NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BIBLIOGRAFIA ADHD NOVEMBRE 2019

Acta Paediatr Int J Paediatr. 2019.

META-ANALYSIS FOUND THAT STUDIES MAY HAVE OVERESTIMATED CAESAREAN SECTION RISKS FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER BY IGNORING CONFOUNDING FACTORS.

Xu L-L, Zhang X, Zhou G-L, et al.

Aim: Epidemiological studies on associations between Caesarean sections (C-sections) and attention-deficit hyperactivity disorder (ADHD) have been inconsistent, and we performed a meta-analysis.

Methods: We systematically searched PubMed and Embase to December 2018 and included nine hospital-based and population registry studies published in 2011-2018. These covered a total study cohort of more than 2.5 million people in eight countries: Australia, Brazil, Denmark, Finland, Germany, Sweden, Turkey and the UK. The analysis provided summary odds ratios (ORs) and 95% confidence intervals (CI) while taking heterogeneity into account.

Results: We found that that C-sections were associated with a small increase in the risk of ADHD (OR 1.14, 95% CI 1.11, 1.17, I2 0%) in offspring. In subgroup analyses, the association remained for both infants born after elective C-sections (OR, 1.15, 1.11, 1.19, I2 0%) and emergency C-sections (OR, 1.13, 1.1, 1.17, I2 45.4%). However, these were only marginally significant when we pooled data from siblings from other pregnancies (OR, 1.06, 1.00-1.13, I2 0%), implying that the association was due to confounding.

Conclusion: The statistically significant association between C-sections and ADHD in children can be partially explained by unmeasured confounding. Further research controlling for important confounders is required before firm conclusions can be drawn

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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.

Acta Paediatr Int J Paediatr. 2019.

HIGH PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADOLESCENTS WITH SEVERE OBESITY SEEKING BARIATRIC SURGERY.

Leib S, Gilon MT, Stein D, et al.

Aim: To examine the prevalence of attention-deficit/hyperactivity disorder (ADHD) and related post-surgical weight loss in adolescents with severe obesity seeking bariatric surgery.

Methods: The study population included 84 adolescents (age 13-19-áyears; 44 males, 40 females) with severe obesity who sought bariatric surgery at the Sheba Medical Centre in Israel during the years 2011-2017. Anthropometric and clinical data were collected from medical records. A subgroup of 20 participants filled questionnaires that evaluated ADHD-like symptoms, eating behaviours and quality of life. Data on adolescents that ultimately underwent surgery (n-á=-á45) were also obtained.

Results: The prevalence of ADHD was 28.6% in adolescents seeking bariatric surgery, much higher than that of the general adolescent population of Israel (17.1%, P-á<.001). There were no significant differences in reductions of weight, body mass index, body mass index standard deviation scores and body fat percent between participants with or without ADHD. In the subgroup that filled questionnaires, higher scores on ADHD-Rating Scale at baseline were associated with greater excess weight loss.

Conclusion: The prevalence of ADHD in adolescents seeking bariatric surgery was very high. Diagnosed ADHD was not related to post-surgical weight loss, whereas baseline ADHD-related behaviour was associated with higher post-surgical weight loss

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Am J Epidemiol. 2019;188:1923-31.

ANTIBIOTIC EXPOSURE IN THE FIRST YEAR OF LIFE AND THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A POPULATION-BASED COHORT STUDY.

Hamad AF, Alessi-Severini S, Mahmud SM, et al.

Early childhood antibiotic exposure induces changes in gut microbiota reportedly associated with the development of attention-deficit/hyperactivity disorder (ADHD). We conducted a population-based cohort study to examine the association between antibiotic use in the first year of life and ADHD risk. We included children born in Manitoba, Canada, between 1998 and 2017. Exposure was defined as having filled 1 or more antibiotic prescriptions during the first year of life. ADHD diagnosis was identified in hospital abstracts, physician visits, or drug dispensations. Risk of developing ADHD was estimated using Cox proportional hazards regression in a high-dimensional propensity score-matched cohort (n = 69,738) and a sibling cohort (n = 67,671). ADHD risk was not associated with antibiotic exposure in the matched-cohort (hazard ratio = 1.02, 95% confidence interval: 0.97, 1.08) or in the sibling cohort (hazard ratio = 0.96, 95% confidence interval: 0.89, 1.03). In secondary analyses of the matched cohort, ADHD risk increase was observed in those exposed to 4 or more antibiotic courses or a duration longer than 3 weeks. These associations were not observed in the sibling cohort. We concluded that antibiotic exposure in the first year of life does not pose an ADHD risk on a population level

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Am J Med Genet Part B Neuropsychiatr Genet. 2019.

TYROSINEMIA TYPE 1 AND SYMPTOMS OF ADHD: BIOCHEMICAL MECHANISMS AND IMPLICATIONS FOR TREATMENT AND PROGNOSIS.

Barone H, Bliksrud YT, Elgen IB, et al.

Hereditary tyrosinemia Type 1 (HT-1) is a rare metabolic disease where the enzyme catalyzing the final step of tyrosine breakdown is defect, leading to accumulation of toxic metabolites. Nitisinone inhibits the degradation of tyrosine and thereby the production of harmful metabolites, however, the concentration of tyrosine also increases. We investigated the relationship between plasma tyrosine concentrations and cognitive functions and how tyrosine levels affected enzyme activities of human tyrosine hydroxylase (TH) and tryptophan hydroxylase 2 (TPH2). Eight Norwegian children between 6 and 18 years with HT-1 were assessed using questionnaires measuring Attention Deficit Hyperactivity Disorder (ADHD)-symptoms and

executive functioning. Recent and past levels of tyrosine were measured and the enzyme activities of TH and TPH2 were studied at conditions replicating normal and pathological tyrosine concentrations. We observed a significant positive correlation between mean tyrosine levels and inattention symptoms. While TH exhibited prominent substrate inhibition kinetics, TPH2 activity also decreased at elevated tyrosine levels. Inhibition of both enzymes may impair syntheses of dopamine, noradrenaline, and serotonin in brain tissue. Inattention in treated HT-1 patients may be related to decreased production of these monoamines. Our results support recommendations of strict guidelines on plasma tyrosine levels in HT-1. ADHD-related deficits, particularly inattention, should be monitored in HT-1 patients to determine whether intervention is necessary

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Anadolu Psikiyatr Derg. 2019;20:651-58.

EFFECTS OF PARENTS' ATTACHMENT STYLES AND ATTENTION DEFICIT SYMPTOMS ON SOCIAL RESPONSIVENESS IN CHILDREN WITH ADHD.

Gumustas F, Yulaf Y.

Objective: The aim of this study is to investigate the effects of parental attachment styles and parental inatten-tiveness symptoms on social responsiveness problem scores of school age children diagnosed with attention deficit hyperactivity disorder (ADHD).

Methods: One hundred and seventy-nine children with ADHD diagnosed between 7 and 12 years and their parents were the sample of the study. The Schedule for Affective Disorders and Schizo-phrenia for School-Age Children Present and Lifetime Version was used to determine the presence of psychiatric disorders in the children. Parents were asked to fill out the Parental Attachment Scale, Wender Utah Rating Scale, and Social Responsiveness Scale.

Results: As a result of the path analysis, it was shown that avoidant and ambivalent attachment levels of mothers had a significant increase effect on the levels of social responsiveness of children and mothersΓÇÖ attention deficit symptoms mediated this effect. The attachment style scores of fathers were not correlated with social responsiveness of children.

Conclusion: In children with attention deficit hyperactivity disorder comorbid with social responsiveness problems, it is recommended to consider the attachment patterns of parents, especially mothers, and possible attention deficit symptoms

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Anadolu Psikiyatr Derg. 2019;20:642-50.

METHYLPHENIDATE TREATMENT OUTCOMES AND GENDER DIFFERENCES IN ATTENTIONAL DEFICIT AND HYPERACTIVITY DISORDER WITH EPILEPSY: A FOLLOW-UP STUDY.

Cam RP, et al.

Objective: The aim of this study is to investigate the methylphenidate (MPH) treatment response in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) with and without epilepsy.

Methods: Ninety-four children and adolescents with ADHD consisting of 47 with and 47 without epilepsy were enrolled into the study. The patients were evaluated by DSM-IV-TR, the Stroop test, the Conners Parent and Teacher Rating Scales. The groups were matched with regard to age, gender, ADHD subtype and comorbidity. The Stroop test was performed three times: During baseline (S-1); at the third month of the MPH treatment (S-2); after drug holiday of the treatment with MPH which lasted for six months (S-3). Stroop total time (ST) and Stroop total error+correction (SEC) scores were analyzed.

Results: The mean ST-3 and SEC-3 scores were significantly higher in cases with ADHD-attention deficit (ADHD-AD) subtype with the epilepsy group compared to ADHD-combined type (ADHD-CT) in the epilepsy group, whereas there was no significant difference detected in the non-epilepsy groups. While in the boys with/ without epilepsy and the girls without epilepsy and were demonstrated significant reductions in all recorded ST and SEC scores during/after treatment in comparison with the initial scores, a similar relationship could not be shown for the girls with epilepsy.

Conclusion: It is noted that gender and the ADHD subtypes may affect drug choice in patient with ADHD cases comorbid with epilepsy. One of the noticeable results of our study is was that the Stroop scores is no significant change with methylphenidate treatment in especially in girls with ADHD and epilepsy

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Anadolu Psikiyatr Derg. 2019;20:659-66.

DISTURBED EATING BEHAVIOR AND OBESITY IN DRUG NA+»VE CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Aykutlu HC, G+Ârker I.

Objective: In recent studies, attention deficit hyperactivity disorder (ADHD) was found to be linked with disturbed eating behavior and obesity. However, more studies needed to assess this relationship in pediatric age group. Therefore, eating behavior, dietary habits and obesity prevalence were evaluated in children who were newly diag-nosed with ADHD.

Methods: Eighty-six children with ADHD between the ages of 6 and 9 without medical treatment and chronic medical disease were included in the study group. 86 age and sex matched children without chronic medical and psychiatric disease were obtained as the control group. Sociodemographic Data Form, Children's Eating Behavior Questionnaire (CEBQ), the Turgay DSM-IV Based Disruptive Behavior Disorders Child and Adolescent Rating and Screening Scale (T-DSM-IV-S) and Schedule for Affective Disorders and Schizophrenia for School Age Children were applied to all cases. Weight and height of all cases were measured. Weight and height z scores, body mass index percentiles were calculated.

Results: CEBQ desire to drink subscale scores were found significantly higher in ADHD group than controls. CEBQ food responsiveness, emotional overeating and desire to drink subscale scores were found as positively correlated with T-DSM-IV-S ADHD total scores in ADHD group. It was found that children with ADHD eat more often, prefer to consume less water than controls. Higher rates of obesity and overweight, lower rates of underweight were found statistically significant in ADHD group.

Discussion: Our findings provide evidence that children who are newly diagnosed with ADHD could have impaired eating behaviors, high rates of obesity and overweight. Therefore, it is important to evaluate growth measures and dietary habits in this population. (Anatolian Journal of Psychiatry 2019; 20(6):659-666)

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An Pediatr. 2019.

RECOMMENDATIONS OF THE SPANISH SOCIETY OF PAEDIATRIC CARDIOLOGY AND CONGENITAL HEART DISEASE AS REGARDS THE USE OF DRUGS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS WITH A KNOWN HEART DISEASE, AS WELL AS IN THE GENERAL PAEDIATRIC POPULATION: POSITION STATEMENT BY THE SPANISH PAEDIATRIC ASSOCIATION.

Perez-Lescure PJ, Centeno MF, Collell HR, et al.

Introduction: Approved drugs for attention deficit hyperactivity disorder (ADHD) in Spain are methylphenidate, lisdexamphetamine, atomoxetine and guanfacine. Due to adverse cardiovascular effects, mainly increased blood pressure and heart rate, its use in patients with known or undiagnosed heart disease may be controversial.

Objective: To obtain a consensus document from the Spanish Society of Paediatric Cardiology and Congenital Heart Diseases (SECPCC) and experts from other Agencies and Societies as a guide for the paediatric cardiologist and physicians who treat children and adolescents with ADHD.

Methodology: An analysis was performed on the bibliography and Clinical Practice Guidelines, technical data sheets approved by the Spanish Agency of Medicines and Health Devices, and the Spanish Ministry of Health Guidelines. A Working Group was formed, with a Coordinator, as well as members of the Clinical Cardiology Working Group and Arrhythmia Group of the SECPCC. This Group produced a preliminary document that was reviewed by a group of external experts and a group of internal experts of the SECPCC with a consensus being reached on the final document.

Results: The recommendations of the SECPCC and the group of experts are presented on cardiovascular evaluation prior to treatment in children and adolescents with no known cardiovascular disease and with

known cardiovascular disease. The recommendations of the SECPCC and the group of experts are also presented on the use of medications for ADHD in children and adolescents with cardiological symptoms with no evidence of heart disease, congenital heart disease, cardiomyopathy, Marfan syndrome and other aortic diseases, hypertension, and arrhythmias

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Annals of Physical and Rehabilitation Medicine. 2019.

EXECUTIVE FUNCTIONS AND ATTENTION 7 YEARS AFTER SEVERE CHILDHOOD TRAUMATIC BRAIN INJURY: RESULTS OF THE TRAUMATISME GRAVE DE L'ENFANT (TGE) COHORT.

Le FC, et al.

Objectives: Severe childhood traumatic brain injury (TBI) leads to long-standing executive function and attention deficits, with negative consequences for participation, academic outcome and independence. This study aimed to assess executive function and attention 7 years after severe childhood TBI in comparison with a matched control group and to investigate associated factors.

Methods: Children (< 15 years) with severe accidental TBI consecutively admitted in a single trauma center over 3 years were included in the Traumatisme Grave de l'Enfant (TGE) prospective longitudinal study. Of the 81 children initially included, 65 survived. At 7 years post-TBI, executive functions and attention were assessed in 27 participants (42 % of the 65 survivors) by using a combination of computerized tasks from the Test of Attentional Performance (TAP) and the Behavioral Rating of Executive Functions (BRIEF) questionnaire. Patients were compared to a group of 27 typically developing controls who were matched for sex, age and parental education level.

Results: Among the 27 participants, mean (SD) age at injury was 7.7 (4.6) years, and mean length of coma 5.6 (4.6) days. Regarding the TAP, the number of errors was significantly higher (P = 0.003) and reaction time marginally slower (P = 0.08) in the TBI than control group. The BRIEF questionnaire completed by parents indicated significantly more executive difficulties in the TBI than control group (Behavior Regulation Index, P = 0.005; Metacognitive index, P = 0.02; Global Executive Composite, P = 0.012). Correlations between BRIEF and TAP scores did not reach statistical significance. BRIEF total score was correlated moderately with length of coma (r = 0.40, P = 0.037), and TAP scores were correlated with the Full-Scale Intellectual Quotient (total number of errors: r = -0.48; P = 0.01; mean reaction time: r = 0.51; P = 0.009).

Conclusions: Executive and attention deficits were evident 7 years after severe childhood TBI. Computerized tasks and questionnaires provide complementary and non-redundant information. Systematic long-term follow-up should be provided until the transition to adulthood, to assess ongoing development and to implement timely tailored interventions

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Asian J Psychiatry. 2020;47.

BLOOD AND HAIR ZINC LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A META-ANALYSIS.

Luo J, Mo Y, Liu M.

We summarized the observational studies on the correlation between zinc and attention deficit hyperactivity disorder (ADHD) since 1986, extracted relevant data for meta-analysis to determine the relationship between zinc and ADHD. We searched PubMed, Scopus, Cochrane Library, EMBASE (included EMBASE and Medline), Web of Science and Clinical Trials.gov databases from inception to April 8, 2019. We assessed the blood zinc, hair zinc and ADHD by combined the standardized mean difference (SMD) and 95% confidence interval (CI). Statistical analysis was performed using Stata 14.0. We included 11 studies for meta-analysis. Of these, 8 studies comprising 1311 participants reported blood zinc and 3 studies comprising 206 participants reported hair zinc. The zinc levels in blood (SMD: -0.91, 95% CI: -1.88-0.07, P(SMD) < 0.068), and hair (SMD: 1.42, 95% CI: -4.49-7.33, P(SMD) = 0.638) not significantly compare ADHD with controls. Nevertheless, high heterogeneity (I2 > 97.3%) emerged among the included studies. The subgroup analysis showed that the heterogeneity of samples >100 group was significantly reduced. The sensitivity analysis found that the results changed significantly after excluding the only cross-sectional study. In

conclusion, our meta-analysis showed that there was no statistically significant difference in blood zinc and hair zinc levels between ADHD children and adolescents compared with healthy children and adolescents

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Biological Trace Element Research. 2019.

ICP-MS ASSESSMENT OF HAIR ESSENTIAL TRACE ELEMENTS AND MINERALS IN RUSSIAN PRESCHOOL AND PRIMARY SCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Tinkov AA, Mazaletskaya AL, Ajsuvakova OP, et al.

The objective of the present study was to investigate the relationship between hair essential trace element and mineral content and ADHD in preschool (4ΓÇô6 years old) and primary school children (6ΓÇô10 years old) in relation to age and gender. Hair essential trace element and mineral content in 90 Russian children with ADHD and 90 age- and gender-matched neurotypical controls were assessed using inductively coupled plasma mass-spectrometry after microwave digestion. The obtained data demonstrate that hair Co, Cu, Mn, Si, and Zn contents in ADHD children was significantly reduced by 18%, 10%, 27%, 16%, and 19% as compared to the control values, respectively. The most significant decrease in children with ADHD was observed for hair Mg levels, being 29% lower than those in neurotypical children. After adjustment for age and gender, the observed difference in hair element content was more characteristic for preschool children and girls, respectively. Multiple linear regression analysis demonstrated that in a crude model (hair element levels as predictors), only hair Zn content was significantly inversely associated with ADHD (+¦ = ΓêÆ 0.169; p = 0.025). Adjustment for anthropometric parameters (model 2) did not increase the predictive ability of the model, although it improved the association between hair Zn and ADHD in children (+¦ = ΓêÆ 0.194; p = 0.014). Hypothetically, the observed alterations may at least partially contribute to neurobehavioral disturbances in children with ADHD. Moreover, the results of the present study raise the question about the potential benefits of Zn and Mg supplementation in children with ADHD. However, further detailed studies are required to investigate micronutrient deficiencies in ADHD

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BMC Pediatr. 2019;19.

PRENATAL PET KEEPING AND CAREGIVER-REPORTED ATTENTION DEFICIT HYPERACTIVITY DISORDER THROUGH PREADOLESCENCE IN A UNITED STATES BIRTH COHORT.

Cassidy-Bushrow AE, Sitarik AR, Johnson-Hooper TM, et al.

Background: While the keeping of pets has been shown to protect against childhood allergic disease and obesity, less is known regarding potential associations of prenatal pet keeping and attention deficit hyperactivity disorder (ADHD). We sought to examine the associations between prenatal dog or cat keeping with caregiver-reported ADHD in preadolescents in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort (N = 1258).

Methods: At an interview with the caregiver at child age 10-12 years, caregivers reported if the WHEALS child had ever been diagnosed with ADHD. Similarly, during an interview with the mother prenatally, pet keeping (defined as dog or cat kept inside ΓëÑ1 h/day) was ascertained. Logistic regression models were fit to examine the association of prenatal pet keeping (dog keeping and cat keeping, separately) with ADHD.

Results: A subset of 627 children were included in the analyses: 93 who had ADHD and 534 with neurotypical development. After accounting for confounders and loss to follow-up, maternal prenatal dog exposure was associated with 2.23 times (95% CI: 1.15, 4.31; p = 0.017) greater odds of ADHD among boys. Prenatal dog keeping was not statistically significantly associated with ADHD in girls (odds ratio = 0.27, 95% CI: 0.06, 1.12; p = 0.070). Prenatal cat keeping was not associated with ADHD.

Conclusions: In boys, but not girls, maternal prenatal dog keeping was positively associated with ADHD. Further study to confirm these findings and to identify potential mechanisms of this association (e.g., modification of the gut microbiome, exposure to environmental toxicants or pet-related medications) is needed

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BMC Psychiatry. 2019;19.

DOES THE TREATMENT OF ANXIETY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) USING COGNITIVE BEHAVIORAL THERAPY IMPROVE CHILD AND FAMILY OUTCOMES? PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Sciberras E, Efron D, Patel P, et al.

Background: Up to 60% of children with Attention-Deficit/Hyperactivity Disorder (ADHD) meet diagnostic criteria for at least one anxiety disorder, including Social, Generalized and/or Separation Disorder. Anxiety in children with ADHD has been shown to be associated with poorer child and family functioning. Small pilot studies suggest that treating anxiety in children with ADHD using cognitive-behavioral therapy (CBT) has promising benefits. In a fully powered randomized controlled trial (RCT), we aim to investigate the efficacy of an existing CBT intervention adapted for children with ADHD and comorbid anxiety compared with usual care.

Methods: This RCT is recruiting children aged 8-12 years (N = 228) from pediatrician practices in Victoria, Australia. Eligibility criteria include meeting full diagnostic criteria for ADHD and at least one anxiety disorder (Generalized, Separation or Social). Eligible children are randomized to receive a 10 session CBT intervention (Cool Kids) versus usual clinical care from their pediatrician. The intervention focuses on building child and parent skills and strategies to manage anxiety and associated impairments including cognitive restructuring and graded exposure. Minor adaptations have been made to the delivery of the intervention to meet the needs of children with ADHD including increased use of visual materials and breaks between activities. The primary outcome is change in the proportion of children meeting diagnostic criteria for an anxiety disorder at 5 months randomization. This will be assessed via diagnostic interview with the child's parent (Anxiety Disorders Interview Schedule for Children V) conducted by a researcher blinded to intervention condition. Secondary outcomes include a range of child (e.g., anxiety symptoms, ADHD severity, behavior, quality of life, sleep, cognitive functioning, school attendance) and parent (e.g., mental health, parenting behaviors, work attendance) domains of functioning assessed at 5 and 12 months post-randomization. Outcomes will be analyzed using logistic and mixed effects regression.

Discussion: The results from this study will provide evidence on whether treating comorbid anxiety in children with ADHD using a CBT approach leads to improvements in anxiety and/or broader functional outcomes.

Trial registration: This trial was prospectively registered: Current Controlled Trials ISRCTN59518816 (https://doi.org/10.1186/ISRCTN59518816). The trial was first registered 29/9/15 and last updated 15/1/19

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BMJ Open. 2019;9.

EVIDENCE OF POTENTIAL OVERDIAGNOSIS AND OVERTREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS: PROTOCOL FOR A SCOPING REVIEW.

Kazda L, Bell K, Thomas R, et al.

Introduction Worldwide, attention deficit hyperactivity disorder (ADHD) diagnosis rates in children and adolescents have been increasing consistently over the past decades, fuelling a debate about the underlying reasons for this trend. While many hypothesise that a substantial number of these additional cases are overdiagnosed, to date there has been no comprehensive evaluation of evidence for or against this hypothesis. Thus, with this scoping review we aim to synthesise published evidence on the topic in order to investigate whether existing literature is consistent with the occurrence of overdiagnosis and/or overtreatment of ADHD in children and adolescents.

Methods and analysis The proposed scoping review will be conducted in the context of a framework of five questions, developed specifically to identify areas in medicine with the potential for overdiagnosis and overtreatment. The review will adhere to the Joanna Briggs Methodology for Scoping Reviews. We will search Medline, Embase, PsycINFO and the Cochrane Library electronic databases for primary studies published in English from 1979 onwards. We will also conduct forward and backward citation searches of included articles. Data from studies that meet our predefined exclusion and inclusion criteria will be charted into a standardised extraction template with results mapped to our predetermined five-question framework in the form of a table and summarised in narrative form.

Ethics and dissemination The proposed study is a scoping review of the existing literature and as such does not require ethics approval. We intend to disseminate the results from the scoping review through publication in a peer-reviewed journal and through conference presentations. Further, we will use the findings from our scoping review to inform future research to fill key evidence gaps identified by this review

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BMJ Open. 2019;9.

BIOMARKER RESEARCH IN ADHD: THE IMPACT OF NUTRITION (BRAIN) - STUDY PROTOCOL OF AN OPEN-LABEL TRIAL TO INVESTIGATE THE MECHANISMS UNDERLYING THE EFFECTS OF A FEW-FOODS DIET ON ADHD SYMPTOMS IN CHILDREN.

Stobernack T, De Vries SPW, Rodrigues PR, et al.

Introduction Attention deficit hyperactivity disorder (ADHD) is the most common childhood behavioural disorder, causing significant impediment to a child's development. It is a complex disorder with numerous contributing (epi)genetic and environmental factors. Currently, treatment consists of behavioural and pharmacological therapy. However, ADHD medication is associated with several side effects, and concerns about long-term effects and efficacy exist. Therefore, there is considerable interest in the development of alternative treatment options. Double-blind research investigating the effects of a few-foods diet (FFD) has demonstrated a significant decrease in ADHD symptoms following an FFD. However, an FFD requires a considerable effort of both child and parents, limiting its applicability as a general ADHD treatment. To make FFD intervention less challenging or potentially obsolete, we need to understand how, and in which children, an FFD affects ADHD behaviour and, consequently, the child's well-being. We hypothesise that an FFD affects brain function, and that the nutritional impact on ADHD is effectuated by a complex interplay between the microbiota, gut and brain, that is, the microbiota-gut-brain axis.

Methods and analysis The Biomarker Research in ADHD: the Impact of Nutrition (BRAIN) study is an open-label trial with researchers blinded to changes in ADHD symptoms during sample processing and initial data analyses.

Ethics and dissemination The Medical Research and Ethics Committee of Wageningen University has approved this study (NL63851.081.17, application 17/24). Results will be disseminated through peer-reviewed journal publications, conference presentations, (social) media and the BRAIN study website. A summary of the findings will be provided to the participants. Trial registration number NCT03440346. Study dates Collection of primary outcome data started in March 2018 and will be ongoing until 100 children have participated in the study. Sample data analysis will start after all samples have been collected

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Brain Connectivity. 2019;9:711-29.

INTEGRATION AND SEGREGATION OF THE BRAIN RELATE TO STABILITY OF PERFORMANCE IN CHILDREN AND ADOLESCENTS WITH VARIED LEVELS OF INATTENTION AND IMPULSIVITY.

Machida K, Johnson KA.

It is common to find that individuals with attention-deficit/hyperactivity disorder (ADHD) produce more variable responses when performing cognitive tasks. The neural mechanism associated with heightened response time variability (RTV) is not well understood in ADHD nor in typically developing individuals. One potential mechanism that might be associated with increased RTV is functional connectivity of the brain, and specifically inefficient connections. This study examined the relationships among functional connectivity of the brain, RTV, and levels of ADHD symptoms, using a cross-sectional developmental design. Twenty children aged 9-12 years and 49 adolescents aged 15-18 years completed the Sustained Attention to Response Task with flanker interference while electroencephalography (EEG) was recorded. The Conners 3 questionnaire was used to measure the participants' levels of ADHD symptoms. Parameters reflecting different aspects of RTV were computed using ex-Gaussian and fast Fourier transform techniques. Functional connectivity between 64 electrodes was computed for the task period, and global efficiency reflecting functional integration and modularity reflecting strength of functional segregation were computed. Greater global efficiency in the theta band was associated with decreased RTV. Increased integration during

the task may help to combine information more efficiently and produce stable responses. When congruent flankers were present, children with greater modularity in the beta band showed greater tau, which is thought to reflect attentional lapses. This association was not observed when incongruent flankers were present. Brains with increased strength of segregated activity might be more prone to attentional lapses, especially during simpler tasks

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Brain Connectivity. 2019;9:673-91.

PARSING HETEROGENEITY IN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH INDIVIDUAL CONNECTOME MAPPING.

Dajani DR, Burrows CA, Nebel MB, et al.

Traditional diagnostic systems for neurodevelopmental disorders define diagnostic categories that are heterogeneous in behavior and underlying neurobiological alterations. The goal of this study was to parse heterogeneity in a core executive function (EF), cognitive flexibility, in children with a range of abilities (N = 132; children with autism spectrum disorder, attention-deficit/hyperactivity disorder [ADHD], and typically developing children) using directed functional connectivity profiles derived from resting-state functional magnetic resonance imaging data. Brain regions activated in response to a cognitive flexibility task in adults were used to guide region-of-interest selection to estimate individual connectivity profiles in this study. We expected to find subgroups of children who differed in their network connectivity metrics and symptom measures. Unexpectedly, we did not find a stable or valid subgrouping solution, which suggests that categorical models of the neural substrates of cognitive flexibility in children may be invalid. Exploratory analyses revealed dimensional associations between network connectivity metrics and ADHD symptomatology and EF ability across the entire sample. Results shed light on the validity of conceptualizing the neural substrates of cognitive flexibility categorically in children. Ultimately, this work may provide a foundation for the development of a revised nosology focused on neurobiological substrates as an alternative to traditional symptom-based classification systems

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Brain Sciences. 2019;9.

INTEGRATED ANALYSIS OF MICRORNA AND MRNA EXPRESSION PROFILES: AN ATTEMPT TO DISENTANGLE THE COMPLEX INTERACTION NETWORK IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Nuzziello N, Craig F, Simone M, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder, whose etiology and pathogenesis are still largely unknown. In order to uncover novel regulatory networks and molecular pathways possibly related to ADHD, we performed an integrated miRNA and mRNA expression profiling analysis in peripheral blood samples of children with ADHD and age-matched typically developing (TD) children. The expression levels of 13 miRNAs were evaluated with microfluidic qPCR, and differentially expressed (DE) mRNAs were detected on an Illumina HiSeq 2500 genome analyzer. The miRNA targetome was identified using an integrated approach of validated and predicted interaction data extracted from seven different bioinformatic tools. Gene Ontology (GO) and pathway enrichment analyses were carried out. Results showed that six miRNAs (miR-652-3p, miR-942-5p, let-7b-5p, miR-181a-5p, miR-320a, and miR-148b-3p) and 560 genes were significantly DE in children with ADHD compared to TD subjects. After correction for multiple testing, only three miRNAs (miR-652-3p, miR-148b-3p, and miR-942-5p) remained significant. Genes known to be associated with ADHD (e.g., B4GALT2, SLC6A9 TLE1, ANK3, TRIO, TAF1, and SYNE1) were confirmed to be significantly DE in our study. Integrated miRNA and mRNA expression data identified critical key hubs involved in ADHD. Finally, the GO and pathway enrichment analyses of all DE genes showed their deep involvement in immune functions, reinforcing the hypothesis that an immune imbalance might contribute to the ADHD etiology. Despite the relatively small sample size, in this study we

were able to build a complex miRNA-target interaction network in children with ADHD that might help in deciphering the disease pathogenesis. Validation in larger samples should be performed in order to possibly suggest novel therapeutic strategies for treating this complex disease

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Brain Sciences. 2019;9.

IS A VIRTUAL REALITY TEST ABLE TO PREDICT CURRENT AND RETROSPECTIVE ADHD SYMPTOMS IN ADULTHOOD AND ADOLESCENCE?

Areces D, et al.

Despite the persistence of attention deficit hyperactivity disorder (ADHD) into adulthood and adolescence, there are few objective, reliable instruments (based on patient performance) that have been shown to be able to predict current and retrospective ADHD symptoms. The present study aimed to explore whether a validated VR test called Nesplora Aquarium is able to predict ADHD symptoms in adults and adolescents, based on both current and retrospective self-reports. A non-clinical sample of 156 adults and adolescents (70 women and 86 men) between 16 and 54 years of age (M = 21.23, SD = 8.04) took part in the study. Virtual reality (VR) variables such as the number of correct answers, omission and commission errors, among others, were used to predict current and retrospective self-reported symptoms of ADHD using multiple regression models. Correct answers and omission errors in the VR test significantly predicted both current and retrospective ADHD symptoms. However, only the number of perseveration errors and gender were able to significantly predict retrospective ADHD symptoms. These findings suggest that inattention problems tend to remain after adolescence, while perseveration errors (which have been related to impulsive behavior) and gender differences tend to diminish

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Child Adolesc Psychiatry Ment Health. 2019;13.

EXECUTIVE FUNCTIONING AND NEURODEVELOPMENTAL DISORDERS IN EARLY CHILDHOOD: A PROSPECTIVE POPULATION-BASED STUDY.

Otterman DL, Koopman-Verhoeff ME, White TJ, et al.

Background: Executive functioning deficits are common in children with neurodevelopmental disorders. However, prior research mainly focused on clinical populations employing cross-sectional designs, impeding conclusions on temporal neurodevelopmental pathways. Here, we examined the prospective association of executive functioning with subsequent autism spectrum disorder (ASD) traits and attention-deficit/hyperactivity disorder (ADHD) traits.

Methods: This study included young children from the Generation R Study, a general population birth cohort. The Brief Rating Inventory of Executive Function-Preschool Version was used to assess parent-reported behavioral executive functioning when the children were 4 years old. ASD traits were assessed at age 6 (n = 3938) using the parent-reported Social Responsiveness Scale. The Teacher Report Form was used to assess ADHD traits at age 7 (n = 2749). Children with high scores were screened to determine possible clinical ASD or ADHD diagnoses. We were able to confirm an ASD diagnosis for n = 56 children by retrieving their medical records and established an ADHD diagnosis for n = 194 children using the Diagnostic Interview Schedule for Children-Young Child version (DISC-YC). Data were analyzed using hierarchical linear and logistic regressions.

Results: Impaired executive functioning was associated with more ASD and ADHD traits across informants (for ASD traits and diagnoses: +¦ = 0.33, 95% CI [0.30-0.37]; OR = 2.69, 95% CI [1.92-3.77], respectively; for ADHD traits and diagnoses: +¦ = 0.12, 95% CI [0.07-0.16]; OR = 2.32, 95% CI [1.89-2.85], respectively). Deficits in all subdomains were associated with higher levels of ASD traits, whereas only impaired inhibition, working memory, and planning/organization were associated with more ADHD traits.

Conclusions: The findings of the current study suggest a graded association of executive functioning difficulties along the continuum of ASD and ADHD and that problems in executive functioning may be a precursor of ASD and ADHD traits from an early age onwards

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Clin EEG Neurosci. 2019.

INDIVIDUALIZED NEUROFEEDBACK TRAINING MAY HELP ACHIEVE LONG-TERM IMPROVEMENT OF WORKING MEMORY IN CHILDREN WITH ADHD.

Dobrakowski P, +üebecka G.

Background. Children with attention deficit hyperactivity disorder (ADHD) may suffer from working memory deficits, which can adversely affect their academic performance. Neurofeedback training may enhance working memory and provide a solution to this problem.

Aim. To investigate the effect of frequency-neurofeedback on working memory in children with ADHD and to check if the effect is long-lasting.

Method. Forty-eight children with ADHD (aged 6-12 years) were randomly assigned either to a neurofeedback with training parameters chosen to take into account each child's peak alpha frequency (PAF) or to a waiting list control group. Each trained child underwent 19-channel electroencephalography (EEG). All children had average intelligence and none were receiving treatment, such as medications, for ADHD. Prior to the training, MOXO and n-back tests were performed. Next, neurofeedback training sessions with frequency bands for theta and beta ranges determined using each child's PAF were carried out for 10 weeks. Training parameters were set to increase amplitudes in the low beta range and to decrease amplitudes in the theta and high beta frequency ranges. The n-back test was performed again right after the training and then a year later.

Results. During the first n-back test, children from both groups responded correctly to more than 43% of the stimuli. During the second test, children from the waiting list responded correctly to an average of 49% of the stimuli, while children who underwent the neurofeedback training were correct, on average, 69% of the time (significant difference, P <.001). During the third n-back test a year later, children from the waiting list responded correctly to 53% of the stimuli, while those who underwent the neurofeedback training responded correctly to nearly 71%.

Conclusion. This study found a statistically significant improvement in a measure of working memory in children who did 10 to 12 sessions of neurofeedback training with training frequency ranges for theta and beta defined according to each child's PAF. The beneficial effects were still present a year after training

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CNS and Neurological Disorders - Drug Targets. 2019;18:496-501.

THE EFFECT OF VITAMIN D3 SUPPLEMENTATION ON SERUM BDNF, DOPAMINE, AND SEROTONIN IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Seyedi M, Gholami F, Samadi M, et al.

Background & Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood. The exact etiology of this disease is unknown, but it is believed to be related to the disorder of catecholaminergic and serotonergic systems. Also, serum vitamin D levels in patients with ADHD is lower. Several studies have also shown the effect of vitamin D on the synthesis pathways of dopamine, serotonin, and a number of neurotrophic factors. Therefore, this study aimed to investigate the effect of vitamin D3 supplementation on serum levels of Brain-Derived Neurotrophic Factor (BDNF), dopamine, and serotonin in school-aged children with ADHD.

Methods: Eighty-six children with ADHD were divided into two groups, based on randomized permuted blocks. Patients received 2000 IU vitamin D/day or a placebo for 12 weeks. Serum levels of BDNF, dopamine, serotonin, and 25-hydroxyvitamin D [25(OH)D] were measured at baseline and at the end of the study.

Results: Serum levels of 25(OH)D and dopamine significantly increased in the vitamin D group, compared to the placebo group ($p < 0.05$). However, serum BDNF and serotonin levels did not change significantly.

Conclusion: Vitamin D3 supplementation in children with ADHD can increase serum dopamine levels, but further studies are needed to determine the effects of vitamin D on neurotrophic factors and serotonin

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Cognitive Neuropsychiatry. 2019.

A NEW SEMI-NONVERBAL TASK GLANCE, MODERATE ROLE OF COGNITIVE FLEXIBILITY IN ADHD CHILDREN'S THEORY OF MIND.

Mohammadzadeh A, Khorrami BA, Tehrani DM, et al.

Introduction: Studies have documented both executive functions (EF) impairment in children with Attention Deficit / Hyperactivity Disorders (ADHD) and Theory of Mind (ToM), yielding mixed results, possibly because of a variety of tasks used, all requiring different levels of language skills.
Aim: To investigate the relationship between ToM and EF with non-language-based tasks.
Methods: Thirty ADHD (7-9 years old) were compared to thirty controls (age and IQ matched). Participants ToM was assessed using the Animated Triangles task and two EF tasks, namely spatial control test, the Stockings Of Cambridge (SOC) and rule and acquisition test, the Intra-Extra Dimensional set shift (IED) from the neuropsychological battery of the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Results: ADHD group had a significant ToM and EF impairment relative to the control group. ToM was not significantly correlated with EF; however, the performance on IED tasks affected the performance on ToM tasks.
Discussion: The study provides evidence for a link between the abilities to attribute correct mental states to others, planning and shifting attention in ADHD children, suggesting the ability to rely on cognitive flexibility in the face of a changing environment plays a role in explaining the association between ToM and EF

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Complement Ther Clin Pract. 2019 Aug;36:170-75.

EFFECT OF SWEET ALMOND SYRUP VERSUS METHYLPHENIDATE IN CHILDREN WITH ADHD: A RANDOMIZED TRIPLE-BLIND CLINICAL TRIAL.

Motaharifard MS, Effatpanah M, Karimi M, et al.

BACKGROUND AND PURPOSE: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common health disorders among children. Some patients do not respond to methylphenidate or cannot tolerate its side effects. Sweet almond syrup as a Persian Medicine preparation has been used for many years. This study aims to evaluate the efficacy and safety of sweet almond for ADHD children.
MATERIALS AND METHODS: Fifty children aged 6-14 years with ADHD were recruited to the study. The participants were randomly assigned to two groups to receive either methylphenidate or sweet almond syrup. The outcomes were assessed using the Parent and Teacher ADHD Rating Scale every two weeks for 8 weeks.
RESULTS: Results showed that the two treatments had similar effects on symptom reduction in ADHD children. No significant differences were observed between the two groups (F=2.3, df=1, p=0.13, F=0.57, df=1, p=0.47).
CONCLUSION: Sweet almond may be an effective treatment for ADHD children

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Contemporary Clinical Trials Communications. 2019;16.

RATIONALE AND DESIGN OF AN INTERNATIONAL RANDOMIZED PLACEBO-CONTROLLED TRIAL OF A 36-INGREDIENT MICRONUTRIENT SUPPLEMENT FOR CHILDREN WITH ADHD AND IRRITABLE MOOD: THE MICRONUTRIENTS FOR ADHD IN YOUTH (MADDY) STUDY.

Johnstone JM, Leung B, Gracious B, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder affecting up to 9% of children and substantial numbers of adults. Existing pharmacologic treatments often improve symptoms, but concerns exist over side effects, stigma, potential long-term health effects, and

residual irritability, often treated with adjunctive antipsychotics. To address public and clinician demand for non-pharmacologic evidence-based treatments, this study will examine efficacy of a 36-ingredient micronutrient (vitamin/mineral) supplement as treatment for children with ADHD and irritability.
Methods: An international team of experts in ADHD, mood dysregulation, nutrition, epidemiology, and clinical trials conferred to develop/refine a protocol powered to detect a medium effect. The study will employ a fully-blind randomized controlled trial (RCT) design, comparing the micronutrient supplement to matched placebo in 135 children aged 6-12 with ADHD symptoms and irritability, based on the parent-rated Child and Adolescent Symptom Inventory-5 (CASI-5). Irritability will be measured by at least one symptom of oppositional defiant disorder (ODD) or disruptive mood dysregulation disorder (DMDD). Based on research suggesting an irritable ADHD subtype, the primary outcome will be a composite score comprised of the CASI-5 subscales: ADHD, ODD, DMDD, and the Peer Conflict Scale, which assesses anger and aggression perpetrated towards peers. Participants will provide biological samples (blood, urine, saliva, hair and stool) to explore the micronutrients mechanisms of action.
Discussion: This study is the first adequately powered RCT in North America to examine both behavioral responses to, and biological mechanisms of, micronutrients for ADHD and irritability in children. If found efficacious, broad-spectrum micronutrients, given at therapeutic doses, may provide an evidence-based alternative to prescription medications for ADHD and associated irritability.
Trial registration: NCT03252522. Registered 26 July 2017

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Curr Psychiatry Rep. 2019;21.
UNDERSTANDING CHRONIC AGGRESSION AND ITS TREATMENT IN CHILDREN AND ADOLESCENTS.
Magalotti SR, Neudecker M, Zaraa SG, et al.
Purpose of review: Youth aggression is common and has a significant burden on individuals, families, and society. However, its treatment is often a challenge for clinicians. Thus, this review will examine the current understanding of youth aggression, conceptualize aggression as a symptom rather than its own disorder, and provide an overview of treatment strategies.
Recent findings: Youth aggression is associated with complex genetic, neurobiological, and environmental risks. Prevention strategies are of the utmost importance for at-risk families and youth. Psychosocial interventions are the first line treatment. But if not fully effective, then pharmacologic interventions including psychostimulants, alpha-2 agonists, atomoxetine, and risperidone have shown benefits. Other medications, such as SSRIs, can be useful in certain scenarios.
Summary: It is important to conceptualize youth aggression as being a trans-diagnostic symptom in psychopathology. Determining the underlying cause of aggression will help to guide treatment

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Environ Int. 2019;133.
ASSOCIATION OF WATER FLUORIDE AND URINARY FLUORIDE CONCENTRATIONS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CANADIAN YOUTH.
Riddell JK, Malin AJ, Flora D, et al.
Background: Exposure to fluoride has been linked with increased prevalence of attention deficit hyperactivity disorder (ADHD) in the United States and symptoms of inattention in Mexican children. We examined the association between fluoride exposure and attention outcomes among youth living in Canada.
Method: We used cross-sectional data collected from youth 6 to 17 years of age from the Canadian Health Measures Survey (Cycles 2 and 3). Urinary fluoride concentration adjusted for specific gravity (UFSG) was available for 1877 participants. Water fluoride concentration measured in tap water samples was available for 980 participants. Community water fluoridation (CWF) status was determined by viewing reports on each city's website or contacting the water treatment plant. We used logistic regression to test the association between the three measures of fluoride exposure and ADHD diagnosis. Linear regression was used to examine the relationship between the three measures of fluoride exposure and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

Results: UFSG did not significantly predict ADHD diagnosis or hyperactive/inattentive symptoms. A 1 mg/L increase in tap water fluoride level was associated with a 6.1 times higher odds of an ADHD diagnosis (95% CI = 1.60, 22.8). A significant interaction between age and tap water fluoride level (p = .03) indicated a stronger association between tap water fluoride and hyperactivity/inattention symptoms among older youth. A 1 mg/L increase in water fluoride level was associated with a 1.5 SDQ score increase (95% CI: 0.23, 2.68, p = .02) for youth at the 75th percentile of age (14 years old). Similarly, there was a significant interaction between age and CWF. At the 75th percentile of age (14 years old), those living in a fluoridated region had a 0.7-point higher SDQ score (95% CI = 0.34, 1.06, p < .01) and the predicted odds of an ADHD diagnosis was 2.8 times greater compared with youth in a non-fluoridated region (aOR = 2.84, 95% CI: 1.40, 5.76, p < .01).
Discussion: Exposure to higher levels of fluoride in tap water is associated with an increased risk of ADHD symptoms and diagnosis of ADHD among Canadian youth, particularly among adolescents. Prospective studies are needed to confirm these results

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Environ Res. 2019.
A SYSTEMATIC REVIEW AND META-ANALYSIS EXAMINING THE INTERRELATIONSHIPS BETWEEN CHEMICAL AND NON-CHEMICAL STRESSORS AND INHERENT CHARACTERISTICS IN CHILDREN WITH ADHD.
Nilsen FM, Tulve NS.
Children may be more vulnerable to the combined interactions of chemical and non-chemical stressors from their built, natural, and social environments when compared to adults. Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood neurodevelopmental disorder and is considered a major public health issue, as 75% of childhood cases persist into adulthood. ADHD is characterized by developmentally inappropriate levels of hyperactivity, impulsivity, and inattention, with the neurotransmitter serotonin regulating these symptoms. Monoamine oxidase A (MAOA) aids in serotonin uptake and is often implicated in behavioral and emotional disorders, including ADHD. When children are exposed to cigarette smoke, bisphenol A (BPA), or organophosphate pesticides, MAOA activity is inhibited. Non-chemical stressors, such as traumatic childhood experiences, and lifestyle factors, complicate the relationship between genotype and exposures to chemical stressors. But the co-occurrence among outcomes between exposures to chemical stressors, non-chemical stressors, and the low activity MAOA genotype suggest that mental illness in children may be influenced by multiple interacting factors. In this systematic review, we examine the existing literature that combines exposures to chemical and non-chemical stressors (specifically childhood trauma), MAOA characteristics, and ADHD diagnosis to investigate the interrelationships present. We observe that chemical (lead [Pb], phthalates/plasticizers, persistent organic pollutants, and cigarette smoke) exposure is significantly related to ADHD in children. We also observed that existing literature examining the interaction between MAOA, exposures to chemical stressors, and traumatic experiences and their effect on ADHD outcomes is sparse. We recommend that future studies investigating childhood ADHD include chemical and non-chemical stressors and inherent characteristics to gain a holistic understanding of childhood mental health outcomes

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Epidemiol Psychiatr Sci. 2019 Dec;28:692-96.
PREVALENCE, INCIDENCE AND PERSISTENCE OF ADHD DRUG USE IN JAPAN.
Okumura Y, Usami M, Okada T, et al.

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Eur Child Adolesc Psychiatry. 2019 Aug;28:1037-64.

BARRIERS AND FACILITATORS TO UNDERSTANDING OF ADHD IN PRIMARY CARE: A MIXED-METHOD SYSTEMATIC REVIEW.

French B, Sayal K, Daley D.

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder affecting up to 5% of children and adults and is underdiagnosed in many European countries. The process of access to care for this disorder is complex and variable across countries. In general, those affected, or their caregiver, will seek help through their primary care practitioners who are then often responsible for referral to other professionals for diagnosis and provision of treatment. Previous studies have highlighted that many barriers to recognition exist in primary care settings (such as misconceptions, lack of education or lack of resources), preventing access to care for this population and potentially affecting diagnosis rate. This systematic review aims to establish the barriers and facilitators with regard to attitudes, beliefs and experiences of ADHD within primary care. Electronic searches of multiple databases identified 3898 articles of which 48 met our inclusion criteria-primary care professionals from any country, understanding, knowledge, awareness, attitude and recognition of ADHD. Four main themes were identified: (1) need for education, (2) misconceptions and stigma, (3) constraints with recognition, management and treatment, and (4) multidisciplinary approach. The findings suggest many interacting factors are at play in the recognition of ADHD by primary care practitioners with a strong recurring theme of a significant need for better education on ADHD. Implications for research and practice are discussed, suggesting that educational interventions for primary care practitioners could improve the recognition of ADHD in this setting

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Eur Child Adolesc Psychiatry. 2019;28:1659-69.

OVERWEIGHT IN FAMILY MEMBERS OF PROBANDS WITH ADHD.

Geuijen PM, Buitelaar JK, Fliers EA, et al.

The widely reported association between ADHD and overweight may be attributable to genetic and environmental factors also present in unaffected family members. Therefore, the purpose of this study was to examine the association between ADHD and overweight within families. A cohort was used of families with at least one member with ADHD, recruited as part of the Dutch node of the International Multicenter ADHD Genetics (IMAGE) study, with assessments taking place between 2003 and 2006, 2009 and 2012, and 2013 and 2015. The three assessment waves yielded N = 1828 youth assessments and N = 998 parent assessments from N = 447 unique families. Overweight was defined as a body mass index (BMI) ΓëÑ 85th percentile for youth of the same age and sex; overweight in adults as a BMI ΓëÑ 25. Effects of age, gender, and medication use (psychostimulants, antipsychotics, and melatonin) were taken into account. Generalized estimation equations were used to correct for within-family and within-subject correlations. There was no difference in risk between ADHD-affected youth and their unaffected siblings (OR 0.92, 95% CI 0.78ΓÇô1.09). However, compared to population prevalence data, all ADHD family members alike were at increased risk for being overweight: ADHD-affected youth (OR 1.33, 95% CI 1.13ΓÇô1.59), unaffected siblings (OR 1.73, 95% CI 1.45ΓÇô2.08), mothers (OR 1.74, 95% CI 1.40ΓÇô2.17) and fathers (OR 1.78, 95% CI 1.46ΓÇô2.15). Parental overweightΓÇöbut not parental ADHDΓÇöwas predictive of offspring overweight (mothers OR 1.40; 95% CI 1.14ΓÇô1.73, fathers OR 1.83; 95% CI 1.41ΓÇô2.36). Being overweight runs in ADHD families, yet is not specifically linked to ADHD within families. Shared unhealthy lifestyle factors (including nutrition, sleep, exercise, stress) as well as genetic factors shared by family members likely explain the findings

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Eur Child Adolesc Psychiatry. 2019.

ASSOCIATION BETWEEN PRENATAL EXPOSURE TO A 1-MONTH PERIOD OF REPEATED ROCKET ATTACKS AND NEUROPSYCHIATRIC OUTCOMES UP THROUGH AGE 9: A RETROSPECTIVE COHORT STUDY.

Barzilay R, Lawrence GM, Berliner A, et al .

Exposure to gestational stress is implicated in increased risk for neuropsychiatric disorders in offspring. We assessed association between prenatal exposure to a 1-month period of repeated rocket attacks during the 2006 Second Lebanon War in Northern Israel and emergence of childhood neuropsychiatric disorders from birth through 9-áyears of age. Children born to women who were pregnant during the war (N = 6999) were identified and compared to children in the same district born a year later (N = 7054), whose mothers were not exposed to rocket attacks during pregnancy. Multivariable regression models assessed risk for attention deficit hyperactivity disorder, autism, epilepsy, depression and/or anxiety, or any of these disorders (composite outcome) in offspring. Models controlled for multiple confounders including parents' demographics, parity, maternal use of psychotropic medications during pregnancy, post-partum depression and parental psychiatric history. Results show that exposed and comparison groups did not differ with respect to demographics, parity or psychiatric history. Exposed and comparison groups were similar with regard to gestational age and weight at birth. Multivariable models did not demonstrate an association between exposure to rocket attacks during pregnancy and neuropsychiatric outcomes by age 9. No interactions were found between exposure and gestational trimester at exposure or childΓÇÖs sex. Our findings suggest that in utero exposure to isolated, 1-month repeated rocket attacks on a civilian population was not associated with major neuropsychiatric outcomes in children by age 9. Future studies should evaluate whether this exposure is associated with psychiatric and/or other health-related outcomes later in life

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Evidence-Based Practice in Child and Adolescent Mental Health. 2019;4:170-86.

INTERVENTIONS FOR TRANSITIONING ADOLESCENTS WITH ADHD TO EMERGING ADULTHOOD: DEVELOPMENTAL CONTEXT AND EMPIRICALLY-SUPPORTED TREATMENT PRINCIPLES.

LaCount PA, Hartung CM, Canu WH, et al.

The developmental transition between adolescence to emerging adulthood (ages 18-25) is a critical juncture particularly for individuals with attention-deficit/hyperactivity disorder (ADHD). However, there are no known published studies on treatments for ADHD that aim to improve the transition from adolescence to emerging adulthood. We sought to facilitate future transition intervention research and provide empirically-supported treatment principles and corresponding targets for clinicians with this manuscript. We review two key areas of research to inform transition planning interventions for adolescents with ADHD: (a) domains of impairment (e.g., occupational, social) within the developmental context of the transition to emerging adulthood and (b) existing treatment research on interventions for adolescents and adults with ADHD. After evaluating and synthesizing these areas of research, we highlight and discuss targets for treatment that are promising for addressing the unique needs of adolescents with ADHD transitioning to emerging adulthood. We also discuss treatment modalities which may be particularly suited for ADHD within this developmental context. Many treatment elements were indicated, ranging from empirically-supported focuses on compensatory skills (e.g., organization, time management, planning [OTMP]) to more theoretically relevant techniques, such as health and lifestyle behaviors (e.g., physical exercise). Further, certain treatment modalities, such as parent-teen collaborative models and group-based approaches, seemed particularly suited for adolescents with ADHD transitioning to emerging adulthood. Limitations of existing research on the transition to emerging adulthood for those diagnosed with ADHD and areas for future research are discussed in greater detail

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Fetal and Pediatric Pathology. 2019.

ASSOCIATION OF MTHFR 677C > T AND 1298A > C POLYMORPHISMS WITH SUSCEPTIBILITY TO ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Sadeghiyeh T, Dastgheib SA, Lookzadeh MH, et al.

Background: The associations of MTHFR polymorphisms with risk of attention deficit and hyperactivity disorder (ADHD) are poorly elucidated. This study was performed to evaluate the association of MTHFR polymorphisms with ADHD risk in Iranian children.

Methods: This case control study included 214 children with ADHD and 220 healthy subjects. The MTHFR 677C > T and 1298A > C polymorphisms were genotyped by an ABI PRISMs 7500 real-time PCR System.

The odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association.
Results: The MTHFR 1298A > C polymorphism CC genotype (OR= 1.526, 95% CI 1.004-2.320, p = 0.048) and C allele (OR= 1.336, 95% CI 0.1023-1.745, p = 0.034) were associated with an increased risk of ADHD. There was no significant association between MTHFR 677C > T polymorphism and increased risk of ADHD.
Conclusions: Our results revealed that the MTHFR 1298A > C polymorphism but not the MTHFR 677 C > T is associated with increased risk of ADHD in Iranian children

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Front Human Neurosci. 2019;13.
ERROR-RELATED DYNAMICS OF REACTION TIME AND FRONTAL MIDLINE THETA ACTIVITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) DURING A SUBLIMINAL MOTOR PRIMING TASK.
Keute M, Stenner M-P, Mueller M-K, et al.
Post-error slowing (PES) is an established performance monitoring readout. Several previous studies have found that PES is reduced in children and adolescents with attention-deficit hyperactivity disorder (ADHD). We analyzed reaction time data, along with electroencephalography (EEG) data, from a response priming experiment in children and adolescents with ADHD (N = 28) and typically developing (TD) controls (N = 15) between 10 and 17 years of age. We report dynamic reaction time changes before and after errors: whereas TD controls readjusted their response speed to their individual average speed after committing an error, this reaction time adjustment appeared to be delayed and decreased in ADHD patients. In the EEG, error trials were accompanied by increased frontal midline theta activity, which was attenuated in ADHD compared to TD. We conclude that PES has a different time course rather than being fully absent in ADHD and discuss relationships with our EEG findings and potential implications for performance monitoring in ADHD

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Front Human Neurosci. 2019;13.
ELECTROPHYSIOLOGICAL CORRELATES OF RESPONSE TIME VARIABILITY DURING A SUSTAINED ATTENTION TASK.
Machida K, Murias M, Johnson KA.
Individuals with Attention Deficit Hyperactivity Disorder (ADHD) tend to perform cognitive tasks with greater Response Time Variability (RTV). Greater RTV in ADHD may be due to inefficient functional connectivity of the brain during information processing. This study aimed to investigate the relationship between brain connectivity, RTV, and levels of ADHD symptoms. Twenty-eight children aged 9-12 years and 49 adolescents aged 15-18 years performed the Sustained Attention to Response Task (SART) while EEG was recorded. The participants levels of ADHD symptoms were measured using self- and parent-rated questionnaires. The ex-Gaussian analysis and The Fast Fourier Transform were used to measure multiple aspects of RTV. Functional connectivity between 64 electrodes was computed during task performance, and global efficiency and modularity were calculated, reflecting integration and segregation of the brain, respectively. There was a positive association between multiple RTV measures and the level of ADHD symptoms, where participants with higher levels of ADHD symptoms showed greater RTV, except for sigma from the ex-Gaussian analysis. More efficient brain network activity, measured by global efficiency, was associated with reduced RTV. Children showed greater RTV and less efficient brain network activity compared with the adolescents. These findings support the view that stable responses are achieved with more integrated (and efficient) brain connectivity

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Frontiers in Pediatrics. 2019;7.

INFANTS OF MOTHERS WITH DIABETES AND SUBSEQUENT ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RETROSPECTIVE COHORT STUDY.

Lin C-H, Lin W-D, Chou I-C, et al.

Background: Maternal diabetes mellitus (DM) increases the risk of fetal, neonatal, and long-term complications in offspring. Although this has been widely known for decades, data are limited regarding the effect of maternal pregestational and gestational diabetes on the subsequent neurodevelopmental outcome of offspring. This study investigated whether infants of mothers with diabetes (IDMs) were associated with a risk of subsequent attention deficit hyperactivity disorder (ADHD).

Objectives: We collected data from newborn infants born to mothers with gestational or pregestational diabetes at China Medical University Children's Hospital between January 1, 2006, and December 31, 2012. These patients were followed to evaluate their risk of ADHD (IDM group) compared with that for those born to mothers without DM (non-IDM group). Several assumed perinatal risk factors accompanying the IDMs were also analyzed.

Results: Overall, 104 patients with average gestational ages of 36.5 weeks were included in the IDM group. Additionally, 110 patients with average gestational ages of 36.6 weeks were included in the non-IDM group. Compared with non-IDMs (reference), the overall risk of ADHD in IDMs was 2.6 [95% confidence interval (CI)P, 1.11ΓÇô5.90; p = 0.03]. Furthermore, the risk of ADHD among male (OR, 3.78; 95% CI, 1.37-10.3; p = 0.001) and full-term infants [odds ratio (OR), 4.5; 95% CI, 1.16ΓÇô17.6; p = 0.03] in the IDMs was higher than that in the non-IDM group. No significant differences were found among IDMs for the assumed perinatal risk factors that were analyzed.

Conclusions: The study revealed a higher incidence rate of ADHD in IDMs, especially male and full-term infants. It is crucial for pediatricians to identify the early symptoms neurodevelopmental disorders, especially ADHD, in children of diabetic mothers to initiate proper assessment and treatment

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Hum Brain Mapp. 2019.

ALTERED BRAIN MORPHOLOGY IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT COMORBID CONDUCT DISORDER/OPPOSITIONAL DEFIANT DISORDER.

Vetter NC, Backhausen LL, Buse J, et al.

About 50% of attention deficit hyperactivity disorder (ADHD) patients suffer from comorbidity with oppositional defiant disorder/conduct disorder (ODD/CD). Most previous studies on structural morphology did not differentiate between pure (ADHD-only) and comorbid ADHD (ADHD+ODD/CD). Therefore, we aimed to investigate the structural profile of ADHD-only versus ADHD+ODD/CD spanning the indices subcortical and cortical volume, cortical thickness, and surface area. We predicted a reduced total gray matter, striatal, and cerebellar volume in both patient groups and a reduced amygdalar and hippocampal volume for ADHD+ODD/CD. We also explored alterations in prefrontal volume, thickness, and surface area. We acquired structural images from an adolescent sample ranging from 11 to 17 years, matched with regard to age, pubertal status, and IQΓÇöincluding 36 boys with ADHD-only, 26 boys with ADHD+ODD/CD, and 30 typically developing (TD) boys. We analyzed structural data with FreeSurfer. We found reductions in total gray matter and total surface area for both patient groups. Boys with ADHD+ODD/CD had a thicker cortex than the other groups in a right rostral middle frontal cluster, which was related to stronger ODD/CD symptoms, even when controlling for ADHD symptoms. No group differences in local cortical volume or surface area emerged. We demonstrate the necessity to carefully differentiate between ADHD and ADHD+ODD/CD. The increased rostral middle frontal thickness might hint at a delayed adolescent cortical thinning in ADHD+ODD/CD. Patients with the double burden ADHD and ODD or CD seem to be even more affected than patients with pure ADHD

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Indian Journal of Dermatology. 2019;64:451-55.

THE ASSOCIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ATOPIC DERMATITIS: A STUDY AMONG IRANIAN CHILDREN.

Atefi N, Rohaninasab M, Shooshtari M, et al.

Background: The co-occurrence of attention-deficit/hyperactivity disorder (ADHD) with atopic dermatitis (AD) has been well described in some recent association studies; however, we did not have any perspective on this relationship in our country.
Aim and Objective: Hence, the present study aimed to assess the prevalence of ADHD in children with AD.
Materials and Methods: This cross-sectional study was performed on 95 consecutive children and adolescents (aged 4-18 years) who were referred to dermatology clinics at the two hospitals in Tehran during 2017 with atopic dermatitis. The evidence of atopy was assessed using the 2003 National Survey of Children's Health. The diagnosis of ADHD was based on the Conner Rating Scale. The sleep disorder was also assessed by the Pittsburg sleep quality questionnaire.
Results: The prevalence of hyperactivity and attention deficit in our AD patients was 20.0% and 29.47%, respectively. Furthermore, patients with sleep problem were significantly more likely to have hyperactivity disorder (odds ratio [OR]: 2.91, 95% confidence interval [CI]: 1.04-8.16, P = 0.04). According to the results of multiple logistic regression analyses, flexor involvement was the only predictor of hyperactivity disorder in the final model. The univariate and multivariate analyses showed that having attention deficit was associated with having cheek involvement (OR = 3.63, 95% CI: 1.44-9.14, P = 0.01) and sleep problem (OR = 3.68, 95% CI: 1.45-9.33, P = 0.01).
Conclusion: It seems that neurocognitive disturbances due to sleep restriction in AD children may be one of the main trigger, especially for attention deficit

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Int J Behav Nutr Phys Act. 2019 Jun;16:52.

SHAPING HEALTHY HABITS IN CHILDREN WITH NEURODEVELOPMENTAL AND MENTAL HEALTH DISORDERS: PARENT PERCEPTIONS OF BARRIERS, FACILITATORS AND PROMISING STRATEGIES.

Bowling A, Blaine RE, Kaur R, et al.

OBJECTIVE: Prevalence of pediatric neurodevelopmental and mental health disorders (ND/MHD) is increasing in the United States and globally. ND/MHD are associated with higher risk of poor dietary, physical activity (PA), screen, and sleep habits in youth, contributing to elevated lifetime chronic disease risk. ND/MHD symptoms can present unique challenges to parenting, create competing parenting priorities, and may decrease parental capacity to instill healthy habits. Unfortunately, literature characterizing parenting of health habits in youth with ND/MHD is sparse. The objective of this study was to describe barriers to, facilitators of, and practical strategies for parenting healthy lifestyle habits in children and teens with ND/MHD.
METHODS: We conducted semi-structured interviews with parents whose children with diagnosed ND/MHD were attending a Boston-area therapeutic day school serving K-10th grade. Interviews allowed parents to focus on parenting PA, diet, sleep, and/or screen habits as context for questions. Interviews were transcribed, double-coded using constant comparative methods, and summarized into themes using NVivo 11.
RESULTS: We interviewed 24 parents; average age of their child with ND/MHD was 11.2 years (range: 8-15). Most had a son (75%) with multiple ND/MHD (88%); diagnoses included autism spectrum disorder (50%), attention deficit-hyperactivity disorder (67%), anxiety (67%), and other mood disorders (58%). Major barriers to parenting all types of health habits included depleted parent resources, child dysregulation, lack of supportive programming available to children with ND/MHD, and medication side effects. Major facilitators included participation in specialized therapeutic options, adaptive community programs and schools, as well as parents' social capital. Effective parenting strategies included setting clear, often structural boundaries, using positive reinforcement, allowing agency by presenting healthy choices, and use of role modeling to promote healthy habits. Almost one third of parents extensively discussed the role of pets or therapy animals as key to establishing and maintaining healthy routines, particularly PA and screen-time management.

CONCLUSIONS: Parenting healthy habits in children with ND/MHD is difficult and is undermined by competing demands on parenting resources. To reduce chronic disease disparities and promote health in this population, future research must better adapt existing health promotion materials and programs to more practically support parents in multiple settings including home, schools and community organizations

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Int J Evid Based Healthc. 2019 Jun;17 Suppl 1:S34-S37.

THE ASSOCIATION BETWEEN MODE OF BIRTH DELIVERY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW PROTOCOL OF EPIDEMIOLOGICAL EVIDENCE.

Klugarova J, Janouskova K, Prochazka M, et al.

Caesarean section is currently the most frequently performed intervention after episiotomy in obstetrics and one of the most common abdominal operations overall. Rates of caesarean section have been rising globally. Given the increasing rate worldwide it is therefore necessary and important to understand how caesarean section affects child development. Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioural disorder in children. ADHD is characterized by a combination of symptoms including inattention, impulsivity and hyperactivity. Caesarean section may affect psychological development through changes in microbiota or stress response, and birth by caesarean section can be associated with a small increased risk of ADHD. In the current literature, there is no systematic review or protocol of the systematic review answering the question of whether the mode of delivery has influence on the risk of ADHD development.The objective of this review is to synthesize the best available evidence regarding the epidemiological association between the mode of delivery (caesarean section versus vaginal delivery) as exposure and ADHD as the outcome.A three-step strategy will be utilized in this review, aiming to find both published and unpublished studies. The initial search will be conducted using the MEDLINE, CINAHL and EMBASE. The second search will involve 21 databases and sources. Following the Preferred Reporting Items for Systematic Review and Meta-analysis statement analysis of title, abstracts and full texts, critical appraisal and data extraction will be carried out on selected studies using standardized instruments developed by Joanna Briggs Institute. All steps will be performed by two independent reviewers. If possible, statistical meta-analysis using Joanna Briggs Institute within the System for the Unified Management, Assessment and Review of Information will be pooled. Statistical heterogeneity will be assessed.The results will be disseminated by publishing in a peer-reviewed journal. Ethical assessment is not needed - we will search/evaluate the existing sources of literature

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Int J Soc Psychiatry. 2019 May;65:217-24.

PROFILE OF TRANSCULTURAL PATIENTS IN A REGIONAL CHILD AND ADOLESCENT MENTAL HEALTH SERVICE IN GIPPSLAND, AUSTRALIA: THE NEED FOR A MULTIDIMENSIONAL UNDERSTANDING OF THE COMPLEXITIES.

Basu S, Isaacs AN .

BACKGROUND: Several childhood stressors related to immigration have been documented, and it is important for clinicians to understand and address the various factors that may lead to or act as maintaining factors of mental disorders in children and adolescents.

AIMS: To describe the cultural profile of transcultural patients presenting to a Child and Adolescent Mental Health Service (CAMHS) in regional Victoria and identify the most common disorders and psychosocial stressors they presented with.

METHOD: Descriptive analysis was applied to 101 case records of patients with a transcultural background who attended the CAMHS of Latrobe Regional Hospital in Gippsland Victoria from 2013 to 2017. The Adverse Childhood Experience questionnaire was retrospectively applied to capture psychosocial stressors such as 'bullying', 'racism' and 'family conflict', sexual abuse, physical violence, parents with mental illness and parental substance use.

RESULTS: Almost 60% of patients were male and over 46% Aboriginal. Those from a non-Aboriginal background belonged to 19 different cultural entities, the most common of which was a mixed Asian and European heritage. The most common diagnoses were disruptive mood dysregulation disorder (38.6%),

attention-deficit hyperactivity disorder (32.7%) and developmental trauma disorder (26.7%). The most common psychosocial stressors were conflict and death in the family (44.6%), domestic violence (41.6%) and emotional abuse (34.7%). 'Parent in jail' and 'domestic violence' were associated with having an Aboriginal background (p < .005). 'Cultural differences with parent' was associated with a non-Aboriginal background (p < .005).
CONCLUSION: This study provides a snapshot of challenges faced by children from different cultural backgrounds while adjusting in a rural area in Australia. A broad-based formulation and cultural awareness by clinicians can enable a better understanding of the complexities, guide management plans and inform public health policies for primary prevention and early intervention

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Int J Pediatr Otorhinolaryngol. 2020;130.
COCHLEAR IMPLANT OUTCOMES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: COMPARISON WITH CONTROLS.
Omidvar S, Jeddi Z, Doosti A, et al.
Objectives: The coincidence of attention-deficit/hyperactivity disorder (ADHD) and hearing loss in the children has adverse effects in speech, cognition, communication and motor development. This can influence cochlear implant (CI) outcomes negatively. The aim of this study was to compare auditory, language, speech, cognition, communication and motor outcomes between CI children with versus without ADHD.
Methods: Nineteen CI children with ADHD and twenty-three age and gender matched children without ADHD at the Shiraz CI center ranging in age from 37 to 60 months were participated in this cross-sectional study. The developmental quotient in auditory, receptive and expressive language, speech and cognition skills was evaluated through Newsha Developmental Scale. The Persian version of the Ages and Stages Questionnaire (ASQ) was used to assess children's developmental status in fine and gross movements, communication, problem solving, and personal-social domains. A comparison of the results between two groups was made by the Mann-Whitney test.
Results: CI children with ADHD had significantly lower Newsha developmental quotients in cases of auditory, receptive and expressive language, speech and cognition skills compared to the control group (P = 0.027 to <0.001). A significant difference was observed between children with and without ADHD in fine and gross movements, communication, problem solving, and personal-social domains of ASQ at 60 months (P = 0.029 to 0.003).
Conclusion: Children with ADHD showed decreased ability in auditory, language, speech, cognition, motor and communication skills following CI compared to children without ADHD. It can guide clinician to provide these children with more specific rehabilitation program to improve their skills

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J Am Acad Child Adolesc Psychiatry. 2019 Jan;58:22-24.
SUICIDAL AND SELF-HARMING PRESCHOOLERS.
Dervic K, Oquendo MA.
Research on suicidal ideation (SI) and suicidal behavior (SB) in very young children is scarce. However, in clinical settings, child psychiatrists encounter these constellations repeatedly. Although death by suicide before 10 years of age is rare, suicidal thoughts, and sometimes behaviors, do occur. Indeed, the prevalence of suicidal thoughts and behaviors, considered together, in preschoolers is reported to be 4% to 13%.(1-3) Along the more severe end of the suicidal spectrum, a frequency of SB and/or attempts of 1.6% (5 of 306 children)(2) and of suicidal plans or attempts of 2% to 3%(3) were reported for children 3 to 7 years old. Although the variability in reported prevalence rates might be influenced by factors such as the specific definition of SI/SB used(1) and reporting bias (assessment of SI/SB by parent/primary caregiver report), expressions of SI/SB in preschool age are strongly associated with distress, psychopathology (eg, depression, attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, posttraumatic stress disorder, impulsivity, nonsuicidal self-directed aggression, abuse/neglect, runaway behavior), parental psychopathology, and family instability.(2-6) Notably, the presence of SI/SB in preschool

age was a predictor of school-age SI/SB in a prospective longitudinal study.(2) Indeed, almost three-fourths of preschoolers with SI/SB reported these behaviors as school-aged children (7-12 years), too,(2) which underlines the importance of proper assessment and timely intervention

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J Autism Dev Disord. 2019 Sep;49:3898-905.

ANXIETY LEVELS OF CHILDREN WITH DEVELOPMENTAL DISORDERS IN JAPAN: BASED ON REPORTS PROVIDED BY PARENTS.

Ishimoto Y, Yamane T, Matsumoto Y.

A large number of children with developmental disorders like autism spectrum disorder (ASD), learning disabilities, and attention deficit hyperactivity disorder have high anxiety. It has also been shown that the high anxiety has harmful effects on them, directly and indirectly. In this study, we conducted a survey on community samples on the level of anxiety of children with developmental disorders in Japan that had hardly been studied so far, and compared them with the anxiety in children in a general population sample in previous studies. Analysis on the 203 participants showed that children with developmental disorders have high anxiety as compared to children as in previous studies in other countries. Particularly children with ASD had a higher anxiety compared with children with developmental disorders without ASD

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J Ment Health. 2019 Jun;28:282-88.

THE ROLE OF MOTHERS' AFFILIATE STIGMA AND CHILD'S SYMPTOMS ON THE DISTRESS OF MOTHERS WITH ADHD CHILDREN.

Charbonnier E, Caparos S, Tremoliere B.

BACKGROUND: Mothers of ADHD children often display high levels of distress. Understanding the origin of such distress in a view to reducing it is an essential part of the clinical management of ADHD children. Studies have shown that children's symptoms are linked to mothers' stigma and that such stigma can cause mothers' distress. However, no study has explored the links between symptoms, stigma and distress.

AIM: We tested (1) whether children's symptoms are sources of affiliate stigma, which in turn contributes to generating mothers' distress and (2) whether such relationship is stronger in mothers of male ADHD children.

METHOD: 159 French mothers of an ADHD child were recruited. Four indices were used to assess mothers' distress: anxiety, depression, self-esteem and life satisfaction. Children's ADHD symptoms and mothers' affiliate stigma were also measured and contrasted with distress.

RESULTS: Mothers' distress was positively related with both affiliate stigma and children's ADHD symptoms, but this was only true in mothers of male ADHD children. The relationship between children's symptoms and mothers' distress was mediated by affiliate stigma.

CONCLUSIONS: Psychosocial interventions in mothers of ADHD children must integrate affiliate stigma and should be adjusted according to child's gender

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JAMA Netw Open. 2019 Mar;2:e190154.

FAMILY HISTORY OF MENTAL AND NEUROLOGICAL DISORDERS AND RISK OF AUTISM.

Xie S, Karlsson H, Dalman C, et al.

Importance: Familial aggregation of mental and neurological disorders is often observed in autism spectrum disorders (ASD), but reports have generally focused on single disorders and are limited to first-degree relatives.

Objectives: To examine family history of mental and neurological disorders among first- to fourth-degree relatives and risk of ASD with and without intellectual disability (ID) in index persons.

Design, Setting, and Participants: In this population-based cohort study, 567436 index persons were identified from the Stockholm Youth Cohort, an ongoing longitudinal register-linkage cohort study of the total population aged 0 to 17 years residing in Stockholm County, Sweden. Index persons were nonadopted

singleton births born between 1984 and 2009 who were at least 2 years of age at the end of follow-up on December 31, 2011, had resided in Stockholm County for at least 2 years since birth, and could be linked to both biological parents. Data analysis was conducted from May 2017 to December 2018.
Exposure: Mental and neurological diagnoses of relatives of the index persons.
Main Outcomes and Measures: Diagnosis of ASD, with or without co-occurring ID, in the index persons.
Results: The cohort included 567436 index persons (291191 [51.3%] male; mean [SD] age at the end of follow-up, 14.3 [7.5] years). The prevalence of ASD with and without ID was 0.4% and 1.5%, respectively. Positive family history of mental and neurological disorders was associated with higher odds of ASD in index persons; 6895 (63.1%) of index persons with ASD had a parent with history of mental and/or neurological disorders, compared with 252454 (45.4%) of index persons without ASD. Family history of multiple disorders was associated with higher odds of ASD in index persons, including history of ASD (odds ratio among first-degree relatives for ASD with and without ID: 14.2, 9.0), intellectual disability (7.6, 2.3), attention-deficit/hyperactivity disorder (3.3, 4.7), obsessive compulsive disorder (1.9, 2.1), schizophrenia and other nonaffective psychotic disorders (2.1, 1.8), depression (1.4, 2.0), bipolar disorder (1.4, 2.2), personality disorder (2.1, 2.6), cerebral palsy (2.2, 1.5), and epilepsy (2.0, 1.3). The more closely related the affected family member was, the higher the odds was of ASD for the index person. ASD without intellectual disability was associated with more disorders compared to ASD with intellectual disability. ASD with intellectual disability exhibited a weaker familial association with other mental disorder diagnoses but a stronger familial association with some neurological diagnoses as compared to ASD without intellectual disability.
Conclusions and Relevance: This study suggests that family history of mental and neurological disorders is associated with increased risk of ASD. The familial component of ASD etiology may differ by presence or absence of co-occurring ID

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JAMA Netw Open. 2019 Jan;2:e186606.
ASSOCIATION OF PRENATAL EXPOSURE TO VALPROATE AND OTHER ANTIEPILEPTIC DRUGS WITH RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OFFSPRING.
Christensen J, Pedersen L, Sun Y, et al.
Importance: Valproate is an antiepileptic drug (AED) used in the treatment of epilepsy and many other neurological and psychiatric disorders. Its use in pregnancy is associated with increased risks of congenital malformations and adverse neurodevelopment in the offspring and may be associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD).
Objective: To determine whether prenatal exposure to valproate and other AEDs is associated with an increased risk of ADHD in the offspring.
Design, Setting, and Participants: This was a population-based cohort study of all live-born singleton children in Denmark from January 1, 1997, to December 31, 2011 (N = 913302). Information on prenatal exposure to AEDs, including valproate, was obtained from the Danish National Prescription Registry and all children with ADHD were identified (children with diagnosed ADHD in the Danish Psychiatric Central Research Register or children who redeemed a prescription for ADHD medication). The cohort was followed up from birth until the day of the ADHD diagnosis, death, emigration, or December 31, 2015, whichever came first. Data were analyzed in September 2018.
Exposures: Maternal use of valproate and other AEDs in pregnancy.
Main Outcomes and Measures: Cox regression estimates of the hazard ratio of ADHD. Estimates were adjusted for potential confounders.
Results: The cohort included 913302 children (mean age at end of study, 10.1 years; median age, 9.4 years; interquartile range, 7.2-12.8 years; 468708 [51.3%] male). A total of 580 were identified as having been exposed to valproate during pregnancy; of them, 49 (8.4%) had ADHD. Among the 912722 children who were unexposed to valproate, 29396 (3.2%) had ADHD. Children with prenatal valproate exposure had a 48% increased risk of ADHD (adjusted hazard ratio, 1.48; 95% CI, 1.09-2.00) compared with children with no valproate exposure. The absolute 15-year risk of ADHD was 4.6% (95% CI, 4.5%-4.6%) in children unexposed to valproate and 11.0% (95% CI, 8.2%-14.2%) in children who were exposed to valproate in pregnancy. No associations were found between other AEDs and ADHD.

Conclusions and Relevance: Maternal use of valproate, but not other AEDs, during pregnancy was associated with an increased risk of ADHD in the offspring. These findings have important implications for the counseling of women of childbearing potential using valproate

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JAMA Netw Open. 2019 Jan;2:e186694.

ASSOCIATION OF CHILDHOOD SOCIAL-EMOTIONAL FUNCTIONING PROFILES AT SCHOOL ENTRY WITH EARLY-ONSET MENTAL HEALTH CONDITIONS.

Thomson KC, Richardson CG, Gadermann AM, et al.

Importance: More than 50% of lifetime mental health disorders develop by early adolescence, and yet it is not well understood how early childhood social-emotional functioning varies in populations or how differences in functioning may be associated with emerging mental health conditions.

Objectives: To identify profiles of social-emotional functioning at kindergarten school entry (age 5 years) and to examine to what extent profiles are related to early-onset mental health conditions (ages 6-14 years).

Design, Setting, and Participants: This prospective cohort study followed up a population cohort of 34552 children in British Columbia, Canada, from birth (born 1996-1998) to age 14 years (last follow-up, December 31, 2011). Data were analyzed from the Developmental Trajectories cohort that links British Columbia child development data from the Early Development Instrument (EDI) to British Columbia Ministry of Health and Ministry of Education records. Data were analyzed between May and September 2017.

Exposures: Early childhood social-emotional functioning (defined as social competence, internalizing, and externalizing symptoms) rated by the children's kindergarten teachers.

Main Outcomes and Measures: Occurrences of physician-assessed mental health conditions throughout childhood and early adolescence, including depression, anxiety, conduct disorder, and attention-deficit/hyperactivity disorder (ADHD), calculated from billing codes from the International Classification of Diseases, Ninth Revision recorded in provincial health insurance data.

Results: Data from 34323 children (mean [SD] age, 5.7 [0.3] years; 17538 [51.1%] were boys) were analyzed at kindergarten and followed up to age 14 years (15204 completed follow-up). Latent profile analysis identified 6 unique social-emotional functioning profiles at school entry, with 41.6% of children (n = 14262) exhibiting comparative vulnerabilities in internalizing or externalizing behaviors. Prevalence of mental health conditions from ages 6 to 14 years was 4.0% for depression, 7.0% for anxiety, 5.5% for conduct disorder, 7.1% for ADHD, and 5.4% for multiple conditions. Zero-inflated Poisson analyses showed an association between social-emotional functioning profiles at kindergarten school entry and physician-assessed mental health conditions by age 14 years (range of adjusted odds ratios: depression, 1.10 [95% CI, 0.76-1.60] to 2.93 [95% CI, 1.93-4.44]; anxiety, 1.00 [95% CI, 0.74-1.36] to 1.73 [95% CI, 1.11-2.70]; conduct disorder, 2.17 [95% CI, 1.41-3.34] to 6.91 [95% CI, 4.90-9.74]; ADHD, 1.46 [95% CI, 1.11-1.93] to 8.72 [95% CI, 6.46-11.78]; and multiple conditions, 1.20 [95% CI, 0.88-1.63] to 6.81 [95% CI, 4.91-9.44]). Children with higher teacher ratings of aggression and hyperactivity had more frequent consultations for conduct disorder, ADHD, and multiple conditions.

Conclusions and Relevance: This study's findings suggest that more than 40% of children enter the school system with relative vulnerabilities in social-emotional functioning that are associated with early-onset mental health conditions. The results raise important questions for using population-level early childhood development monitoring in the context of universal and proactive mental health strategies

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JAMA Network Open. 2019;2.

TRENDS IN THE PREVALENCE AND INCIDENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG ADULTS AND CHILDREN OF DIFFERENT RACIAL AND ETHNIC GROUPS.

Chung W, Jiang S-F, Paksarian D, et al.

Importance: An increasing prevalence of adult attention-deficit/hyperactivity disorder (ADHD) diagnosis and treatment has been reported in clinical settings and administrative data in the United States. However, there are limited data on recent trends of adult ADHD diagnosis among racial/ethnic subgroups.

Objective: To examine trends, including associated demographic characteristics, psychiatric diagnoses, and negative outcomes, in the prevalence and incidence of adult ADHD diagnosis among 7 racial/ethnic groups during a 10-year period.
Design, Setting, and Participants: This cohort study investigated trends in the diagnosis of ADHD in adults who identified as African American or black, Native American, Pacific Islander, Latino or Hispanic, non-Hispanic white, Asian American, or other using the Kaiser Permanente Northern California health plan medical records. A total of 5282877 adult patients and 867453 children aged 5 to 11 years who received care at Kaiser Permanente Northern California from January 1, 2007, to December 31, 2016, were included. Data analysis was performed from January 2017 through September 2019. Exposures: Period of ADHD diagnosis.
Main Outcomes and Measures: Prevalence and incidence of licensed mental health clinician-diagnosed ADHD in adults and prevalence of licensed mental health clinician-diagnosed ADHD in children aged 5 to 11 years.
Results: Of 5282877 adult patients (1155790 [21.9%] aged 25-34 years; 2667562 [50.5%] women; 2204493 [41.7%] white individuals), 59371 (1.12%) received diagnoses of ADHD. Prevalence increased from 0.43% in 2007 to 0.96% in 2016. Among 867453 children aged 5 to 11 years (424449 [48.9%] girls; 260236 [30.0%] white individuals), prevalence increased from 2.96% in 2007 to 3.74% in 2016. During the study period, annual adult ADHD prevalence increased for every race/ethnicity, but white individuals consistently had the highest prevalence rates (white individuals: 0.67%-1.42%; black individuals: 0.22%-0.69%; Native American individuals: 0.56%-1.14%; Pacific Islander individuals: 0.11%-0.39%; Hispanic or Latino individuals: 0.25%-0.65%; Asian American individuals: 0.11%-0.35%; individuals from other races/ethnicities: 0.29%-0.71%). Incidence of ADHD diagnosis per 10000 person-years increased from 9.43 in 2007 to 13.49 in 2016. Younger age (eg, >65 years vs 18-24 years: odds ratio [OR], 0.094; 95% CI, 0.088-0.101; P <.001), male sex (women: OR, 0.943; 95% CI, 0.928-0.959; P <.001), white race (eg, Asian patients vs white patients: OR, 0.248; 95% CI, 0.240-0.257; P <.001), being divorced (OR, 1.131; 95% CI, 1.093-1.171; P <.001), being employed (eg, retired vs employed persons: OR, 0.278; 95% CI, 0.267-0.290; P <.001), and having a higher median education level (OR, 2.156; 95% CI, 2.062-2.256; P <.001) were positively associated with odds of ADHD diagnosis. Having an eating disorder (OR, 5.192; 95% CI, 4.926-5.473; P <.001), depressive disorder (OR, 4.118; 95% CI, 4.030-4.207; P <.001), bipolar disorder (OR, 4.722; 95% CI, 4.556-4.894; P <.001), or anxiety disorder (OR, 2.438; 95% CI, 2.385-2.491; P <.001) was associated with higher odds of receiving an ADHD diagnosis. Adults with ADHD had significantly higher odds of frequent health care utilization (OR, 1.303; 95% CI, 1.272-1.334; P <.001) and sexually transmitted infections (OR, 1.289; 95% CI 1.251-1.329; P <.001) compared with adults with no ADHD diagnosis.
Conclusions and Relevance: This study confirmed the reported increases in rates of ADHD diagnosis among adults, showing substantially lower rates of detection among minority racial/ethnic subgroups in the United States. Higher odds of negative outcomes reflect the economic and personal consequences that substantiate the need to improve assessment and treatment of ADHD in adults.

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JAMA Psychiatry. 2019.
ASSOCIATION OF CORD PLASMA BIOMARKERS OF IN UTERO ACETAMINOPHEN EXPOSURE WITH RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN CHILDHOOD.
Ji Y, Azuine RE, Zhang Y, et al.
Importance: Prior studies have raised concern about maternal acetaminophen use during pregnancy and increased risk of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in their children; however, most studies have relied on maternal self-report.
Objective: To examine the prospective associations between cord plasma acetaminophen metabolites and physician-diagnosed ADHD, ASD, both ADHD and ASD, and developmental disabilities (DDs) in childhood.
Design, Setting, and Participants: This prospective cohort study analyzed 996 mother-infant dyads, a subset of the Boston Birth Cohort, who were enrolled at birth and followed up prospectively at the Boston Medical Center from October 1, 1998, to June 30, 2018.

Exposures: Three cord acetaminophen metabolites (unchanged acetaminophen, acetaminophen glucuronide, and 3-[N-acetyl-l-cystein-S-yl]-acetaminophen) were measured in archived cord plasma samples collected at birth.
Main Outcomes and Measures: Physician-diagnosed ADHD, ASD, and other DDs as documented in the child's medical records.
Results: Of 996 participants (mean [SD] age, 9.8 [3.9] years; 548 [55.0%] male), the final sample included 257 children (25.8%) with ADHD only, 66 (6.6%) with ASD only, 42 (4.2%) with both ADHD and ASD, 304 (30.5%) with other DDs, and 327 (32.8%) who were neurotypical. Unchanged acetaminophen levels were detectable in all cord plasma samples. Compared with being in the first tertile, being in the second and third tertiles of cord acetaminophen burden was associated with higher odds of ADHD diagnosis (odds ratio [OR] for second tertile, 2.26; 95% CI, 1.40-3.69; OR for third tertile, 2.86; 95% CI, 1.77-4.67) and ASD diagnosis (OR for second tertile, 2.14; 95% CI, 0.93-5.13; OR for third tertile, 3.62; 95% CI, 1.62-8.60). Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen buden and ADHD and acetaminophen burden and ASD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex, for which point estimates for the ORs vary from 2.3 to 3.5 for ADHD and 1.6 to 4.1 for ASD.
Conclusions and Relevance: Cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD and ASD in a dose-response fashion. Our findings support previous studies regarding the association between prenatal and perinatal acetaminophen exposure and childhood neurodevelopmental risk and warrant additional investigations.

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JAMA Psychiatry. 2019;76:1119-21.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, HYPOMANIA, AND BIPOLAR DISORDER IN YOUTH.
Moran LV, Guvenek-Cokol PE, Perlis RH.

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J Abnorm Child Psychol. 2019 Nov;47:1759-70.
USING REPEATED-MEASURES DATA TO MAKE STRONGER TESTS OF THE ASSOCIATION BETWEEN EXECUTIVE FUNCTION SKILLS AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMATOLOGY IN EARLY CHILDHOOD.
Willoughby MT, Wylie AC, Blair CB.
Theoretical models of Attention deficit/hyperactivity disorder (ADHD) have long implicated executive function (EF) skills as contributing to the etiology, maintenance, and changes in ADHD symptomatology over time. Although there is interest making within-person inferences (i.e., deficits in EF skills give rise to ADHD behaviors), most of the evidence has been derived from studies that conflated between- and within-person sources of variance. Here, we use repeated-measures data to test within-person association between EF skills and ADHD behaviors. Participants included 1160 children from the Family Life Project, an ongoing prospective longitudinal study of child development in low-income, nonmetropolitan communities. We tested the magnitude of the association between EF skills and ADHD behaviors when children were 3, 4, and 5 years old. Consistent with meta-analyses, unadjusted bivariate associations between EF and ADHD (which reflect combined between- and within-person variation) were of moderate magnitude (rs = -0.20 to -0.30). However, after controlling for all time-invariant, between-person sources of variation, the within-person associations between EF skills and ADHD behaviors were weak (ßs -0.04 to -0.05, ps = 0.01). These results suggest that EF skills may contribute less prominently to ADHD behaviors in early childhood than is commonly assumed and provoke broader questions about developmental models of ADHD

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J Adolesc Health. 2019;65:784-89.

QUANTIFYING THE PROTECTIVE EFFECTS OF STIMULANTS ON FUNCTIONAL OUTCOMES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A FOCUS ON NUMBER NEEDED TO TREAT STATISTIC AND SEX EFFECTS.

Biederman J, DiSalvo M, Fried R, et al.

Purpose: The aim of the study was to help quantify the protective effects of stimulant treatment on important functional outcomes in attention-deficit/hyperactivity disorder (ADHD) using the number needed to treat (NNT) statistic and examine whether these effects are moderated by sex.

Methods: Subjects were derived from three independent samples, two similarly designed case-control, 10-year prospective follow-up studies of boys and girls with and without ADHD grown up and a cross-sectional randomized clinical trial of lisdexamfetamine on driving performance and behavior. For all studies, subjects were evaluated with structured diagnostic interviews. To measure psychopharmacologic treatment in the follow-up studies, we collected information about each subject's stimulant medication use, age at onset, and age at termination of treatment. Subjects in the driving study underwent two driving simulation assessments (premedication and after 6 weeks of treatment on lisdexamfetamine or placebo). For each outcome, we ran a logistic regression model that included an interaction between sex and treatment status. Lifetime rates were used to calculate the NNT statistic. We also calculated adjusted NNT statistics that accounted for sex, age, socioeconomic status, and family intactness.

Results: The NNTs were very low, ranging from 3 to 10. No interaction effects with sex were detected (all p > .05). The adjusted NNTs mostly remained the same with the exception of any substance use disorder, which increased after controlling for age.

Conclusions: Stimulants have strong protective effects on functional outcomes in youth with ADHD that are not moderated by sex. These results support the critical importance of early identification and treatment of children with ADHD of both sexes

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J Appl Behav Anal. 2019;52:1076-88.

ACCUMULATED REINFORCERS INCREASE ACADEMIC RESPONDING AND SUPPRESS PROBLEM BEHAVIOR FOR STUDENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Robinson N, St.Peter CC.

We compared rates of academic responses and problem behavior during mathematics with distributed and accumulated reinforcer arrangements for 3 students with Attention-Deficit Hyperactivity Disorder who engaged in chronic, severe problem behavior. All 3 students engaged in more academic responding and less problem behavior when reinforcers accumulated throughout the session, relative to conditions in which reinforcers were distributed throughout the session or withheld completely. We then conducted concurrent-chain analyses to evaluate student preference for the reinforcer arrangements. Two students preferred distributed reinforcers, even though this arrangement continued to produce problem behavior. One student preferred accumulated reinforcers. Our data replicate previous findings regarding the efficacy of accumulated-reinforcer arrangements, but suggest that students do not always prefer the most efficacious reinforcer arrangement

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J Autism Dev Disord. 2019.

ADAPTATION OF DIAGNOSIS FROM AUTISM SPECTRUM DISORDER TO SOCIAL COMMUNICATION DISORDER IN ADOLESCENTS WITH ADHD.

Tsai L-H, Lin J-W.

Here, we describe a case in which an original diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and Asperger's syndrome was later adapted to social communication disorder, to meet the new guidelines. First, separate diagnostic labels of autism disorder, Asperger's disorder, and PDD-NOS have been replaced by one umbrella term autism spectrum disorder. Second, the new DSM-5 criteria are more stringent than the old criteria. For example, observation of a higher number of symptoms is necessary to meet the criteria, such as restricted interests and repetitive behaviors. Third, the communication and social interaction domains are

combined into one, titled social/communication deficits. Finally, requirement of a delay in language development is no longer necessary to establish a diagnosis of autism

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Journal of Behavioral Addictions. 2019;8:81-82.

SERIAL MULTIPLE MEDIATION EFFECTS OF SELF-CONTROL AND AGGRESSION IN THE RELATIONSHIP BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND INTERNET GAMING ADDICTION IN ADOLESCENTS USING THREE-WAVE LONGITUDINAL DATA.

Yim HW, Jeong H, Jo S-J, et al.

This study aims to investigate serial multiple mediation effect of self-control and aggression in the relationship between ADHD symptoms and risk of IGD in adolescents using 3 wave iCURE study. The study participants consisted of 1,754 secondary school students (male: 1,005 (57.3%), female: 749 (46.7%). We hypothesized that ADHD symptoms (T1) would indirectly infuence development of risk of IGD (T3) through causally linked multiple mediators of self-control (T1) and aggression (T2). The model was tested for serial multiple mediation to see how they would be impact on each other. The total effect of ADHD (T1) on risk of IGD (T3) was signifcant (+¦ = 0.40, 95%CI: 0.26-0.57). Serial-multiple mediation effects of self- control (T1) and aggression (T2), single mediation effect of self-control (T1), and single mediation effect of aggression (T2) were found to be statistically signifcant in the relationship between ADHD (T1) on risk of IGD (T3) (+¦ = 0.044, 95%CI: 0.024-0.075, +¦ = 0.09, 95%CI: 0.045-0.159, and +¦ = 0.046, 95%CI: 0.018-0.09, respectively). These results may help us to see how ADHD symptoms (T1) and risk of IGD are linked and what the fundamental mediators are in the chain

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Journal of Behavioral Addictions. 2019;8:99-100.

SOCIAL MEDIA DISORDER, ADHD-SYMPTOMS, AND MENTAL HEALTH: LONGITUDINAL INVESTIGATIONS OF DIRECTIONALITY AMONG ADOLESCENTS.

Boer M, Stevens GWJM, Finkenauer C, et al.

Cross-sectional research shows that symptoms of social media disorder (SMD) and symptoms of Attention Defcit Hyperactivity Disorder (ADHD) are related. Due to the lack of longitudinal studies, the direction of this relation remains unknown. The present study aims to address this gap by investigating the bidirectional relation between ADHD-symptoms and SMD- symptoms using longitudinal data. Also, the direction of the relation between ADHD-symptoms and frequency of social media use was examined. A three-wave longitudinal study among Dutch secondary school students aged 11 - 15 years was used (n = 543). Findings from a random intercept cross-lagged panel model suggest a unidirectional relation, whereby SMD-symptoms increased ADHD-symptoms over time. Furthermore, no longitudinal associations between frequency of social media use and ADHD-symptoms were found. This implies that disordered use of social media, rather than highly-engaged use of social media, has harmful implications for adolescents' ADHD-symptoms. In addition, bidirectional re- lations between SMD-symptoms and mental health outcomes will be examined, including life satisfaction and depression symptoms. Findings of these studies are considered to be an important step towards understanding the relation between disordered use of social media and adolescent mental health. Promising directions for continuing longitudinal research will be discussed

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J Child Adolesc Psychopharmacol. 2019;29:725.

RE: "DASOTRALINE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SIX-WEEK, PLACEBO-CONTROLLED, FIXED-DOSE TRIAL" BY FINDLING ET AL. (J CHILD ADOLESC PSYCHOPHARMACOL 2019;29:80-89).

Mosholder AD, Kim J, Davis M, et al.

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J Child Adolesc Psychopharmacol. 2019;29:688-704.

MINERAL-VITAMIN TREATMENT ASSOCIATED WITH REMISSION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND RELATED PROBLEMS: 1-YEAR NATURALISTIC OUTCOMES OF A 10-WEEK RANDOMIZED PLACEBO-CONTROLLED TRIAL.

Darling KA, Eggleston MJF, Retallick-Brown H, et al.

Objective: This article presents 1-year follow-up of a randomized placebo-controlled trial with open-label extension evaluating the efficacy of a broad-spectrum micronutrient (vitamins and minerals) intervention. The object was to determine if dominant treatment at follow-up was associated with differential psychological outcomes.

Methods: Ninety percent of the original sample of 93 children with attention-deficit/hyperactivity disorder (ADHD) were followed 52 weeks postbaseline. Assessments included measures of ADHD, mood, anxiety, and general function based on parent/clinician report. Outcome was considered based on dominant therapy at 52 weeks (trial micronutrients [n = 19], medications [n = 21], and no treatment [n = 35]). Nine children were not categorized due to inconsistent therapies.

Results: Based on dominant treatment, more of those who stayed on trial micronutrients (84%) were identified as "Much" or "Very Much" improved overall relative to baseline functioning, compared to 50% of those who switched to psychiatric medications and only 21% of those who discontinued treatment [¤ç2(2) = 19.476, p < 0.001]. Fifteen (79%) of those still taking micronutrients, 8 (42%) of those using medications, and 7 (23%) of those who discontinued treatment were considered remitters based on parent-reported ADHD [¤ç2(2) = 15.3, p < 0.001]. Those who stayed on micronutrients were more likely to have failed medication treatment in the past. The micronutrient group also displayed better outcomes on measures of parent-rated hyperactivity and anxiety, and clinician-rated general function and mood, with moderate to large between-group effect sizes (micronutrients vs. medication: ES = 0.73-1.01; micronutrients vs. no treatment: ES = 0.54-1.01). Most common reasons for stopping trial micronutrients were cost and number of pills to swallow. No continued side effects were associated with micronutrients.

Conclusions: Children who benefitted from micronutrients in the short term maintained changes at follow-up, without side effects. While both those who continued micronutrients and those who switched to medication showed improved ADHD symptoms, psychiatric medication use was associated with deterioration in mood and anxiety. Inherent selection bias limits generalizability

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J Child Adolesc Psychopharmacol. 2019;29:670-87.

THE EFFECT OF VITAMIN D SUPPLEMENTATION ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Gan J, Galer P, Ma D, et al.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted to assess the benefits and harms of vitamin D supplementation for attention-deficit/hyperactivity disorder (ADHD) patients.

Methods: We followed the standard methodological procedures of the Cochrane Handbook for Systematic Reviews of Intervention. PubMed, Embase, the Cochrane Central Register of Controlled Trials, Science and Conference Proceedings Citation Index-Social Science and Humanities (Web of Science), ClincalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform were searched for RCTs in January 2019. Independently, two authors (J.G., T.X.) extracted data, assessed the risk of bias, combined the data, and graded evidence quality using the Grading of Recommendations Assessment, Development, and Evaluation approach. Our primary outcomes were assessed through rating scales of ADHD severity. Secondary outcomes measured were the possible adverse effects of vitamin D supplementation and vitamin D status after supplementation for ADHD.

Results: We included four RCTs with 256 children addressing vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms. Vitamin D supplementation demonstrated a small but statistically significant improvement in ADHD total scores, inattention scores, hyperactivity scores, and behavior scores. The improvement was likely limited due to the low to very low quality of evidence in the literature. There was no statistically significant improvement in oppositional scores. Reported adverse events

in the vitamin D group were mild and not significantly different from the control group. Vitamin D supplementation increased serum vitamin D levels and the ratio of patients with sufficient vitamin D levels.
Conclusions: Vitamin D supplementation as adjunctive therapy to methylphenidate appeared to reduce ADHD symptoms without serious adverse events, associated with improved vitamin D status. However, considering the generally low strength of evidence, well-designed RCTs are needed to determine the efficacy and safety of vitamin D supplementation for both children and adults with ADHD, especially in the setting of a combination of vitamin D and other ADHD treatments

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J Child Neurol. 2019.
CLINICAL FEATURES OF TOURETTE SYNDROME.
Gill CE, Kompoliti K .
Tourette syndrome is a multifaceted disorder characterized by multiple motor and at least one vocal tics that start in childhood, persist for at least 1 year, and cannot be attributed to another medical condition or exposure to medications/drugs. Clinical diagnostic criteria are available, and identification of tics is typically straightforward based on characteristic appearance and features. Diagnostic uncertainty can rarely arise in cases of mild tics, atypical features, certain psychiatric comorbidities, and other non-tic movement disorders. Comorbid psychopathology, including attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive behaviors/obsessive-compulsive disorder, affects the majority of patients and is correlated with disease severity and the presence of additional psychiatric behaviors. The severity of tics often improves after adolescence, whereas psychiatric symptoms typically persist. The subset of patients in whom tics persist into adulthood experience higher rates of anxiety, and lower self-esteem, socioeconomic status, and quality of life; the relative contribution of motor tics and psychopathology is not fully understood. This article summarizes the clinical features of Tourette syndrome, including major diagnostic criteria, unique features of tics, and key aspects that differentiate tics from common mimics and chameleons. Comorbid psychiatric conditions and their impact on phenotype and quality of life are described. Finally, current understanding of the natural history is summarized, including limited research in adults with Tourette syndrome

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J Child Psychol Psychiatry. 2019 Nov;60:1219-29.
INTRAINDIVIDUAL VARIABILITY OF SLEEP/WAKE PATTERNS IN ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Langberg JM, Breaux RP, Cusick CN, et al.
Background: Prior studies examining the sleep of adolescents with and without attention-deficit/hyperactivity disorder (ADHD) have relied on mean values such as average sleep duration, which masks intraindividual variability (IIV). The objective was to investigate whether adolescents with ADHD have greater IIV of sleep/wake patterns than adolescents without ADHD using actigraphy and daily sleep diaries.
Method: Adolescents (ages 13.17 ± 0.40 years; 45% female) with (n = 162) and without (n = 140) ADHD were recruited from middle schools at two sites. Participants wore actigraphs and completed sleep diaries for an average of 2 weeks.
Results: Multilevel models were conducted with sex, sleep medication use, ADHD medication use, number of days with data, and social jetlag controlled for in analyses. For actigraphy, adolescents with ADHD had greater variability for time in bed, sleep onset and offset, and wake after sleep onset than adolescents without ADHD. For sleep diary data, adolescents with ADHD had greater variability in bedtime, wake time, sleep duration, sleep onset latency, sleep quality, and night wakings than adolescents without ADHD. Social jetlag was a significant predictor of variability in sleep measures based on both actigraph and daily diaries; however, ADHD status was not associated with social jetlag.
Conclusions: This is the first study to show that adolescents with ADHD have more variable sleep/wake patterns than their peers using both objective and subjective sleep measures. IIV of sleep/wake patterns may be important for clinicians to assess and monitor as part of treatment. Research is needed to understand the

mechanisms underlying increased IIV of sleep/wake patterns in adolescents with ADHD and potential consequences for daytime functioning

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J Child Psychol Psychiatry. 2019 Nov;60:1230-41.

IMPACT OF A BEHAVIORAL INTERVENTION, DELIVERED BY PEDIATRICIANS OR PSYCHOLOGISTS, ON SLEEP PROBLEMS IN CHILDREN WITH ADHD: A CLUSTER-RANDOMIZED, TRANSLATIONAL TRIAL.

Hiscock H, Mulraney M, Heussler H, et al.

Background: We have demonstrated the efficacy of a brief behavioral intervention for sleep in children with ADHD in a previous randomized controlled trial and now aim to examine whether this intervention is effective and cost-effective when delivered by pediatricians or psychologists in community settings.
Methods: Translational, cluster-randomized trial of a behavioral intervention versus usual care from 19th January, 2015 to 30th June, 2017. Participants (n = 361) were children aged 5–13 years with ADHD and parent report of a moderate/severe sleep problem who met criteria for American Academy of Sleep Medicine criteria for chronic insomnia disorder, delayed sleep–wake phase disorder, or were experiencing sleep-related anxiety. Participants were randomized at the level of the pediatrician (n = 61) to intervention (n = 183) or usual care (n = 178). Families in the intervention group received two consultations with a pediatrician or a psychologist covering sleep hygiene and tailored behavioral strategies.
Results: In an intention-to-treat analysis, at 3 and 6 months respectively, the proportion of children with moderate to severe sleep problems was lower in the intervention (28.0%, 35.8%) compared with usual care group (55.4%, 60.1%; 3 month: risk ratio (RR): 0.51, 95% CI 0.37, 0.70, p < .001; 6 month: RR: 0.58; 95% CI 0.45, 0.76, p < .001). Intervention children had improvements across multiple Children's Sleep Habits Questionnaire subscales at 3 and 6 months. No benefits of the intervention were observed in other domains. Cost-effectiveness of the intervention was AUD 13 per percentage point reduction in child sleep problem at 3 months.
Conclusions: A low-cost brief behavioral sleep intervention is effective in improving sleep problems when delivered by community clinicians. Greater sample comorbidity, lower intervention dose or insufficient clinician supervisions may have contributed to the lack benefits seen in our previous trial

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J Child Psychol Psychiatry. 2019 Nov;60:1191-99.

ASSESSING PHENOTYPIC AND POLYGENIC MODELS OF ADHD TO IDENTIFY MECHANISMS OF RISK FOR LONGITUDINAL TRAJECTORIES OF EXTERNALIZING BEHAVIORS.

Li JJ.

Background: Children with ADHD frequently engage in higher rates of externalizing behaviors in adulthood relative to children without. However, externalizing behaviors vary across development. Little is known about how this risk unfolds across development. Phenotypic and polygenic models of childhood ADHD were used to predict individual differences in adult externalizing trajectories. Supportive parenting, school connectedness, and peer closeness were then examined as causal mechanisms.
Methods: Data were from the National Longitudinal Study of Adolescent to Adult Health (N = 7,674). Externalizing behavior was measured using data from age 18 to 32 and modeled using latent class growth analysis. Child ADHD was measured using retrospective self-report (phenotypic model) and genome-wide polygenic risk scores (polygenic model). Multiple mediation models examined the direct and indirect effects of the phenotypic and polygenic models (separately) on externalizing trajectories through the effects of adolescent supportive parenting, school connectedness, and peer closeness.
Results: Phenotypic and polygenic models of ADHD were associated with being in the High Decreasing (3.2% of sample) and Moderate (16.1%) adult externalizing trajectories, but not the severe Low Increasing trajectory (2.6%), relative to the Normal trajectory (78.2%). Associations between both models of ADHD on the High Decreasing and Moderate trajectories were partially mediated through the effects of school connectedness, but not supportive parenting or peer closeness.

Conclusions: Findings shed light on how childhood ADHD affects downstream psychosocial processes that then predict specific externalizing outcomes in adulthood. They also reinforce the importance of fostering a strong school environment for adolescents with (and without) ADHD, as this context plays a critical role in shaping the development of externalizing behaviors in adulthood

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J Clin Exp Neuropsychol. 2019 Nov;41:933-45.

A MULTI-FACTORIAL PERSPECTIVE ON ADHD AND ODD IN SCHOOL-AGED CHILDREN: WHAT IS THE ROLE OF COGNITIVE REGULATION, TEMPERAMENT, AND PARENTAL SUPPORT?

Frick MA, Brocki KC.

Introduction: It is well established that attention-deficit/hyperactivity disorder (ADHD) is a disorder of self-regulation. As such, ADHD is associated with disturbed cognitive regulation, extreme temperament traits, and deficient extrinsic regulation such as parenting. Despite these associations, cognitive regulation, temperament, and parenting have not previously been examined simultaneously in relation to ADHD symptoms in school-aged children. To bridge this gap of knowledge, we examined effects of these important aspects of self-regulation on symptoms of inattention, hyperactivity/impulsivity, and comorbid symptoms of oppositional defiant disorder (ODD) in children with and without a diagnosis of ADHD.

Method: The sample consisted of 77 children aged 8 to 12 years (~40% had a diagnosis of ADHD). We assessed cognitive regulation (i.e., complex inhibition and working memory) during a lab visit and parents rated child temperament (negative affect, surgency, and effortful control) and parental support. Parents and teachers rated ADHD and ODD symptoms in the child. We performed continuous analyses, informed by a dimensional perspective on ADHD.

Results: Working memory contributed independently to inattention (ß = -.19, p < .05). Effortful control contributed independently to inattention and hyperactivity/impulsivity (ßs = -.50 and -.49, ps < .01). Negative affect contributed to ODD symptoms as moderated by parental support (ß = .58, p < .01). Specifically, for children who received lower levels of parental support there was a significant positive association between negative affect and ODD symptoms.

Conclusions: The results propose that both cognitive regulation and effortful control influence ADHD symptoms. Moreover, different factors seem to be involved in ADHD and ODD, with regulatory deficits specifically related to ADHD symptoms, and elevated negative affect specifically related to ODD symptoms. Interestingly, parenting moderated the relationship between negative affect and ODD symptoms, with a suggested protective effect of high parental support for children with high levels of negative affect

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Journal of Clinical Medicine. 2019;8.

STRESS EXPOSURE AND THE COURSE OF ADHD FROM CHILDHOOD TO YOUNG ADULTHOOD: COMORBID SEVERE EMOTION DYSREGULATION OR MOOD AND ANXIETY PROBLEMS.

Hartman CA, Rommelse N, van der Klugt CL, et al.

Background: Compared to typically developing individuals, individuals with attention-deficit-hyperactivity disorder (ADHD) are on average more often exposed to stressful conditions (e.g., school failure, family conflicts, financial problems). We hypothesized that high exposure to stress relates to a more persistent and complex (i.e., multi-problem) form of ADHD, while low-stress exposure relates to remitting ADHD over the course of adolescence.

Method: Longitudinal data (ages 11, 13, 16, and 19) came from the Tracking AdolescentsΓÇÖ Individual Life Survey (TRAILS). We selected children diagnosed with ADHD (n = 244; 167 males; 77 females) from the TRAILS clinical cohort and children who screened positive (n = 365; 250 males; 115 females) and negative (gender-matched: n = 1222; 831 males; 391 females) for ADHD from the TRAILS general population sample cohort (total n = 1587). Multivariate latent class growth analysis was applied to parent-and self-ratings of stress exposure, core ADHD problems (attention problems, hyperactivity/impulsivity), effortful control, emotion dysregulation (irritability, extreme reactivity, frustration), and internalizing problems (depression, anxiety, somatic complaints).

Results: Seven distinct developmental courses in stress exposure and psychopathology were discerned, of which four related to ADHD. Two persistent ADHD courses of severely affected adolescents were associated with very high curvilinear stress exposure peaking in mid-adolescence: (1) Severe combined type with ongoing, severe emotional dysregulation, and (2) combined type with a high and increasing internalization of problems and elevated irritability; two partly remitting ADHD courses had low and declining stress exposure: (3) inattentive type, and (4) moderate combined type, both mostly without comorbid problems.
Conclusions: High-stress exposure between childhood and young adulthood is strongly intertwined with a persistent course of ADHD and with comorbid problems taking the form of either severe and persistent emotion dysregulation (irritability, extreme reactivity, frustration) or elevated and increasing irritability, anxiety, and depression. Conversely, low and declining stress exposure is associated with remitting ADHD and decreasing internalizing and externalizing problems. Stress exposure is likely to be a facilitating and sustaining factor in these two persistent trajectories of ADHD with comorbid problems into young adulthood. Our findings suggest that a bidirectional, continuing, cycle of stressors leads to enhanced symptoms, in turn leading to more stressors, and so forth. Consideration of stressful conditions should, therefore, be an inherent part of the diagnosis and treatment of ADHD, to potentiate prevention and interruption of adverse trajectories

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J Clin Sleep Med. 2019;15:1433-42.

RATES OF MENTAL HEALTH SYMPTOMS AND ASSOCIATIONS WITH SELF-REPORTED SLEEP QUALITY AND SLEEP HYGIENE IN ADOLESCENTS PRESENTING FOR INSOMNIA TREATMENT.

Van Dyk TR, Becker SP, Byars KC.

Study Objectives: Despite high prevalence rates of both psychopathology and sleep problems during adolescence, as well as frequent co-occurrence, little is known about the mental health of adolescents presenting for insomnia evaluation and treatment. This study describes (1) rates of mental health symptoms and (2) associations of mental health symptoms with sleep behaviors and schedules in adolescents presenting to a behavioral sleep medicine clinic within an accredited sleep disorders center.
Methods: As a part of routine clinical care, 376 adolescents (ages 11 to 18 years) presenting for insomnia evaluation completed measures of insomnia and sleep behavior. Their caregiver reported on mental health diagnoses and symptoms.
Results: Adolescents had high rates of mental health diagnoses (75%) and clinically elevated symptoms (64%). Affective, anxiety, and attention deficit-hyperactivity disorder (ADHD) symptoms were most commonly reported. Mental health symptoms were related to sleep behaviors and insomnia severity, with ADHD symptoms and affective problems most consistently associated with disrupted sleep.
Conclusions: Health providers should assess for mental health problems in youth presenting with sleep-related concerns. Intervening with both sleep and mental health problems should be considered to most effectively improve functioning

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J Fam Psychol. 2019 Nov.

LIFETIME CAREGIVER STRAIN AMONG MOTHERS OF ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Babinski DE, Mazzant JR, Merrill BM, et al.

The lifetime maternal caregiver strain (CS) associated with raising a child with attention-deficit/hyperactivity disorder (ADHD) into adolescence and young adulthood was examined in the Pittsburgh ADHD Longitudinal Study (PALS), a longitudinal study of individuals diagnosed with ADHD in childhood and recontacted in adolescence and young adulthood for yearly follow-up. Mothers of adolescents/young adults with (n = 364, 89.6% male; Mage = 19.79) and without childhood ADHD (n = 240, 88.8% male; Mage = 18.97) rated their lifetime maternal CS at Wave 3. Adolescent/young adult (AYA) ADHD and ODD severity measured at Wave 1, AYA delinquency measured at Wave 2, and school disciplinary actions combined from Waves 1 and 2 were explored as mediators of the association between childhood ADHD and lifetime maternal CS at Wave 3 using path analysis. AYA gender and age, parental marital status, maternal depression and ADHD, and

highest parental education were included as covariates. Greater lifetime CS was reported among mothers of adolescents/young adults with versus without childhood ADHD. In the mediation model, direct effects of childhood ADHD on AYA ADHD and ODD severity, delinquency, and school discipline problems emerged, and direct effects of AYA ODD severity, delinquency, and school discipline problems on lifetime CS emerged. AYA ODD, delinquency, and school discipline mediated the association between childhood ADHD and lifetime maternal CS. These findings extend research on childhood ADHD to identify AYA sequelae contributing to maternal CS. Future research on the transaction between AYA functional impairment and maternal CS across the transition from adolescence into adulthood is needed to clarify opportunities for intervention

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J Neural Transm. 2019 Nov;126:1513-16.

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

Dorman Ilan S, 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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Journal of Neurogenetics. 2019.

DOPAMINERGIC GENE ANALYSIS INDICATES INFLUENCE OF INATTENTION BUT NOT IQ IN EXECUTIVE DYSFUNCTION OF INDIAN ADHD PROBANDS.

Maitra S, Chatterjee M, Sinha S, et al.

Organizational inefficiency and inattention are speculated to be the reason for executive deficit (ED) of ADHD probands. Even with average IQ, probands often perform poorly due to higher inattention. Pharmacotherapy, cognitive behavioural therapy, and counselling provide only symptomatic relief. Several candidate genes showed involvement with ADHD; the most consistent are dopamine receptor 4 (DRD4) and solute carrier family 6 member 3 (SLC6A3). We analyzed association of rarely investigated DRD4 and SLC6A3 variants with ADHD core traits in Indo-Caucasoid probands. ED, inattention, organizational efficiency, and IQ were measured by Barkley Deficit in Executive Functioning-Child & Adolescent scale, DSM-IV-TR, ConnersΓÇÖ Parent Rating Scale-revised, and WISC respectively. Target sites were analyzed by PCR, RFLP, and/or Sanger sequencing of genomic DNA. DRD4 variants mostly affected inattention while SLC6A3 variants showed association with IQ. Few DRD4 and SLC6A3 variants showed dichotomous association with IQ and inattention. DRD4 Exon3 VNTR >4R showed negative impact on all traits excepting IQ. Inattention showed correlation with attention span, organizational efficiency, and ED, while IQ failed to do so. We infer that IQ and attention could be differentially regulated by dopaminergic gene variants affecting functional efficiency in ADHD and the two traits should be considered together for providing better rehabilitation

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Journal of Pain Research. 2019;12:2925-32.

CHRONIC PAIN AND HEALTH-RELATED QUALITY OF LIFE IN WOMEN WITH AUTISM AND/OR ADHD: A PROSPECTIVE LONGITUDINAL STUDY.

Asztely K, Kopp S, Gillberg C, et al.

Purpose: To investigate the prevalence of chronic pain and its association with healthrelated quality of life (HRQoL) in a group of women, diagnosed with autism spectrum disorder (ASD) and/or attention deficit hyperactive disorder (ADHD) in childhood.

Patients and methods: Prospective longitudinal 16-19 years follow-up study of 100 Swedish females diagnosed with ASD and/or ADHD in childhood/adolescence. Seventyseven of the women were included in the current sub-study, using validated measures of pain perception and quality of life.
Results: A large majority of the women (76.6%) reported chronic pain. HRQoL was low overall and lower still for those reporting chronic pain. Women with ADHD who had ongoing treatment with stimulants reported a significant lower prevalence of chronic widespread pain (CWP) than those not treated.
Conclusion: Comorbidity with chronic pain is common in women with ASD and/or ADHD and important to address in the clinic since it is associated with an already low HRQoL. Treatment for ADHD might reduce the pain in some cases

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J Sleep Res. 2019.
EVENING CIRCADIAN PREFERENCE IS ASSOCIATED WITH SLEEP PROBLEMS AND DAYTIME SLEEPINESS IN ADOLESCENTS WITH ADHD.
Becker SP, Kapadia DK, Fershtman CEM, et al.
Adolescence is a developmental period characterized by disruptions in sleep and changes in circadian preferences. Although adolescents with attention-deficit/hyperactivity disorder (ADHD) are at even higher risk of sleep disruption than their peers, no study has examined whether circadian preference is associated with sleep problems and daytime sleepiness in adolescents with ADHD. This study provides an initial test of the hypothesis that greater evening preference would be associated with more sleep problems and daytime sleepiness in adolescents diagnosed with ADHD. Participants were 80 adolescents (69% male), aged 13ΓÇô17 years, with ADHD. Adolescents completed measures assessing circadian preference, pubertal development, anxiety/depressive symptoms and weeknight sleep duration. Both adolescents and parents completed measures of sleep problems and daytime sleepiness. In regression analyses controlling for a number of other variables (i.e., age, sex, pubertal development, ADHD medication use, and ADHD, oppositional defiant disorder and internalizing symptom severity), greater evening preference was associated with both adolescent- and parent-reported sleep problems and daytime sleepiness. Greater evening preference remained significantly associated with each of these sleep problems and daytime sleepiness when also controlling for weeknight sleep duration. This is the first study to demonstrate that evening circadian preference is associated with both sleep problems and daytime sleepiness in adolescents with ADHD. The results indicate that it is important to consider circadian function as research examining sleep in adolescents with ADHD continues to advance

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J Am Acad Child Adolesc Psychiatry. 2019.
TRAJECTORIES OF GROWTH ASSOCIATED WITH LONG-TERM STIMULANT MEDICATION IN THE MULTIMODAL TREATMENT STUDY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Greenhill LL, Swanson JM, Hechtman L, et al.
Objective: To estimate long-term stimulant treatment associations on standardized height, weight, and body mass index trajectories from childhood to adulthood in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA).
Method: Of 579 children with DSM-IV ADHD-combined type at baseline (aged 7.0ΓÇô9.9 years) and 289 classmates (local normative comparison group [LNCG]), 568 and 258 respectively, were assessed 8 times over 16 years (final mean age = 24.7). Parent interview data established subgroups with self-selected Consistent (n = 53, 9%), Inconsistent (n = 374, 66%), and Negligible (n = 141, 25%) stimulant medication use, as well as patients starting stimulants prior to MTA entry (n = 211, 39%). Height and weight growth trajectories were calculated for each subgroup.
Results: Height z scores trajectories differed among subgroups (F = 2.22, p <.0001) and by stimulant use prior to study entry (F = 2.22, p <.001). The subgroup-by-assessment interaction was significant (F = 2.81, p <.0001). Paired comparisons revealed significant subgroup differences at endpoint: Consistent was shorter than Negligible (0.66 z units /4.06 cm /1.6 inches, t = 3.17, p < 0.0016), Consistent shorter than Inconsistent

(0.45 z units /2.74 cm /1.08 inches, t = 2.39, p <.0172), and the Consistent shorter than LNCG (0.54 z units/+3.34 cm/ 1.31 inches, t = 3.30, p < 0.001). Weight z scores initially diverged among subgroups, converged in adolescence, and then diverged again in adulthood when the Consistent outweighed the LNCG (+ 3.561 z units /+7.47 kg /+16.46 lb, p <.0001).
Conclusion: Compared with those negligibly medicated and the LNCG, 16 years of consistent stimulant treatment of children with ADHD in the MTA was associated with changes in height trajectory, a reduction in adult height, and an increase in weight and body mass index.
Clinical trial registration information: Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); https://clinicaltrials.gov/; NCT00000388

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Korean J Pediatr. 2019;62:374-79.

THE MATERNAL PREPREGNANCY BODY MASS INDEX AND THE RISK OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Jenabi E, Bashirian S, Khazaei S, et al.

Background: Attention deficit hyperactivity disorder (ADHD) symptoms have a major impact on individuals, families, and society. Therefore identification risk factors of ADHD are a public health priority.
Purpose: This is meta-analysis evaluated the association between maternal prepregnancy body mass index and the risk of ADHD among the resulting offspring.
Methods: The search identified studies published through December 2018 in the PubMed, Web of Science, and Scopus databases. The odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CI) extracted from eligible studies were used as the common measure of association among studies.
Results: A significant association was found between overweight women and the risk of ADHD among children with the pooled HR and OR estimates (HR, 1.27 and 95% CI, 1.17-1.37; OR, 1.28 and 95% CI, 1.15-1.40, respectively). This association was significant between obese women and the risk of ADHD among children and adolescents with the pooled estimates of HR and OR (HR, 1.65 and 95% CI, 1.55ΓÇô1.76; OR, 1.42 and 95% CI, 1.23ΓÇô1.61).
Conclusion: The current epidemiological studies present sufficient evidence that prepregnancy overweight and obesity are significantly associated with an increased risk of ADHD among children and adolescents. These findings provide a new approach to preventing ADHD by controlling weight gain in the prenatal period, which should be considered by policymakers

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Lancet Psychiatry. 2019 Jun;6:493-505.

GENOTYPE-PHENOTYPE ASSOCIATIONS IN CHILDREN WITH COPY NUMBER VARIANTS ASSOCIATED WITH HIGH NEUROPSYCHIATRIC RISK IN THE UK (IMAGINE-ID): A CASE-CONTROL COHORT STUDY.

Chawner SJRA, Owen MJ, Holmans P, et al.

BACKGROUND: Several copy number variants (CNVs) are associated with a high risk of neurodevelopmental and psychiatric disorders (referred to as ND-CNVs). We aimed to characterise the effect of ND-CNVs on childhood development and investigate whether different ND-CNVs lead to distinct and specific patterns of cognitive and behavioural outcomes.
METHODS: In this case-control study, we used data from the Intellectual Disability and Mental Health: Assessing the Genomic Impact on Neurodevelopment (IMAGINE-ID) study. Children aged 4 years and older with pathogenic CNV or single nucleotide variants were recruited via the UK National Health Service (NHS) medical genetic clinic network and via patient support groups to complete broad online phenotyping, from whom children aged 6-19 years with at least one of a specific group of ND-CNVs (1q21.1 [proximal duplication, and distal deletion and duplication], 2p16.3 deletion, 9q34.3 deletion, 15q11.2 deletion, 15q13.3 deletion and duplication, 16p11.2 [proximal deletion and duplication, and distal deletion], and 22q11.2 deletion and duplication) and their families were approached for a deep phenotyping, home-based assessment, and we report on this sample here. We invited siblings of index children to participate as controls, for whom the presence of ND-CNVs was excluded by use of microarray results and also medical

records where possible. We systematically assessed the children for psychiatric disorders and broader traits of neurodevelopmental, cognitive, and psychopathological origin and compared results of ND-CNV carriers with control siblings to test the hypothesis that phenotypes would differ by genotype, both quantitatively in terms of severity and qualitatively in the pattern of associated impairments. FINDINGS: Between Oct 1, 2014, and Dec 31, 2018, of 2819 children recruited, 258 (9%) had one ND-CNV of interest, with 13 CNVs across nine loci, and underwent a home-based assessment. 106 control siblings were enrolled. 186 (80%) of ND-CNV carriers met criteria for one or more psychiatric disorder (odds ratio [OR] 13.8, 95% CI 7.2-26.3, compared with controls). The risk of attention-deficit hyperactivity disorder (OR 6.9, 3.2-15.1), oppositional defiant disorder (OR 3.6, 1.4-9.4), any anxiety disorder (OR 2.9, 1.2-6.7), and autism spectrum disorder traits (OR 44.1, 15.3-127.5) was particularly high compared with controls. ND-CNV carriers were impaired across all neurodevelopmental, cognitive, and psychopathological traits compared with controls. Only moderate quantitative and qualitative differences in phenotypic profile were found between genotypes. Overall, the range of phenotypes was broadly similar for all ND-CNV genotypes. Traits did show some evidence of genotypic specificity, with rank-based analyses showing moderate qualitative and quantitative profile differences between ND-CNVs; however, the specific genotype accounted for a low proportion of variance in cognitive and behavioural outcomes (approximately 5-20% depending on the trait).
INTERPRETATION: The 13 ND-CNVs studied have a similar range of adverse effects on childhood neurodevelopment, despite subtle quantitative and qualitative differences. Genomic risk for neuropsychiatric disorder has pleiotropic effects on multiple processes and neural circuits and indicates that future research should avoid being narrowly focused on single phenotypes.
FUNDING: UK Medical Research Council and Medical Research Foundation

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Lancet Psychiatry. 2019 Jun;6:528-37.
EMERGING CHALLENGES IN PHARMACOTHERAPY RESEARCH ON ATTENTION-DEFICIT HYPERACTIVITY DISORDER-OUTCOME MEASURES BEYOND SYMPTOM CONTROL AND CLINICAL TRIALS.
Wong ICK, Banaschewski T, Buitelaar J, et al.
Although pharmacological therapies are recommended as a key component in the treatment of attention-deficit hyperactivity disorder, their use continues to prompt intense debate. Despite considerable research efforts, several gaps in the knowledge base and several questions over the quality of evidence exist. Particular issues surrounding pharmacological treatments include uncertainties about long-term effectiveness and safety, safety profiles in adults, and the comparative effectiveness of different medications. In this Review, we focus on four key methodological issues for future research: (1) the use of appropriate trial designs; the need for (2) outcome measures targeting effectiveness beyond symptom control and (3) safety outcome measures; and (4) the application of clinical and administrative research databases to assess real-world outcomes. Potential solutions include increased use of randomised placebo-controlled withdrawal trials and large pharmacoepidemiological studies that use electronic health-care records on the long-term effectiveness and safety of medications. Pragmatic head-to-head randomised trials would also provide direct evidence on comparative effectiveness and safety profiles

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Med Lett Drugs Ther. 2019 Aug;61:126-28.
Jornay PM -- evening-dosed methylphenidate for ADHD.
Anon.

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Mental Health and Physical Activity. 2019;17.

MOTOR COMPETENCE MODERATES RELATIONSHIP BETWEEN MODERATE TO VIGOROUS PHYSICAL ACTIVITY AND RESTING EEG IN CHILDREN WITH ADHD.

Yu C-L, Chueh T-Y, Hsieh S-S, et al.

Background: Children with ADHD display abnormal electroencephalographic (EEG) activity, in particular an elevated theta to beta ratio (TBR) during the resting state.

Aims: To assess whether the motor competence (MC) and moderate to-vigorous physical activity (MVPA) were associated with TBR, and whether MC moderated the relationship between MVPA and TBR.

Methods: Data from a total of 73 children with ADHD (69 boys and 4 girls, mean age = 9.92 years, SD = 1.56 years) were analyzed. EEG readings were taken as participants rested with their eyes open. MC was assessed using the Movement ABC-2 measure, and MVPA was evaluated using an ActiGraph accelerometer.

Results: MC was negatively associated with TBR, and an interaction between MVPA and MC on TBR was observed. It was found that there was a negative correlation between MVPA and TBR in those with high MC, whereas the relationship was positive in those with low MC.

Conclusions and implications: The current study found that increased MC was associated with less deviant cortical activity in the resting state, as measured by TBR, and that MC moderated the relationship between MVPA and TBR after controlling for age. It highlights the importance of increasing motor competence within physical activity to improve cortical functioning of children with ADHD

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Minerva Pediatr. 2019 Jun;71:310-12.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN GENETICALLY-DETERMINED INTELLECTUAL DISABILITY.

Operto FF, Mazza R, Campanozzi S, et al.

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Minerva Pediatr. 2019;71:313-25.

EARLY MONITORING OF FATTY ACID PROFILE IN CHILDREN WITH ATTENTION DEFICIT AND/OR HYPERACTIVITY DISORDER UNDER TREATMENT WITH OMEGA-3 POLYUNSATURATED FATTY ACIDS .

Checa-Ros A, Haro-Garc+¡a A, Seiquer I, et al.

BACKGROUND: Cognitive effects of omega-3 polyunsaturated fatty acids (¤ë-3 PUFAs) might make them helpful in attention deficit/hyperactivity disorder (ADHD). However, the results derived from supplementation studies in children depend on the respective combinations and the study period. We aimed to investigate the serum fatty acid profile, attention scores and the tolerability in a group of ADHD children after receiving methylphenidate (MPH) and ¤ë-3 PUFAs for 1 month.

METHODS: A combination of MPH (1 mg/kg/day) and eicosapentaenoic (EPA, 70 mg/day) + docosahexaenoic acids (DHA, 250 mg/day) was administered to 40 ADHD children (7-15 years). An analysis of serum fatty acids by gas chromatography and an assessment of attention by using the Magallanes Scale of Visual Attention (MSVA) were carried out before and after 1 month of treatment.

RESULTS: Our data revealed significant decreases of several 6 PUFAs, like arachidonic acid ($P<0.0259$). EPA and DHA concentrations increased by 27% and 3% respectively, and the ¤ë-6/¤ë-3 index slightly decreased. The quality of attention significantly increased ($P<0.026$) and an improvement of ADHD core symptoms was reported both by parents and by teachers. No severe side effects occurred.

CONCLUSIONS: Results demonstrate that the combination of MPH and EPA+DHA at the tested doses has positive clinical effects and an adequate safety profile. Therefore, our study suggests that ¤ë-3 PUFAs may represent a feasible and a safe adjuvant therapy in children with ADHD and might enhance the effects of MPH. Further long-term follow-up studies are required to confirm these initial findings

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Mol Psychiatry. 2019.

INHIBITION-RELATED MODULATION OF SALIENCE AND FRONTOPARIETAL NETWORKS PREDICTS COGNITIVE CONTROL ABILITY AND INATTENTION SYMPTOMS IN CHILDREN WITH ADHD.

Cai W, Griffiths K, Korgaonkar MS, et al.

Attention-deficit hyperactivity disorder (ADHD) is associated with pervasive impairments in attention and cognitive control. Although brain circuits underlying these impairments have been extensively investigated with resting-state fMRI, little is known about task-evoked functional brain circuits and their relation to cognitive control deficits and inattention symptoms in children with ADHD. Children with ADHD and age, gender and head motion matched typically developing (TD) children completed a Go/NoGo fMRI task. We used multivariate and dimensional analyses to investigate impairments in two core cognitive control systems: (i) cingulo-opercular ΓÇ£salienceΓÇØ network (SN) anchored in the right anterior insula, dorsal anterior cingulate cortex (rdACC), and ventrolateral prefrontal cortex (rVLPFC) and (ii) dorsal frontoparietal central executive (FPN) network anchored in right dorsolateral prefrontal cortex (rDLPFC) and posterior parietal cortex (rPPC). We found that multivariate patterns of task-evoked effective connectivity between brain regions in SN and FPN distinguished the ADHD and TD groups, with rDLPFC-rPPC connectivity emerging as the most distinguishing link. Task-evoked rdACC-rVLPFC connectivity was positively correlated with NoGo accuracy, and negatively correlated with severity of inattention symptoms. Brain behavior relationships were robust against potential age, gender, and head motion confounds. Our findings highlight aberrancies in task-evoked modulation of SN and FPN connectivity in children with ADHD. Crucially, cingulo-frontal connectivity was a common locus of deficits in cognitive control and clinical measures of inattention symptoms. Our study provides insights into a parsimonious systems neuroscience model of cognitive control deficits in ADHD, and suggests specific circuit biomarkers for predicting treatment outcomes in childhood ADHD

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Mol Psychiatry. 2019.

THE NOREPINEPHRINE TRANSPORTER GENE MODULATES INTRINSIC BRAIN ACTIVITY, VISUAL MEMORY, AND VISUAL ATTENTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shang C-Y, Lin H-Y, Gau SSF.

The norepinephrine transporter gene (SLC6A2) and deficits in visual memory and attention were associated with attention-deficit/hyperactivity disorder (ADHD). The present study aimed to examine whether the SLC6A2 rs36011 (T)/rs1566652 (G) haplotype affected the intrinsic brain activity in children with ADHD and whether these gene-brain modulations were associated with visual memory and attention in this population. A total of 96 drug-naive children with ADHD and 114 typically developing children (TDC) were recruited. We analyzed intrinsic brain activity with regional homogeneity (ReHo) and degree centrality (DC). Visual memory and visual attention were assessed by the delayed matching to sample (DMS) and rapid visual information processing (RVIP) tasks, respectively. The SNP genotyping of rs36011 and rs1566652 was performed. Children with ADHD showed lower ReHo and DC in the cuneus and lingual gyri than TDC. The TG haplotype was associated with significantly increased DC in the right precentral and postcentral gyri. Significant interactions of ADHD status and the TG haplotype were found in the right postcentral gyrus and superior parietal lobule for ReHo. For the ADHD-TG group, we found significant correlations of performance on the DMS and RVIP tasks with ReHo in bilateral precentral-postcentral gyri and the right postcentral gyrus-superior parietal lobule and DC in bilateral precentral-postcentral gyri. A novel gene-brain-behavior association was identified in which the intrinsic brain activity of the sensorimotor and dorsal attention networks was related to visual memory and visual attention in ADHD children with the SLC6A2 rs36011 (T)/rs1566652 (G) haplotype

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Nature Neuroscience. 2019.

AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER HAVE A SIMILAR BURDEN OF RARE PROTEIN-TRUNCATING VARIANTS.

Satterstrom FK, Walters RK, Singh T, et al.

The exome sequences of approximately 8,000 children with autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD) and 5,000 controls were analyzed, finding that individuals with ASD and individuals with ADHD had a similar burden of rare protein-truncating variants in evolutionarily constrained genes, both significantly higher than controls. This motivated a combined analysis across ASD and ADHD, identifying microtubule-associated protein 1A (MAP1A) as a new exome-wide significant gene conferring risk for childhood psychiatric disorders

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Neuropsychopharmacology. 2019.

AUDITORY SENSORY GATING IN YOUNG ADOLESCENTS WITH EARLY-ONSET PSYCHOSIS: A COMPARISON WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Lemvigh CK, Jepsen JRM, Fagerlund B, et al.

Numerous studies have demonstrated impaired sensory gating in schizophrenia and this impairment has been proposed as a candidate biomarker for the disorder. The typical age of onset for schizophrenia is early adulthood, however a sizable group of patients present with psychotic symptoms before the age of 18, commonly referred to as early-onset psychosis (EOP). How an earlier onset influences sensory gating is currently unknown. Impaired sensory gating may not be specific to psychosis, but rather a shared disturbance of neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD). Therefore, the current study investigated P50 suppression in young adolescents (12ΓÇô17 years old) with either EOP (N = 55) or ADHD (N = 28) and age and gender matched healthy controls (HC) (N = 71). In addition to P50 suppression, N100 and P200 suppression data were also analyzed. No significant group differences in either raw mean P50 amplitude or mean P50 gating ratios were observed between EOP, ADHD, and HC. Additionally, we observed no P50 suppression deficit in those EOP patients diagnosed with schizophrenia (N = 39). Similarly, we observed no differences in N100 or P200 between the three groups. Healthy levels of P50 suppression were found in both patient groups. The results are in line with some previous studies showing healthy levels of P50 suppression in the early phases of schizophrenia. Our findings do not support P50 sensory gating as a valid biomarker for EOP or ADHD

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Niger J Clin Pract. 2019 Sep;22:1241-51.

PATTERN OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG PRIMARY SCHOOL CHILDREN IN ILE-IFE, SOUTH-WEST, NIGERIA.

Oke OJ, Oseni SB, Adejuyigbe EA, et al.

Background: One of the most common neurodevelopmental problems affecting behavior of children all over the world is attention deficit hyperactivity disorder (ADHD). Studies on ADHD prevalence in Africa used either parents' or teachers' disruptive behavioral disorder rating scale (DBDRS) to diagnose ADHD, but this study diagnose ADHD using both parents and teachers DBDRS simultaneously among primary school pupils in Ile-Ife.

Materials and Methods: The study was conducted among 1,385 primary school pupils in Ile-Ife using multistage random sampling. The parents' and teachers' DBDRS were used simultaneously to screen children who had ADHD.

Results: Sixty-five (4.7%) of the pupils had ADHD. Among the 65 pupils with ADHD, 28 (43%) had the inattentive subtype, 25 (38.5%) had the combined subtype, whereas 12 (18.5%) had hyperactive/impulsive subtype. The prevalence of ADHD was significantly higher in the younger age group than the older age groups (chi(2) = 7.153, P = 0.007). There was no significant association found between the prevalence of ADHD and the social class (chi(2) = 3.852, P = 0.146).

Conclusion: ADHD prevalence of 4.7% was found among the children in Ile-Ife. Assessment of children for ADHD was done by parents at home and teachers in the school with DBDRS. The inattentive subtype was the most common and the hyperactive subtype was the least seen in the study. Early diagnosis and treatment of this disorder will bring better outcome in the children

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Nord J Psychiatry. 2019.

THE CLINICAL RELEVANCE OF ASKING YOUNG PSYCHIATRIC PATIENTS ABOUT CHILDHOOD ADHD SYMPTOMS.

Richter M, Spangenberg H, Ramklint M, et al.

Aim: The aim of this study was to explore the relevance of asking young psychiatric patients about childhood symptoms of attention deficit hyperactivity disorder (ADHD).

Method: A total of 180 young adults (18ΓÇô25 years of age) from a general psychiatric out-patient clinic in Uppsala filled in the Child and Adolescent Psychiatric Screening Inventory-Retrospect (CAPSI-R) as part of the diagnostic procedure. The study population was divided into groups based on number and subtype of reported ADHD symptoms, inattention (IN) or hyperactivity/impulsivity (HI). The clinical characteristics associated with different symptoms of ADHD were explored.

Results: The groups with five or more self-reported ADHD childhood symptoms, of either IN or HI, had more psychiatric comorbid conditions, a significantly higher co-occurrence of substance use disorders and personality disorders, and experienced more psychosocial and environmental problems.

Conclusion: High level of self-reported ADHD childhood symptoms in young psychiatric patients identified a group more burdened with psychiatric comorbid conditions and more psychosocial problems. This group should be offered a thorough diagnostic assessment of ADHD

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Nord J Psychiatry. 2019.

EVALUATION OF A NEW MODEL FOR ASSESSMENT AND TREATMENT OF UNCOMPLICATED ADHDΓÇÔEFFECT, PATIENT SATISFACTION AND COSTS.

Wernersson R, Johansson J, Andersson M, et al.

Aim: Attention-deficit/hyperactivity disorder (ADHD) is the most common diagnosis within child- and adolescent psychiatry. Waiting lists and delayed care are major issues. The aim was to evaluate if standardized care (SC) for assessment and treatment of uncomplicated ADHD would reduce resource utilization and increase satisfaction with preserved improvement within the first year of treatment.

Method: Patients 6-12 years with positive screen for uncomplicated ADHD at the brief child and family phone interview (BCFPI), a routine clinical procedure, were triaged to SC. The control group consisted of patients diagnosed with ADHD in 2014 and treated as usual. BCFPI factors at baseline and follow-up after one year and resource utilization were compared.

Results: Patients improved in ADHD symptoms (Cohen's d = 0.78, p < 0.001), child function (Cohen's d = 0.80, p < 0.001) and in family situation (Cohen's d = 0.61, p < 0.001) without group differences. Parents of SC patients participated more often in psychoeducational groups (75.5 vs. 49.5%, p < 0.001). SC had shorter time to ADHD diagnosis (8.4 vs. 15.6 weeks, p = 0.01) and to medication (24.6 vs. 32.1 weeks, p = 0.003). SC families were more satisfied with the waiting time (p = 0.01), otherwise there were no differences in satisfaction between the groups. Families of SC patients had fewer visits (4.7 vs. 10.8, p < 0.001) but used the same number of phone calls (6.3 vs. 6.2, p = 0.71). Costs were 55% lower.

Conclusions: A SC for ADHD can markedly reduce costs with preserved quality. As resources are limited, child psychiatry would benefit from standardization

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Nord J Psychiatry. 2019.

PROCESSING SPEED AS A MARKER TO STIMULANT EFFECT IN CLINICAL SAMPLE OF CHILDREN WITH HIGH FUNCTIONING AUTISM SPECTRUM DISORDER.

Peled J, Cassuto H, Berger I.

Background: Patients with co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) and ASD might benefit from stimulants. There is a progressive increase in prescribing ADHD aimed medications for children diagnosed with Autism Spectrum Disorder (ASD), despite scarce knowledge and no distinct clinical guidelines for that matter.

Aim: This study aims to analyze the effect of stimulant on processing speed performance and attention indices in children with ASD and ADHD. Methods: Forty children aged 6ΓÇô18 years diagnosed with ASD who also met the criteria for ADHD were recruited. All children performed a computerized performance test for the assessment of cognitive attention performance three times: twice while they are drug na+»ve and once an hour after taking a single dose of 10 mg. methylphenidate (MPH). This performance was compared to a group of children diagnosed with ADHD only without ASD.

Results: A significant difference ($p < 0.001$) was found only in the parameter of measuring cognitive processing speed. This effect is significantly different from the response of the ADHD only group.

Conclusions: The reaction to MPH among ASD children is different than among ADHD children. In ASD, MPH significantly improved cognitive processing speed without changing other measured attention parameters. Improving processing speed, might improve every day functioning in children with ASD who also met the criteria for ADHD, in other means than expected. This unique response suggests new research targets for treatment with stimulants in ASD and ADHD children and its influence on cognitive parameters

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Nord J Psychiatry. 2019.

RELIABILITY AND VALIDATION OF SWEDISH TRANSLATION OF BELIEFS ABOUT MEDICATION SPECIFIC (BMQ-SPECIFIC) AND BRIEF ILLNESS PERCEPTION QUESTIONNAIRE (B-IPQ) FOR USE IN ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Emilsson M, Berndtsson I, Gustafsson PA, et al.

Objectives: The purpose of this study was to assess the reliability and validity of Swedish translations of the Beliefs about Medicines Questionnaire-Specific (BMQ-Specific) and Brief Illness Perception Questionnaire (B-IPQ) for use in adolescents with ADHD.

Methods: Forward and backward translations of the BMQ-Specific and B-IPQ scales to Swedish were conducted and reviewed by adolescents with ADHD and professionals. The validity and reliability of both questionnaires were investigated in a cross-sectional study of 101 adolescents (13ΓÇô17-áyears) on a long-term prescription of ADHD medication recruited from two child and adolescent psychiatric outpatient clinics in Sweden.

Results: Regarding the BMQ-Specific, principal component analysis (PCA) loadings confirmed the previously defined components of Specific-Necessity and Specific-Concern. The PCA for B-IPQ revealed two components, the first one, B-IPQ Consequences, captured questions regarding perceptions of the implication of having ADHD (items 1, 2, 5, 6 and 8) and the second one, B-IPQ-Control, the perceptions of the capability to manage the ADHD disorder (items 3, 4 and 7). The Cronbach alpha coefficients for BMQ-Specific-Necessity scale was +¦ = 0.80, for BMQ-Specific-Concern scale +¦ = 0.75, B-IPQ Consequences +¦ = 0.74 and for B-IPQ-Control +¦ = 0.44.

Conclusions: The present results prove the Swedish translation of BMQ-Specific and B-IPQ to be valid and reliable for utilization in adolescents with ADHD. The PCA confirmed the original components for BMQ-Specific and the recent findings of two main B-IPQ components describing emotional and cognitive implications versus the capability for self-care maintenance of ADHD

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Nord J Psychiatry. 2019.

SACCADE EYE MOVEMENT IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Huang J-H, Chan Y-S.

Objects: This study aims to investigate the saccade/anti-saccade eye movement in children with attention deficit/hyperactivity disorder (ADHD).

Methods: Twelve children (8.8 -¦ 0.8 years) diagnosed with ADHD (DSM-V) and 12 control (9.1 -¦ 0.3 years) were invited to participate in the experiment where the iView Hi-SPEED eyetracker, with the sample rate at 500 Hz Binocular, was employed. The visual guided saccade (VGS) task was used to collect saccade latency and accuracy values. The anti-saccade task was used to collect saccade latency and accuracy values as well as the percentage of direction errors (PDE).

Results: Children with ADHD showed a significant difference in latency in the 7.5-¦ target and imprecision in both targets (7.5-¦ and 15-¦) during the VGS task. Moreover, the ADHD group exhibited shorter latency (15-¦ target) and significantly higher numbers in the Percentage of Direction Errors in the anti-saccade tasks than the control group.

Conclusions: The results suggest that children with ADHD have the following difficulties: precise oculomotor control, oculomotor response inhibition function and basic visual attention

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Nord J Psychiatry. 2019.

HOW DO ADOLESCENTS WITH ADHD PERCEIVE AND EXPERIENCE STRESS? AN INTERVIEW STUDY.

Oster C, Ramklint M, Meyer J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is linked to high levels of perceived stress in adult populations. Thus, it is not surprising that stress managing techniques are being included in treatment protocols for adults with ADHD. There is, however, a paucity of studies on perceived stress in adolescents with ADHD.

Aims: This study aims to explore how adolescents with ADHD perceive and experience stress (and stressors) using a qualitative approach.

Methods: Explorative interviews were conducted with 20 adolescents (Mean age: 16.30) diagnosed with ADHD in conjunction with group treatment therapy. Data were analysed using qualitative content analysis.

Results: Stress and ADHD, as well as stress, anxiety and ill-health, were described as closely intertwined. The result is presented in four categories: stress is often present, triggers of stress, stress affects daily life, and stress can be handled and prevented. A relation was found between stress and feelings of helplessness, ill-health and anxiety. Stress was viewed as being out of proportion with reality and was driven by such factors as ADHD symptoms, school demands, unpredictable situations and relational problems. Several negative consequences of stress were reported, including postponing schoolwork and the tendency to give up. Some participants also reported performing better when stressed. Accepting help from others, practising acceptance, settling down and controlling oneself, and planning in advance were seen as helpful stress managing techniques.

Conclusions: Stress should be considered among other problems related to ADHD. Psychoeducation about stress, stress managing techniques and coaching should be included in the treatment of adolescents with ADHD

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Nurs Res. 2019 Jul;68:275-84.

POVERTY, TOXIC STRESS, AND EDUCATION IN CHILDREN BORN PRETERM.

Kelly MM, Li K.

BACKGROUND: Preterm birth, defined as birth before the completion of 37 weeks of gestation, is a multifactorial global epidemic with psychosocial, economic, and physical ramifications affecting the child, family, and community at large. Toxic stress-the results of exposure to adverse childhood experiences-results in changes to brain structure and function that negatively affects future health.

OBJECTIVES: The aim of this study was to apply the eco-bio-developmental (EBD) model of poverty and preterm birth to the cross-sectional data of the 2016 National Survey of Children's Health to evaluate the associations between poverty, toxic stress, and prematurity on neurodevelopmental and educational outcomes.
METHODS: A subset of data representing children ages 6-11 years old (n = 15,010) from the 2016 National Survey of Children's Health was used for multivariate analysis of demographic variables and neurodevelopmental and educational outcome variables. Pearson's chi-square, logistic regression, and interaction effects explored the relationships between prematurity, toxic stress, and poverty.
RESULTS: Children in this sample born preterm had a higher incidence of toxic stress, poverty, developmental delay, learning disability, intellectual disability, speech/language disorders, attention-deficit disorder (ADD)/attention-deficit/hyperactivity disorder (ADHD), autism, and special education/early intervention plans. The combination of poverty, toxic stress, and preterm birth significantly increased the risk of these conditions. After accounting for gender, insurance coverage, race, and parental education, children in the sample born preterm were more likely to experience developmental delay, intellectual disability, speech/language disorder, learning disability, and ADD/ADHD. Toxic stress increased the incidence of ADD/ADHD and autism in both the preterm and full-term samples.
DISCUSSION: The negative effect of poverty and toxic stress on children born preterm, as depicted by the eco-bio-developmental model, is supported by this analysis. Healthcare providers are encouraged to address the tripartite vulnerability resulting from prematurity, poverty, and toxic stress

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Nurse Pract. 2019 Jul;44:37-42.
NPs' USE OF GUIDELINES TO DIAGNOSE AND TREAT CHILDHOOD ADHD.
Jansen M.
Current research on NPs' use of the American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents is limited. This cross-sectional survey examined 89 NPs in Upstate New York regarding self-reported practice behaviors based on the guideline. Most NPs followed at least 50% of the AAP guideline for diagnosis and treatment. However, use of all criteria was less than optimal

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Orv Hetil. 2019 Aug;160:1311-18.
THE MOST COMMON FOOD ALLERGY IN CHILDREN IS COW'S MILK PROTEIN ALLERGY.
Lendvai-Emmert D, Emmert V, Fusz K, et al.
Introduction and aim: The aim of our research is to evaluate and compare commonly performed diagnostic tests, and to examine the psychological disorders induced by this food allergy. Children with symptoms suggesting cow's milk protein allergy were included in this study (n = 47). Blood and saliva samples were collected from the participants. Parents were asked to fill in a questionnaire constructed by the research team (containing the DSM-5 symptoms checklist about attention deficit hyperactivity disorder).
Method: One of the most widely used diagnostic tool is the skin allergy test, which was performed in 47 subjects (n = 47, mean age: 7.36 years); only 2 children showed positive test result for cow's milk. Lymphocyte transformation test was observed to be positive in 8 children (17%), 4 subjects demonstrated questionable results. In our sub-study about psychological symptoms (n = 43, mean age: 7.88 years), the score was according to the attention deficit hyperactivity disorder symptom checklist before the diet (6.88, SD: 4.43) and showed significant decrease after 3 months of the elimination diet (4.48, SD: 3.69, p = 0.001). Scores of children with sleep disorder (10.62, SD: 4.23) also represented a significant reduction after 3 months of the diet (6.69, SD: 4.59, p = 0.009). Salivary cortisol levels did not show significant changes before and after elimination diet.
Results: According to our data, skin allergy testing and lymphocyte transformation test are not reliable diagnostic tools for establishing the diagnosis.

Conclusion: We conclude that a significant improvement in clinical symptoms can only be achieved with a strict elimination diet. Orv Hetil. 2019; 160(33): 1311-1318

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Paediatr Perinat Epidemiol. 2019;33:482-89.

COMBINED ASSOCIATION OF BTEX AND MATERIAL HARDSHIP ON ADHD-SUGGESTIVE BEHAVIOURS AMONG A NATIONALLY REPRESENTATIVE SAMPLE OF US CHILDREN.

Dellefratte K, Stingone JA, Claudio L.

Background: Previous research shows that environmental and social factors contribute to the development of attention-deficit/hyperactivity disorder (ADHD).

Objective: To determine the relationship between early-life exposure to common ambient air pollutants (benzene, toluene, ethylbenzene, and xylene, also known as BTEX), household material hardship (a measure of socio-economic status), and ADHD-suggestive behaviours in kindergarten-age children.

Methods: Pollutant exposure estimated from the 2002 National Air Toxics Assessment at-áeach child's residential ZIP code at enrolment was linked to the Early Childhood Longitudinal Study Birth Cohort (n-á=-á4650). Material hardship was assigned as a composite score of access to food, health care, and housing. Kindergarten teachers rated children's behaviours and activity in the classroom using a five-point Likert scale. Children with summary scores in the bottom decile were classified as displaying ADHD-suggestive behaviours. Logistic regression models were constructed to estimate the association between both BTEX exposure and material hardship on ADHD-suggestive behaviours.

Results: The odds of displaying ADHD-suggestive behaviours were greater in children with combined high-level exposure to BTEX and in those experiencing material hardship (odds ratio 1.54, 95% confidence interval [CI] 1.12, 2.11, and OR 2.12, 95% CI 1.25, 3.59, respectively), adjusting for covariates. These associations were stronger when restricting the study population to urban areas. There was no evidence of interaction between early life BTEX exposure and material hardship, although the effects of BTEX exposure were slightly greater in magnitude among those with higher material hardship scores.

Conclusions: Children exposed to air toxics, material hardship, or both early in life are more likely to display signs of ADHD-suggestive behaviours as assessed by their kindergarten teachers. The associations between exposures to air pollution and to socio-economic hardship were observed in all children but were particularly strong in those living in urban areas

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Pediatr Pulmonol. 2019.

STARTING EARLY: AN INTERNATIONAL FOCUS ON MENTAL HEALTH IN CHILDREN LIVING WITH CYSTIC FIBROSIS.

Georgiopoulos AM.

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Pediatr Int. 2019;61:1043-47.

SEIZURES IN CHILDREN WITH EPILEPSY AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Goker Z, Yilmaz A, Eraslan AN, et al.

Background: Epilepsy is an important disorder that is sometimes accompanied by inattention problems. This study explored the features of seizures in children with epilepsy, with or without attention-deficit/hyperactivity disorder (ADHD).

Methods: Between January 2017 and January 2018, data records of children with epilepsy aged 5ΓÇô18-áyears admitted to hospital were retrospectively collected. SPSS 17.0 was used for analyses and $P < 0.05$ was accepted as significant.

Results: Of 301 patients with epilepsy, 32 of them had ADHD. Median age at diagnosis of epilepsy in the epilepsy + ADHD group was lower than in the epilepsy alone group (6 vs 8-áyears; z = ΓêÆ2.989, P = 0.003). The two groups were similar in terms of duration of epilepsy, seizure types and features of complicated versus non-complicated epilepsy, number of anti-epileptic drugs (AED) used (for all, $P > 0.05$). The epilepsy

+ ADHD group had a significantly higher prevalence of intellectual disability (31.3% vs 12.6%; ¤ç2(1) = 7.9, P = 0.014) and specific learning disorder (12.5% vs 1.9%; ¤ç2(1) = 11.1, P = 0.009) than the epilepsy alone group (¤ç2(1) = 11.1, P = 0.009). ADHD medication use was identified in 68.8% of children in the epilepsy + ADHD group.
Conclusion: Attention-deficit-hyperactivity disorder was identified in 11.8% of 5-18-year-old children (32/301) with epilepsy in a 1-year period. ADHD is more frequent in children with epilepsy in childhood (5-11 years of age). Epilepsy diagnosis is more frequent in younger children with ADHD. Children with epilepsy and ADHD, also have a significantly higher prevalence of intellectual disability and specific learning disorder. Younger children diagnosed with epilepsy should be carefully monitored for ADHD

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Pediatriya - Zhurnal im G N Speranskogo. 2019;98:114-22.
MODERN APPROACHES TO DIAGNOSIS AND TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Korabelnikova EA.
Attention deficit hyperactivity disorder (ADHD) is an urgent problem due to the high incidence rate, reaching 3-5% in the child population. The article discusses diagnostic criteria for ADHD and manifestation peculiarities in different age periods. It also duscusses etiopathogenesis of ADHD as a multifactorial developmental disorder; reviews main groups of drugs used for the pharmacological correction of the disease, among which nootropics, in particular aminophenylbutyric acid (Anvifen), occupy a special place. Author discusses and justifies the need for an integrated approach to ADHD treatment, which should combine pharmacotherapy, neuropsychological correction and psychotherapy with a child, parents and teachers

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PeerJ. 2019;2019.
ESTIMATING BIOLOGICAL ACCURACY OF DSM FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER BASED ON MULTIVARIATE ANALYSIS FOR SMALL SAMPLES.
Abramov DM, Lazarev VV, Gomes SC, et al.
Objective. To estimate whether the Diagnostic and Statistical Manual of Mental Disorders (DSM) is biologically accurate for the diagnosis of Attention Deficit/ Hyperactivity Disorder (ADHD) using a biological-based classifier built by a special method of multivariate analysis of a large dataset of a small sample (much more variables than subjects), holding neurophysiological, behavioral, and psychological variables.
Methods. Twenty typically developing boys and 19 boys diagnosed with ADHD, aged 10-13 years, were examined using the Attentional Network Test (ANT) with recordings of event-related potentials (ERPs). From 774 variables, a reduced number of latent variables (LVs) were extracted with a clustering of variables method (CLV), for further reclassification of subjects using the k-means method. This approach allowed a multivariate analysis to be applied to a significantly larger number of variables than the number of cases.
Results. From datasets including ERPs from the mid-frontal, mid-parietal, right frontal, and central scalp areas, we found 82% of agreement between DSM and biological-based classifications. The kappa index between DSM and behavioral/psychological/neurophysiological data was 0.75, which is regarded as a substantial level of agreement.
Discussion. The CLV is a useful method for multivariate analysis of datasets with much less subjects than variables. In this study, a correlation is found between the biological-based classifier and the DSM outputs for the classification of subjects as either ADHD or not. This result suggests that DSM clinically describes a biological condition, supporting its validity for ADHD diagnostics

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PLoS ONE. 2019;14.

ASSOCIATIONS BETWEEN COGNITIVE PERFORMANCE AND SIGMA POWER DURING SLEEP IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, HEALTHY CHILDREN, AND HEALTHY ADULTS.

Bestmann A, Conzelmann A, Baving L, et al.

Sigma power during sleep is associated with cognitive abilities in healthy humans. We examined the relationship between sigma power in sleep EEG and intelligence and alertness in schoolchildren with ADHD (n = 17) in comparison to mentally healthy children (n = 16) and adults (n = 23). We observed a positive correlation between sigma power in sleep stage 2 and IQ in healthy adults but a negative correlation in children with ADHD. Furthermore, children with ADHD showed slower reaction times in alertness testing than both control groups. In contrast, only healthy children displayed a positive correlation between sigma power and reaction times. These data suggest that the associations between sigma power and cognitive performance underlie distinct developmental processes. A negative association between IQ and sigma power indicates a disturbed function of sleep in cognitive functions in ADHD, whereas the function of sleep appears to be matured early in case of motor-related alertness performance

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PLoS ONE. 2019;14:e0211873.

PSYCHIATRIC COMORBID PATTERNS IN ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: TREATMENT EFFECT AND SUBTYPES.

Tsai FJ, Tseng WL, Yang LK, et al.

Psychiatric comorbidities are common in individuals with attention-deficit/hyperactivity disorder (ADHD). In this study, we sought to evaluate the effects of medication and childhood ADHD subtypes on psychiatric comorbidities among adults with ADHD as compared to healthy adult controls. We assessed 121 drug-naive adults with ADHD, 93 treated adults with ADHD, and 145 healthy controls (age 18-36 years) using semi-structured psychiatric interviews, intelligence tests, and medical records. Drug-naive adults with ADHD had more comorbidities than treated adults with ADHD and controls. Childhood ADHD-combined subtype, relative to ADHD-inattentive subtype, was associated with higher risks of comorbidities. Current medication treatment was associate with a higher risk for anxiety disorders, and longer treatment duration was associated with lower risks of mood disorders and sleep disorders. Our results indicate that no medication treatment, short treatment duration, and childhood ADHD-combined subtype are associated with increased risks for psychiatric comorbidities among adults with ADHD

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Prim Care Companion J Clin Psych. 2019;21.

NOVEL INTERACTIVE EYE-TRACKING GAME FOR TRAINING ATTENTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Garcia-Baos A, et al.

Objective: To assess whether the eye-tracking approach of the RECOGNeyes game has potential therapeutic benefits for children with neurodevelopmental disorders, in particular attention-deficit/hyperactivity disorder (ADHD). RECOGNeyes is a computer game that is played using the eyes as the game controller. The rationale behind the game is that individuals with ADHD have an underdeveloped attention control system. This attention control system is underdeveloped not because they lack this capacity but because this ability has not been sufficiently developed. The game was designed as an intervention for training visual attention in ADHD.

Methods: The sample included 28 children aged 8-15 years (18 aged < 12 y and 10 aged = 12 y) previously diagnosed with ADHD (DSM-5 criteria). The participants were randomly divided into 2 groups. The experimental group played RECOGNeyes with eye-tracker for 3 weeks (3 times/week) at home, while the control group played the game using the mouse. Different attentional parameters were assessed before and after training. The study was conducted from January 2018-June 2018.

Results: Participants from the eye-tracker group showed an improvement posttest compared to pretest in impulsivity (P =.0067), reaction time (P <.0001), and fixation gaze control (P <.0001). No changes were found in mouse control between pretest and posttest assessments.
Conclusion: RECOGNeyes is a child-friendly, interactive game combined with eye-tracking technology that seems to provide an improvement in the visual attention system, which is especially indicated for ADHD patients. This game might be used as an alternative to pharmacologic therapy and may provide new insights into the treatment of ADHD

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Prim Care Companion J Clin Psych. 2019;21.

A CASE OF SEDATION SECONDARY TO A TRIAL OF LISDEXAMFETAMINE.

Majeed MH, Wasiq S, Mumtaz A, et al.

The American Academy of Child and Adolescent Psychiatry1-áhas endorsed stimulants and behavioral therapy as the mainstay treatment for attention-deficit/hyperactivity disorder (ADHD). Lisdexamfetamine dimesylate is a prodrug usually prescribed for the treatment of ADHD and binge-eating disorder. Common side effects include anorexia, decreased appetite, irritability, nausea, and insomnia.2-áWe present the case of a 6-year-old boy diagnosed with ADHD who, when administered a trial of lisdexamfetamine, developed excessive daytime sleepiness (EDS)

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;98.

ALTERED RESTING FUNCTIONAL NETWORK TOPOLOGY ASSESSED USING GRAPH THEORY IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang Y, Zuo C, Xu Q, et al.

Notwithstanding an extensive literature about attention-deficit/hyperactivity disorder (ADHD) and brain structure and function, the controversy of ADHD resulting from dysfunction or developmental delay remains unclear. Graph analysis studies have reached consensus about the pattern of increased integration and decreased randomness during childhood and early adulthood. Here, we hypothesized that ADHD is a neurodevelopmental disorder resulting from developmental delay and would show a pattern of decreased integration and increased randomness during childhood and early adulthood compared with typically developing children. To test this hypothesis, publicly available resting-state fMRI data from 102 children with ADHD and 143 typically developing controls (TDC) were compared using graph theoretical analysis. Functional connectivity was estimated using Pearson correlation analysis, and network topology was characterized using small-world (SW) and minimum spanning tree (MST) properties. The mean strength of global connectivity was significantly weaker in those with ADHD and was related to ADHD diagnosis scores. Significant group differences were observed for SW(clustering coefficient, path length, global and local efficiency) and MST (leaf number, kappa and hierarchy) topology. In addition, except for global efficiency, all of these parameters showed significant correlations with ADHD-related disability. The topology of SW and MST showed less integration and more randomness, which confirmed that ADHD is a disorder associated with developmental delay. Moreover, the topology of resting-state functional networks in children with ADHD that show abnormalities was associated with the degree of disability, which can be considered neurological hallmarks of neurodevelopmental disorders and may facilitate the evaluation and monitoring of clinical status in individuals with ADHD

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Psychol Assess. 2019 Jul;31:851-60.

THE ADHD SYMPTOM INFREQUENCY SCALE (ASIS): A NOVEL MEASURE DESIGNED TO DETECT ADULT ADHD SIMULATORS.

Courrege SC, Skeel RL, Feder AH, et al.

The current project outlines the development of the Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Infrequency Scale (ASIS), a stand-alone measure designed to identify individuals feigning or exaggerating symptoms to receive a diagnosis of ADHD. Over the course of 3 studies, valid data was collected from 402 participants assigned to control, simulator, ADHD diagnosed, or possible undiagnosed ADHD groups. Group assignment was based on self-reported history of ADHD diagnosis including information about the credentials of diagnosing professional and methods used. The ASIS includes an Infrequency Scale (INF) designed to detect rarely reported symptoms of ADHD and several clinical scales designed to measure genuine symptoms. The final version of the ASIS demonstrated high internal consistency for the INF (alpha = .96) and the ADHD Total scales (alpha= .96). Convergent validity for the ADHD Total was established through a strong correlation with Barkley Adult ADHD Rating Scale-IV (r = .92). Initial validation of the INF yielded high discriminability between groups (d = 2.76; 95% confidence interval [2.17, 3.36]). The final INF scale demonstrated strong sensitivity (.79-.86) and excellent specificity (.89). Using our study's malingering base rate of 29%, positive and negative predictive values were strong (.71-.79 and .92-.93, respectively). Additional information is provided for a range of base rates. Current results suggest that the ASIS has potential as a reliable and valid measure of ADHD that is sensitive to malingering when compared to a sample of individuals self-reporting a history of ADHD diagnosis

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Psychotherapy and Psychosomatics. 2019;88:65.

THE ASSOCIATION BETWEEN SOMATIC SYMPTOMS AND BRAIN CONNECTIVITY WITHIN DEFAULT MODE NETWORK IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kim H, Kim SM, Han DH, et al.

Background: To assess the correlation between somatic symptoms and brain connectivity within default mode network (DMN) in children with Attention Deficit Hyperactivity Disorder (ADHD).

Methods: 20 ADHD adolescents with somatic symptoms, 20 ADHD adolescents without somatic symptoms and age and sex matched 20 healthy adolescents were recruited. At baseline and after 6-month methylphenidate treatment, all adolescents underwent resting-state functional magnetic resonance imaging.

Results: Both ADHD children with somatic symptoms and ADHD children without somatic symptoms showed greater Functional Connectivity (FC) from Posterior Cingulate Cortex (PCC) seed to right insular (salience network), compared to healthy control (T=4.65, FDRq=.03). ADHD children with somatic symptoms showed increased FC from PCC to right parahippocampal gyrus (posterior DMN) (T=3.58, uncorrected p<.001) but decreased FC from PCC to right medial frontal gyrus (anterior DMN) (T=3.19, uncorrected p<.001), compared to ADHD children without somatic symptoms. After 6-month methylphenidate treatment, the FC from PCC seed to right medial frontal cortex increased in ADHD children with somatic symptoms (T=4.01, uncorrected p<.001). In addition, somatic symptoms also showed improvement. During the treatment, the changes in the severity of somatic symptoms was negatively correlated with the changes in the FC between PCC and right medial frontal cortex in ADHD children with somatic symptoms (r=-0.49, p<.01).

Conclusions: Six months methylphenidate treatment of ADHD would increase the FC of anterior and posterior DMN as well as improve somatic symptoms. The somatic symptoms of ADHD children were not associated with somatosensory network but associated with the FC of DMN

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Res Dev Disabil. 2020;96.

FREQUENCY COUPLING OF LOW AND HIGH FREQUENCIES IN THE EEG OF ADHD CHILDREN AND ADOLESCENTS IN CLOSED AND OPEN EYES CONDITIONS.

Rodriguez-Martinez EI, Angulo-Ruiz BY, Arjona-Valladares A, et al.

The present report examines the possible differences in absolute Power Spectral Density (PSD), the topography of brain rhythms, and low frequency (delta and theta) vs. beta PSD when attention deficit disorder (ADHD) children and controls are compared. These results would potentially be useful to test the validity of the developmental lag and differential developmental models for ADHD. The EEG resting state under the experimental conditions of open and closed eyes were recorded in samples of control subjects and children with ADHD (6ΓÇô17 years old). The PSD from 0 to 46 Hz was calculated and ANOVAs were performed to compare the groups of subjects in the two experimental conditions. To observe differences in the co-maturation of the brain rhythms between the groups of subjects, correlations of the PSD of all frequency ranges were computed. These results showed an increase in delta power in children with ADHD compared to control subjects. The topographies of the different brain rhythms were similar in children with ADHD and controls. The maturational power-to-power frequency-coupling between low frequencies and beta rhythms was lower in children with ADHD. The increased delta PSD in ADHD and the similar brain rhythms topographies in children with ADHD and controls support the developmental lag model, whereas the decreased co-maturation of low frequencies vs. beta PSD in children with ADHD suggests a differential maturation rate for low and beta frequencies in children with ADHD compared to controls

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Res Soc Work Pract. 2019 Nov;29:939-48.

THE EFFECTIVENESS OF NEUROFEEDBACK IN AN OUTPATIENT SETTING: A MULTILEVEL MODELING APPROACH.

Ward KP, Porter NA, Wood DS.

Purpose: Neurofeedback is an increasingly common therapeutic intervention for mental disorders. Most of the existent neurofeedback via electroencephalography (EEG-nf) research uses controlled studies to examine whether EEG-nf is an efficacious treatment for attention deficit hyperactivity disorder (ADHD). Less is known regarding the effectiveness of EEG-nf in clinical settings for symptoms other than ADHD. The purpose of this study was to examine whether EEG-nf sessions were associated with a reduction in hyperactivity, emotional dysregulation, anxiety, and depression symptoms.

Method: Multilevel growth curve models were used to analyze secondary data from 83 EEG-nf patients from an outpatient clinic.

Results: EEG-nf sessions were associated with a decrease in mental disorder symptoms generally, but this trend slowed over time.

Discussion: Findings suggest that practitioners should adhere to a relatively brief (approximately 30 sessions) EEG-nf protocol. Findings also encourage more research dedicated to examining the effectiveness of EEG-nf on a variety of mental health symptoms treated in community settings

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Rev Saude Publica. 2019;53:96.

MENTAL DISORDERS AND SUICIDE RISK IN EMERGING ADULTHOOD: THE 1993 PELOTAS BIRTH COHORT.

Gomes AP, Soares ALG, Kieling C, et al.

OBJECTIVE: To assess the prevalence of some mental disorders and suicide risk, and the association between them in youths.

METHODS: Data from the 1993 Pelotas Birth Cohort (Brazil) was used. The prevalence of mental disorders at 22 years [major depressive disorder (MDD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), attention-deficit/ hyperactivity disorder (ADHD), bipolar disorders type 1 and 2 (BD1; BD2), post-traumatic stress disorder (PTSD), and antisocial personality disorder (APD)] and of suicide risk were assessed using the Mini International Neuropsychiatric Interview (n = 3,781). Comorbidity between disorders was also assessed. Association of each mental disorder and the number of disorders with suicide risk was assessed using Poisson regression.

RESULTS: The prevalence of any mental disorder was 19.1% (95%CI 17.8-20.3), and GAD was the most prevalent (10.4%; 95%CI 9.5-11.4). The prevalence of current suicide risk was 8.8% (95%CI 5.9-9.7). All disorders (except APD) and the suicide risk were higher among women. Mental disorders were associated with a higher suicide risk, with the highest risks being observed for MDD (RR = 5.6; 95%CI 4.1-7.8) and PTSD (RR = 5.0; 95%CI 3.9-6.3). The higher the number of co-occurring mental disorders, the higher the risk of suicide.
CONCLUSIONS: Our findings showed that about 20% of the youths had at least one mental disorder. However, this prevalence is underestimated since other relevant mental disorders were not assessed. Mental disorders were associated with higher suicide risk, especially the comorbidity between them

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Scand J Psychol. 2019 Aug;60:304-08.

GRADE EFFECTS ON TEACHER RATINGS OF ADHD SYMPTOMS AMONG PRIMARY SCHOOL STUDENTS.

Oner O, Vatanartiran S, Karadeniz S.

Several studies have reported that being younger for grade increases the risk of having attention deficit hyperactivity disorder (ADHD) diagnosis and being on ADHD medication among students. The aim of this study was to investigate this association in a low-middle income country setting. Sample included 2,627 children from first to fourth grades. We compared students who were older than the 75th and younger than the 25th percentiles in consecutive grades. Teachers completed SNAP-4 scale. Results indicated that teacher rated ADHD symptoms were 2.5 to 3.6 times more common in students who were younger for their grade, after age, gender, and Fluid IQ scores were controlled. Teacher SNAP-4 scores were also significantly associated with grade. Our results suggested that the phenomenon of higher rates of teacher rated ADHD symptoms among younger for grade students was not limited to Western countries and that the teacher reported symptom loads were higher in these children

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Sci Total Environ. 2020;699.

PRENATAL AND CHILDHOOD PHTHALATE EXPOSURE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER TRAITS IN CHILD TEMPERAMENT: A 12-YEAR FOLLOW-UP BIRTH COHORT STUDY.

Ku H-Y, Tsai T-L, Wang P-L, et al.

Temperamental tendencies may form the basis of personality development, and specific personality constellations are associated with increased incidences of behavioural problems. Phthalic acid ester (PAE) has been associated with symptoms of attention deficit hyperactivity disorder (ADHD) in cross-sectional studies. We hypothesised that early-life exposure to PAE affects the temperaments of children, particularly ADHD traits. In this study, we analysed the temperament evaluations completed at least once by maternalΓÇôinfant pairs (n = 208) when the child was aged 2, 5, and/or 11 years between 2000 and 2012. We measured seven PAE metabolites in the urine of the mothers during pregnancy and their children using liquid chromatography-electrospray ionisation-tandem mass spectrometry. These metabolites included mono-methyl phthalate, mono-ethyl phthalate, mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), and three metabolites of di (2-ethylhexyl) phthalate. The phthalate metabolite levels in pregnant women were significantly associated with a decreased threshold of responsiveness (coefficients from ΓêÆ0.21 to ΓêÆ0.46) and increased distractibility (coefficients from 0.23 to 0.46) in pre-school children. After adjustment for maternal exposure, the phthalate metabolite concentrations of the children exhibited significantly increased odds ratios (ORs) with respect to the ADHD symptom traits. Specifically, mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), the sum of the DEHP metabolites, and MBzP yielded ORs and 95% confidence intervals of 2.98 (1.05ΓÇô8.48), 3.28 (1.15ΓÇô9.35), and 9.12 (1.07ΓÇô78.06), respectively, for every log10 creatinine unit (g/g creatinine) increase. Thus, early-life phthalate exposure was found to be associated with the behavioural characteristics of children, particularly temperamental traits associated with ADHD

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Sleep. 2019;42.

SHOOTING A HIGH-DENSITY ELECTROENCEPHALOGRAPHIC PICTURE ON SLEEP IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Miano S, Amato N, Garbazza C, et al.

Study Objectives: Sleep-related slow-wave activity (SWA) has been recognized as a marker of synaptic plasticity. In children affected by attention deficit hyperactivity disorder (ADHD), SWA is mainly located in the central rather than frontal regions, reflecting a maturational delay. A detailed subjective and objective sleep investigation, including a full night video-polysomnography (PSG-HD-EEG), was performed on 30 consecutive drug na+»ve outpatients with a diagnosis of ADHD. They received a diagnosis of sleep disorders in 29/30 cases, and most of them had a past history of sleep problems. They had a higher apnea-hypopnea index at PSG, and slept less than 9 hr at actigraphy. We aimed to describe the SWA behavior in the same group of children with ADHD. Materials and Methods: The full-night PSG-HD EEG of children with ADHD was compared with the one of the 25 healthy controls. The scalp SWA mapping, the decrease of SWA during the night, and the EEG source of SWA were analyzed. Results: At scalp topography, the focus of SWA was observed over the centro-parietal-occipital regions in participants with ADHD ($p < 0.01$), which remained significant in the subgroups divided between subgroups according to the sleep diagnosis ($p < 0.01$). The physiological decrease in SWA was more evident in control participants. The source analysis revealed a greater delta power over the posterior cingulate in participants with ADHD ($p < 0.01$). Conclusions: Our results confirm static and dynamic changes in SWA behavior in children with ADHD, which may reflect a maturational delay occurring at a vulnerable age, as a consequence of chronic sleep deprivation

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Transl Psychiatry. 2019;9.

HIGH-DOSE EICOSAPENTAENOIC ACID (EPA) IMPROVES ATTENTION AND VIGILANCE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND LOW ENDOGENOUS EPA LEVELS.

Chang JPC, Su K-P, Mondelli V, et al.

No studies have examined the relationship between endogenous polyunsaturated fatty acids (PUFAs) levels and treatment response to PUFAs. We conducted a 12-week, double-blind, placebo-controlled trial comparing the effects of high-dose eicosapentaenoic acid (EPA, 1.2 g) and placebo on cognitive function (continuous performance test) in n = 92 youth (age 6ΓÇô18-years-old) with Attention Deficit Hyperactivity Disorder (ADHD). Blood erythrocytes PUFAs were measured before and after treatment, to examine the effects of baseline endogenous EPA levels on treatment response and the effects of EPA treatment on PUFAs levels. Secondary measures included other ADHD symptoms, emotional symptoms, and levels of plasma high-sensitivity c-reactive protein (hs-CRP) and brain-derived neurotrophic factor (BDNF). Overall, EPA group improved more than placebo group on focused attention (variability, Effect size (ES) = 0.38, p = 0.041); moreover, within youth with the lowest baseline endogenous EPA levels, EPA group improved more than placebo group in another measure of focused attention (hit reaction time, HRT, ES = 0.89, p = 0.015) and in vigilance (HRT interstimulus interval changes, HRTISIC, ES = 0.83, p = 0.036). Interestingly, EPA group improved less than placebo group in impulsivity (commission errors), both overall and in youth with the highest baseline EPA levels, who also showed less improvement in other ADHD and emotional symptoms. EPA increased blood erythrocytes EPA by 1.6-fold but not DHA levels, and did not affect hs-CRP and BDNF plasma levels. In conclusion, EPA treatment improves cognitive symptoms in ADHD youth, especially if they have a low baseline endogenous EPA level, while youth with high EPA levels may be negatively affected by this treatment

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Transl Psychiatry. 2019;9.

MOTOR CORTEX FACILITATION: A MARKER OF ATTENTION DEFICIT HYPERACTIVITY DISORDER CO-OCCURRENCE IN AUTISM SPECTRUM DISORDER.

Pedapati EV, Mooney LN, Wu SW, et al.

The neural correlates distinguishing youth with Autism Spectrum Disorder (ASD-) and ASD with co-occurring Attention Deficit Hyperactivity Disorder (ASD+) are poorly understood despite significant phenotypic and prognostic differences. Paired-pulse transcranial magnetic stimulation (TMS) measures, including intracortical facilitation (ICF), short interval cortical inhibition (SICI), and cortical silent period (CSP) were measured in an age matched cohort of youth with ASD- (n = 20), ASD + (n = 29), and controls (TDC) (n = 24). ASDΓêÆ and ASD+ groups did not differ by IQ or social functioning; however, ASD+ had significantly higher inattention and hyperactivity ratings. ICF (higher ratio indicates greater facilitation) in ASD+ (Mean 1.0, SD 0.19) was less than ASDΓêÆ (Mean 1.3, SD 0.36) or TDC (Mean 1.2, SD 0.24) (F2,68 = 6.5, p = 0.003; post-hoc tests, ASD+ vs either TDC or ASDΓêÆ, p Γëñ 0.05). No differences were found between groups for SICI or age corrected active/resting motor threshold (AMT/RMT). Across all ASD youth (ASDΓêÆ and ASD+), ICF was inversely correlated with worse inattention (Conners-3 Inattention (r = ΓêÆ0.41; p < 0.01) and ADHDRS-IV Inattention percentile (r = ΓêÆ0.422, p < 0.01) scores. ICF remains intact in ASDΓêÆ but is impaired in ASD+. Lack of ICF is associated with inattention and executive function across ASD. Taken with the present findings, ADHD may have a distinct electrophysiological ΓÇ£signatureΓÇØ in ASD youth. ICF may constitute an emerging biomarker to study the physiology of ADHD in ASD, which may align with disease prognosis or treatment response

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Wei Sheng Yan Jiu. 2019 Jul;48:577-82.

CORRELATION BETWEEN SINGLE NUCLEOTIDE POLYMORPHISMS OF NEUROTROPHIC FACTORS AND EXECUTIVE FUNCTION CHARACTERISTICS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Wang N, Wang Z, Yan F, et al.

OBJECTIVE: To investigate the correlation between the polymorphisms of(brain derived neurotrophic factor, BDNF)BDNF gene rs11030104 and rs2030324 and executive function in children with attention deficit hyperactivity disorder(ADHD).

METHODS: A total of 206 ADHD children and 212 control children were enrolled in the study. Five mL peripheral venous blood was extracted from each subject and genomic DNA was extracted. The genotypes of rs11030104 and rs2030324 loci were genotyped by PCR/sequencing. The selection was tested by Wisconsin Classification Card Test, Stroop Color-Word Task, Reaction/Nonresponse Task and Stop Signal Task.

RESULTS: The distribution of rs2030324 locus gene frequency was different between ADHD group and control group. G allele was the risk factor of ADHD(chi~2=4. 481, P=0. 034; OR=1. 520, 95%CI 1. 031-2. 243); rs11030101 locus gene frequency distribution and genotype distribution had statistical significance between the two groups, and A allele was related to ADHD susceptibility(OR=1. 601, 95%CI 1. 052-2. 436). The error interference score of Stroop test in ADHD group was higher than that in control group(P<0. 05), but there was no significant difference in response time interference score between the two groups(P>0. 05). The SCWT scores of different genotypes of BDNF rs2030324 in ADHD group were different. Compared with AA type and AG type, the SCWT error interference scores of GG type ADHD patients were higher. There was no significant difference among rs11030101 genotypes. The WCST scores of ADHD group were lower than those of control group. The variation of Go/no-go scores in ADHD group was higher than that of control group in missed count, mistaken count and correct reaction time. The variation of SST and correct reaction time in ADHD group were higher than that of control group, but the genotype distribution of rs11030104 and rs2030324 loci had no significant correlation with WCST, Go/no-go and SST scores.

CONCLUSION: Children with ADHD have executive dysfunction. ADHD children with BDNF rs2030324 GG genotype showed poor Stroop executive function

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COGITUM IN CHILDREN'S NEUROLOGY AND PSYCHIATRY (EXPERIENCE IN THE PRACTICAL USE).

Goryunova AV, Shevchenko YS, Goryunov AV.

The authors review current data on the role of the synthetic aspartic acid analogue N-acetyaspartate (NAA) in various biochemical metabolic reactions in the CNS. Its importance as a biomarker for neuropsychiatric disorders identified using magnetic resonance spectroscopy (MRS) is noted. The authors present their own results of the use of cogitum, a synthetic analogue of NAA, in children with the effects of traumatic brain injury, mental retardation, hyperactivity disorder and in the complex therapy of schizotypal disorder. Effects of cogitum on cognitive deficit, asthenia are evaluated. The neurotrophic effect of the drug, which specifically affects cognitive and asthenic disorders in these diseases, is shown

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brain sciences

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Article

Integrated Analysis of microRNA and mRNA Expression Profiles: An Attempt to Disentangle the Complex Interaction Network in Attention Deficit Hyperactivity Disorder

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Abstract: Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder, whose etiology and pathogenesis are still largely unknown. In order to uncover novel regulatory networks and molecular pathways possibly related to ADHD, we performed an integrated miRNA and mRNA expression profiling analysis in peripheral blood samples of children with ADHD and age-matched typically developing (TD) children. The expression levels of 13 miRNAs were evaluated with microfluidic qPCR, and differentially expressed (DE) mRNAs were detected on an Illumina HiSeq 2500 genome analyzer. The miRNA targetome was identified using an integrated approach of validated and predicted interaction data extracted from seven different bioinformatic tools. Gene Ontology (GO) and pathway enrichment analyses were carried out. Results showed that six miRNAs (miR-652-3p, miR-942-5p, let-7b-5p, miR-181a-5p, miR-320a, and miR-148b-3p) and 560 genes were significantly DE in children with ADHD compared to TD subjects. After correction for multiple testing, only three miRNAs (miR-652-3p, miR-148b-3p, and miR-942-5p) remained significant. Genes known to be associated with ADHD (e.g., *B4GALT2, SLC6A9 TLE1, ANK3, TRIO, TAF1,* and *SYNE1*) were confirmed to be significantly DE in our study. Integrated miRNA and mRNA expression data identified critical key hubs involved in ADHD. Finally, the GO and pathway enrichment analyses of all DE genes showed their deep involvement in immune functions, reinforcing the hypothesis that an immune imbalance might contribute to the ADHD etiology. Despite the relatively small sample size, in this study we were able to build a complex miRNA-target interaction network in children with ADHD that might help in deciphering the disease pathogenesis. Validation in larger samples should be performed in order to possibly suggest novel therapeutic strategies for treating this complex disease.

Keywords: circulating biomarkers; microRNA; transcriptome; targetome; bioinformatics; high-throughput next-generation sequencing (HT-NGS)

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterized by inappropriate and impairing inattention, impulsivity, and hyperactivity [1]. The disease occurs in 2%–10% of school-age children [2], more frequently identified in young males [3]. Persistence rates of ADHD in adulthood range from 40% to 75%, with a worldwide prevalence of 3.4% [4,5].

ADHD is considered a complex disorder caused by environmental [6], epigenetic [7], and genetic factors [8,9]. In the general population, the risk of ADHD is estimated to be around 20% in the first-degree relatives of probands [2]. Several candidate genes [10–13] have been implicated in ADHD susceptibility, and a recent genome-wide association study (GWAS) identified significant risk loci located within or nearby genes involved in neurodevelopment processes [8].

To date, many critical features still need to be clarified about ADHD: the etiology and pathogenesis of the disease are still largely unknown, and its diagnosis continues to be heatedly debated, as it is based on the observation of behavioral signs and verbal reports, rather than on measurable biological parameters; moreover, personalized and efficient therapeutic approaches are missing. Given the clinical heterogeneity of ADHD and its high comorbidity with other psychopathological disorders [14], there is an urgent need to identify useful molecular signatures that help in deciphering the disease pathogenetic mechanisms, thus facilitating the diagnosis and possibly addressing new therapeutic strategies.

Micro-ribonucleic acids (miRNAs), highly evolutionarily conserved endogenous small noncoding RNAs, have been investigated as biomarkers for the diagnosis of ADHD, as well as for monitoring its progression and response to treatment [15–17]. MiRNAs configure complex molecular networks where they may regulate hundreds of genes individually, and up to 80% of the human genome collectively [18–20]. Lines of evidence confirm the role of miRNAs in ADHD etiology, pathogenesis, and diagnosis; nevertheless, the studies are still few in number and do not overlap with each other [15–17,21]. The first study reported a decreased expression of five miRNAs in children with ADHD compared to controls [15]. Recently, five dysregulated serum miRNAs were identified in a more comprehensive set of 84 miRNAs, whereas the first and only global screening technology exploring the miRNA profile in ADHD was performed in the Chinese population, which identified 13 miRNAs as potential ADHD diagnostic biomarkers [16].

The aim of this study was to identify critical key hubs and aberrant miRNA-based regulatory networks in order to provide deeper insight into the genetic mechanisms underlying this multifactorial and complex disease, thus helping to clarify the gray areas of ADHD. To this purpose, we investigated the expression profile of several circulating miRNAs in children with ADHD employing a miRNA panel tested for the study of other neurological diseases [22]. Using a high-throughput next-generation sequencing (HT-NGS) approach, we also performed a genome-wide profiling of the mRNA fraction in order to identify differentially expressed (DE) target genes with an unbiased approach, and to search for miRNA-target interaction network(s) possibly related to ADHD.

2. Materials and Methods

Figure 1 shows the flow chart of our study design (details below).

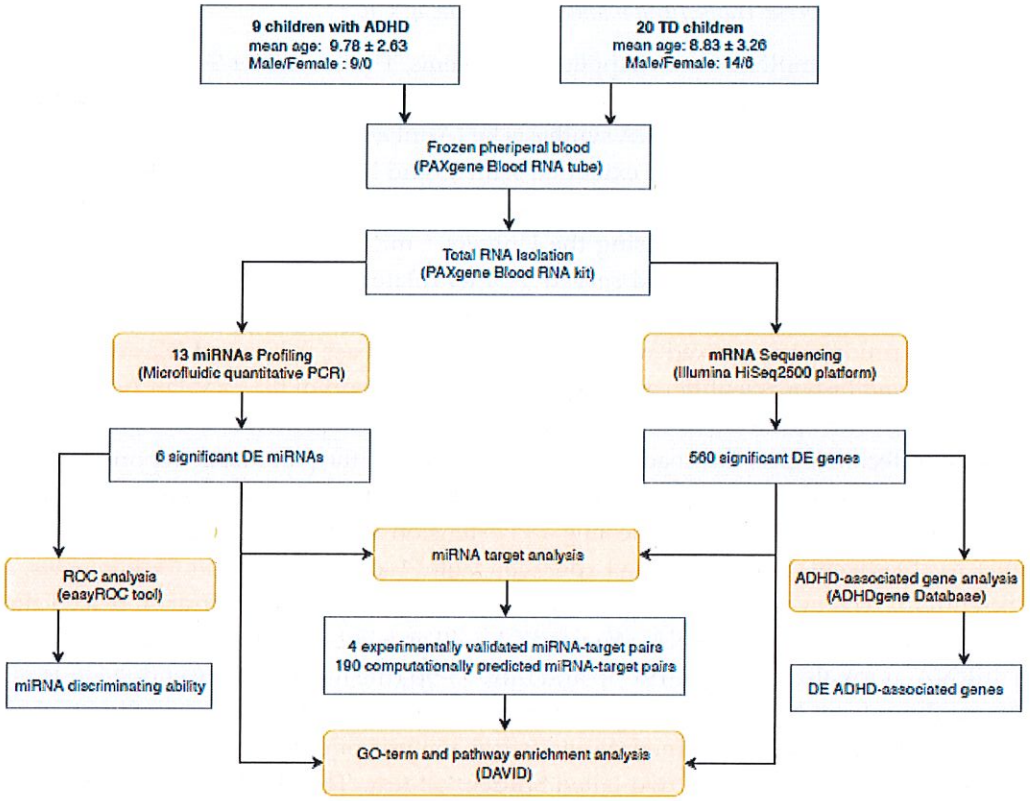

Figure 1. Flow chart describing the study design.

2.1. Study Population

The study recruited children diagnosed with ADHD, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, among those diagnosed, followed-up, and consecutively presenting at the Child Neuropsychiatric Unit, University of Bari, Italy. ADHD patients were less than 18 years old and they were not previously exposed or under concomitant psychotropic drugs. Children with a history of comorbid major psychiatric disorders, such as autism spectrum disorder, bipolar disorders, major depression, obsessive-compulsive disorders, psychotic disorders, epilepsy, or severe head injury, were excluded.

Age-matched typically developing (TD) children were recruited from the same geographic area; they did not show clinical signs or instrumental evidence for any of the aforementioned major psychiatric disorders.

The study was approved by the Ethics Committee of Azienda Ospedaliera Policlinico, University of Bari. Written informed consent (according to the Declaration of Helsinki) was obtained from the parents or legal tutors of the children enrolled in the investigation.

2.2. Sample Preparation

Peripheral blood samples were collected from children with ADHD and controls and stored at –20 °C in 3 ml PAXgene Blood RNA Tubes (PreAnalytiX Qiagen/BD, Hombrechtikon, Switzerland). Total RNA was isolated using the PAXgene Blood RNA Kit (PreAnalytiX Qiagen/BD, Hilden, Germany). RNA quantity and quality were measured using Nanodrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA) and RNA 6000 Pico chip on Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA), respectively. Samples with RNA integrity number (RIN) scores higher than 7 and with A260/A280 values in the 1.8–2.2 range were processed for further analyses.

2.3. miRNA Profiling: Reverse Transcription and Microfluidic qPCR

TaqMan Advanced miRNA Cards (Applied Biosystems, Thermo Fisher Scientific) were employed for miRNA quantitative analysis. Approximately 8 ng of total RNA/sample was reverse transcribed using a TaqMan Advanced miRNA cDNA synthesis kit (Applied Biosystems, Thermo Fisher Scientific). The ends of each mature miRNA were extended with 5′-end ligation of an adaptor sequence and 3′ poly-A tailing, and recognized by universal RT primers (Applied Biosystems, Thermo Fisher Scientific). The obtained cDNA was amplified using the Universal miR-Amp Primers (Applied Biosystems, Thermo Fisher Scientific), diluted, and served as a template for microfluidic qPCR analysis with TaqMan Advanced miRNA Cards (Applied Biosystems, Thermo Fisher Scientific). Briefly, 25 µL of preamplified product was mixed with 50 µL of TaqMan Fast Advanced Master Mix (Applied Biosystems, Thermo Fisher Scientific) and dispensed into each port of the TaqMan Advanced miRNA Card. The reaction was performed on ABI PrismVR 7900HT sequence detection system (Applied Biosystems, Life Technologies, Carlsbad, CA, USA) according to the parameters reported in a previous study [22]. In detail, thermal cycling parameters were 10 min at 92 °C to enzyme activation, 40 cycles of denaturation at 95 °C for 1 s, and annealing and extension at 60 °C for 20 s.

Raw Ct-values were calculated using Expression Suite™ software v1.1 (Life Technologies, Thermo Fisher Scientific). The cycle number at which the reaction crossed an arbitrarily placed threshold (Ct) was determined for each miRNA. We used Ct = 40 as a cut-off. The relative expression levels of each miRNA, normalized to miR-191-5p and miR-93-5p (the most suitable endogenous reference miRNAs resulting from NormFinder and GeNorm tools), were calculated according to the $2^{-\Delta\Delta Ct}$ method, detailed in [23]. We performed the statistical analysis of miRNAs (DE) with the Expression Suite™ software, which consists of two-tailed Student's *t*-test. The obtained *p*-value was corrected for multiple comparisons using Benjamini–Hochberg's method. A *p*-value <0.05 was considered statistically significant.

The miRNA's ability to discriminate the compared groups (ADHD versus TD) was determined using receiver-operating characteristic (ROC) analysis, calculated with the easyROC web-tool [24]. Statistical significance was set at p-value < 0.05; the Youden cut-off method was used to determine cut-off values. The associated *p*-values and area under ROC (AUC) were calculated for each miRNA.

2.4. mRNA Profiling: HT-NGS

mRNA libraries were prepared using the TruSeq Stranded mRNA Sample Preparation kit (Illumina). Briefly, 1 µg of total RNA was used for poly-A mRNA selection with oligo-dT beads, followed by thermal mRNA fragmentation and reverse transcription (RT). The obtained cDNAs were 3′-end adenylated and ligated to Illumina paired-end sequencing adapters and subsequently amplified by 12 cycles of PCR. The libraries were fluorimetrically quantified and analyzed, pooled together to obtain equimolar concentrations into a multiplex sequencing pool, and sequenced to generate 2 bp × 100 bp paired-end reads (around 30 million reads/sample) using an Illumina HiSeq2500 platform.

2.5. mRNA Profiling: Bioinformatic Analyses

RNA-Seq data of ADHD and TD samples were processed, according to an in-house developed bioinformatics pipeline based on the standard tools developed for NGS data elaboration: sequencing quality was assessed with FastQC [25]; mRNA reads were mapped with STAR [26]; multireads were evaluated with RSEM [27] and MultiDEA [28] tools; differential expression analysis was performed with DESeq2 [29], which used Benjamini–Hochberg for correction. The change in the expression was considered statistically significant if the adjusted *p*-value was <0.05.

In order to identify genes closely related to ADHD, the list of DE genes, obtained through the previous pipeline, was matched to public available ADHD-associated genetic factors by using ADHDgene Database [30]. This database contains multitype genetic factors associated with ADHD (including SNPs, CNVs, VNTR, microsatellites, genes, chromosomal regions, and biological

pathways) and obtained from both deep literature screening with manual curation and extended functional analyses.

2.6. miRNA Target Analysis

Seven publicly available tools of predicted and validated miRNA-target interactions were used: miRanda [31], DIANA-microT-CDS [32], rna22 [33], mirDB [34], and TargetScan [35] collect predicted miRNA targets; two databases, miRtarbase [36] and DIANA-TarBase [37], contain validated miRNA-target interactions.

In order to reduce the probability of false positive results, only those miRNA/mRNA bindings that were confirmed by reporter gene assays in the previously mentioned databases, or computationally predicted by at least three algorithms, were finally selected.

2.7. Pathway Analysis

Functional and pathway enrichment analysis of identified DE genes were performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID v6.814, https://david.ncifcrf.gov/) tool and analyzed by one-tailed Fisher's exact test followed by the Benjamini correction with a threshold p-value < 0.05.

3. Results

This study included 9 children with ADHD with a mean age of 9.78 (SD 2.63) and 20 TD subjects with a mean age of 8.83 (SD 3.26). No statistically significant difference was detected between the two groups by age ($p = 0.171$). A gender-related discrepancy was registered, since the ADHD patients were all males compared to 14 males and 6 females in the TD group ($p = 0.0316$); to avoid any biases due to gender differences, all the comparisons were performed between the ADHD patients and both the 20 TD subjects and the 14 male TD. Since the results did not change (Table S1), we decided to show here the first set of data to increase the significance of the comparison.

The ADHD patients showed impairment of concentration, processing speed, working memory, and cognitive flexibility performances, as documented by a complete neuropsychological evaluation routinely performed at the study entry [38]. No significant interindividual variabilities were recorded among them.

3.1. Differentially Expressed miRNAs in ADHD

We evaluated the expression of 13 miRNAs (let-7a-5p, let-7b-5p, miR-25-3p, miR-125a-5p, miR-942-5p, miR-221-3p, miR-652-3p, miR-182-5p, miR-185-5p, miR-181a-5p, miR-320a, miR-99b-5p, and miR-148b-3p) in children with ADHD using a miRNA panel tested for the study of other neurological diseases [22].

The comparison of miRNA expression levels within the study groups revealed six mature miRNAs significantly DE between ADHD and TD (Figure 2). After Benjamini–Hochberg correction for multiple testing, only miR-652-3p, miR-148b-3p, and miR-942-5p remained significant (adjusted p-value, adj. p-value < 0.05). Despite this result, given the small sample size and the functional significance of the over-threshold miRNAs, we enclosed in the analysis of the targeted mRNAs all the six miRNAs (p-value < 0.05) (see discussion for comments).

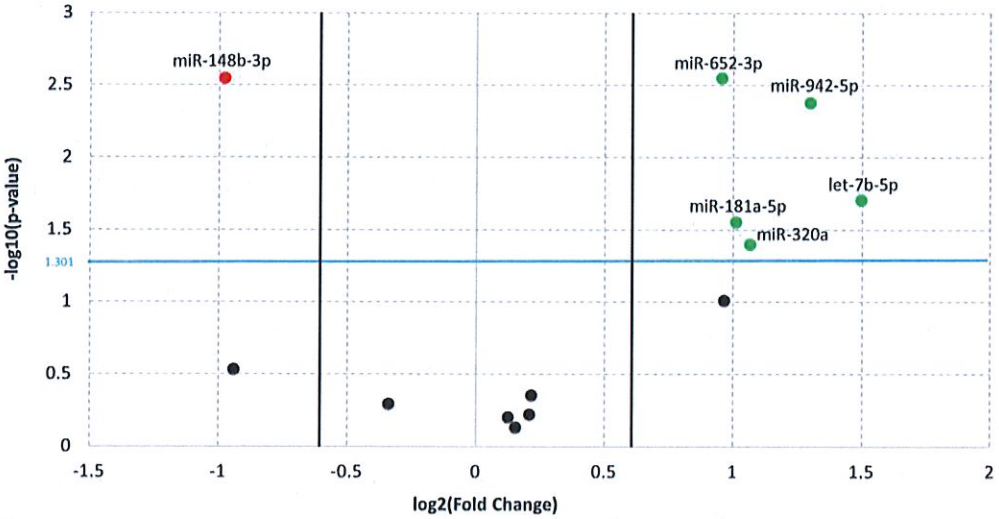

Figure 2. Volcano plot of qPCR data referring to the comparison of miRNAs expressions between ADHD and TDs. The *Y*-axis values show the negative logarithm base 10 (log10) of the p-values; the blue horizontal line on the plot represents the threshold p-value used for this analysis (0.05). The values in the *X*-axis indicate the $\log_2$ differences in estimated relative expression of the miRNAs of interest; the vertical lines represent the thresholds for the $\log_2$ fold change (equivalent to a fold change of 1.5). Thus, the red dot corresponds to downregulated miRNA, whereas the green dots correspond to upregulated miRNAs.

In detail, results from the microfluidic qPCR analysis showed statistically significant upregulation of miR-652-3p (Fold Change FC = 1.94; p-value = 2.84×10^{-3}), miR-942-5p (FC = 2.46; p-value = 4.22×10^{-3}), let-7b-5p (FC = 2.82; p-value = 1.98×10^{-2}), miR-181a-5p (FC = 2.02; p-value = 2.82×10^{-2}), and miR-320a (FC = 2.09; p-value = 4.02×10^{-2}) and statistically significant downregulation of miR-148b-3p (FC = 1.97; p-value = 2.85×10^{-3}) in children with ADHD compared to TDs (Table 1).

Table 1. List of significant dysregulated miRNAs. For each miRNA, the $\log_2$FC, p-value, and the corresponding adjusted p-value from qPCR analysis have been detailed. The ROC section shows the results of AUC and associated p-value. The total number of miRNA targets (experimentally validated by reporter gene assays or computationally predicted by at least three algorithms) and the list of previously ADHD-associated target genes have been indicated.

miRNA	Regulation	qPCR			ROC		Target	ADHD-Associated Target Genes
		$\log_2$FC	p-Value	adj. p-Value	AUC	p-Value		
miR-652-3p	up	0.95594	2.84×10^{-3}	1.83×10^{-2}	0.733	2.33×10^{-2}	89	*B4GALT2, ANK3, SLC6A9*
miR-148b-3p	down	−0.97755	2.85×10^{-3}	1.83×10^{-2}	0.878	5.46×10^{-6}	8	
miR-942-5p	up	1.29942	4.22×10^{-3}	1.83×10^{-2}	0.811	1×10^{-4}	2	*TLE1*
let-7b-5p	up	1.49735	1.98×10^{-2}	6.45×10^{-2}	0.772	1.16×10^{-2}	9	
miR-181a-5p	up	1.01275	2.82×10^{-2}	7.33×10^{-2}	0.75	1.82×10^{-2}	75	*TAF1, TRIO, SYNE1*
miR-320a	up	1.06673	4.02×10^{-2}	8.72×10^{-2}	0.778	1.16×10^{-2}	8	

As detailed before, in order to prevent any misleading results due to the gender ratio discrepancy between the two study groups, we ran the same analysis by comparing the miRNA expressions of the ADHD (all males) versus the 14 TD males, and we confirmed that the same six miRNAs were significantly different between the two groups (Table S1).

To discriminate between the compared groups, we performed receiver-operating characteristic (ROC) analysis using the easyROC tool [24]. The independent miRNA analysis showed significant diagnostic values for all the DE miRNAs (p-value < 0.05). The six miRNAs provided values of the area under the curve (AUC) higher than 0.7, discriminating ADHD from TD (Figure 3). The best AUC values were observed for miR-320a (0.811; p-value =1×10^{-4}) and miR-148b-3p (0.878; p-value = 5.5×10^{-6}).

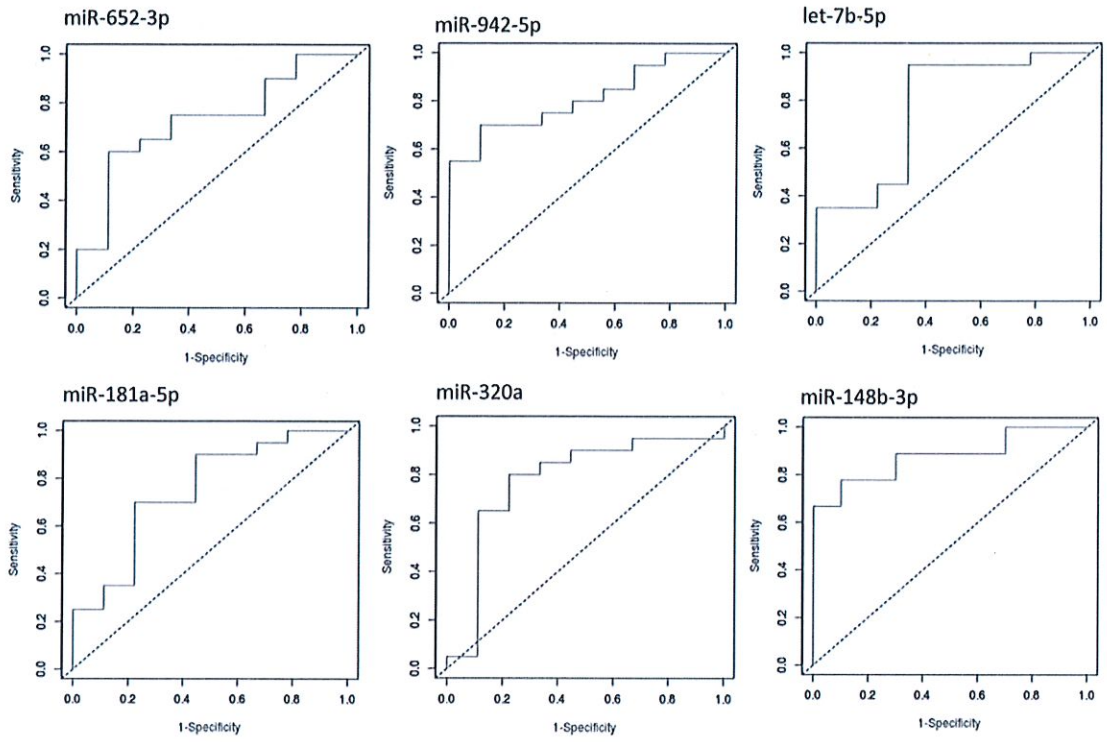

Figure 3. ROC curves generated by using the relative expression data of six DE miRNAs of interest. The diagram is a plot of sensitivity (true-positive rate) versus specificity (false-positive rate). AUC provides an estimate of the miRNA's ability to discriminate between the compared groups.

3.2. *Identification of DE mRNAs*

In order to obtain a list of mRNAs involved in ADHD susceptibility, differential expression analysis of RNA-Seq data between the two subgroups (ADHD vs. TD) was performed, using three criteria already tested in previous analyses [22,23]: (1) an average absolute fold change between the two study groups greater than 1.5; (2) a mean number of reads greater than 25; and (3) statistical significance (adjusted *p*-value, adj. *p*-value) lower than 0.05.

As result, 560 genes (200 upregulated and 360 downregulated) showed significant DE in children with ADHD compared to TD subjects (Table S2).

3.3. *Target Analysis*

To identify the miRNA targetome, the 560 DE mRNAs and the 6 DE miRNAs were selected for gene target analysis, using an integrated approach of validated and predicted interaction data extracted from seven different bioinformatic tools. Using databases containing experimentally validated miRNA-target interactions (miRtarbase and DIANA-Tarbase), four miRNA-target pairs, validated by reporter gene assays, were selected. Furthermore, since the prediction of the target site of existing algorithms can be still characterized by low precision and poor sensitivity, we integrated the predictions of at least three out of five miRNA-target interaction tools (miRanda, RNA22, mirDB, TargetScan, DIANA-microT-CDS) according to published guidelines [39].

This extensive analysis was able to uncover 190 predicted miRNA-target pairs, including 131 target genes; three miRNA-target pairs (miR-181a-5p/PHLPP2, let-7b-5p/E2F2, and let-7b-5p/IGF2BP2) were found overlapping between the experimentally validated and computationally predicted miRNA-target interactions.

We therefore constructed the miRNA-based network (Figure 4) including the DE miRNAs and their associated DE targets using Cytoscape v3.6.0 [40]. Interestingly, eight target genes (*KLHL14, ASH1L, MACF1, ZNF318, EPHA4, LAMC1, PPARGC1B*, and *SYNPO*) were shared by three miRNAs.

The DE genes were matched to publicly available ADHD-associated genetic factors contained in the ADHDgene Database [41], and we confirmed several miRNA targets previously associated to ADHD (TLE1, ANK3, TRIO, TAF1, SYNE1).

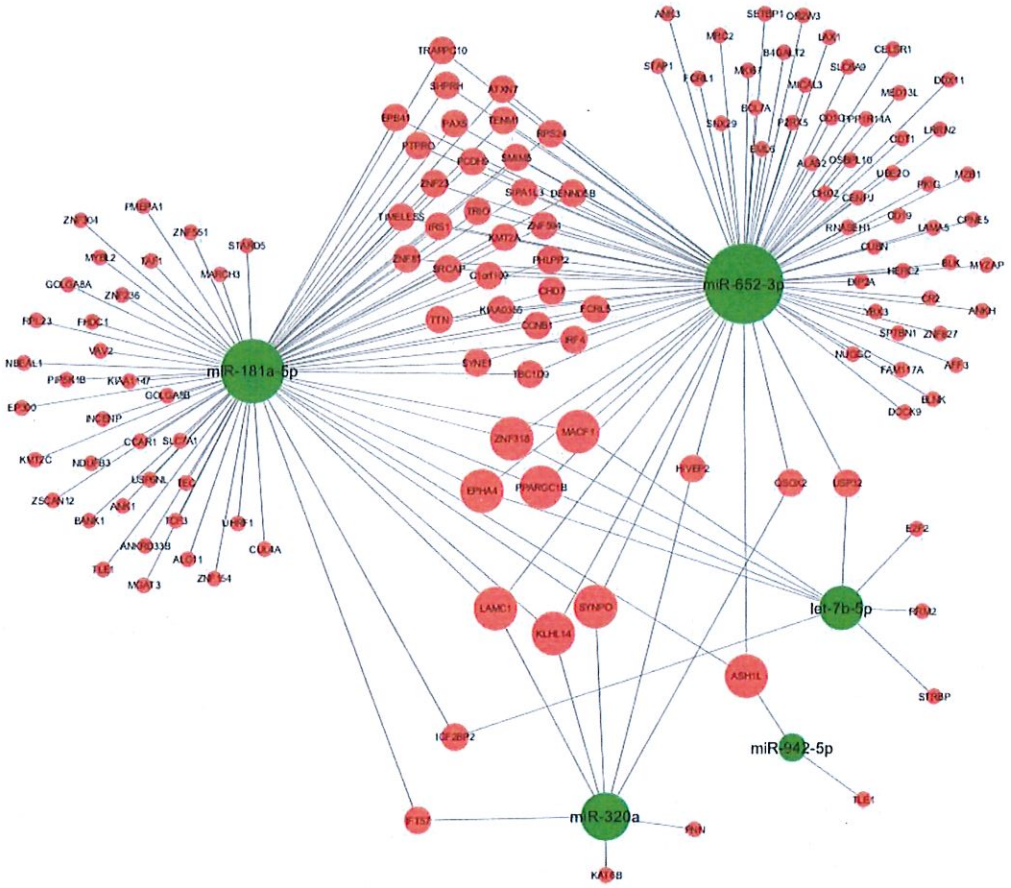

Figure 4. Graphical representation of miRNA-based targetome using Cytoscape v3.6.0. Only computationally predicted (three out of five algorithms) and/or validated miRNA-target interactions are shown. Green nodes represent miRNAs, red nodes represent target genes. The size of the nodes is proportional to the degree of the nodes (i.e., number of incoming and outcoming edges).

3.4. GO-Term and Pathway Enrichment Analysis

To explore the potentially involved physiological functions, all target genes were subjected to Gene Ontology (GO) and pathway enrichment analysis using the DAVID 6.8 Functional Annotation Tool (http://david.abcc.ncifcrf.gov/). The three GO categories (biological processes, cellular components, and molecular functions) were used to describe the gene product attributes (Figure 5A). Meanwhile, the results of pathway enrichment analysis revealed the main pathways in which the target genes were involved (Figure 5B). Almost all the GO-term results were closely related to immune system functions, such as complement activation (adj. p-value = 2.63×10^{-34}), regulation of immune response (adj. p-value = 2.41×10^{-23}), Fc-epsilon receptor signaling (adj. p-value = 3.38×10^{-21}), antigen binding (adj. p-value = 2.73×10^{-31}). The pathway analysis also revealed the enrichment of immune-related pathways, such as classical antibody-mediated complement activation (adj. p-value = 2.29×10^{-35}), CD22-mediated B cell receptor regulation (adj. p-value = 7.46×10^{-35}), Fc-epsilon receptor activation (adj. p-value = 3.83×10^{-34}), B cell receptor signaling (adj. p-value = 1.10×10^{-33}). Details of significantly implicated pathways and GO terms are reported in Table S3.

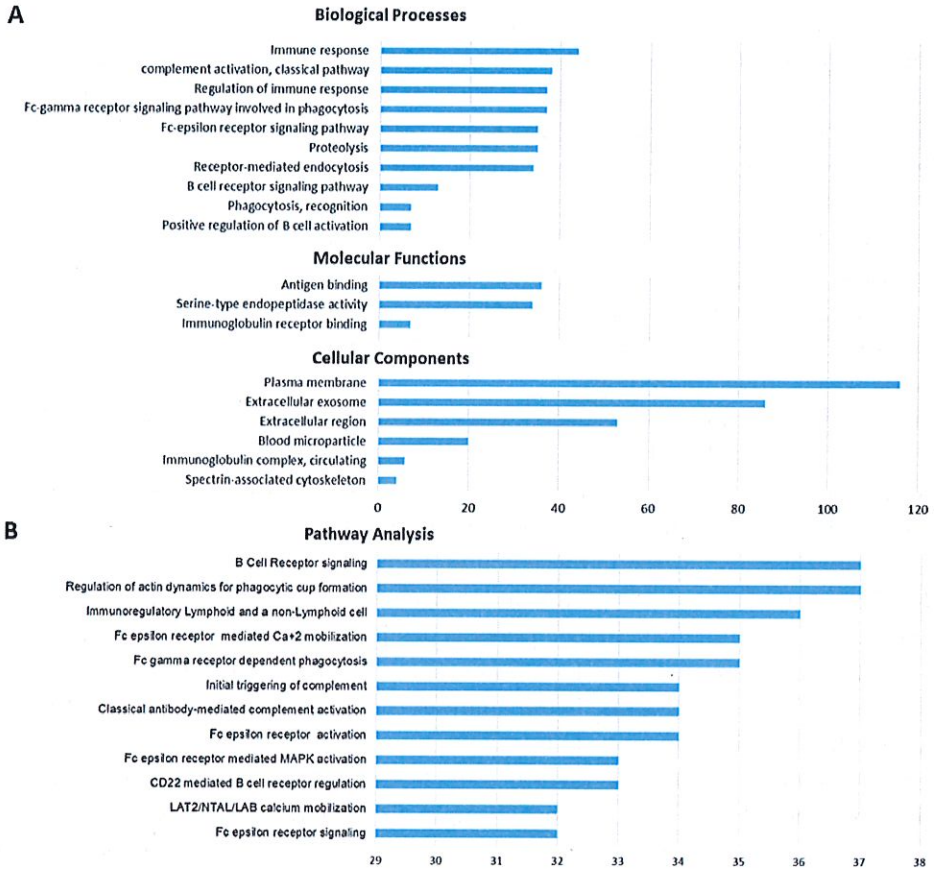

Figure 5. The histograms illustrate the category of enriched GO terms (**A**) and enriched pathways (**B**) for the DE genes. The horizontal axis represents the number of genes.

4. Discussion

To our knowledge, this is the first report that evaluates combined miRNA and mRNA expressions in children with ADHD. None of the three miRNAs that finally resulted DE in our analysis have been found to be implicated in the pathophysiology of ADHD, although this evidence may be explained (e.g., by some methodological bias). In fact, as in our approach, most of the studies investigated preselected miRNAs involved in other neurological disorders and/or in neurobiology mechanisms based on literature reviews or miRNA databases [15,17,21]; therefore, we may have omitted some potential miRNAs associated with ADHD, as they are involved in unknown biological mechanisms. On the other hand, Wang et al. [16] used for the first time a global screening technology (NGS) to explore miRNA profiles in ADHD of Han Chinese individuals recruited from a single site in Taiwan, but the study identified 13 different miRNAs as potential ADHD biomarkers. However, given the complex pathophysiology of ADHD, it is reasonable to hypothesize that the underlying biological mechanisms may not be identical across ethnicities.

In our investigation, starting from a panel of miRNAs dysregulated in diseases like Pediatric Multiple Sclerosis (PedMS) [22], we identified six DE miRNAs (miR-652-3p, miR-942-5p, let-7b-5p, miR-181a-5p, miR-320a, and miR-148b-3p) in children with ADHD compared to TDs, although only three of them (miR-652-3p, miR-148b-3p, and miR-942-5p) survived from the multiple comparisons correction. The overlap of these miRNAs in ADHD and PedMS might be explained by common underlying mechanisms (e.g., their cognitive dysfunctions), since ADHD-like symptoms have been described in about 27% of PedMS cases [42]. According to the literature, miR-652-3p and miR-148b-3p were also found to be associated with autism [43]; this evidence may be justified by the clinical comorbidity between the two diseases that also seem to share some genetic background, thus

complicating the differential diagnosis between them [44–47]. Furthermore, in our analysis, several DE miRNA targets were found to be associated with neuropsychiatric disorders, such as schizophrenia (TTN, SYNPO) [48,49], depressive disorder (PPARGC1B, TIMELESS) [50–52], and autism (TAF1, TRIO) [53,54]. Given the high overlap of DE miRNAs and mRNAs in ADHD and these disorders, it is more likely that given dysregulated miRNA-target networks may be specific to ADHD, rather than single miRNAs and/or genes.

Using for the first time a HT-NGS approach to profile mRNA expression in ADHD, we also obtained a plethora of DE genes compared to TDs. In the resulting miRNA-targets network, the targets with the largest degree values (in terms of number of incoming and outcoming edges) were KLHL14, ASH1L, MACF1, ZNF318, EPHA4, LAMC1, and PPARGC1B, suggesting that they might be critical elements in the ADHD physiopathology.

Several of these downregulated targets have been previously associated to ADHD, such as TLE1 [55], ANK3 [55,56], TRIO [57], TAF1 [58], SYNE1 [59]. Notably, TLE1 is essential for the maintenance of neuronal survival and its expression is reduced in neurons primed to die [60]. Since decreased subcortical volumes have been observed in ADHD patients, it is possible that a selective neuronal vulnerability is implicated in these volumetric losses [61]. Moreover, ANK3 is involved in neuronal development, playing a critical role in intellectual functioning, and its decreased expression can lead to different cognitive/psychiatric phenotypes [62]. Finally, TRIO regulates the neuronal development of the hippocampus, as well as the neuronal migration and axon guidance, by modulating RhoG that resulted in being upregulated in our analysis. Both RhoG and its regulator TRIO were found closely related to the learning functions in mice [63].

Recently, a genome-wide analysis identified the first significant genetic variants associated with ADHD in 12 independent loci [8]. The most strongly associated locus on chromosome 1 covered a gene-rich 250 kb region, including B4GALT2 and SLC6A9 that resulted in DE genes targeting both by miR-652-3p, one of the confirmed miRNAs in our analysis. Although the index variant was intronic to both genes, it might affect the gene expression levels in different manners. For example, variants in introns can introduce novel splice sites, activate novel promoters, introduce/eliminate enhancer activity, or modify RNA structure and, consequently, the accessibility of the target site to the RISC complex (mRNA secondary structure fold during transcription).

In our analysis, many other identified miR-652-3p targets were related to mechanisms possibly associated with the ADHD pathophysiology. Among them, HIVEP2 has been reported in patients characterized by developmental delay and intellectual disability [64], and CHD2 was found implicated in the development of selected neural circuits (i.e., cortical and hippocampal circuits) and long-term memory [65]. KLHL14 (one of the largest degree value nodes in Figure 4) and SYNE1 have been found to be involved in GABAergic interneuron circuitry and glutamate receptor internalization at postsynaptic sites, respectively [66,67]. Glutamate and GABA are essential excitatory and inhibitory neurotransmitters in the brain, and both seem to be involved in the frontostriatal signaling as well as related to the dysfunctions of the inhibiting impulse observed in ADHD subjects [68]. Indeed, magnetic resonance spectroscopy studies showed decreased prefrontal GABA levels in children with ADHD [69]. In addition, SYNE1 deficiency is one of the most common genetic causes of cerebellar ataxia, which may be of interest given the reported evidence of the cerebellum involvement in the pathophysiology of ADHD [70]. Cerebellar symptoms have been associated with difficulties in spatial working memory in children and adolescents with ADHD [71] and variability in their reaction time, which represents one of the candidate endophenotypes in this disorder [72].

Finally, the GO and pathway enrichment analysis of all the DE genes in our study reported their prevalent involvement in immune functions, such as complement activation, regulation of immune response, B cell receptor signaling, innate immunity, complement cascade, and adaptive immunity. Although from a limited number of cases, these results support the hypothesis that an immune imbalance may contribute to ADHD etiology, possibly requiring a predisposing genetic background [73], or it may be at least partially causative of the clinical symptoms [74–76]. Interestingly,

several significant enriched pathways pointed to the Fc-epsilon receptor, a key player in adaptive immunity and immediate allergic reactions through the binding of immunoglobulin antibodies that recognize an immune insult and elicit an inflammatory response with the production of cytokines. If confirmed in independent evaluations, this finding may generate novel hypotheses to explore in the pathogenesis of ADHD, with the potential to improve the search for more efficient targeted treatments.

5. Conclusions

In conclusion, in this study we were able to draw a genetic profile of juvenile ADHD that may help in deciphering the disease's pathogenesis. In spite of several already mentioned limitations, we believe in fact that our findings might provide preliminary but solid suggestions about some molecular networks that may be evoked during the occurrence of the disease. A larger cohort study and additional experimental approaches (e.g., protein level of mRNA targets) need to be performed to confirm these preliminary results.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3425/9/10/288/s1, Figure S1: title, Table S1: title, Video S1: title. Table S1: List of significant dysregulated miRNAs in ADHD (all males) compared to 14 TD males, Table S2: Datasets of DE mRNAs and miRNAs, Table S3: Lists of significant GO categories and pathways associated with ADHD.

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Attention deficit hyperactivity disorder in genetically-determined intellectual disability

A child aged 6 years and 6 months came to our observation for important motor restlessness, behavioral dyscontrol with hetero-aggressive behavior, develop-mental delay, sleep disturbance and dysmorphic features.

He was the only child of healthy and non-consanguineous parents. Two maternal cousins were report-edly diagnosed with small head and intellectual disability. Pregnancy was characterized by fetal growth arrest at 33 weeks. He was born by urgent caesarean section after 39 weeks of gestation; birth weight was 2220 g. At birth, he had neonatal jaundice. Maternal breastfeeding lasted 3 months, then it was integrated.

At the age of 6 months, a neurosurgical evaluation and cerebral echo scan were performed with detection of microcephaly and thinning of the corpus callosum.

The patient exhibited developmental delay: he began to walk at 16 months and started talking at 4 years. He also showed emotional spasms up to 4 years of age.

Growth was normal up to 4 years, when the patient began to manifest hyperphagia resulting in significant weight gain. He soon developed a severe sleep disturbance with frequent night awakenings and nocturnal pavor.

At the age of 4 years, the child was admitted for diagnosis to another hospital. Genetic investigations were performed, and CGH-Array revealed a *de-novo* 7.6-Mb duplication in chromosome 8 (8q24.23q24.3) and a *de novo* 5,8 Mb deletion in chromosome 13 (13q33.3q34). Duplication includes the following disease genes: TRAPPc9, SLURP1, CYP11B2, CYP11B1, FAM83H, PLEC and SLC39A4; deletion includes IRS2, COL4A1, ING1, F7, F10, PRZ and GRK1.

Ophthalmologic evaluation revealed hypermetropic astigmatism; otolaryngology evaluation showed adenoid hypertrophy of grade 3; electroencephalogram in sleep showed pseudo-pointy activities in frontotemporal regions; orthopedic evaluation and echocardiogram were reported as normal.

A diagnosis of "*genetically based moderate intellectual disability, severe linguistic impairment, hyperactive and impulsive behavior and attention disorder*" was made.

Immediately upon entry into the school, he showed important motor restlessness, behavioral dyscontrol and hetero-aggressive behaviors, also reported by teachers.

When the patient came to our observation, on physical examination he presented with grade 1 obesity (Body Mass Index: 32.1 kg/m²); two *café-au-lait* spots with a diameter of 2 cm on the left and right buttocks and bilateral short and stubby fingers were observed (Figure 1). He also had facial dysmorphic features: reduction of the bifrontal diameter and microcephaly (COF: 50 cm, equal to 10th percentile), moon facies, enlarged nasal bridge, hypertelorism, hypoplastic supraorbital ridges, straight eyebrows, thin upper lip (Figure 2, 3). Neurological examination showed global clumsiness, mildly enlarged based gait with external rotation of the feet. Regarding to language skills, understanding was sufficient for simple orders, while the expressive language was represented by word-sentence or bi-term phrase.

On the instrumental evaluation level, we performed ultrasound abdomen with detection of fatty liver, endocrinological consulting, cardiological evaluation, otolaryngology evaluation, electroencephalogram in sleep (reported as normal) and brain MRI, that showed thinning of the corpus callosum.

Figure 1.—Short and stubby fingers.

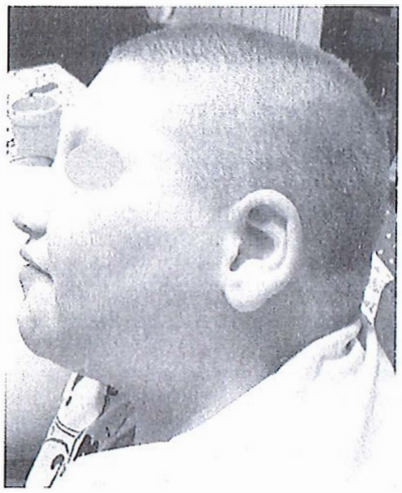

Figure 2.—Patient's head profile.

Figure 3.—Reduction of the bifrontal diameter, moon facies, enlarged nasal bridge, hypertelorism, hypoplastic supraorbital ridges, straight eyebrows, thin upper lip.

Our patient also underwent neuropsychological examination. The child was assessed with the Leiter International Performance Scale-Revised (Leiter-R), whereas the adaptive behavior profile has been investigated using Vineland Adaptive Behavior Scales (VABS). Parents completed several rating scales that measured symptoms of ADHD: Conner's Rating Scale-Revised (CRS-R), Child Behavior Checklist (CBCL), Swanson, Nolan, and Pelham Version IV Scale for ADHD (SNAP-IV). CRS-R was also completed by teachers. We also used Developmental Disabilities Children's Global Assessment Scale (DD-CGAS) in order to measure functional impairment, in addition to symptomatology.

The overall non-verbal IQ score was 60, thus attesting a mild degree of cognitive disability; on VABS, the equivalent score was 2 years, with low scores, in all four domains of Communication, Daily living skills, Socialization and Motor skills; DD-CGAS score was 40, attesting a moderate degree of functional impairment.

We made a diagnosis of "*genetically-based moderate intellectual disability, ADHD, microcrania, and facial dysmorphisms.*"

The patient was given 10 mg of methylphenidate once daily for 3 days, then 15 mg every 24 hours, and finally 20 mg once daily. No adverse effects have been observed.

School teachers and parents were involved in the management of hyperactivity with behavioral modification techniques and special education was planned.

Over a follow-up period of 2 years, clinical controls were performed every 3 months. Height, weight, heart rate, blood pressure, blood tests and electrocardiogram were monitored every 3 months; whereas neuropsychological assessment was performed every 6 months with the administration of CBCL, VABS and DD-CGAS. Cognitive assessment was repeated after 1 and 2 years, confirming mild cognitive disability.

All the rating scales administered in follow-up, showed a gradual improvement since the beginning of drug therapy: CBCL showed an improvement in externalizing behaviors (inattention, hyperactivity, oppositional behaviors); VABS showed a gradual improvement of personal and social autonomy (equivalent age scores of 3 years); DD-CGAS scores indicated better functioning, reaching a score of 65 at the end of the follow-up period. We also witnessed the gradual regularization of sleep patterns.

We present the case of a patient in which drug therapy with methylphenidate has been successful, without adverse effects, despite the presence in comorbidity of intellectual disability and ADHD. The improvement seen in ADHD symptoms and behavioral problems was certainly also due to non-pharmacological treatment measures, as stated during the neuropsychological evaluation.

In the literature, few studies investigated the effect of methylphenidate in ADHD children with intellectual disability[1-3] and even less studied patient's improve-

ments through neuropsychological evaluation using VABS,[4] DD-CGAS[5] and CBCL as instruments.

In our experience, methylphenidate treatment and non-pharmacological measures can improve behavioral issues also in children with intellectual disability and ADHD.

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La particolare fragilità dei bambini con patologie neuropsichiatriche

Maria Antonella Costantino, Presidente della Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

Lo scenario: numerosità e complessità delle patologie neuro-psichiatriche infantili, che rendono i bambini con tali patologie particolarmente fragili

I disturbi neuropsichici dell'età evolutiva sono estremamente frequenti e determinano un *Global Burden of Disease* superiore a quello delle malattie cardiovascolari. Coinvolgono tra il 10 e il 20% della popolazione infantile e adolescenziale, con disturbi molto diversi tra loro per tipologia, decorso e prognosi, per la maggior parte determinati da un complesso intreccio tra predisposizione genetica, vulnerabilità neurobiologica e variabili ambientali. Includono sia i disturbi neurologici (conseguenti a malattie acquisite o genetiche del sistema nervoso, con sequele spesso gravemente invalidanti), sia i disturbi di sviluppo (disabilità intellettiva, disturbi dello spettro autistico, disturbi specifici del linguaggio e dell'apprendimento, disturbo da deficit di attenzione con iperattività ecc.), sia i disturbi psichiatrici (psicosi, disturbi affettivi, disturbi della condotta, disturbi del comportamento alimentare e molti altri).

Le nuove conoscenze nell'ambito delle neuroscienze e della specificità del neurosviluppo, associate a una maggiore attenzione sociale, permettono diagnosi sempre più tempestive e interventi terapeutici e riabilitativi efficaci, che consentono di prevenire o ridurre

il carico emotivo, sanitario e sociale dei disturbi, di migliorare la qualità di vita degli utenti e di supportare le famiglie nel percorso.
La comorbidità tra disturbi del neurosviluppo è frequentissima, e pone una serie di interrogativi importanti per la ricerca, ma anche per la clinica e per l'organizzazione dei servizi (Thapar et al., 2017). Mentre infatti la maggior parte delle evidenze in letteratura e delle linee guida sono disturbo-specifiche, la maggior parte dei fruitori dei servizi di neuropsichiatria hanno più disturbi contemporaneamente, che interferiscono a vicenda in positivo o in negativo e modificano la risposta alle cure, richiedendo attenta integrazione e personalizzazione dei percorsi diagnostici e terapeutici.
In meno di dieci anni vi è stato un raddoppio degli utenti seguiti nei servizi di Neuropsichiatria dell'Infanzia e dell'Adolescenza (NPIA) (Saponaro e Bruno, 2017), con una prevalenza di accesso 4 volte superiore a quella dei servizi di salute mentale adulti (SISM); 8 volte superiore a quella dei servizi per le dipendenze patologiche (SIDER); 20 volte superiore a quella dell'area psicologica dei consultori (Report, 2016). Molte le cause di questi aumenti di richiesta assistenziale: aumentata consapevolezza della popolazione, cambiamento dei criteri diagnostici, introduzione di strategie di *screening* e individuazione precoce che consentono la diagnosi anche di disturbi lievi che in passato non erano individuati, aumentata sopravvivenza di soggetti con gravi disabilità, presenza di modificazioni ambientali rilevanti e molto rapide che impattano sullo sviluppo e sul livello atteso di funzionamento (indispensabilità di buone competenze di lettoscrittura, aspetti educativi ed economici, inquinamento ecc.).

I pregiudizi duri a morire

Gli utenti e le loro famiglie sono oggetto di pregiudizi marcati, che interferiscono con diagnosi e terapia, con l'inclusione sociale e soprattutto con la programmazione sanitaria. Nonostante cambiamenti molto rilevanti nella sensibilità della popolazione e una generale buona capacità di inclusione sociale del nostro Paese, la tendenza a negare l'esistenza dei disturbi neuropsichici è purtroppo ancora molto marcata, e frequenti e ripetute sono le campagne contro l'eccessiva medicalizzazione, quelle che sottolineano il diritto dei bambini a essere vivaci e diversi senza per questo essere "etichettati", e soprattutto quelle che stigmatizzano le verosimili colpe della famiglia, della scuola e dell'ambiente nella genesi dei comportamenti disfunzionali. Conseguentemente la maggior parte delle famiglie giunge alla diagnosi tardivamente, è spesso gravata da un rilevante senso di colpa, ed è in difficoltà a ingaggiarsi in pieno negli interventi necessari, anch'essi oggetto di frequenti attacchi sia per quanto riguarda le terapie non farmacologiche (banalizzate e invase da approcci non scientifici) che per quanto riguarda le terapie psicofarmacologiche (in Italia utilizzate con tassi 20 volte inferiori al resto d'Europa).

Mentre la solidarietà per un bambino con una grave malattia del corpo e per la sua famiglia è immediata e totale, così ancora non è per un bambino che si comporta in modo diverso dagli altri, facilmente considerato male educato, o pigro, o ridicolo, o addirittura "cattivo", e altrettanto facilmente isolato o bullizzato.

Gli attuali servizi di neuropsichiatria infantile, soprattutto territoriali, non sono assolutamente adeguati

Infatti:

- solo 1 utente su 2 riesce ad accedere ai servizi territoriali di NPIA per il percorso diagnostico;
- solo 1 utente su 3 riesce a ricevere un intervento terapeutico-riabilitativo;
- il numero medio di prestazioni ricevute da ciascun utente è basso e in diminuzione, e chi accede riceve un numero di trattamenti inferiore a quanto sarebbe auspicabile;
- solo 1 utente su 3 che ha necessità di ricovero ordinario o in urgenza riesce ad accedere a un reparto di NPIA;
- il supporto alle famiglie e la formazione al contesto non riescono a essere garantiti;
- molti interventi basati sulle più recenti evidenze scientifiche non sono ancora disponibili;
- solo 1 utente su 10 riesce a effettuare il passaggio a un servizio per l'età adulta.

Utenti e famiglie restano in lista d'attesa per mesi o addirittura anni, e le famiglie si trovano a ricorrere sempre più al privato, con costi rilevanti che in tempi di crisi economica sono sempre meno in grado di sostenere.
La prevalenza trattata è ampiamente insufficiente rispetto alla prevalenza attesa, attestandosi al 6-8% della popolazione nelle poche regioni con una situazione più favorevole, e scendendo in altre anche al di sotto del 4%, con disuguaglianze intra- e inter-regionali in aumento e conseguente non equità di risposte per i bambini e i ragazzi e per le loro famiglie.
In alcune regioni, i servizi di NPIA non esistono come tali e sono presenti solo singoli operatori sparsi nei distretti. In altre, i servizi territoriali di NPIA sono strutturati da decenni come servizi multiprofessionali che garantiscono risposte anche riabilitative a un bacino di utenza di riferimento, pur con una sempre maggiore flessibilità. Anche nelle situazioni meglio organizzate, mancano le strutture semiresidenziali e residenziali terapeutiche e i letti per il ricovero ospedaliero, in particolare per quanto riguarda la risposta ai disturbi psichiatrici. Non in tutti i servizi sono presenti le figure professionali necessarie (NPIA, psicologi, logopedisti, TNPMEE, fisioterapisti, assistenti sociali, educatori professionali, infermieri, tecnici, amministrativi ecc.). Non è in genere nota la prevalenza degli utenti trattati nei servizi di riabilitazione, né soprattutto quanti di essi siano contemporaneamente seguiti anche in

servizi di NPIA, né è strutturato un sistema coordinato su un territorio vasto, che includa i centri di riferimento, la riabilitazione infantile ex art. 26 e le strutture di NPIA dei singoli territori e condivida percorsi diagnostici e terapeutici. Inoltre, in genere, la presa in carico è possibile solo fino a quando è attivo un intervento terapeutico-riabilitativo diretto sul bambino, poi si interrompe e utente e famiglia vengono inviati ai servizi territoriali di NPIA. Particolarmente critica appare la situazione in Campania, Calabria, Marche, Abruzzo, Molise, ma anche in Liguria e Sardegna.
Infine, la criticità forse più rilevante è rappresentata dalla mancanza di un sistema informativo nazionale e di monitoraggio dedicato ai disturbi neuropsichici dell'età evolutiva, che includa le informazioni relative ai percorsi di cura effettivamente erogati, alla loro appropriatezza e agli esiti ottenuti.

Cosa oggi si sta facendo per correggere le lacune assistenziali e proteggere questi bambini "particolarmente" fragili?

Non molto.
Un segnale senz'altro positivo può essere considerato il documento di Linee di Indirizzo per i disturbi dell'età evolutiva, approvato dalla Conferenza Stato-Regioni nel Luglio del 2019. Tuttavia alcune Regioni, e in particolare il Veneto, hanno imposto l'eliminazione dal testo base dell'indicazione puntuale dei diversi livelli assistenziali.
Questa modifica è purtroppo un significativo limite alla futura efficacia migliorativa dei servizi, e permetterà il perpetuarsi delle diseguaglianze regionali.
Appare sempre più urgente avviare non solo interventi mirati di sensibilizzazione (l'esempio di quanto avvenuto in seguito alle campagne per l'autismo è molto interessante), ma anche soprattutto a colmare i vuoti enormi che esistono in questo ambito e garantisca finalmente risposte appropriate, eque e tempestive per i bambini e gli adolescenti con disturbi neuropsichici, per garantire non solo la loro salute e quella delle loro famiglie, oggi e soprattutto in proiezione per il loro futuro, ma anche il benessere di tutta la società.

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(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
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(in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016, N. 1077 del 02/02/2017 N. 1938 del 15/02/2019) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Percorsi diagnostico-terapeutici per l'ADHD*".

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