation from additivity for cardiovascular toxicity in rats. *J. Appl. Toxicol.* **2015**, *35*, 918–926. [CrossRef] [PubMed]
16. Beier, E.E.; Inzana, J.A.; Sheu, T.-J.; Shu, L.; Puzas, J.E.; Mooney, R.A. Effects of Combined Exposure to Lead and High-Fat Diet on Bone Quality in Juvenile Male Mice. *Environ. Health Perspect.* **2015**, *123*, 935–973. [CrossRef]
17. World Health Organization. Childhood Lead Poisoning. 2010. Available online: <http://www.who.int/ceh/publications/leadguidance.pdf> (accessed on 11 December 2018).
18. Centers for Disease Control and Prevention. Sources of Lead. 2015. Available online: <https://www.cdc.gov/nceh/lead/tips/sources.htm> (accessed on 11 December 2018).
19. Centers for Disease Control and Prevention. Lead Toxicity. Where Is Lead Found? 2017. Available online: <https://www.atsdr.cdc.gov/csem/csem.asp?csem=34&po=5> (accessed on 11 December 2018).
20. Sanders, T.; Liu, Y.; Buchner, V.; Tchounwou, P.B. Neurotoxic Effects and Biomarkers of Lead Exposure: A Review. *Rev. Environ. Health* **2009**, *24*, 15–45. [CrossRef] [PubMed]
21. Shukla, V.; Shukla, P.; Tiwari, A. Lead poisoning. *Indian J. Med. Spec.* **2018**, *9*, 146–149. [CrossRef]
22. Amadi, C.N.; Igweze, Z.N.; Orisakwe, O.E. Heavy metals in miscarriages and stillbirths in developing nations. *Middle East Fertil. Soc. J.* **2017**, *22*, 91–100. [CrossRef]

23. Hossain, N.; Nazli, E.W. Environmental factors implicated in the causation of adverse pregnancy outcome. *Semin. Perinatol.* **2007**, *31*, 240–242. [CrossRef]
24. Vorvolakos, T.; Arseniou, S.; Samakouri, M. There is no safe threshold for lead exposure: A literature review. *Psychiatriki* **2016**, *27*, 204–214. [CrossRef]
25. World Health Organization. Lead Poisoning and Health. 2018. Available online: <http://www.who.int/news-room/fact-sheets/detail/lead-poisoning-and-health> (accessed on 26 August 2018).
26. Daneshparvar, M.; Mostafavi, S.A.; Jeddi, M.Z.; Yunesian, M.; Mesdaghinia, A.; Mahvi, A.H.; Akhondzadeh, S. The Role of Lead Exposure on Attention-Deficit/ Hyperactivity Disorder in Children: A Systematic Review. *Iran J. Psychiatry* **2016**, *11*, 1–14.
27. He, J.; Ning, H.; Huang, R. Low blood lead levels and attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis. *Environ. Sci. Pollut. Res.* **2017**. [CrossRef] [PubMed]
28. Friedenreich, C.M. Methods for pooled analyses of epidemiologic studies. *Epidemiology* **1993**, *4*, 295–302. [CrossRef]
29. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.; Clarke, M.; Devereaux, P.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* **2009**, *339*. [CrossRef] [PubMed]
30. SIGN. A Guideline Developer’s Handbook. 2008. Available online: https://www.sign.ac.uk/assets/sign50_2015.pdf (accessed on 11 September 2018).
31. Baker, A.; Young, K.; Potter, J.; Madan, I. A review of grading systems for evidence-based guidelines produced by medical specialties. *Clin. Med.* **2010**, *10*, 358–363. [CrossRef]
32. Sackett, D.L. Evidence-based medicine. *Semin. Perinatol.* **1997**, *21*, 3–5. [CrossRef]
33. Huang, S.; Hu, H.; Sánchez, B.N.; Peterson, K.E.; Ettinger, A.S.; Lamadrid-Figueroa, H.; Schnaas, L.; Mercado-García, A.; Wright, R.O.; Basu, N.; et al. Childhood Blood Lead Levels and Symptoms of Attention Deficit Hyperactivity Disorder (ADHD): A Cross-Sectional Study of Mexican Children. *Children’s Health* **2016**. [CrossRef] [PubMed]
34. Zhang, R.; Huo, X.; Ho, G.; Chen, X.; Wang, H.; Wang, T.; Ma, L. Attention-deficit/hyperactivity symptoms in preschool children from an E-waste recycling town: Assessment by the parent report derived from DSM-IV. *BMC Pediatrics* **2015**. [CrossRef] [PubMed]
35. Ji, Y.; Hong, X.; Wang, G.; Chatterjee, N.; Riley, A.W.; Lee, L.-C.; Surkan, P.J.; Bartell, T.R.; Zuckerman, B.; Wang, X.; et al. A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences. *J. Pediatrics* **2018**. [CrossRef] [PubMed]
36. Choi, W.J.; Kwon, H.J.; Lim, M.H.; Lim, J.A.; Ha, M. Blood lead, parental marital status and the risk of attention-deficit/hyperactivity disorder in elementary school children: A longitudinal study. *Psychiatry Res.* **2016**, *236*, 42–46. [CrossRef] [PubMed]
37. Neugebauer, J.; Wittsiepe, J.; Kasper-Sonnenberg, M.; Schöneck, N.; Schölmerich, A.; Wilhelm, M. The influence of low-level pre- and perinatal exposure to PCDD/Fs, PCBs, and lead on attention performance and attention-related behavior among German school-aged children: Results from the Duisburg Birth Cohort Study. *Int. J. Hyg. Environ. Health* **2015**. [CrossRef] [PubMed]
38. Forns, J.; Fort, M.; Casas, M.; Cáceres, A.; Guxens, M.; Gascon, M.; Garcia-Esteban, R.; Julvez, J.; Grimalt, J.O.; Sunyer, J.; et al. Exposure to metals during pregnancy and neuropsychological development at the age of 4 years. *NeuroToxicology* **2014**. [CrossRef] [PubMed]
39. Sioen, I.; Den Hond, E.; Nelen, V.; Van de Mieroop, E.; Croes, K.; Van Larebeke, N.; Nawrot, T.S.; Schoeters, G. Prenatal exposure to environmental contaminants and behavioral problems at age 7–8 years. *Environ. Int.* **2013**, *59*, 225–231. [CrossRef]
40. Yang, R.; Zhang, Y.; Gao, W.; Lin, N.; Li, R.; Zhao, Z. Blood Levels of Trace Elements in Children with Attention-Deficit Hyperactivity Disorder: Results from a Case-Control Study. *Biol. Trace Element Res.* **2018**. [CrossRef] [PubMed]
41. Lee, M.J.; Chou, M.C.; Chou, W.J.; Huang, C.W.; Kuo, H.C.; Lee, S.Y.; Wang, L.J. Heavy Metals’ Effect on Susceptibility to Attention-Deficit/Hyperactivity Disorder: Implication of Lead, Cadmium, and Antimony. *Int. J. Environ. Res. Public Health* **2018**. [CrossRef] [PubMed]
42. Joo, H.; Lim, M.H.; Ha, M.; Kwon, H.J.; Yoo, S. J.; Choi, K.H.; Paik, K.C. Secondhand Smoke Exposure and Low Blood Lead Levels in Association With Attention-Deficit Hyperactivity Disorder and Its Symptom

- Domain in Children: A Community-Based Case–Control Study. *Nicotine Tob. Res.* **2017**, *19*, 94–101. [[CrossRef](#)] [[PubMed](#)]
43. Park, J.H.; Seo, J.H.; Hong, Y.S.; Kim, Y.M.; Kang, J.W.; Yoo, J.H.; Chueh, H.W.; Lee, J.H.; Kwak, M.J.; Kim, J.; et al. Blood lead concentrations and attention deficit hyperactivity disorder in Korean children: A hospital-based case control study. *BMC Pediatrics* **2016**, *16*, 156. [[CrossRef](#)] [[PubMed](#)]
 44. Yu, C.J.; Du, J.C.; Chiou, H.C.; Feng, C.C.; Chung, M.Y.; Yang, W.; Chen, Y.S.; Chien, L.C.; Hwang, B.; Chen, M.L. Sugar-Sweetened Beverage Consumption Is Adversely Associated with Childhood Attention-Deficit/Hyperactivity Disorder. *Int. J. Environ. Res. Public Health* **2016**. [[CrossRef](#)]
 45. Yu, C.J.; Du, J.C.; Chiou, H.C.; Yang, S.H.; Liao, K.W.; Yang, W.; Chung, M.Y.; Chien, L.C.; Hwang, B.; Chen, M.L. Attention Deficit/Hyperactivity Disorder and Urinary Nonylphenol Levels: A Case–Control Study in Taiwanese Children. *PLoS ONE* **2016**. [[CrossRef](#)]
 46. Chan, T.J.; Gutierrez, C.; Ogunseitan, O.A. Metallic Burden of Deciduous Teeth and Childhood Behavioral Deficits. *Int. J. Environ. Res. Public Health* **2015**. [[CrossRef](#)]
 47. Hong, S.B.; Im, M.H.; Kim, J.W.; Park, E.J.; Shin, M.S.; Kim, B.N.; Yoo, H.J.; Cho, I.H.; Bhang, S.Y.; Hong, Y.C.; et al. Environmental Lead Exposure and Attention Deficit/Hyperactivity Disorder Symptom Domains in a Community Sample of South Korean School-Age Children. *Children's Health* **2015**. [[CrossRef](#)]
 48. Kim, S.; Arora, M.; Fernandez, C.; Landero, J.; Caruso, J.; Chen, A. Lead, mercury, and cadmium exposure and attention deficit hyperactivity disorder in children. *Environ. Res.* **2013**. [[CrossRef](#)]
 49. Dikme, G.; Arvas, A.; Gür, E. The relation between blood lead and mercury levels and chronic neurological diseases in children. *Turk. Arch. Ped.* **2013**, *48*, 221–225. [[CrossRef](#)]
 50. Faraone, S.V.; Asherson, P.; Banaschewski, T.; Biederman, J.; Buitelaar, J.K.; Ramos-Quiroga, J.A.; Rohde, L.A.; Sonuga-Barke, E.J.S.; Tannock, R.; Franke, B.; et al. Attention-deficit/hyperactivity disorder. *Nat. Rev. Dis. Primers* **2015**. [[CrossRef](#)]
 51. Who, H.D.; Kim, D.W.; Hong, Y.S.; Kim, Y.M.; Seo, J.H.; Choe, B.M.; Park, J.H.; Kang, J.W.; Yoo, J.H.; Chueh, H.W.; et al. Dietary patterns in children with attention-deficit/hyperactivity disorder (ADHD). *Nutrients* **2014**, *6*, 1539–1553.
 52. Li, Y.; Zhang, H.; Kuang, H.; Fan, R.; Cha, C.; Li, G.; Luo, Z.; Pang, Q. Relationship between bisphenol A exposure and attention-deficit/hyperactivity disorder: A case-control study for primary school children in Guangzhou, China. *Environ. Pollut.* **2018**, *235*, 141–149. [[CrossRef](#)] [[PubMed](#)]
 53. Perera, F.P.; Chang, H.; Tang, D.; Roen, E.L.; Herbstman, J.; Margolis, A.; Huang, T.J.; Miller, R.L.; Wang, S.; Rauh, V. Early-Life Exposure to Polycyclic Aromatic Hydrocarbons and ADHD Behavior Problems. *PLoS ONE* **2014**. [[CrossRef](#)] [[PubMed](#)]
 54. Richardson, J.R.; Taylor, M.M.; Shalat, S.L.; Guillot, T.S.; Caudle, M.W.; Hossain, M.M.; Mathews, T.A.; Jones, S.R.; Cory-Slechta, D.A.; Miller, G.W. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. *FASEB J.* **2015**, *29*, 1960–1972. [[CrossRef](#)] [[PubMed](#)]
 55. Gulson, B.L.; Cameron, M.A.; Smith, A.J.; Mizon, K.J.; Korsch, M.J.; Vimpani, G.; McMichael, A.J.; Pisaniello, D.; Jameson, C.W.; Mahaffey, K.R. Blood Lead–Urine Lead Relationships in Adults and Children. *Environ. Res.* **1998**, *78*, 152–160. [[CrossRef](#)] [[PubMed](#)]
 56. Dalton, J.E.; Bolen, S.D.; Mascha, E.J. Publication Bias: The Elephant in the Review. *Anesth. Analg.* **2016**, *123*, 812–813. [[CrossRef](#)] [[PubMed](#)]
 57. Bussing, R.; Fernandez, M.; Harwood, M.; Hou, W.; Garvan, C. W.; Eyberg, S.M.; Swanson, J.M. Parent and Teacher SNAP-IV Ratings of Attention Deficit/Hyperactivity Disorder Symptoms: Psychometric Properties and Normative Ratings from a School District Sample. *Assessment* **2008**, *15*, 317–328. [[CrossRef](#)] [[PubMed](#)]
 58. Skelly, A.C.; Dettori, J.R.; Brodt, E.D. Assessing bias: The importance of considering confounding. *Evid.-Based Spine-Care J.* **2012**, *3*, 9–12. [[CrossRef](#)]



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