NEWSLETTER

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BIBLIOGRAFIA ADHD MAGGIO 2022

Acta Paediatr. 2022 Jun;111:1167-75.

NEURODEVELOPMENTAL DISORDERS AND SOMATIC DIAGNOSES IN A NATIONAL COHORT OF CHILDREN BORN BEFORE 24 WEEKS OF GESTATION.

Morsing E, Lundgren P, et al.

AIM: This study investigated childhood diagnoses in children born extremely preterm before 24Â weeks of gestation.

METHODS: Diagnoses of neurodevelopmental disorders and selected somatic diagnoses were retrospectively retrieved from national Swedish registries for children born before 24 weeks from 2007 to 2018. Their individual medical files were also examined.

RESULTS: We studied 383 children born at a median of 23.3 (range 21.9-23.9) weeks, with a median birthweight of 565 (range 340-874) grams. Three-quarters (75%) had neurodevelopmental disorders, including speech disorders (52%), intellectual disabilities (40%), attention deficit hyperactivity disorder (30%), autism spectrum disorders (24%), visual impairment (22%), cerebral palsy (17%), epilepsy (10%) and hearing impairment (5%). More boys than girls born at 23 weeks had intellectual disabilities (45% vs. 27%, pÂ <Â 0.01) and visual impairment (25% vs. 14%, pÂ <Â 0.01). Just over half of the cohort (55%) received habilitation care. The majority (88%) had somatic diagnoses, including asthma (63%) and failure to thrive/short stature (39%).

CONCLUSION: Most children born before 24 weeks had neurodevelopmental disorders and/or additional somatic diagnoses in childhood and were referred to habilitation services. Clinicians should be aware of the multiple health and developmental problems affecting these children. Resources are needed to identify their long-term support needs at an early stage

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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.

Adolesc Psychiatry. 2021;11:225-39.

CUMULATIVE EFFECTS OF PRENATAL AND CONCURRENT MATERNAL DISTRESS ON PSYCHIATRIC DISORDERS IN ADOLESCENT OFFSPRING.

Mortaji N, Savoy C, Boylan K, et al.

Background: Mental disorders affect 20% of children and adolescents globally and are among the most chronic and costly problems affecting youth. Offspring exposure to maternal disorders (depression, anxiety, and/or stress) prenatally as well as in adolescence increases the risk of psychopathology in adolescence.

Objective: Exposure to maternal distress in pregnancy, as well as in adolescence, has independently been linked to psychopathology in youth. However, our understanding of the cumulative effects of exposure to maternal distress over time remains incomplete.

Methods: 1964 participants enrolled in the 2014 Ontario Child Health Study (OCHS) aged 12-17 years completed the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). Maternal prenatal distress was defined as mother-reported depression and/or anxiety during pregnancy requiring treatment. Maternal concurrent distress was self-reported when offspring were 12-17 years of age using the Kessler Psychological Distress Scale (K6). We examined associations between increasing levels of exposure to maternal distress (no exposure, prenatal exposure only, concurrent exposure only, both prenatal and concurrent exposure) and the risk of psychiatric disorder in 12-17-year-olds.

Results: The odds of major depressive disorder (OR=1.29, 95% CI: 1.01-1.67) and ADHD (OR=1.30, 95% CI: 1.02-1.65) increased with increasing exposure to maternal distress. Associations between increasing levels of maternal distress and several psychiatric disorders were amplified in males.

Conclusion: The accumulation of exposure to maternal distress over time predicts offspring psychopathology in adolescence and emphasizes the significance of the early detection of maternal distress and ongoing monitoring and intervention to reduce the burden of mental disorders in offspring

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Alcohol Alcohol. 2022 May;57:385-95.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ALCOHOL AND OTHER SUBSTANCE USE DISORDERS IN YOUNG ADULTHOOD: FINDINGS FROM A CANADIAN NATIONALLY REPRESENTATIVE SURVEY.

Fuller-Thomson E, Lewis DA, Agbeyaka S .

Aim: (a) To document the prevalence and odds of (i) alcohol use disorders, (ii) cannabis use disorders, (iii) other drug use disorders and (iv) any substance use disorder (SUD), among young adults with and without ADHD, and (b) to investigate the degree to which the association between ADHD and SUDs is attenuated by socio-demographics, early adversities and mental health.

Method: Secondary analysis of the nationally representative Canadian Community Health Survey-Mental Health (CCHS-MH). The sample included 6872 respondents aged 20-39, of whom 270 had ADHD. The survey response rate was 68.9%.

Measurements: Substance Use Disorder: World Health Organization's Composite International Diagnostic Interview criteria, SUDs, were derived from lifetime algorithms for alcohol, cannabis and other substance abuse or dependence. ADHD was based on self-report of a health professional's diagnosis.

Findings: One in three young adults with ADHD had a lifetime alcohol use disorder (36%) compared to 19% of those without ADHD ($P < 0.001$). After adjusting for all control variables, those with ADHD had higher odds of developing alcohol use disorders (OR = 1.38, 95% CI: 1.05, 1.81), cannabis use disorders (OR = 1.46, 95% CI: 1.06, 2.00), other drug use disorders (OR = 2.07, 95% CI: 1.46, 2.95) and any SUD (OR = 1.69, 95% CI: 1.28, 2.23). History of depression and anxiety led to the largest attenuation of the ADHD-SUD relationship, followed by childhood adversities and socioeconomic status.

Conclusions: Young adults with ADHD have a high prevalence of alcohol and other SUDs. Targeted outreach and interventions for this extremely vulnerable population are warranted.

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Am J Obstet Gynecol. 2022.

CHORIOAMNIONITIS AND RISK OF LONG-TERM NEURODEVELOPMENTAL DISORDERS IN OFFSPRING: A POPULATION-BASED COHORT STUDY.

Tsamantioti E, Lisonkova S, Muraca G, et al.

Background: Evidence indicates that in utero exposure to chorioamnionitis might increase the risk of neurodevelopmental disorders in the offspring. However, findings on this topic have been inconsistent.

Objective: To examine the association between chorioamnionitis and neurodevelopmental disorders in offspring. Study

Design: This was a retrospective population-based cohort study in Sweden. A total of 2,228,280 singleton live births and stillbirths between 1998 and 2019 were included in our study population. Data on maternal characteristics and neurodevelopmental disorders in offspring were obtained by individual record-linkages of nationwide Swedish registries. Chorioamnionitis was identified using the National Medical Birth Register. Inpatient and outpatient diagnoses were obtained for cerebral palsy, autism, attention deficit hyperactivity disorder, epilepsy, and intellectual disability. Multivariable Cox proportional hazards regression was used to estimate the association between chorioamnionitis and each neurodevelopmental disorder with adjusted hazard ratios and 95% confidence intervals. A causal mediation analysis of the relationship between chorioamnionitis and neurodevelopmental disorders with preterm delivery (<37 weeks) was performed.

Results: A total of 5770 (0.26%) offspring were exposed to chorioamnionitis during pregnancy. During the study's follow-up time there were 4752 (0.21%) cases of cerebral palsy, 17,897 (0.80 %) cases of epilepsy, 50,570 (2.27 %) cases of autism, 114,087 (5.12%) cases of attention deficit hyperactivity disorder, and 14,574 (0.65%) cases of intellectual disability. After adjusting for potential confounders, exposure to chorioamnionitis increased the hazard ratios of cerebral palsy (adjusted hazard ratio, 7.43; 95% confidence interval, 5.90-9.37), autism (adjusted hazard ratio, 1.43; 95% confidence interval, 1.21-1.68), attention deficit hyperactivity disorder (adjusted hazard ratio, 1.17; 95% confidence interval, 1.03-1.33), and intellectual disability (adjusted hazard ratio, 1.99; 95% confidence interval, 1.53-2.58), whereas chorioamnionitis was not significantly associated with higher rates of epilepsy in offspring. Mediation analysis revealed that these associations were mainly explained through preterm delivery; however, increased risk was also observed among term infants.

Conclusion: Chorioamnionitis increases the risk of neurodevelopmental disorders, particularly cerebral palsy, autism, attention deficit hyperactivity disorder, and intellectual disability. These associations were mainly mediated through preterm delivery. Efforts for timely identification and appropriate interventions to treat infections during pregnancy will have sustained benefits in reducing the burden of neurologic complications in children at the population level

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Arch Suicide Res. 2022 Jan;26:280-89.

DIFFERENCES IN COMORBIDITIES BETWEEN CHILDREN AND YOUTH WITH SUICIDE ATTEMPTS VERSUS IDEATION PRESENTING TO THE EMERGENCY DEPARTMENT.

Claudius I, Axeen S.

OBJECTIVE: The aim of this work was to explore identified risk factors for suicidal ideations and attempts and the differences in these risk factors between emergency department encounters among youth seeking medical care for suicide attempt and those with suicidal ideation.

METHOD: This was a retrospective analysis of suicide-related claims for emergency department visits from nine state-level Healthcare Cost and Utilization Project databases for youth aged 5 through 19 years. Risk factors were estimated by identifying comorbidities recorded in first five diagnosis codes. Odds ratios comparing rates of these comorbidities in encounters for suicide attempts compared to encounters for suicidal ideation were estimated using multivariate logistic regression.

RESULTS: In all, 169,047 encounters for suicide-related behavior were identified. We found higher odds of concurrent anxiety, personality disorders, and alcohol-related diagnoses and lower odds of a comorbid psychosis diagnosis, attention deficit hyperactivity disorder, and other substance-related diagnoses in the population of suicide attempters compared to patients with suicidal ideation alone.

CONCLUSION: The odds of diagnoses of specific comorbidities differed in youth encounters for suicide attempts compared to encounters for suicidal ideation

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Asian J Psychiatr. 2022 May;71:103054.

PREVALENCE OF AUTISM SPECTRUM DISORDER AMONG SAUDI CHILDREN BETWEEN 2 AND 4 YEARS OLD IN RIYADH.

Albatti TH, Alsaghan LB, Alsharif MF, et al.

OBJECTIVES: We aimed to estimate the prevalence of autism spectrum disorder between 2 and 4 years old in Riyadh, Saudi Arabi

Methods: A cross-sectional study was conducted among Saudi children aged 2-4 years between December 2017 and March 2018 at five different hospitals in Riyadh.

RESULTS: A Total of 398 children were included. The prevalence of ASD was estimated to be (2.51%, 1:40, 25 per 1000)), with a male to female ratio of 3:1.

CONCLUSION: The estimated high prevalence rate of ASD is close to recent trends in international studies. Future population-based studies are required

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Asian J Psychiatr. 2022 May;71:103071.

QUALITY OF WEB-BASED INFORMATION ON ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Singh S, Saini R, Sagar R.

BACKGROUND AND OBJECTIVE: The limited literature available on quality of online health information about attention deficit hyperactivity disorder (ADHD), reported mixed findings and was more than five years old. This study aimed to assess the content quality, readability, aesthetics, and interactivity of current web-based information on ADHD.

METHODS: We screened first 50 links obtained on searching for ADHD using two popular search engines (Google and Bing), out of which 44 websites were selected for quality assessment. They were analysed using pre-decided study Performa, which included previously validated DISCERN instrument for content quality. Flesch-Kincaid grade level score and Flesch-Kincaid readability index were calculated for assessing readability.

RESULTS: About 61.4% of websites had DISCERN score 40, suggestive of good content quality. However, only 38.6% and 13.6% of websites were written at recommended reading level of eighth and sixth grade respectively. The DISCERN score had significant positive correlation with aesthetics and interactivity scores. Websites with the Health On Net (HON) label had better content quality. No significant difference in the readability, aesthetics, and interactivity of websites with and without the HON label.

CONCLUSION: This study underscores the need for improving readability of web-based information on ADHD, and highlight important areas for improving the overall quality of websites. The use of HONCode label might guide general public in gauging the content quality of online health information, but not its readability or presentation

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Assessment. 2022 Jul;29:1086-98.

CONVERGENT AND DISCRIMINANT VALIDITY OF THE CHILD AND ADOLESCENT BEHAVIOR INVENTORY SCALE SCORES WITH WELL-ESTABLISHED PSYCHOPATHOLOGY AND ACADEMIC ACHIEVEMENT MEASURES IN ADOLESCENTS WITH ADHD.

Burns GL, Becker SP.

The convergent and discriminant validity of the parent version of the Child and Adolescent Behavior Inventory (CABI) symptom and impairment scale scores were evaluated with the scale scores from multiple methods including a semistructured diagnostic interview, rating scales, and an academic achievement test. Participants were 82 adolescents (70% male, 78% non-Hispanic White) aged 13 to 17 years (M = 15.01) diagnosed with attention-deficit/hyperactivity disorder (77% predominantly inattentive presentation) and parents. CABI scale scores showed moderate (rs = .42 to .49) to substantial (rs = .62 to .91) convergent correlations with scores from similar measures. CABI scale scores also showed significant discriminant validity (convergent correlation significantly larger than discriminant correlation) with the scores on the other measures. These findings provide additional support for use of the CABI in research and clinical practice, and copies of the scale and norms are freely available

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Autism Res. 2022 Jun;15:1008-17.

AN ATLAS OF GENETIC CORRELATIONS BETWEEN GESTATIONAL AGE AND COMMON PSYCHIATRIC DISORDERS.

Yao Y, Li C, Meng P, et al.

We aim to systematically explore the potential genetic correlations between five major psychiatric disorders and gestational ages. Genome-wide association study (GWAS) summary datasets of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BD), schizophrenia (SCZ) and major depressive disorder (MDD) in discovery were downloaded from the Psychiatric GWAS Consortium (PGC) website. Suggestive (Raw $p < 0.05$) genetic associations in the discovery phrase were further replicated in independent GWASs which downloaded from PGC, the FinnGen study or Integrative Psychiatric Research (iPSYCH) website. GWASs of gestational duration, preterm and post-term birth were derived from previous studies of infants from the Early Growth Genetics (EGG) Consortium, the iPSYCH study, and the Genomic and Proteomic Network for Preterm Birth Research (GPN). We calculated genetic correlations using linkage disequilibrium score (LDSC) regression. Mendelian randomization (MR) analyses were performed to investigate the causal effects. We identified four suggestive genetic correlations between psychiatric disorders and gestational age factors in discovery LDSC and two replicated in a confirmation LDSC: gestational duration and ADHD (rg = -0.1405, FDR p = 0.0406), post-term birth and SCZ (rg = -0.2003, FDR p = 0.0042). We also observed causal effect of post-term birth on SCZ by MR (PWeighted median = 0.037, PInverse variance weighted = 0.007). Our analysis suggested no significant evidence of horizontal pleiotropy and heterogeneity. This study showed the genetic correlation evidences between gestational age phenotypes and psychiatric disorders, providing novel clues for understanding the pathogenic factors of common psychiatric disorders. LAY SUMMARY: Whereas gestational age factors were reported to be associated with psychiatric disorders, the genetic relationship and causality remain to be revealed. The present study reported the first large-scale genetic correlations investigation of the associations between gestational age phenotypes and psychiatric disorders. Results indicate causal relationships between post-term birth and schizophrenia (SCZ), as well as suggestive genetic correlations between gestational duration and attention deficit/hyperactivity disorder (ADHD). This study provided novel clues for understanding the pathogenic factors of common psychiatric disorders

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Autism Res. 2022 Apr;15:740-50.

ASSOCIATION BETWEEN ATOPIC DISEASES AND NEURODEVELOPMENTAL DISABILITIES IN A LONGITUDINAL BIRTH COHORT.

Qu X, Lee LC, Ladd-Acosta C, et al.

Reports on the association between the prevalence of atopic diseases and neurodevelopmental disabilities (NDs) have been inconsistent in the literature. We investigated whether autism spectrum disorder (ASD), attention deficit-hyperactivity disorders (ADHD), and other NDs are more prevalent in children with asthma, atopic dermatitis (AD) and allergic rhinitis (AR) compared to those without specific atopic conditions. A total of 2580 children enrolled at birth were followed prospectively, of which 119 have ASD, 423 have ADHD, 765 have other NDs, and 1273 have no NDs. Atopic diseases and NDs were defined based on physician diagnoses in electronic medical records. Logistic regressions adjusting for maternal and child characteristics estimated the associations between NDs (i.e., ASD, ADHD, and other NDs) and asthma, AD and AR, respectively. Children with asthma, AD or AR had a greater likelihood of having ADHD or other NDs compared with children without specific atopic conditions. The association between ASD and asthma diminished after adjusting for maternal and child factors. Either mothers or children having atopic conditions and both mothers and children with atopic conditions were associated with a higher prevalence of ADHD in children, compared with neither mothers nor children having atopic conditions. Children diagnosed with multiple atopic diseases were more likely to have NDs compared with those without or with only one type of atopic disease. In conclusion, in this U.S. urban birth cohort, children with atopic diseases had a higher co-morbidity of NDs. The findings have implications for etiologic research that searches for common early life antecedents of NDs and atopic conditions. Findings from this study also should raise awareness among health care providers and parents about the possible co-occurrence of both NDs and atopic conditions, which calls for coordinated efforts to screen, prevent and manage NDs and atopic conditions

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Biol Psychiatry. 2022;91:S110-S111.

P58. IMPACT OF GENETIC AND ENVIRONMENTAL RISK FACTORS ON ADHD DIAGNOSIS AMONG SCHOOL AGED CHILDREN IN THE ABCD STUDY.

Kunitoki K, Hughes D, Roffman J.

Background: Risk for ADHD is associated with both genetic and environmental factors, but the relative burden of these classes of risk remains uncertain. We sought to determine attributable risk estimates for known genetic and environmental risk factors in a large study of youth age 9-10.

Methods: Using baseline data from 2,984 children participating in the Adolescent Brain Cognitive Development (ABCD) Study, we extracted ADHD diagnosis (past, present, unspecified) from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), along with a total of 15 variables selected a priori based on the ADHD literature: neighborhood unsafety, economic hardship, screen time, extracurricular activities, divorce, lack of prenatal vitamins, unplanned pregnancy, c-section, preterm birth, drug abuse, pregnancy or birth complications. Among participants with European ancestry, ADHD polygenic risk score (PRS) was calculated based on PGC summary statistics. We calculated relative risk and population attributable fraction (PAF) for each risk factor, along with estimated weighted overall PAF accounting for overlapping variance principal component analysis.

Results: The prevalence of all ADHD among this cohort was 19.8%. Weighted overall PAF for ADHD diagnosis was 0.43. Weighted PAF across environmental factors was 0.39, compared to 0.046 for ADHD polygenic risk.

Conclusions: Common environmental exposures cumulatively confer substantially greater risk for ADHD compared to that attributable to genetic loading, as presently indexed. As several of these environmental factors are potentially modifiable, these findings suggest the possibility of prevention in some cases of ADHD.

Supported By: R01MH124694, R01MH120402

Keywords: ADHD, Environmental Risk Factors, Genetic Risk, Prevention

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Biol Psychiatry. 2022;91:S86.

SUPERFICIAL WHITE MATTER FIBRES MICROSTRUCTURE IS ASSOCIATED WITH ATTENTION DEFICITS IN CHILDREN WITH CONCUSSION.

Stojanovski S, Ameis S, Wheeler A.

Background: Attention problems are common sequelae of concussion in children. Superficial white matter fibers in the brain are particularly vulnerable to concussion in children due to their protracted myelination and the change in tissue density where they are located at the grey-white matter interface beneath the cortex.

Methods: Children (9-10-year old) with concussion (N=324) and without concussion (N=339) from the Adolescent Brain Cognitive Development Study were matched on: age, sex, pubertal status, total combined family income, parental education, race and ethnicity, and medications. To assess superficial white matter microstructure constrained spherical deconvolution and particle filtering tractography was applied to multishell diffusion weighted MRI data to generate length thresholded tractogram streamlines weighted by fractional anisotropy (FA), fiber density (AFD) and fiber orientations (NuFO). Attention was assessed with the CBCL attention problem scale. Differences in attention and white matter microstructure between groups and associations between attention and white matter microstructure were assessed with linear mixed effects models.

Results: Children with concussion had more clinically significant attention syndrome scale scores (p=4.9x10-6) and elevated FA (p=2.0x10-16), AFD (4.9x10-8) and NuFO (2.3x10-16) in superficial white matter compared to children without concussion. In children with concussion there were significant interactions between FA and age (p=0.002) as well as NuFO and age (p=0.03) that indicated that in younger children lower values were associated with better attention and in older children higher values were associated with better attention.

Conclusions: These data suggest that the maturational trajectory of superficial white matter fiber microstructure may be altered by concussion and impair attention. Supported By: RESTRACOMP SICKKIDS

Keywords: Concussion, Attention, White Matter Microstructure, Diffusion- Weighted Magnetic Resonance Imaging, Adolescent Brain Cognitive Development (ABCD) Study

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Biol Psychiatry. 2022;91:S114-S115.

P68. Atypical Network Properties During Rest and Task Performance in Youth With ADHD Symptoms: A Bifactor Model Approach.

Reimann G, Stier AJ, Moore TM, et al.

Background: When neural networks deviate from typical development, the resulting dysfunction is thought to contribute to varying forms of psychopathology. Although childhood networks are crucial for understanding neural and psychological development, research in this domain has been limited by psychological comorbidities, small sample sizes, and a reliance on traditional diagnostic categories.

Methods: To combat these limitations, the present study examined the efficiency of functional networks in association with a bifactor model of four psychopathology dimensionsΓÇögeneral psychopathology, internalizing, conduct problems, and attention-deficit/hyperactivity disorder (ADHD)ΓÇöin a sample of 3,568 children from the Adolescent Brain and Cognitive DevelopmentSM Study (ABCD Study-«). Local and global graph theory metrics were calculated at rest and during tasks of reward processing, inhibition, and working memory. We examined the dimensionsΓÇÖ associations with functional network attributes using structural equation modeling.

Results: Greater ADHD symptoms were associated with lower modularity across rest (p =.01), reward processing (p =.001), inhibition (p <.001), and working memory (p =.008). Further, greater ADHD symptoms were associated with reduced local efficiency in the motor network at rest (p =.008). These findings indicate nonoptimal short-range communication and a lack of information hub formation specific to the ADHD dimension.

Conclusions: Uniquely, our dimensional model disentangles the variance specific to ADHD from the common variance shared across psychopathology symptoms to examine its associated network properties. Using a large sample size and powerful dimensional and graph theory frameworks, we illustrate deficits in within-network communication may be a neurobiological marker of ADHD.

Supported By: NIDA; NIMH; NCATS; NARSAD; Sloan Research; Lifespan Brain Institute of the University of Pennsylvania and the Children's Hospital of Philadelphia Keywords: ADHD, Graph Theory, Childhood and Adolescence, Dimensional Psychopathology

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Biol Psychiatry. 2022;91:S114.

P67. Chronic Exposure to Psychostimulants in Pediatric ADHD Moderates Striatal Resting-State Functional Connectivity and Symptom Severity Over Two Years.

Kaminski A, You X, Vaidya C.

Background: Acute administration of psychostimulants, the most common medication for Attention-Deficit/Hyperactivity Disorder (ADHD), attenuates symptoms via upregulation of striatal dopamine activity. Less is known about the effects of long-term psychostimulant exposure. We explored exposure-dependent changes in striatal resting-state functional connectivity (rs-FC) and their relation to symptom outcome across two years in the Adolescent Brain Cognitive Development dataset.

Methods: Subjects (n=196; mean age=9.9 years at baseline; 11.9 years at year 2 [Y2]) were included if they had ADHD diagnosis, IQ>70, CBCL ADHD Problems scores, and >5 minutes of low motion (<0.2mm FD) rs-FC data, at both timepoints. Subjects were psychostimulant na+»ve (n=116) or treated (n=80). We calculated change in seed-based rs-FC (Y2-baseline) between left and right ventral striatum, caudate, and putamen, and 10 large-scale functional networks. A stepwise logistic regression identified connections where rs-FC change predicted exposure, and then linear regression tested whether this rs-FC change interacted with exposure to predict Y2 ADHD severity, controlling for baseline ADHD severity, gender, IQ, family income, and maternal education, and correcting for number of models.

Results: FC change was associated with psychostimulant exposure in 9 connections (Adj. R2=0.24). Of these, FC between left ventral-striatum and bilateral sensorimotor network interacted with psychostimulant exposure to explain Y2 ADHD severity (b=-16.80, p=0.003; Adj. R2=0.35). FC became more positive for exposed (mean: baseline=0.06, Y2=0.08) but not na+»ve (mean: baseline=0.10, Y2=0.07) subjects (t(178.75)=-2.10, p=0.037).

Conclusions: Stronger rs-FC between left ventral-striatum, a reward region, and primary sensory and motor cortices over two years predicted symptom outcome in ADHD children treated with psychostimulants.

Keywords: Attention Deficit Hyperactivity Disorder, Long-term Psychostimulant Exposure, Corticostriatal Functional Connectivity

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Biol Psychiatry. 2022;91:S111-S112.

P60. META-ANALYSIS OF CELL TYPE-SPECIFIC DNA METHYLATION OF CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.

Meijer M, Klein M, Caramaschi D, et al.

Background: The interplay of genetic factors and environmental adversities in ADHD can be reflected by cell type-specific DNA methylation (DNAm). Previous methylome-wide association studies (MWAS) for ADHD have been performed in bulk tissue only, where meaningful DNAm signal could be left undetected. We aim to identify cell type-specific DNAm profiles associated with childhood ADHD symptoms.
Methods: First, we performed array-based (<850.000 sites) cell type-specific MWAS meta-analyses of childhood ADHD symptoms (age-range 4-13 years) in cord- (N=1543) and peripheral blood (N=2009) from the PACE consortium. Then we expanded the coverage of the epigenome to 28 million sites based on methyl-binding-domain sequencing in peripheral blood (N=583; Great Smoky Mountain Study; mean-age 13.5 years). Using epigenomic deconvolution, DNAm associations in the five major blood cells were calculated.
Results: Associations between DNAm and ADHD symptoms were identified in cord blood monocytes (PDE6B, FDR=0.012), CD8T cells (KCNA3, HAND2, both FDR=0.016), and NK cells (KIFC1, FDR=0.043). In peripheral blood, only CD8T cells (RPL31P11, FDR=4.48*10-6 and KCNJ5, FDR=0.0021) showed associations. In the broader coverage analysis, we detected 24 and 16 significant CpG sites (FDR<0.05) in monocytes and granulocytes, respectively. None of these hits were covered by the arrays, and some overlapping genes showed opposite effect sizes in the different cell types, which signal was masked in bulk tissue. Downstream analyses of gene ontology term enrichment showed consistent results between cord and peripheral blood.
Conclusions: We identified the first ADHD-DNAm associations at a cell type-specific level, bringing us closer to understanding the role of specific cell types in the etiology of ADHD.
Supported By: Donders Centre for Medical Neuroscience of the Radboudumc; Dutch National Science Agenda; European's Comission's Horizon 2020 Programme

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Biol Psychiatry. 2022;91:S116.

P72. RIGHT CAUDATE VOLUME AND PARENT RATINGS OF EXECUTIVE FUNCTIONS IN PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Hai T, Swansburg R, Chenji S, et al.

Background: The caudate has been implicated in pediatric ADHD. However, previous studies have not investigated the relationship between the caudate and executive function using commonly used parent rating scales.
Methods: Twenty-four children with ADHD (M=11.64; males =12) and 25 typically developing children (TDC; M = 11.09 years; n=14 males) underwent a high-resolution Magnetic Resonance Imaging (MRI) T1-weighted sequence. FreeSurfer 6.0 was used for subcortical volume reconstruction. Parents completed behaviour ratings measuring executive function skills (BRIEF-2). Data were analyzed using Multivariate Analysis of Covariance and Spearman correlations.
Results: Parents of children with ADHD reported significantly more executive function challenges on the BRIEF-2 compared to the TDC group, F (5,43) = 20.89, p <.001, partial eta square =.71). However, no significant difference was observed in the caudate volume between the children with ADHD and TDC groups, F (4,41) =.79, p>.05, partial eta square =.07). Spearman correlations did demonstrate negative correlations between right caudate volume and parent ratings of emotion regulation (r = -.52, p =.009) in the ADHD group.
Conclusions: Our study showed significant executive function difficulties based on parent ratings, but no volumetric difference was observed in the caudate. Right caudate was related to parent ratings of executive function in pediatric ADHD participants. Future studies are required to replicate current findings and determine if the right caudate volume can be a biomarker of ADHD.
Supported By: Alberta children's hospital research institute

Keywords: ADHD, Executive Functions, Subcortical Volume, Pediatric Populations

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Biol Psychiatry. 2022;91:S110.

P57. METHYLPHENIDATE ENHANCES SPONTANEOUS FLUCTUATIONS IN REWARD AND COGNITIVE CONTROL NETWORKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CONTROL TRIAL.

Mizuno Y, Cai W, Supekar K, et al.

Background: Methylphenidate, the first-line treatment for attention-deficit/hyperactivity disorder (ADHD), is thought to influence brain networks involved in attention and cognitive control by increasing dopaminergic neurotransmission in the nucleus accumbens (NAc), but this hypothesis has yet to be systematically tested.
Methods: In a randomized placebo-controlled double-blind crossover trial, 34 children with ADHD were scanned twice with resting-state functional MRI under methylphenidate and placebo conditions, along with assessments of sustained attention using a continuous performance task. Spontaneous activity in the NAc, salience and default mode networks as well as functional connectivity of the NAc were examined.
Results: Methylphenidate increased spontaneous fluctuations regionally in the NAc, and at the network level, in the salience and default mode networks. In addition, methylphenidate-induced changes in spontaneous activity patterns in the default mode network were associated with changes in reaction time variability during a sustained attention task. Methylphenidate increased NAc connectivity with the anterior insula node of the salience network, and decreased NAc connectivity with the posterior cingulate cortex, ventromedial prefrontal cortex, and angular gyrus nodes of the default mode network. Brain-wide levels of spontaneous activity and NAc functional connectivity differentiated methylphenidate and placebo conditions with a high degree of accuracy.
Conclusions: Methylphenidate enhances weak spontaneous neural activity in multiple brain circuits associated with reward processing and cognitive control in children with ADHD, resulting in more stable sustained attention. Our findings identify a novel neurobiological mechanism underlying methylphenidate treatment in ADHD, and inform the development of clinically useful biomarkers for evaluating treatment outcomes.
Supported By: NIH; JSPS; MEXT; AMED
Keywords: Methylphenidate, ADHD, Nucleus Accumbens, Salience Network, Default Mode Network

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Biol Psychiatry. 2022;91:S115-S116.

P70. BASELINE STRIATAL ACTIVATIONS DURING DELAY DISCOUNTING IN YOUTH WITH ADHD CORRELATE WITH AFFECTIVE SYMPTOMS 1 TO 3 YEARS LATER.

Conroy S, Butcher T, Dzemidzic M, et al.

Background: ADHD in youth confers risk for developing subsequent psychopathology in multiple domains. Brain activation during impulsive decision-making tasks potentially offer predictive information. We examined relationships between baseline striatal activation during a delay discounting (DD) fMRI task and affective symptoms that emerged at 1, 2, and 3-year follow-ups.
Methods: Non-depressed youth with ADHD and a disruptive behavior disorder (age 12.0-¦0.6 years) underwent fMRI and comprehensive assessments. Activations in striatal regions during the [Delay>Baseline] contrast were extracted. Psychiatric symptoms at follow up (1, 2, and 3 years) were assessed using the depression, anxiety, and repetitive thoughts and behaviors (RTB) domains of the self-report Cross-Cutting Symptoms (CCS) Scale of the KSADS. We assessed baseline DD-fMRI activation and correlation with follow-up CCS scores (Spearman's rho).
Results: At 1 year (n=44), activations in right putamen correlated with depressive symptoms (¤ü=-0.298, p=0.05) while left nucleus accumbens core correlated with RTB (¤ü=0.384, p=0.010). At 2 years (n=40), correlations were found between depressive symptoms and left ventral anterior (VA) putamen (¤ü=0.512, p=0.001) and left putamen (¤ü=0.399, p=0.011); and RTB with left VA putamen (¤ü=0.366; p=0.020). At 3 years (n = 36), associations were found between anxiety and left VA putamen (¤ü=0.381, p=0.022), and RTB with left VA putamen (¤ü=0.411, p=0.015).
Conclusions: Striatal activations during delay discounting in youth with ADHD at baseline may predict degree of subsequent affective psychiatric symptoms, particularly with the VA putamen and RTB.

Interestingly, the VA putamen has been implicated in both impulsivity and compulsive behavior, which may shed light on the relationship in this population.
Supported By: NIDA R01DA039764 (LAH); NIAAA R00AA023296 (BGO)
Keywords: ADHD, Delay-Discounting, Affective Disorders, BOLD fMRI

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Biomedical Signal Processing and Control. 2022;76.

ADHD DETECTION USING DYNAMIC CONNECTIVITY PATTERNS OF EEG DATA AND CONVLSTM WITH ATTENTION FRAMEWORK.

Bakhtyari M, Mirzaei S.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental behavioral disorder. It is common in children, can be carried over into adulthood, and is associated with inattention, hyperactivity, and impulsive behavior. Physicians typically use the patient's description and questionnaires to diagnose this disorder. Due to its subjective nature, this procedure can lead to false diagnoses, which may cause irreparable distress to the patient's life. Since mental disorders are dependent on the brain function, researchers use biological signals such as electroencephalography (EEG) to help diagnose ADHD. In this study, we propose a new feature extraction scheme based on evaluating dynamic connectivity tensors among EEG channels for constructing the input formulation of the classification model. The tensors contain correlations among the EEG channels over different time frames. This method allows preserving both temporal and spatial structures of the EEG data while reducing the input dimensions of the model. We then employ a neural network model consisting of a convolutional long short-term memory (ConvLSTM) and an attention mechanism to classify ADHD patients and the control group. This model can encode the spatiotemporal representation of EEG recordings and identify dependencies between temporal segments. Convolution is responsible for encoding and finding spatial dependencies between electrodes. LSTM explores the relationships between different time blocks, and finally, attention focuses on the most relevant parts of the sequence. We evaluate the proposed approach by performing experiments on the EEG dataset, including 400 instances with 30 s length collected from 46 children with ADHD and 45 children in the control group. We achieved an average accuracy of 99.34% on this dataset, and our best model has an accuracy of 99.75%, both are the highest among the work done in this field

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BJPsych Open. 2020;6.

SOCIAL GRADIENTS IN THE RECEIPT OF MEDICATION FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND YOUNG PEOPLE IN SHEFFIELD.

Nunn SPT, Kritsotakis EI, Harpin V, et al.

Background Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterised by inattention and hyperactivity-impulsivity that can affect people throughout their life course. A social gradient exists in the prevalence of ADHD in the UK. Studies in other countries have shown that social gradients also exist in the receipt of medication for ADHD. Socioeconomic position is potentially an unrecognised and modifiable factor in children and young people's receipt of medication for ADHD in the UK.
Aim The aim of the study was to investigate if socioeconomic position could explain in part whether or not children and young people in Sheffield are receiving medication for ADHD.
Method We used multivariate logistic regression modelling to investigate whether socioeconomic position could explain variation in receipt of medication for ADHD in children and young people in a cross-sectional study. We collected data from 1354 children and young people with a diagnosis of ADHD across three Sheffield centres between January and December 2016. Independent variables were age, gender, religion, ethnicity, comorbidities, and Index of Multiple Deprivation decile (derived from home postcode).
Results Our results showed a social gradient in the receipt of medication for ADHD ($P<0.01$); an increase in one decile of the Index of Multiple Deprivation was associated with 10% lower odds of receipt of medication for ADHD (adjusted odds ratio 0.90, 95% CI 0.84-0.97).

Conclusion Children and young people from more deprived backgrounds are more likely to receive medication for ADHD. This is the first time that a social gradient in children and young people's receipt of medication for ADHD has been shown in a UK sample

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BMC Med. 2022;20.

THE IMPACT AND CAUSAL DIRECTIONS FOR THE ASSOCIATIONS BETWEEN DIAGNOSIS OF ADHD, SOCIOECONOMIC STATUS, AND INTELLIGENCE BY USE OF A BI-DIRECTIONAL TWO-SAMPLE MENDELIAN RANDOMIZATION DESIGN.

Michalsson M, Yuan S, Melhus H, et al.

Background: Previous studies have reported associations between attention-deficit/hyperactivity disorder (ADHD) and lower socioeconomic status and intelligence. We aimed to evaluate the causal directions and strengths for these associations by use of a bi-directional two-sample Mendelian randomization (MR) design.
Methods: We used summary-level data from the largest available genome-wide association studies (GWAS) to identify genetic instruments for ADHD, intelligence, and markers of socioeconomic status including the Townsend deprivation index, household income, and educational attainment. Effect estimates from individual genetic variants were combined using inverse-variance weighted regression.
Results: A genetically predicted one standard deviation (SD) increment in the Townsend deprivation index conferred an odds ratio (OR) of 5.29 (95% confidence interval (CI) 1.89ΓÇô14.76) for an ADHD diagnosis (p<0.001). A genetically predicted one SD higher education level conferred an OR of 0.30 (95% CI 0.25-0.37) (p<0.001), and a genetically predicted one SD higher family income provided an OR of 0.35 (95% CI 0.25 0.49; p<0.001). The associations remained after adjustment for intelligence whereas the lower odds of an ADHD diagnosis with higher intelligence did not persist after adjustment for liability to greater educational attainment (adjusted OR 1.03, 95% CI 0.68 1.56; p=0.87). The MR analysis of the effect of ADHD on socioeconomic markers found that genetic liability to ADHD was statistically associated with each of them (p<0.001) but not intelligence. However, the average change in the socioeconomic markers per doubling of the prevalence of ADHD corresponded only to 0.05-0.06 SD changes.
Conclusions: Our results indicate that an ADHD diagnosis may be a direct and strong intelligence-independent consequence of socioeconomic related factors, whereas ADHD appears to lead only to modestly lowered socioeconomic status. Low intelligence seems not to be a major independent cause or consequence of ADHD

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BMC Psychiatry. 2022 May;22:354.

LATE-MANIFESTATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OLDER ADULTS: AN OBSERVATIONAL STUDY.

Sasaki H, Jono T, Fukuhara R, et al.

BACKGROUND: The age of attention-deficit/hyperactivity disorder onset is usually during the first 12 years of life; however, there have been recent reports of late-onset attention-deficit/hyperactivity disorder. These reports have been limited to that of young adults, and details in older adults remain unknown. As such, we had previously presented the first case report of "very" late-onset attention-deficit/hyperactivity disorder, wherein the symptoms presented in senile age. In this observational study, we aimed to investigate the prevalence and clinical features of such attention-deficit/hyperactivity disorders in older adults visiting our dementia clinic.
METHODS: Four hundred forty-six consecutive patients visiting our specialty outpatient clinic for dementia during the 2-year period from April 1, 2015 to March 31, 2017 were included in this study. First, the patients were examined for the presence or absence of dementia in our specialty outpatient clinic for dementia. Those not diagnosed with dementia were examined for the presence or absence of attention-deficit/hyperactivity disorder in our specialty outpatient clinic for developmental disorders. Finally, these patients who were diagnosed with attention-deficit/hyperactivity disorder were investigated in detail to clarify their clinical characteristics.
RESULTS: Of 446 patients (246 women and 200 men), 7 patients were finally diagnosed with attention-deficit/hyperactivity disorder. Although these 7 patients were initially suspected to have Alzheimer's disease (considering their age, 6 of these 7 patients were suspected to have early onset Alzheimer's disease), it was

found that these symptoms were due to attention-deficit/hyperactivity disorder. These patients had four characteristics in common: (1) they were significantly younger than the complete study population; (2) they predominantly showed inattention-related symptoms; (3) they showed latent manifestation; and (4) they experienced a stressful life event before manifestation.
CONCLUSIONS: Our previous case report suggested that very late-onset attention-deficit/hyperactivity disorder patients could be incorrectly diagnosed with dementia. In this observational study, 1.6% of patients who were initially suspected of having dementia were actually diagnosed with attention-deficit/hyperactivity disorder. This study also showed that the "late-onset" described in our previous report would be better described as "late-manifestation." A clinician should consider late-manifestation of attention-deficit/hyperactivity disorder in the differential diagnosis when encountering dementia patients, especially early onset Alzheimer's disease

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BMC Public Health. 2022 May;22:1070.

AGE WITHIN SCHOOLYEAR AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN SCOTLAND AND WALES.

Fleming M, Bandyopadhyay A, McLay JS, et al.

BACKGROUND: Previous studies suggest an association between age within schoolyear and attention-deficit hyperactivity disorder (ADHD). Scotland and Wales have different school entry cut-off dates (six months apart) and policies on holding back children. We aim to investigate the association between relative age and treated attention deficit hyperactivity disorder (ADHD) in two countries, accounting for held-back children.
METHODS: Routine education and health records of 1,063,256 primary and secondary schoolchildren in Scotland (2009-2013) and Wales (2009-2016) were linked. Logistic regression was used to examine the relationships between age within schoolyear and treated ADHD, adjusting for child, maternity and obstetric confounders.
RESULTS: Amongst children in their expected school year, 8,721 (0.87%) had treated ADHD (Scotland 0.84%; Wales 0.96%). In Wales, ADHD increased with decreasing age (youngest quartile, adjusted OR 1.32, 95% CI 1.19-1.46) but, in Scotland, it did not differ between the youngest and oldest quartiles. Including held-back children in analysis of their expected year, the overall prevalence of treated ADHD was 0.93%, and increased across age quartiles in both countries. More children were held back in Scotland (57,979; 7.66%) than Wales (2,401; 0.78%). Held-back children were more likely to have treated ADHD (Scotland OR 2.18, 95% CI 2.01-2.36; Wales OR 1.70, 95% CI 1.21-2.31) and 81.18% of held-back children would have been in the youngest quartile of their expected year.
CONCLUSIONS: Children younger within schoolyear are more likely to be treated for ADHD, suggesting immaturity may influence diagnosis. However, these children are more likely to be held back in countries that permit flexibility, attenuating the relative age effect

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BMJ Paediatrics Open. 2022;6.

POISONINGS WITH ADHD MEDICATION IN CHILDREN UNDER THE AGE OF 5 YEARS IN AUSTRALIA: A RETROSPECTIVE STUDY, 2004-2019.

Arbaeen A, Wheate NJ, Cairns R.

Objective To describe the temporal relationships in attention-deficit hyperactivity disorder (ADHD) medication poisoning exposures in children; describe patient demographics, medications involved, poisoning exposure reasons and disposition.
Design A population-based, retrospective cohort study of calls to Australia's largest Poisons Information Centre. Poisoning exposure counts and dispensing-adjusted rates were modelled with Poisson, quasi-Poisson and negative binomial regression where appropriate. Setting Calls to the New South Wales Poisons Information Centre and dispensings on the Pharmaceutical Benefits Scheme.
Patients Children under the age of 5 years.
Results There were 1175 poisoning exposures to ADHD psychostimulants, 2004-2019; averaging 73 per year. Accidental poisonings accounted for 94% of cases. Methylphenidate was most frequently implicated (63%). Thirty-four per cent of cases were referred to hospital and a further 21% of calls were made by hospital

staff. Poisoning exposure counts for all ADHD psychostimulants increased by 2.7% (95% CI=0.42% to 4.9%) per year; however, this differed by agent. Methylphenidate poisoning exposures increased by 5.2% per year (95% CI=4.3% to 6.1%), lisdexamfetamine increased by 62% per year (95% CI=48% to 76%), while dexamphetamine poisoning exposures decreased by 5.5% per year (95% CI=-9.5% to -1.4%). These trends are reflected in the number of dispensings; however, dispensings increased at a faster rate than exposures. When poisoning exposures were expressed as dispensing-adjusted rates, there was a 16% decrease (95% CI=-20% to -13%) per year.
Conclusions ADHD medication use has increased, associated with an increased number of paediatric poisoning exposures. However, poisoning exposures per dispensed prescription has decreased. The majority of cases required hospitalisation, indicating the need for further poisoning prevention strategies

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Brain Behav. 2022.

COMPARATIVE EFFICACY OF TARGETED STRUCTURAL PATTERNS OF ELECTROENCEPHALOGRAPHY NEUROFEEDBACK IN CHILDREN WITH INATTENTIVE OR COMBINED ATTENTION DEFICIT HYPERACTIVITY DISORDER .

Wang FH, Sun LY, Cui XM, et al.

Objective: To evaluate and compare the effects of three courses of different structural patterns of electroencephalography neurofeedback on predominantly inattentive attention deficit hyperactivity disorder (ADHD-PI) and combined ADHD (ADHD-CT).
Methods: Thirty-eight ADHD-PI and ADHD-CT children were selected and completed three courses of different structural patterns of electroencephalography neurofeedback according to their ADHD type. Before and after each course, relative power value of electroencephalography, including θ, β, α, SMR and their ratios (θ/β, θ/α), and eighteen integrated visual and auditory continuous performance test (IVA/CPT) quotients were obtained and compared. Data were analyzed by SPSS software, and p <.05 was considered statistically significant.
Results: After one course, θ, three IVA/CPT quotients in both types and two comprehensive quotients in ADHD-CT changed significantly (all p <.05). After two courses, θ/α, θ/β and five IVA/CPT quotients in both types, θ and α in ADHD-PI, four comprehensive quotients, and four respond control quotients in ADHD-CT varied significantly compared to before treatment and after one course (all p <.05). After three courses, α, β, θ, θ/α, θ/β and ten IVA/CPT quotients in both types changed significantly compared to before treatment and after one course (all p <.05). In addition, six IVA/CPT quotients in both types after three courses were significantly higher than those after two courses (all p <.05).
Conclusion: Different structural patterns of electroencephalography neurofeedback targeted for ADHD-CT and ADHD-PI were both effective and feasible. Three courses of EEG neurofeedback were most effective

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Brain Dev. 2022 Aug;44:438-45.

IMPAIRMENT OF AUTONOMIC EMOTIONAL RESPONSE FOR EXECUTIVE FUNCTION IN CHILDREN WITH ADHD: A MULTI-MODAL FNIRS AND PUPILLOMETRIC STUDY DURING THE WISCONSIN CARD SORTING TEST.

Kaga Y, Ohyama T, Goto Y, et al.

OBJECTIVE: Children with attention deficit hyperactivity disorder (ADHD) often experience difficulties with emotional control and a consequent inability to perform tasks. To clarify the effects of emotional behavior on cognitive functions, we aimed to determine the association between emotional changes and executive functions in children with ADHD by measuring the pupil diameter changes associated with emotional changes.
PARTICIPANTS AND METHODS: This study included 14 children with ADHD and 10 typically developing children (TDC) aged between 10 and 16Â years. During the Wisconsin Card Sorting Test (WCST), which is related to context formation and task switching among executive functions, changes in pupil diameter and frontal oxygenated hemoglobin (oxy-Hb) using functional near-infrared spectroscopy (fNIRS) were recorded simultaneously. Pupil diameter changes during "cognitive shift" and "consecutive correction" were compared between both groups.
RESULTS: During cognitive shift, the pupils of children with ADHD contracted, whereas those of the TDC were mydriatic. During consecutive correction, the pupils of children with ADHD were mydriatic, whereas

those of the TDC tended to contract. These results correlated with WCST performance. Moreover, during cognitive shifts, changes in bilateral frontal blood flow were increased in TDC, but not in children with ADHD. **CONCLUSION**: The locus coeruleus-norepinephrine (LC-NE) system plays an important role in pupillary diameter response. These results suggest that the LC-NE system may be dysfunctional in children with ADHD, and the system's abnormality may lead to affective abnormalities in such patients, which results in poor performance on WCST (i.e., impaired executive functions)

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Brain Sciences. 2022;12.

THE ASSOCIATION OF SELF-REPORTED ADHD SYMPTOMS AND SLEEP IN DAILY LIFE OF A GENERAL POPULATION SAMPLE OF SCHOOL CHILDREN: AN INTER-AND INTRAINDIVIDUAL PERSPECTIVE.

Buhr L, Moschko T, de Zarate AER, et al.

Sleep and Attention-Deficit/Hyperactivity Disorder (ADHD) have repeatedly been found to be associated with each other. However, the ecological validity of daily life studies to examine the effect of sleep on ADHD symptoms is rarely made use of. In an ambulatory assessment study with measurement burst design, consisting of three bursts (each 6 months apart) of 18 days each, 70 German schoolchildren aged 10ΓÇô12 years reported on their sleep quality each morning and on their subjective ADHD symptom levels as well as their sleepiness three times a day. It was hypothesized that nightly sleep quality is negatively associated with ADHD symptoms on the inter-as well as the intraindividual level. Thus, we expected children who sleep better to report higher attention and self-regulation. Additionally, sleepiness during the day was hypothesized to be positively associated with ADHD symptoms on both levels, meaning that when children are sleepier, they experience more ADHD symptoms. No association of sleep quality and ADHD symptoms between or within participants was found in multilevel analyses; also, no connection was found between ADHD symptoms and daytime sleepiness on the interindividual level. Unexpectedly, a negative association was found on the intraindividual level for ADHD symptoms and daytime sleepiness, indicating that in moments when children are sleepier during the day, they experience less ADHD symptoms. Explorative analyses showed differential links of nightly sleep quality and daytime sleepiness, with the core symptoms of inattention and hyperactivity/impulsivity, respectively. Therefore, future analyses should take the factor structure of ADHD symptoms into account

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Caries Res. 2022;56:3-14.

DENTAL CARIES IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A META-ANALYSIS.

Drumond VZ, Souza GLN, Pereira MJC, et al.

OBJECTIVES: The aim of the study was to evaluate whether children with attention deficit/hyperactivity disorder (ADHD) are more affected by dental caries than children without ADHD by means of a systematic review and meta-analysis.

DESIGN: Electronic searches were performed in 4 databases (PubMed, Embase, Scopus, and Web of Science) in July 2021. Grey literature search in OpenGrey, a search in Google Scholar, and searches in the reference list of included articles were also conducted. The eligibility criteria were observational studies in which children with ADHD were compared with children without ADHD with respect to the dental caries. Study selection, data extraction, and risk of bias assessment, applying the Joanna Briggs tool were performed by 2 reviewers independently. Meta-analysis and assessment of heterogeneity among studies were conducted with the meta-package of RStudio using the R programming language (R Core Team, Vienna, Austria). Results of meta-analysis were provided in mean difference (MD), odds ratio (OR), and confidence intervals (CIs). For assessment of heterogeneity, Baujat plot and influence analysis plot were obtained.

RESULTS: Thirteen studies were included and 10 were incorporated into meta-analyses. The meta-analysis showed that children with ADHD had a higher decayed, missing, and filled teeth (DMFT) index than their peers without ADHD (I2 = 42%; MD = 0.75 [0.38-1.13]). For decayed, missing, and filled surfaces (I2 = 0; MD = 0.39 [-0.02 to 0.80]) and decayed surfaces (ds) (I2 = 0%; MD = 0.35 [-0.63 to 1.33]), no difference between groups was observed. In addition, children with ADHD had higher odds of having dental caries than their healthy peers (OR = 3.31 [1.25, 8.73]; I2 = 0%). After assessment of heterogeneity among studies,

sensitivity analysis was conducted for DMFT. One study was removed and the significant difference between groups remained. Children with ADHD had a significantly higher DMFT index than their peers without ADHD (MD = 0.98 [CI = 0.75, 1.20]; I2 = 0%) Risk of bias ranged from low to high.
CONCLUSION: The main shortcoming of the included studies is the high risk of bias regarding the strategies to deal with confounding factors. Within its limitations, this systematic review and meta-analysis demonstrated that children with ADHD were more likely to develop dental caries than their healthy counterparts.
FUNDING: No funding.
REGISTRATION: CRD42021238923

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Cereb Cortex. 2022 May;32:2332-42.
CORTICAL GYRIFICATION MORPHOLOGY IN ASD AND ADHD: IMPLICATION FOR FURTHER SIMILARITIES OR DISORDER-SPECIFIC FEATURES?
Gharehgazlou A, Vandewouw M, Ziolkowski J, et al.
Shared etiological pathways are suggested in ASD and ADHD given high rates of comorbidity, phenotypic overlap and shared genetic susceptibility. Given the peak of cortical gyrification expansion and emergence of ASD and ADHD symptomology in early development, we investigated gyrification morphology in 539 children and adolescents (6-17 years of age) with ASD (n=197) and ADHD (n=96) compared to typically developing controls (n=246) using the local Gyrification Index (lGI) to provide insight into contributing etiopathological factors in these two disorders. We also examined IQ effects and functional implications of gyrification by exploring the relation between lGI and ASD and ADHD symptomatology beyond diagnosis. General Linear Models yielded no group differences in lGI, and across groups, we identified an age-related decrease of lGI and greater lGI in females compared to males. No diagnosis-by-age interactions were found. Accounting for IQ variability in the model (n=484) yielded similar results. No significant associations were found between lGI and social communication deficits, repetitive and restricted behaviours, inattention or adaptive functioning. By examining both disorders and controls using shared methodology, we found no evidence of atypicality in gyrification as measured by the lGI in these conditions

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Cereb Cortex. 2022;32:1152-58.
STRUCTURAL BRAIN CHANGES AND ASSOCIATED SYMPTOMS OF ADHD SUBTYPES IN CHILDREN.
Mu S, Wu H, Zhang J, et al.
Attention-deficit/hyperactivity disorder (ADHD) is presumed to be heterogeneous, but the best way to characterize this heterogeneity remains unclear. Although considerable evidence suggests that the 2 different types of ADHD, inattention and combined, have different cognitive and behavioral profiles, and underlying neurobiologies, we currently lack information on whether these subtypes reflect separated brain structure changes. Structural magnetic resonance imaging scans (N = 234), diagnostic, and demographic information were obtained from the ADHD-200 database. Of this sample, 138 were Typically Developing people, 37 were ADHD-Combined, and 59 were ADHD-Inattentive patients. Freesurfer segmentation methods were used to measure cortical thickness, area, and volume, subcortical volume and hipposubfield volume. ADHD-Inattentive patients showed milder clinical symptoms but more serious cognitive injury than ADHD-Combined patients. In addition, dissociable structural brain changes were found in different subtypes of ADHD, particularly in terms of decreased subcortical volume in ADHD-Combined patients compared with Typically Developing people. Clinical symptoms were predominantly related to smaller rh_caudalanteriorcingulate thickness and left-Pallidum volume, whereas verbal IQ injury was correlated strongly with smaller rh_insula area. These findings indicate that there are significant differences in clinical symptoms and gray matter damage between ADHD-Combined and-Inattentive patients. This supports the growing evidence of heterogeneity in the ADHD-Inattentive subtype and the evidence of brain structure differences

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Child Abuse Negl. 2022.

EXPLORING THE RELATIONSHIP BETWEEN ADOPTION AND PSYCHOLOGICAL TRAUMA FOR CHILDREN WHO ARE ADOPTED FROM CARE: A LONGITUDINAL CASE STUDY PERSPECTIVE.

McSherry D, McAnee G.

Children who have been adopted from care are very likely to have experienced early adversity that may result in psychological trauma. A current debate in the field is whether adoption provides a pathway to healing for traumatised children, helping them to recover from past psychological harm, or creates trauma for children through the very nature of being an adopted child. Objective: This study aimed to use longitudinal data pertaining to children who had been adopted from care to examine the relationship between being adopted from care and psychological trauma. Participants and setting: Seventeen adopted children had been interviewed in their adoptive homes during the third wave of the Care Pathways and Outcomes study (McSherry et al., 2013), when they were aged between nine and 14 years old. Ten of these children were selected for specific consideration in this article. Checklists for early adversities and psychological trauma were used to support the creation of case studies that highlighted the extent of psychological trauma in the children's lives. Results: The adopted children either experienced possible pre-care psychological trauma, with the impact of this reducing over time, in utero developmental harm due to their mother's alcohol misuse during pregnancy, inherited an intellectual disability, with the resultant difficulties superseding any concern regarding possible pre-care psychological trauma, or possible psychological trauma when moving from an established foster placement to adoption. Recommendations for policy and practice are provided

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Child Adolesc Ment Health. 2022.

REVIEW: WHICH COMPONENTS OF BEHAVIORAL PARENT AND TEACHER TRAINING WORK FOR CHILDREN WITH ADHD? A METAREGRESSION ANALYSIS ON CHILD BEHAVIORAL OUTCOMES.

Hornstra R, Groenman AP, Van der Oord S, et al.

Background: This metaregression analysis examined which behavioral techniques that are commonly used in behavioral parent and teacher training programs for children with attention-deficit/hyperactivity disorder (ADHD) were related to program effectiveness on children's behavioral outcomes.

Methods: We included 32 randomized controlled trials (N = 2594 children) investigating behavioral parent training, teacher training, or a combination, in children with ADHD under 18 years. Outcomes were symptom counts of total ADHD, inattention, and hyperactivity-impulsivity and behavioral problems. The dosage of techniques was extracted from the intervention manuals. Metaregression was used to assess which techniques and intervention characteristics (setting, delivery method, duration, and home-school collaboration) were associated with intervention effectiveness.

Results: Higher dosage of psycho-education for parents was associated with smaller effects on behavioral problems and, only in case of parent training, also with smaller effects on ADHD symptoms. Higher dosage of teaching parents/teachers to use negative consequences was associated with larger effects on behavioral problems. Individual training compared with group training was associated with larger effects on ADHD and hyperactivity-impulsivity symptoms.

Conclusions: This study provides first insights into the specific techniques that are essential in behavioral parent and teacher training programs for children with ADHD. This knowledge can eventually be used to improve and tailor interventions

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Child Adolesc Ment Health. 2022.

COGNITIVE AND BEHAVIORAL PROFILES IN CHILDREN WITH AUTISM SPECTRUM DISORDER WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Rosello R, Martinez-Raga J, Tomas JM, et al.

Background: Understanding the developmental trajectories of children with autism spectrum disorder (ASD) with and without comorbid ADHD is relevant to tailor care plans. This prospective study assessed, for the first time, cognitive, emotional, behavioral, and learning outcomes in adolescence of children with ASD-ADHD and in those with ASD+ADHD in childhood. Possible predictors of severity of ASD core symptoms in adolescence were also evaluated.

Methods: Forty-five adolescents without intellectual disability, 26 diagnosed in childhood with ASD-ADHD and 19 with ASD+ADHD, were evaluated at baseline (mean age: 8.6 -¦ 1.3) and at 5-year follow-up (mean age: 12.9 -¦ 0.9). Parents and teachers completed questionnaires on executive functions, theory of mind (ToM), emotional/behavioral difficulties (EBD), and learning style at both time points.
Results: Overall different developmental trajectories for the two groups were found. In general, deficits in metacognition processes, ToM skills, EBD, and learning abilities were more pronounced in the ASD+ group. Over time, the ASD+ADHD group, but not the ASD-ADHD, tended to improve in EBD and metacognition but their level of development continued to be lower compared with ASD+ADHD. EBD in childhood were significant predictors of autism core symptoms of adolescents.
Conclusions: Our findings highlight the importance of an early identification of comorbid ADHD symptoms in ASD to offer treatment strategies based on specific developmental trajectories

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Child Psychiatry Hum Dev. 2022 Jun;53:489-501.

INVESTIGATING THE MEASUREMENT INVARIANCE AND METHOD-TRAIT EFFECTS OF PARENT AND TEACHER SNAP-IV RATINGS OF PRESCHOOL CHILDREN.

Lúcio PS, Eid M, Cogo-Moreira H, et al.

The Swanson, Nolan, and Pelham scale version IV (SNAP-IV) is widely used to assess symptoms of attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) in children and adolescents. Nevertheless, there is insufficient data to support its use in preschool children. The study had three goals: First, to test the factorial validity of the three correlated-factors model of ADHD and ODD items of the SNAP-IV. Second, to investigate the measurement invariance of the items over time (6-month longitudinal interval) and by sex. Third, to investigate the convergent validity and method-specific influences on ADHD/ODD assessments with respect to multiple raters (parents/teachers) of children's symptoms. Participants were 618 preschool children (3.5-6 years) at baseline and 6-month follow-up. For model testing, we used confirmatory factor analysis for categorical observed variables. Method and trait effects were examined using the CT-C(M-1) model. The analyses showed partial measurement invariance over time and according to sex. Moreover, strong rater-specific effects were detected. The implication of the results for construct validation of the instrument and clinical assessment of ADHD and ODD traits are discussed

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Child Psychiatry Hum Dev. 2022 Jun;53:538-45.

EXPLORING ELEMENTARY SCHOOLTEACHERS' PERCEPTIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN NORTHERN JORDAN.

AlAzzam M, Tawalbeh L, Abu Al-Rub M, et al.

The purpose of this study was to ascertain elementary schoolteachers' perceptions of attention deficit hyperactivity disorder (ADHD) in northern Jordan. This study utilized a descriptive cross-sectional research design using a self-reporting questionnaire to gather data from elementary schoolteachers in northern Jordan from February to June 2019. The results indicate that elementary schoolteachers in northern Jordan have negative perceptions regarding ADHD and its causes, treatment, and diagnosis. The lack of professional pre-service training and education about children's behavioral problems overall, but especially regarding ADHD knowledge and management of children with ADHD was found to be deficient among our sample of elementary schoolteachers. The pronounced lack of research on teacher management of ADHD in children in Jordan may have contributed to these findings. Structured educational and training programs addressing children with ADHD should be implemented to enhance teachers' knowledge about ADHD and to improve their role in helping the affected children and their families

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Chronobiol Int. 2022 Mar;39:386-97.

RELATIONSHIP BETWEEN SLEEP PROBLEMS AND CHRONOTYPES OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND SERUM GABA, GLUTAMATE AND HOMOCYSTEINE LEVELS.

Miniksar DY, Cansiz MA, Kiliç M, et al.

In this study, we aimed to determine the relationship between chronotype, sleep problems and serum levels of GABA (gamma amminobutyric acid), glutamate and homocysteine in children and adolescents diagnosed with attention deficit and hyperactivity disorder (ADHD) as well as factors affecting this relationship. Sleep problems of 46 children and adolescents aged 7–18 years diagnosed with ADHD and 30 healthy volunteers aged 7–18 years were evaluated with Children's Sleep Habits Questionnaire (CSHQ) while chronotypes were evaluated with Children's Chronotype Questionnaire (CCQ). Serum glutamate, GABA and homocysteine levels were measured using immunosorbent test (ELISA) kits. Sleep problems were significantly more common in the ADHD group compared to the control group ($p < .001$). Serum GABA, glutamate and homocysteine levels were found to be predictor biomarkers for ADHD, independent of total sleep problem score. When the homocysteine levels were above the cut-off point of 9.445 µmol/L, the sensitivity in early diagnosis of ADHD was 84.8% and the specificity was 70.0%. Although ADHD is a disorder in which sleep problems are common, increased serum GABA, glutamate and homocysteine are important in diagnosing ADHD independent of ADHD-related sleep problems. Homocysteine levels may be an important predictor for the presence of ADHD

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Clin Child Fam Psychol Rev. 2022 Jun;25:356-75.

A REVIEW OF PREDICTORS OF PSYCHOSOCIAL SERVICE UTILIZATION IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Green CD, Langberg JM.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders. Professional practice guidelines recommend combined treatment, psychopharmacological and psychosocial, for youth with ADHD. There have been multiple reviews of pharmacological prescription practices and utilization, however, less is known about predictors of ADHD psychosocial service utilization. Given the importance of accessing psychosocial treatment in relation to improving functional impairment, this review synthesizes evidence on predictors of ADHD psychosocial intervention utilization in clinic, community, and school settings. Eighteen studies were identified and included in the review. Findings are summarized across informant profile factors, predisposing characteristics, and barriers and facilitators. The most robust findings were for the impact of symptom severity/impairment, the presence of comorbidities, and age on ADHD psychosocial service utilization. Race/ethnicity, sex, parental knowledge of the disorder and insurance coverage were also identified as key factors. Future avenues of research are provided, and clinical and policy implications targeted at reducing psychosocial treatment disparities in youth with ADHD are discussed

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Clin Neurophysiol. 2022 Jun;138:25-37.

LACK OF AN ASSOCIATION BETWEEN ANTICIPATORY ALPHA OSCILLATIONS AND ATTENTIONAL SELECTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Li B, Guo J, Zhao C, et al.

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is characterized by attention problems. The current study investigated whether and how anticipatory alpha oscillations, the subsequent target-elicited N2 posterior-contralateral component (N2pc) and their relationship contributed to attention problems in children with ADHD.

METHODS: Electroencephalograms (EEGs) were recorded from 8-13-year-old children with ADHD and typically developing children during a cued visuospatial covert attention task.

RESULTS: Children with ADHD could not sustain hemispheric alpha lateralization during the late stage of the cued period. Similar to the pattern of adults, high-accuracy typically developing children showed a strong positive correlation between the degree of cue-induced anticipatory alpha lateralization and the subsequent target-evoked N2pc amplitude, the latter of which further predicted behavioral performance. However, only

the aberrant "cue alpha-target N2pc" temporal relationship was related to symptom severity and behavioral performance in children with ADHD.
CONCLUSIONS: We showed that the temporal association of "cue alpha-target N2pc" was already present in some typically developing children. However, children with ADHD might need more time to develop this temporal association. SIGNIFICANCE: Our results provide neurophysiological evidence that the developmental origin of covert spatial attention is related to the temporal association between low-frequency brain oscillations and event-related potentials (ERPs)

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Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine. 2007;1.
PERCEPTION OF INSPIRATORY RESISTIVE LOADS IN ASTHMATIC CHILDREN WITH ATTENTION DEFICIT DISORDER.
Davenport KL, Julius SM, Davenport PW.
Magnitude estimation (ME) of inspiratory resistive (R) loads has been studied in asthmatic children. Some children have been reported to be unable to perform the perception task. One reason some children may be unable to perform the ME task is Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD). The aim of this study was to determine if asthmatic patients with ADD/ADHD have a perceptual and/or attention deficit in the ME of graded inspiratory R loads. Methods: Asthmatic children aged 11-18 years were classified into ADD/ADHD and asthma control groups. Perception of extrinsic loads was assessed by handgrip ME of inspiratory R loads. A methacholine challenge was performed and the PC20 for each subject determined. Results: There was no significant difference between asthma control and ADD/ADHD groups in the group mean for the slope of ME-R load slopes. The ADD/ADHD subjects had significantly greater variability in ME of R loads. Conclusions: Asthmatic children with ADD/ADHD do not have an impaired perception of extrinsic respiratory loads but do have difficulty attending to the perceptual task. Difficulties in their asthma management may be due to their attention deficit and not their symptom perception

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Clin Neurophysiol. 2022;136:206-18.
LACK OF NEURAL LOAD MODULATION EXPLAINS ATTENTION AND WORKING MEMORY DEFICITS IN FIRST-EPISODE SCHIZOPHRENIA.
Li D, Zhang X, Kong Y, et al.
Objective: Although working memory (WM) deficits are well-recognized core features of schizophrenia, the underlying pathophysiological substrates of impairment in early psychosis before medication remain unclear. One possibility is that deficits in selective attention contribute to WM impairment.
Methods: EEG was acquired from 25 first-episode drug-naive schizophrenia patients and 26 matched controls while they performed a WM task.
Results: Compared with controls, schizophrenia patients showed a deficit in WM capacity in both behavioral and electrophysiological measures. Notably, the increased parieto-occipital pre-encoding stimulus alpha power in patients with schizophrenia predicted their subsequent reduced N2pc and symptom severity, whereas this relationship was absent in controls. Moreover, lacking load effect in neural activities predicted the serious impairment in behavior for schizophrenia.
Conclusions: This pilot study provides preliminary evidence that the lack of load effect in neural activities may serve as potential underlying mechanisms for the impaired selective attention and WM capacity in schizophrenia. Our results emphasize the importance of pre-encoding stimulus alpha power in first-episode drug-naive schizophrenia. Significance: These findings provide a neurophysiological correlate for the subjective reports of working memory deficits in schizophrenia and indicate the potential effective targets for clinical intervention

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CNS Neurol Disord Drug Targets. 2022;21:717-23.

COENZYME Q10 IN THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL.

Gamal F, El AO, Salamah A.

BACKGROUND: Attention Deficit Hyperactivity Disorder is a common child neurobehavioral disorder whose pathogenesis is not completely understood. However, some evidence indicates a crucial link between this disorder and the degree of oxidative stress. Coenzyme Q10 (ubiquinol) is an antioxidant that may play a significant role in the treatment of Attention Deficit Hyperactivity Disorder.
OBJECTIVE: To assess the safety and efficacy of coenzyme Q10 as an add-on drug treatment for attention deficit hyperactivity disorder.
METHODS: Sixty children, aged 6-16 years, with attention deficit hyperactivity disorder, non-responders to atomoxetine treatment for 6 months, were included in this double-blind, randomized, and controlled study. Group 1 received atomoxetine plus coenzyme Q10, and group 2 received atomoxetine plus placebo for 6 months. Follow-up by CONNERS parent rating scale questionnaire (CPRS-48) was performed before and after 1, 3, and 6 months of treatment, and any drug-related side effects were reported.
RESULTS: The addition of coenzyme Q10 to atomoxetine in group 1 improved symptoms in a shorter time with minimal adverse effects. Group 1 showed improvement of about 33.87% in CPRS-48 total score versus 18.24% in group 2. There was a statistically significant decrease in CPRS-48 total score and its three subscales (learning problems, impulsive hyperactive subscale, and 10-items hyperactivity index) in group 1 versus group 2 after six months of treatment (p-value <0.001).
CONCLUSION: Coenzyme Q10 has an important role as an add-on drug treatment for attention deficit hyperactivity disorder by improving symptoms, particularly hyperactivity, and in minimizing atomoxetine adverse effects

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CNS Spectr. 2022 Jun;27:290-97.

USE OF SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS) IN THE TREATMENT OF AUTISM SPECTRUM DISORDER (ASD), COMORBID PSYCHIATRIC DISORDERS AND ASD-ASSOCIATED SYMPTOMS: A CLINICAL REVIEW.

Nanjappa MS, Voyiaziakis E, Pradhan B, et al.

It is challenging to treat symptoms of autism spectrum disorder (ASD), comorbid psychiatric disorders and ASD-associated symptoms. Some of the commonly used medications to treat these can, and frequently do have serious adverse side effects. Therefore, it is important to identify medications that are effective and with fewer side effects and negative outcomes. In this review, we looked at current evidence available for using the serotonin and norepinephrine reuptake inhibitors (SNRIs) class of medications in treating some of these often difficult to treat symptoms and behaviors. An extensive literature search was conducted using EBSCO.host. Our search algorithm identified 130 articles, 6 of which were deemed to meet criteria for the purpose of this review. Each of these six articles was independently reviewed and critically appraised. As a prototype of the SNRIs family, venlafaxine was found to be a useful adjuvant in children and adults with ASD for the treatment of self-injurious behaviors, aggression, and ADHD symptoms when used in doses lower than its antidepressant dosage. However, duloxetine was not found to show any added benefit in treatment of any of the comorbid symptoms and behaviors in ASD when compared to other antidepressants. On the other hand, milnacipran was reported to produce improvements in impulsivity, hyperactivity symptoms, and social functioning through reduction of inattention of ADHD when comorbid with ASD. Overall, SNRIs were shown variable effectiveness in treatment of these comorbid symptoms and behaviors in ASD

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Cogn Neuropsychol. 2021 Jul;38:349-63.

TWO SIDES OF THE SAME COIN: ADHD AFFECTS REACTIVE BUT NOT PROACTIVE INHIBITION IN CHILDREN.

Suarez I, De Los Reyes AC, Grandjean A, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) present a deficit in inhibitory control. Still, it remains unclear whether it comes from a deficit in reactive inhibition (ability to stop the action in progress), proactive inhibition (ability to exert preparatory control), or both.We compared the performance of 39 children

with ADHD and 42 typically developing children performing a Simon choice reaction time task. The Simon task is a conflict task that is well-adapted to dissociate proactive and reactive inhibition. Beyond classical global measures (mean reaction time, accuracy rate, and interference effect), we used more sophisticated dynamic analyses of the interference effect and accuracy rate to investigate reactive inhibition. We studied proactive inhibition through the congruency sequence effect (CSE).Our results showed that children with ADHD had impaired reactive but not proactive inhibition. Moreover, the deficit found in reactive inhibition seems to be due to both a stronger impulse capture and more difficulties in inhibiting impulsive responses. These findings contribute to a better understanding of how ADHD affects inhibitory control in children

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Cogn Neurodyn. 2022.

NEUROFEEDBACK TRAINING FOR CHILDREN WITH ADHD USING INDIVIDUAL BETA RHYTHM.

Hao Z, He C, Ziqian Y, et al.

Neurofeedback training (NFT) is a noninvasive neuromodulation method for children with attention-deficit/hyperactivity disorder (ADHD). Brain rhythms, the unique pattern in electroencephalogram (EEG), are widely used as the training target. Most of current studies used a fixed frequency division of brain rhythms, which ignores the individual developmental difference of each child. In this study, we validated the feasibility of NFT using individual beta rhythm. A total of 55 children with ADHD were divided into two groups using the relative power of individual or fixed beta rhythms as the training index. ADHD rating scale (ADHD-RS) was completed before and after NFT, and the EEG and behavioral features were extracted during the training process. After intervention, the attention ability of both groups was significantly improved, showing a significant increase in beta power, a decrease in scores of ADHD-RS and an improvement in behavioral and other EEG features. The training effect was significantly better with individualized beta training, showing more improvement in ADHD-RS scores. Furthermore, the distribution of brain rhythms moved towards high frequency after intervention. This study demonstrates the effectiveness of NFT based on individual beta rhythm for the intervention of children with ADHD. When designing a NFT protocol and the corresponding data analysis process, an individualized brain rhythm division should be applied to reflect the actual brain state and to accurately evaluate the effect of NFT

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Complement Ther Med. 2022 Aug;67:102826.

DIET AND PHYSICAL EXERCISES FOR PRESCHOOLERS WITH ADHD AND THEIR MOTHERS: AN INTERVENTION STUDY.

Hassan MM, Nuaim AA, Osman SR, et al.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is a serious public health problem. Diet-focused approaches and physical exercise can be used to complement other ADHD management techniques.

OBJECTIVE: To determine the prevalence of ADHD symptoms among preschoolers in nursery schools and to evaluate the educational interventions toward nutrition and physical exercise in mothers and their preschoolers with ADHD symptoms.

RESEARCH METHODOLOGY: A two-phase sampling method was employed. First, a cross-sectional survey was conducted to determine the prevalence of ADHD symptoms in four nursery schools (400 preschoolers aged between 3 and 6 years). Second, an intervention study (a quasi-experimental research design with one group completing the pre-test and the post-test) was performed on 36 preschoolers having ADHD symptoms and their mothers by using the educational intervention for mothers and photos and games about nutrition and physical exercise for the preschoolers with ADHD; mothers of four children out of the 40 refused to participate in the study. Data were analyzed using SPSS version 20. The paired t-test was used to determine significant differences between the groups. Differences were considered significant at $P < 0.05$.

RESULTS: Of the 400 preschoolers, 10% had high ADHD symptoms. The mean score of mothers' knowledge of nutrition and physical exercise improved after the implementation of the program ($p = 0.01$). In addition, preschoolers with ADHD enjoyed the session with photos and games ($p = 0.01$).

CONCLUSIONS AND IMPLICATIONS: Educational intervention significantly improved the knowledge of the mothers. Moreover, preschoolers with ADHD symptoms enjoyed the session with photos and games. This intervention appears to be feasible and promising for further investigation of its effects

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Issues Compr Pediatr Nurs. 2022 Mar;45:22-30.

THE DURATION OF BREASTFEEDING AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN SCHOOL-AGED CHILDREN.

Sepehrmanesh Z, Moraveji A, Ahmadvand A, et al.

Attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood-onset neurodevelopmental disorders. In some recent studies breastfeeding had positive effects on physical health and mental development of children and these studies have recommended further studies in this issue. This study evaluated the relationship between duration of breastfeeding and ADHD. This case-control study was carried out in 2017 on 404 children aged 7–12 (196 children with ADHD and 208 children without ADHD). The questionnaire included items on the risk factors such as the child's sex, age, delivery method, birth weight, birth rank, gestational age, age of mother, duration of breastfeeding, history of neonatal hospitalization, history of drug use in neonatal period, history of drug use in pregnancy, history of hypothyroidism and hyperthyroidism in pregnancy, history of neonatal icter, history of neonatal blood exchange. Data were analyzed using t-test, chi-square and logistic regression. The mean of breastfeeding duration in children with ADHD was 17.05 ± 7.52 months compared with 18.59 ± 6.74 months in control group ($p = .03$). A stepwise logistic regression that included the variables was found to be significant in univariate analysis, demonstrating a significant association between ADHD and breastfeeding duration ($p = .01$), male gender (OR = 2.8), mother hypothyroidism (OR = 4.5) and history of drug use in neonatal period (OR = 1.9). Long-term duration of breastfeeding (more than 12 months) could be a protective factor in ADHD. However, further studies are required

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Crim Behav Ment Health. 2022.

EXAMINING THE INTERPLAY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND TRAIT ANGER AS CONTRIBUTING FACTORS TO INSTITUTIONAL MISCONDUCT AMONG JUSTICE-INVOLVED ADOLESCENTS.

Ramsey KL, Smith SD, Batastini AB, et al.

Background: Although justice-involved adolescents have a higher prevalence of trait anger and of attention-deficit/hyperactivity disorder (ADHD) than adolescents in the general population, these factors have not been examined in relation to institutional misconduct.

Aims: We sought to examine associations between ADHD symptoms and misconduct, including aggression, disruptive behaviours and other rule-violating behaviours among adolescents in a maximum-security residential facility run by the Department of Juvenile Justice and to test the moderating effect of trait anger on such relationships.

Methods: Archival data collected from April 2010 to May 2011 comprising a resident cohort (N=119) of justice-involved adolescents (mean age=16.74) were analysed; 30% were White and 70% Black. Self-report measures of ADHD symptoms and trait anger were collected 2 weeks after their admission to the facility. Behavioural write-ups of rule violations issued by facility staff during the month following the collection of these measures were coded according to the different forms of institutional misconduct.

Results: Analyses revealed that trait anger significantly predicted disruptive behaviours occurring within a 1-month time frame following the administration of the anger measure; it also predicted all other rule violating behaviours except aggression. ADHD symptoms, by contrast, were only marginally predictive. Trait anger did not moderate this small relationship between ADHD symptoms and institutional misconduct.

Conclusions: These findings that adolescents with a chronic tendency to feel angry are more likely to violate a variety of institutional rules during the first few weeks of admission to a juvenile justice maximum-security residential facility suggest that early intervention efforts are needed to minimise harm within the institution and to prevent these adolescents from continuing on this trajectory, which may affect the conditions of their release

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Curr Probl Pediatr Adolesc Health Care. 2022 Feb;52:101132.

EXTREME PREMATURITY: RISK AND RESILIENCY.

Taylor GL, O'Shea TM.

Individuals born extremely preterm (before 28 weeks of gestation) comprise only about 0.7% of births in the United States and an even lower proportion in other high resource countries. However, these individuals account for a disproportionate number of children with cerebral palsy, intellectual deficit, autism spectrum disorder, attention deficit hyperactivity disorder, and epilepsy. This review describes two large multiple center cohorts comprised of individuals born extremely preterm: the EPICURE cohort, recruited 1995 in the United Kingdom and the Republic of Ireland, and the Extremely Low Gestational Age Newborn (ELGAN), recruited 2002-2004 in five states in the United States. The primary focus of these studies has been neurodevelopmental disorders, but also of interest are growth, respiratory illness, and parent- and self-reported global health and well-being. Both of these studies indicate that among individuals born extremely preterm the risks of most neurodevelopmental disorders are increased. Early life factors that contribute to this risk include perinatal brain damage, some of which can be identified using neonatal head ultrasound, bronchopulmonary dysplasia, and neonatal systemic inflammation. Prenatal factors, particularly the family's socioeconomic position, also appear to contribute to risk. For most adverse outcomes, the risk is higher in males. Young adults born extremely preterm who have neurodevelopmental impairment, as compared to those without such impairment, rate their quality of life lower. However, young adults born extremely preterm who do not have neurodevelopmental impairments rate their quality of life as being similar to that of young adults born at term. Finally, we summarize the current state of interventions designed to improve the life course of extremely premature infants, with particular focus on efforts to prevent premature birth and on postnatal efforts to prevent adverse neurodevelopmental outcomes

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Elife. 2022 May;11.

MULTI-TRACT MULTI-SYMPTOM RELATIONSHIPS IN PEDIATRIC CONCUSSION.

Guberman GI, Stojanovski S, Nishat E, et al.

BACKGROUND: The heterogeneity of white matter damage and symptoms in concussion has been identified as a major obstacle to therapeutic innovation. In contrast, most diffusion MRI (dMRI) studies on concussion have traditionally relied on group-comparison approaches that average out heterogeneity. To leverage, rather than average out, concussion heterogeneity, we combined dMRI and multivariate statistics to characterize multi-tract multi-symptom relationships.

METHODS: Using cross-sectional data from 306 previously concussed children aged 9-10 from the Adolescent Brain Cognitive Development Study, we built connectomes weighted by classical and emerging diffusion measures. These measures were combined into two informative indices, the first representing microstructural complexity, the second representing axonal density. We deployed pattern-learning algorithms to jointly decompose these connectivity features and 19 symptom measures.

RESULTS: Early multi-tract multi-symptom pairs explained the most covariance and represented broad symptom categories, such as a general problems pair, or a pair representing all cognitive symptoms, and implicated more distributed networks of white matter tracts. Further pairs represented more specific symptom combinations, such as a pair representing attention problems exclusively, and were associated with more localized white matter abnormalities. Symptom representation was not systematically related to tract representation across pairs. Sleep problems were implicated across most pairs, but were related to different connections across these pairs. Expression of multi-tract features was not driven by sociodemographic and injury-related variables, as well as by clinical subgroups defined by the presence of ADHD. Analyses performed on a replication dataset showed consistent results.

CONCLUSIONS: Using a double-multivariate approach, we identified clinically-informative, cross-demographic multi-tract multi-symptom relationships. These results suggest that rather than clear one-to-one symptom-connectivity disturbances, concussions may be characterized by subtypes of symptom/connectivity relationships. The symptom/connectivity relationships identified in multi-tract multi-symptom pairs were not apparent in single-tract/single-symptom analyses. Future studies aiming to better understand connectivity/symptom relationships should take into account multi-tract multi-symptom heterogeneity.

FUNDING: Financial support for this work came from a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research (G.I.G.), an Ontario Graduate Scholarship (S.S.), a Restracomp Research Fellowship provided by the Hospital for Sick Children (S.S.), an Institutional Research Chair in Neuroinformatics (M.D.), as well as a Natural Sciences and Engineering Research Council CREATE grant (M.D.)

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Environ Res. 2022;212.

MATERNAL SERUM PERSISTENT ORGANIC POLLUTANT EXPOSURE AND OFFSPRING DIAGNOSED ADHD IN A NATIONAL BIRTH COHORT.

Cheslack-Postava K, Rantakokko P, Kiviranta H, et al.

Background: Evidence implicates environmental factors in attention-deficit/hyperactivity disorder (ADHD) risk. Prenatal exposures to polychlorinated biphenyls (PCBs) and the pesticide metabolite p,p-dichlorodiphenyl dichloroethylene (DDE) have been linked to lower cognitive ability, increased impulsivity, and attention related deficits in the offspring. However, information on the relationship of these exposures to the risk of clinically diagnosed ADHD is limited.
Objectives: To determine whether prenatal maternal levels of PCBs or DDE are associated with ADHD diagnosis in the offspring.
Methods: The investigation was conducted in the Finnish Prenatal Study of ADHD (FIPS-ADHD), a case-control study nested in a national birth cohort. Cases were born in 1998 or 1999 and diagnosed with ADHD (ICD-9 314x or ICD-10 F90. x) according to the national Care Register for Health Care. Each case was individually matched to a control on sex, date, and place of birth. PCB congeners (PCB 74, 99, 118, 138, 153, 156, 170, 180, 183, 187) and DDE were quantified from archived prenatal maternal sera from 359 matched case-control pairs using gas chromatography - high triple quadrupole mass spectrometry. Maternal total PCBs were quantified as the sum of concentrations of the measured congeners. Associations with ADHD were examined using conditional logistic regression.
Results: Maternal PCB or DDE levels greater than the 75th percentiles of the control distributions showed no evidence of association with offspring ADHD (PCBs: adjusted odds ratio (aOR) = 1.01, 95% CI = 0.63, 1.60), p = 0.98; DDE: aOR = 1.13, 95% CI = 0.71, 1.81; p = 0.60). Maternal levels of either pollutant dichotomized at the 90th percentile or considered as a continuous variable also did not show evidence for association with offspring ADHD diagnosis.
Discussion: This study did not find evidence for association of maternal prenatal levels of PCBs or DDE with clinical diagnosis of offspring ADHD; however, this does not rule out the possibility of an impact on subclinical phenotypes

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Environ Res. 2022;212.

LIVING PROXIMITY TO PETROCHEMICAL INDUSTRIES AND THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Huang CC, Pan SC, Chin WS, et al.

Evidence regarding the negative neurodevelopmental effects of compound exposure to petrochemicals remains limited. We aimed to evaluate the association between exposure to petrochemical facilities and generated emissions during early life and the risk of attention-deficit/hyperactivity disorder (ADHD) development in children. We conducted a population-based birth cohort study using the 2004 to 2014 Taiwanese Birth Certificate Database and verified diagnoses of ADHD using the National Health Insurance Database. The level of petrochemical exposure in each participant's residential township was evaluated using the following 3 measurements: distance to the nearest petrochemical industrial plant (PIP), petrochemical exposure probability (accounting for monthly prevailing wind measurements), and monthly benzene concentrations estimated using kriging-based land-use regression models. We applied Cox proportional hazard models to evaluate the association. During the study period, 48,854 out of 1,863,963 children were diagnosed as having ADHD. The results revealed that residents of townships in close proximity to PIPs (hazard ratio [HR] = 1.20, 95% confidence interval [CI]: 1.16-1.23, <3 vs. 10 km), highly affected by petrochemical-containing prevailing winds (HR = 1.12, 95% CI: 1.08-1.16, 40% vs. <10%), and with high

benzene concentrations (HR = 1.26, 95% CI: 1.23-1.29, 0.75 vs. <0.55 ppb) were consistently associated with the increased risk of ADHD development in children. The findings of the sensitivity analysis remained robust, particularly for the 2004 to 2009 birth cohort and for models accounting for a longer duration of postnatal exposure. This work provided clear evidence that living near petrochemical plants increases the risk of ADHD development in children. Further studies are warranted to confirm our findings

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Epidemiol Psychiatr Sci. 2022 May;31:e35.

ESTIMATING PREVALENCE OF CHILD AND YOUTH MENTAL DISORDER AND MENTAL HEALTH-RELATED SERVICE CONTACTS: A COMPARISON OF SURVEY DATA AND LINKED ADMINISTRATIVE HEALTH DATA.

Duncan L, Georgiades K, Wang L, et al.

AIMS: Prevalence estimates of child and youth mental disorder and mental health-related service contacts are needed for policy formulation, research, advocacy and resource allocation. Our aim is to compare prevalence estimates of child and youth mental disorder and mental health-related service contacts derived from general population survey data v. linked administrative health data.

METHODS: Provincially representative 2014 Ontario Child Health Study data were linked to administrative health records for 5563 children and youth aged 4-17 in Ontario. Emotional disorders (mood and anxiety) and attention-deficit/hyperactivity disorder were assessed using a standardised diagnostic interview in the survey and using diagnostic codes in administrative health data. Physician-based mental health-related service contacts were assessed using parent self-reports from the survey and administrative data related to mental health-related diagnostic codes. Prevalence estimates were calculated and compared based on one-sample z-tests and ratios of survey data to administrative data-based prevalence. Sensitivity, specificity and agreement between classifications were compared using Îº. Prevalence estimates were calculated by age, sex and geography sub-groups and consistent group differences across data source were counted.

RESULTS: Disorder prevalence and service contact estimates were significantly higher in survey data in all cases, except for mood disorder. Ratios of survey data to administrative data-based prevalence varied, ranging from 0.80 (mood) to 11.01 (attention-deficit/hyperactivity disorder). Specificity was high (0.98-1.00), sensitivity was low (0.07-0.41) and agreement ranged from slight (Îº = 0.13) to moderate (Îº = 0.46). Out of 18 sub-group difference comparisons, half were non-significant in either data source. In the remaining nine comparisons, the only significant differences between groups that were consistent across data source were for sex-based differences (attention-deficit/hyperactivity disorder and service contacts). There were no consistent age- or geography-based differences in prevalence across data sources.

CONCLUSIONS: Our findings suggest that conclusions drawn about prevalence, service contacts and sub-group differences in these estimates are dependent on data source. Further research is needed to understand who and what is being captured by each source. Researchers should conduct data linkage where possible to access and compare multiple sources of information

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Epidemiology. 2022 Jul;33:581-92.

PRENATAL ANTIDEPRESSANT EXPOSURE AND THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD: A COHORT STUDY WITH TRIANGULATION.

Esen BÃ, Ehrenstein V, SÃ¸rensen HT, et al.

BACKGROUND: Uncontrolled confounding from maternal depression and genetic and environmental factors is expected in studies investigating the effect of prenatal antidepressant exposure on the risk of attention-deficit/hyperactivity disorder (ADHD) in childhood and may explain inconsistencies in the existing evidence. We aimed to assess this effect using triangulation.

METHODS: Using population-based health registries, we conducted a nationwide cohort study of all children born in Denmark between 1997 and 2017 and followed through 2018 for ADHD. We assessed the effect of prenatal antidepressant exposure on the risk of ADHD in childhood by comparing children with and without prenatal antidepressant exposure in terms of adjusted incidence rate ratios (IRRs), adjusted incidence rate differences (IRDs), and adjusted risk differences (RDs) and the associated 95% confidence intervals (CIs). We triangulated results from four different analytic approaches: an overall analysis, a negative control analysis, a sibling analysis, and a former-user analysis.

RESULTS: The overall study cohort consisted of 1,253,362 children, among whom 28,910 (2.3%) had prenatal antidepressant exposure. ADHD during follow-up was diagnosed among 1,411 (4.9%) of the exposed and in 37,196 (3.0%) of the unexposed children. Triangulation suggested an IRR of 1.09-1.15; an IRD less than 1 case/1,000 person-years, and an RD of 0.9%-2.2% over an up to 18-year period.
CONCLUSIONS: Based on triangulation, we estimated a modest effect of prenatal antidepressant exposure on the risk of ADHD in childhood. However, considering the limitations of our approaches, this observed association may be partially due to residual biases. See video abstract at, http://links.lww.com/EDE/B935

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Epilepsy Behav. 2021;124.

DRUGS FOR PATIENTS WITH EPILEPSY AND EXCESSIVE DAYTIME SLEEPINESS.

Zaccara G, Bartolini E, Tramacere L, et al.

Excessive daytime sleepiness (EDS) and attentional deficits are often observed in people with epilepsy. They may be the consequence of seizures and subclinical discharges as well as of comorbid conditions as obstructive sleep apnea/hypopnea syndrome (OSAS), attention deficit hyperactivity disorder (ADHD), or other less frequent disorders. Excessive daytime sleepiness may also be caused or worsened by antiseizure medications (ASMs). Several meta-analyses suggested that lamotrigine, lacosamide, and perhaps eslicarbazepine are less sedative than other traditional and new ASMs and, in patients prone to somnolence, might be preferred over ASMs with more sedative properties. In patients with severe EDS and/or ADHD, advantages and risks of a treatment with a psychostimulant need to be considered. Methylphenidate, modafinil, armodafinil, pitolisant, and solriamfetol are authorized for use in ADHD and EDS in patients with narcolepsy and some of them also in OSAS. These agents are off-label for the treatment of EDS associated with epilepsy. They do not have proconvulsant effects, although there are several possible risks for patients with epilepsy. The risks of cardiovascular events and psychiatric symptoms should be carefully evaluated as such disorders can coexist with epilepsy and be triggered by these agents. Finally, combination of psychostimulants with ASMs may be associated with several pharmacokinetic drug-drug interactions

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Eth Human Psychol Psychiatry. 2022;24:41-50.

RECONSIDERING THE SAFETY PROFILE OF STIMULANT MEDICATIONS FOR ADHD.

Ophir Y.

Stimulant medications (e.g., Ritalin) are considered a relatively safe first-line treatment for attention deficit hyperactivity disorder (ADHD), the most common neuropsychiatric diagnosis among children. This study explores the prevalence of side-effects and risks of stimulants, as perceived by 218 Israeli young adults with ADHD who used stimulants. Participants completed questionnaires that addressed representative side-effects (eight side-effects copied from the patient leaflet of Ritalin, as approved by the Israel Ministry of Health, and five additional side-effects), medication dependence, and substance use. Results indicated that almost all side-effects were extremely common significantly and substantially more than the leaflet's estimates. Mood changes such as depression for example, were observed among 66%, compared with the reported 1 in 10,000 users. Suicidal thoughts, which are mentioned as side-effect that occurred with other medications that contain same ingredient, were observed among 3.2%. Side-effects not mentioned in the leaflet, such as zombie-like sensation (72.5%) and alterations in sense-of-self (39.4%), were also very common. Most participants tried quitting the medications (some even resisted taking them as children), mainly to disengage from their medication dependence and cease their adverse-effects, however many struggled coping without the medications and experienced withdrawal reactions, such as decreased mood or motivation as well as increased stress and anxiety. Notably, stimulant use frequency significantly correlated with alcohol and drug use. Although the observational nature of the study limits its generalizability, its findings suggest that the safety profile of stimulants requires further consideration, especially today with the large increase in diagnoses and medication use among millions of children

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Eur J Paediatr Neurol. 2022 May;38:25-32.

VISUAL-PROCESSING DEFICITS IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1: A CLINICAL MARKER OF READING DIFFICULTIES.

Vernet M, Jover M, Bellocchi S, et al.

Today's estimates indicate that nearly 50% of children with Neurofibromatosis type 1 (NF1) suffer from reading disabilities, with a high impact on their academic achievement. In addition to the well-documented importance of phonological skills in reading acquisition and neurodevelopmental disorders, visual-attention processes also appear as important factors in learning to read. The present study aimed at assessing the role of visual-processing dysfunction in the high prevalence of reading disabilities in NF1 children and providing a useful tool for clinician in the early detection of reading impairment in this neurogenetic disorder. Forty-two children with NF1 and 42 typically developing children (TD) participated in the study. All were right-handed and did not present intellectual disability or attention deficit hyperactivity disorder. Visual-attention processes were assessed with the Developmental Eye Movement (DEM) test, together with the NF1 children's reading level. NF1 children with and without reading disabilities were then compared. The results showed that visual-processing deficits were highly present among the NF1 children included in our study. Furthermore, poor readers with NF1 presented an increased risk of visual-processing deficits compared to peers. This finding supports the role of visual-processing deficits in the reading difficulties encountered in nearly half of children with NF1. Finally, in NF1 children without intellectual or attention disability, visual-processing deficits emerge as one of the clinical markers of reading disabilities. The study holds important clinical implications both for the identification, by providing a useful screening tool, and the management of reading disabilities in NF1 children

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Eur J Pediatr. 2022 May;181:1985-95.

PHYSICAL ACTIVITY, SCREEN TIME, AND SLEEP: DO GERMAN CHILDREN AND ADOLESCENTS MEET THE MOVEMENT GUIDELINES?

Hansen J, Hanewinkel R, Galimov A.

The interactions between physical activity (PA), screen time, and sleep affect the health of children and adolescents. This study described the national prevalence estimates of German youth aged 9 to 18 years who meet PA, screen time, and sleep guidelines alone and in combination and examined the associations of demographic and personal characteristics with adherence to guidelines. Data from a 2019-2020 German student survey were used (n=15,786). The target population consisted of children and adolescents enrolled in grades 5-10, with a mean age of 13.0Â years (SD=1.8) and an equal gender distribution (male: 50%). The levels of PA, screen time, and sleep were assessed by self-reports (online questionnaires). The prevalence rates of meeting each guideline individually and in different combinations were calculated, and multilevel logistic regression models were used to examine the associations of demographic and personal characteristics with meeting versus not meeting guidelines. Overall, 9.7% of the respondents met all three guidelines combined, and approximately 25% did not meet any of the guidelines. Half of the participants (50%) met the sleep guidelines, and approximately one third met the screen time (35%) and PA (37%) guidelines alone. Demographic characteristics associated with adherence to meeting all three movement guidelines included younger age, male gender, higher self-reported socioeconomic status, and school type. Personal characteristics related to adherence to meeting all three movement guidelines included better subjective school performance, less frequent attention deficit hyperactivity disorder (ADHD), lower levels of depressive symptoms, lower body mass index (BMI), and not using substances in the past 30 days.

CONCLUSION: A low percentage of German children and adolescents met the movement guidelines. With increasing age, the proportion of young people who follow the recommendations decreases. There is an urgent need for health interventions devoted to youth behavior as a whole.

WHAT IS KNOWN: High levels of PA, low levels of screen time, and optimal sleep duration provide enhanced health benefits in comparison to the adoption of just one of these behaviors. Evidence shows that movement behaviors interact throughout the day and should be studied concurrently.

WHAT IS NEW: Approximately 10% of German children and adolescents met the recommendations on PA, screen time, and sleep, while 25% did not meet any guidelines. Meeting all guidelines was associated with

less frequent ADHD and depressive symptoms, lower BMI, and less frequent substance use in the past 30 days

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Eur Child Adolesc Psychiatry. 2022;31:313-24.

TRAJECTORIES OF DYSREGULATION IN PRESCHOOL AGE.

Asmussen J, Skovgaard AM, Bilenberg N.

Dysregulation of emotions, behaviour and attention is involved in several areas of childhood psychopathology, but knowledge about early developmental trajectories remains scarce. This study aims to explore continuity and associations of dysregulation in preschool age. Dysregulation was measured at age 2 years and again at 5-áyears in a community-based birth cohort of 1099 children using the Child Behavior Checklist, preschool version (CBCL1 5), answered by mothers. Based on the Dysregulation Profile (CBCL-DP) score, we defined four trajectory groups, using the 75th percentile from the Danish norm material as a cut-off. Associations between the four CBCL-DP trajectory groups and potential covariates, including child, parental and family factors, were analysed using univariate and multiple multinomial logistic regression. Nearly half (54%) of the children showed persistent low scores of CBCL-DP, 17% displayed continuing dysregulation problems, 13% had problems that increased from 2-¢ years to 5years, whereas 16% of the children showed reduced problems across preschool age. Persistent dysregulation was associated with maternal postpartum depressive symptoms RRR = 2.20 (95% CI 1.29ΓÇô3.75), low maternal educational level RRR = 1.69 (95% CI 1.08-2.66), and mothers smoking during pregnancy RRR = 2.87 (95% CI 1.09-7.55). Persistent problems of emotional, behavioural and attention regulation in children aged 2 years to 5 years is influenced by maternal educational level and post-partum depression symptoms. The study draws clinical attention to early symptoms of dysregulation and to the importance of addressing the specific needs of mentally vulnerable parents in intervention planning

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Experimental and Clinical Endocrinology and Diabetes. 2022.

FAMILY STRUCTURE IS ASSOCIATED WITH MENTAL HEALTH AND ATTENTION DEFICIT (HYPERACTIVITY) DISORDERS IN ADOLESCENTS WITH TYPE 1 DIABETES.

Baechle C, Stahl-Pehe A, Castillo K, et al .

Objective To analyze the cross-sectional associations of family structure with mental health and attention deficit (hyperactivity) disorders (AD(H)D) in 11- to 17-year-old adolescents with early-onset type 1 diabetes participating in one of three baseline surveys as part of an ongoing cohort study.

Methods Parents (n=1,631) completed the Strengths and Difficulties Questionnaire to screen for their child's mental health and answered questions about their child's diagnosis of AD(H)D. Associations between mental health or AD(H)D and family structure were analyzed using multivariable logistic regression analyses adjusted for various personal and diabetes-related variables.

Results Compared to adolescents living with both parents, adolescents living with one parent and his/her partner had 2.35 (95% confidence interval 1.32; 4.21) higher odds of abnormal screening result and 2.08 (1.09; 3.95) higher odds of a borderline screening result while adolescents living with a single parent had 1.84 (1.07; 3.17)/1.08 (0.53; 2.21) higher odds of abnormal/borderline screening results. The odds ratios for diagnosed attention deficit (hyperactivity) disorder were 2.17 (0.98; 4.84) for adolescents living with one parent and his/her partner and 1.27 (0.54; 3.01) for those living with a single parent vs. both parents.

Conclusions Our results indicate higher odds of mental health problems and AD(H)D in adolescents with type 1 diabetes who do not live with both parents; this finding was most pronounced in individuals living with one parent and his/her partner vs. both parents. Longitudinal studies are needed to verify our results and elucidate the underlying mechanisms

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Fam Pract. 2022 Mar;39:301-10.

PHARMACOTHERAPY INTERVENTIONS FOR ADOLESCENT CO-OCCURRING SUBSTANCE USE AND MENTAL HEALTH DISORDERS: A SYSTEMATIC REVIEW.

Scott K, Becker SJ, Helseth SA, et al.

BACKGROUND: Co-occurring mental health and substance use (SU) disorders among adolescents are common, with two-thirds of adolescents who seek SU treatment also requiring support for mental health. Primary care physicians play a key role in the pharmacological treatment of mental health disorders among adolescents, however, little is known about the impact of these treatments on SU outcomes.

OBJECTIVES: This systematic review summarizes the evidence regarding commonly used pharmacotherapy interventions for mental health and their impact on adolescent SU.

METHODS: Literature searches were conducted across five databases as part of a larger systematic review of adolescent SU interventions. Studies were screened for eligibility by two researchers, and study data were extracted regarding study design, patient and treatment characteristics and results. Risk of bias analyses and qualitative syntheses were completed to evaluate the strength of the evidence and the impact of pharmacotherapy on SU outcomes.

RESULTS: Ten randomized controlled trials exploring seven pharmacotherapies met criteria for inclusion. All studies had low to moderate risk of bias. Four studies evaluated pharmacotherapy for co-occurring depression and SU, three evaluated attention deficit hyperactivity disorder and SU, and three evaluated bipolar disorder and SU. Five of the 10 studies also included a behavioural intervention. We found no evidence that pharmacotherapy for co-occurring mental health diagnoses impacted SU.

CONCLUSION: Family medicine clinicians prescribing pharmacotherapy for mental health should be aware that additional interventions will likely be needed to address co-occurring SU

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Front Psychiatry. 2022;13.

GAME ADDICTION SCALE FOR ADOLESCENTS PSYCHOMETRIC ANALYSES OF GAMING BEHAVIOR, GENDER DIFFERENCES AND ADHD.

Andre F, Munck I, et al.

Background: Internet gaming disorder (IGD) was recently added in the Diagnostic and Statistical Manual of Mental Disorder as a condition for further studies. There is no consensus regarding which rating scales should be used but many scholars suggest the GASA (Game Addiction Scale for Adolescents) and a ranking of the criteria, the core approach to avoid over-diagnosing of disordered gaming. Male gender and ADHD are commonly listed as risk factors for disordered gaming but little is known about sex differences in gaming and gender specific health correlates.

Purpose: The present study aims to evaluate the core approach and the specific indicators of gaming behavior in GASA from a multifactorial perspective and explore the gender differences in a clinical setting, focusing on ADHD.

Patients and Methods: Children and adolescents aged 8-18 years (n = 144) from Child and adolescent psychiatry (CAP) in Skane were assessed with the GASA. Psychometric analyses including confirmatory factor analyses (CFA) and structural equation modeling (SEM) were used to identify well-defined constructs and gender differences. Refined factor scores for single constructs were the outcome of alignment, a procedure for assessing measurement equivalence across gender. New model-based gaming behavior variables were used for descriptive statistics and ANOVA testing of gender differences.

Results: The results confirm that the core approach two-factor model is valid for the CAP sample, as well as a theory based psycho-social model for gaming behavior with over consumption and negative social and emotional consequences. Our findings suggest that negative consequences of over consumption take a social direction for boys and an emotional direction for girls. Also, ADHD was significantly associated with over consumption of video games and the negative consequences thereof for girls.

Conclusion: Guided by psychometric analyses, the GASA could be strengthened by advancing the questionnaire design and by adding complementary items in order to illuminate the complexity of gaming behavior. Our findings suggest that additional research on potential gender related discrepancies of disordered gaming is needed

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Front Psychiatry. 2022;13.

CHARACTERIZING THE NEURAL CORRELATES OF RESPONSE INHIBITION AND ERROR PROCESSING IN CHILDREN WITH SYMPTOMS OF IRRITABILITY AND/OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE ABCD STUDY-«.

Lee KS, Xiao J, Luo J, et al.

Attention-deficit/hyperactivity disorder (ADHD), characterized by symptoms of inattention and/or hyperactivity and impulsivity, is a neurodevelopmental disorder associated with executive dysfunctions, including response inhibition and error processing. Research has documented a common co-occurrence between ADHD and pediatric irritability. The latter is more characterized by affective symptoms, specifically frequent temper outbursts and low frustration tolerance relative to typically developing peers. Shared and non-shared neural correlates of youths with varied profiles of ADHD and irritability symptoms during childhood remain largely unknown. This study first classified a large sample of youths in the Adolescent Brain Cognitive Development (ABCD) study at baseline into distinct phenotypic groups based on ADHD and irritability symptoms (N = 11,748), and then examined shared and non-shared neural correlates of response inhibition and error processing during the Stop Signal Task in a subset of sample with quality neuroimaging data (N = 5,948). Latent class analysis (LCA) revealed four phenotypic groups, i.e., high ADHD with co-occurring irritability symptoms (n = 787, 6.7%), moderate ADHD with low irritability symptoms (n = 901, 7.7%), high irritability with no ADHD symptoms (n = 279, 2.4%), and typically developing peers with low ADHD and low irritability symptoms (n = 9,781, 83.3%). Latent variable modeling revealed group differences in the neural coactivation network supporting response inhibition in the fronto-parietal regions, but limited differences in error processing across frontal and posterior regions. These neural differences were marked by decreased coactivation in the irritability only group relative to youths with ADHD and co-occurring irritability symptoms and typically developing peers during response inhibition. Together, this study provided initial evidence for differential neural mechanisms of response inhibition associated with ADHD, irritability, and their co-occurrence. Precision medicine attending to individual differences in ADHD and irritability symptoms and the underlying mechanisms are warranted when treating affected children and families

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Headache. 2022 May;62:634-41.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND RISK OF MIGRAINE: A NATIONWIDE LONGITUDINAL STUDY.

Hsu TW, Chen MH, Chu CS, et al.

OBJECTIVE: This study explored the risk of migraine in children, adolescents, and young adults with attention deficit hyperactivity disorder (ADHD) and its association with ADHD medications.

BACKGROUND: The prevalence of migraine peaks between the ages of 35 and 39 years. Recent studies have reported a positive association between ADHD and migraine.

METHODS: This longitudinal case-cohort study was conducted using data from the Taiwan National Health Insurance Database. Between 2001 and 2009, we enrolled 81,441 participants with ADHD and a 1:1-matched control cohort for age, sex, and physical and psychiatric comorbidities. All participants had no diagnosis of migraine before enrollment and were followed up to the end of 2011. We examined the risk of newly diagnosed migraine among patients with ADHD and matched controls after adjusting for demographics and physical/psychiatric comorbidities.

RESULTS: Patients with ADHD had a higher incidence of migraine than those in the control group (462/81441 [0.6%] vs. 212/81441 [0.3%] patients, pÂ <Â 0.001). After adjusting for potential confounders, the hazard ratio (HR) was 1.92 (95% CI, 1.64-2.34) for migraine in patients with ADHD versus controls. The subgroup analyses stratified by age showed the HRs were 2.01 (95% CI, 1.63-2.49), 1.94 (95% CI, 1.35-2.79), and 1.31 (95% CI, 0.58-2.98) for children (<12Â years old), adolescents (12-17), and young adults (18-29), respectively, versus controls. When stratified by sex, the HR was 1.97 (95% CI, 1.58-2.46) for men and 1.94 (95% CI, 1.44-2.62) for women versus controls. The cumulative daily dose of ADHD medications was not associated with the risk of migraine.

CONCLUSION: Children and adolescents with ADHD were associated with an increased risk of migraine compared with matched controls. The increased risk was not observed in young adults with ADHD. Further studies are required to examine the mechanisms between migraine and ADHD

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Health Expect. 2022 Jun;25:1094-107.

ELICITING PREFERENCES FOR CONTINUING MEDICATION AMONG ADULT PATIENTS AND PARENTS OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Khan MU, Balbontin C, Bliemer MCJ, et al.

Background: Adherence to medication for attention-deficit hyperactivity disorder (ADHD) is less than optimal. Previous studies have primarily focused on qualitative assessment of factors that influence medication adherence.

Objective: This study aimed to quantify the factors that influence patient and parent preferences for continuing ADHD medication.

Method: A discrete-choice experiment was conducted to investigate preferences. Adults, and parents of children, with ADHD were presented with eight hypothetical choice tasks of three options (Medication A, Medication B, No Medication) described by six attributes related to medication outcomes. Preferences were estimated using a mixed multinomial logit model.

Results: Overall, respondents' preferences (n = 216) for continuing medication were negative (mean [β] = -1.426, p < .001); however, a significant heterogeneity in preferences was observed amongst respondents (standard deviation = 0.805, p < .001). Improvements in education, aggressive behaviour, social behaviour and family functioning, and side effects and stigma, influenced respondents' decision to continue taking medication. The respondents were willing to continue medication if they experienced positive effects, but side effects (even moderate) were the strongest concern for not continuing medication. While side effects were the most important factor for both adult patients and parents of children with ADHD, improvement in education was relatively more important for adults and improvement in aggressive behaviour, social behaviour and family functioning was relatively more important for parents of children with ADHD. Parents were more likely to not continue a medication with severe side effects even at the highest level of improvement in education.

Conclusions: Side effects are the most important factor that influenced preferences for continuing medication for both adults with ADHD, as well as parents of children with ADHD. While overall the respondents preferred not to take/give medication, discrete-choice experiment showed that the relative importance of factors that influenced continuation of medications was different for the two groups.

Patient and public involvement: Adults, and parents of children, with ADHD participated in this study by completing the online questionnaire. The questionnaire was based on findings of research in the literature, as well as earlier focus groups conducted with adults, and parents of children, with ADHD. The face validity of the questionnaire was determined by asking parents of children, and adults, with ADHD (n = 3) to complete the survey and participate in a short discussion on their understanding of the questions and their recommendations on improving the clarity of the survey

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Indian J Pediatr. 2022.

EVALUATION OF SYMPATHETIC AND PARASYMPATHETIC TONE AND REACTIVITY IN ADOLESCENTS WITH SPECIFIC LEARNING DISORDER (DYSLEXIA).

Kosana D, Sagar R, Deepak KK, et al.

Objectives: To evaluate the autonomic function in specific learning disorder (SLD) and comorbid SLD attention-deficit hyperactivity disorder (SLD-ADHD).

Methods: A cross-sectional study was conducted in a tertiary care hospital with 20 adolescent subjects each of confirmed SLD, SLD-ADHD, and healthy control (mean age 15.32 y). Heart-rate variability and autonomic-function tests were carried out using standard protocols.

Results: Heart-rate variability parameters, viz., mean RR interval, number of RR intervals which differ by 50 ms (NN50), percentage NN50, standard deviation of differences between adjacent RR intervals, root square of mean of the sum of the squares of differences between adjacent RR intervals, coefficient of variance and absolute power of high-frequency band (HF) recorded apparently lower levels in SLD and SLD-ADHD as compared to healthy control indicating lower parasympathetic tone. Whereas, higher absolute power of low- frequency band (LF) in SLD and SLD-ADHD than healthy control indicated enhanced sympathetic activity. Higher LF/HF and lower SD1/SD2 ratios in SLD and SLD-ADHD than healthy control indicated higher sympathetic tone over parasympathetic tone. Values of autonomic-function tests such as E:I ratio, change in heart rate during deep-breathing test, 30:15 ratio, and Valsalva ratio showed a decrease

in SLD and SLD-ADHD as compared to healthy control implying reduction in parasympathetic reactivity. Increased values for rise in diastolic blood pressure in the isometric handgrip test and cold pressor test recorded in SLD as compared to healthy control, revealed the increased sympathetic reactivity.
Conclusion: Overall, results of heart-rate variability and autonomic-function tests imply dysregulation of sympathetic and parasympathetic activities with sympathetic dominance in SLD and SLD-ADHD

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Int J Dev Neurosci. 2022 Jun;82:295-302.
HOW AEROBIC EXERCISE IMPROVES EXECUTIVE FUNCTION IN ADHD CHILDREN: A RESTING-STATE FMRI STUDY.
Jiang K, Xu Y, Li Y, et al .
The aim of the study is to explore the functional magnetic resonance imaging (fMRI) characteristics of the improvement in executive function by aerobic exercise in children with attention deficit hyperactivity disorder (ADHD). Seventeen children with ADHD were selected for 8Â weeks of rope skipping aerobic training, and fMRI findings and executive function were examined before and after training. Regional homogeneity (ReHo) and degree centrality (DC) indexes were used in fMRI analysis, whereas the flanker task was used to test executive function. A paired t test was used to compare the fMRI indexes and response time of executive function before and after training. After aerobic exercise, the brain regions in which the ReHo value of ADHD children significantly increased included the left middle frontal gyrus and the right superior frontal gyrus; the brain region in which the DC value increased was the right posterior cingulate cortex. The flanker task response time decreased significantly ($P<0.05$, after correction) after aerobic exercise. The study findings support the hypothesis that aerobic exercise can improve the executive function of ADHD children, and the brain mechanism involved is mainly related to the enhancement of spontaneous prefrontal lobe activity

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Int J Environ Res Public Health. 2022 May;19.
CLINICAL AND SOCIO-DEMOGRAPHIC VARIABLES ASSOCIATED WITH THE DIAGNOSIS OF LONG COVID SYNDROME IN YOUTH: A POPULATION-BASED STUDY.
Merzon E, Weiss M, Krone B, et al.
This study examines the demographic, clinical and socioeconomic factors associated with diagnosis of long COVID syndrome (LCS). Data of 20,601 COVID-19-positive children aged 5 to 18 years were collected between 2020 and 2021 in an Israeli database. Logistic regression analysis was used to evaluate the adjusted odds ratio for the characteristics of the COVID-19 infection and pre-COVID-19 morbidities. Children with LCS were significantly more likely to have been severely symptomatic, required hospitalization, and experienced recurrent acute infection within 180 days. In addition, children with LCS were significantly more likely to have had ADHD, chronic urticaria, and allergic rhinitis. Diagnosis of LCS is significantly associated with pre-COVID-19 ADHD diagnosis, suggesting clinicians treating ADHD children who become infected with COVID-19 remain vigilant for the possibility of LCS. Although the risk of severe COVID-19 infection and LCS in children is low, further research on possible morbidity related to LCS in children is needed

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Int J Environ Res Public Health. 2022 May;19.
EEG GLOBAL COHERENCE IN SCHOLAR ADHD CHILDREN DURING VISUAL OBJECT PROCESSING.
Hernandez-Andrade L, Hermosillo-Abundis AC, Betancourt-Navarrete BL, et al.
Among neurodevelopmental disorders, attention deficit hyperactivity disorder (ADHD) is the main cause of school failure in children. Notably, visuospatial dysfunction has also been emphasized as a leading cause of low cognitive performance in children with ADHD. Consequently, the present study aimed to identify ADHD-related changes in electroencephalography (EEG) characteristics, associated with visual object processing in school-aged children. We performed Multichannel EEG recordings in 16-year-old children undergoing Navon's visual object processing paradigm. We mapped global coherence during the processing of local and global visual stimuli that were consistent, inconsistent, or neutral. We found that Children with ADHD showed significant differences in global weighted coherence during the processing of local and global inconsistent visual stimuli and longer response times in comparison to the control group. Delta and theta EEG bands highlighted important features for classification in both groups. Thus, we advocate EEG coherence and low-

frequency EEG spectral power as prospective markers of visual processing deficit in ADHD. Our results have implications for the development of diagnostic interventions in ADHD and provide a deeper understanding of the factors leading to low performance in school-aged children

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Int J Law Psychiatry. 2022 Jan;80:101726.

CORRELATES AND PREDICTORS OF RE-INCARCERATION AMONG TURKISH ADOLESCENT MALE OFFENDERS: A SINGLE-CENTER, CROSS-SECTIONAL STUDY.

Galer AG, et al.

BACKGROUND: Adolescents involved in the legal system are known to be under elevated risk for repeat offending. There may be many reasons for recidivism. Specifically, we aim to investigate the clinical, socio-demographic, and familial factors and psychopathology among adolescents in a penal institution and to determine risk factors for re-incarceration.

METHODS: This single-center cross-sectional survey was conducted at Tarsus Closed Penal Institution for Children and Youth. This institution is for males only, and all male adolescents detained at the center within the study period were evaluated with semi-structured interviews (K-SADS-PL). The adolescents completed Meaning and Purpose of Life Scale, The EPOCH measure of Adolescent Well-being, Family Sense of Belonging Scale, Children's Alexithymia Scale, Beck Depression Inventory, and State-Trait Anxiety Inventory for themselves. Descriptive and inferential analyses were used. P was set at 0.05.

RESULTS: Ninety adolescent offenders with a mean age of 16.6Â years (SÂ·DÂ =Â 0.7) were enrolled. Mean age at first offense was 14.6Â years (SÂ·DÂ =Â 2.1). The most common reason for offenses was reported as as being with peers who were offenders, too (57.8%). Most common diagnoses were substance use (36.7%), attention deficit/hyperactivity disorder (33.3%), and conduct disorder (26.7%). Rates of offending and conviction in first-degree relatives were 62.2% and 60.0%, respectively, and most of the adolescents had at least one peer with a criminal record (nÂ =Â 71, 78.9%). Re-incarcerated adolescents had lower education, committed more violent crimes, and reported elevated use of substances, suicide attempts, and psychopathology. However, in regression analysis, age of onset was the sole predictor of re-incarceration.

CONCLUSION: Turkish male adolescents in forensic settings may be screened for externalizing disorders and referred for treatment. Re-incarcerated Turkish youth may be more susceptible to peer influence, substance use and externalizing disorders. It may be prudent to systematically screen offending youth for psychiatric disorders regardless of the individual's request for treatment and refer identified cases to treatment. Integration of child and adolescent psychiatrists with penal institutions serving youth may help in this regard

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Int J Methods Psychiatr Res. 2022 Mar;31:e1903.

MORBIDITIES AND MORTALITY OF DIAGNOSED ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) OVER THE YOUTH LIFESPAN: A POPULATION-BASED RETROSPECTIVE COHORT STUDY.

Diallo FB, Pelletier Ã, Vasiliadis HM, et al.

OBJECTIVES: To estimate the prevalence of ADHD, and related comorbidities, mortality, and type of health service use among children and young adults, using different case definitions.

METHODS: We conducted a population-based retrospective cohort study between 2000 and 2018, using the Quebec Integrated Chronic Disease Surveillance System (QICDSS) database. All residents aged less than 25Â years eligible for health insurance coverage were included. We compared outcomes of three indicators (morbidity, services use and mortality) according two different algorithms of ADHD definitions, to the general population.

RESULTS: The cumulative prevalence of ADHD has risen steadily over the past decade, reaching 12.6% in 2017-2018. People with ADHD have a higher prevalence of psychiatric comorbidities, make greater use of medical, mental health services, and are hospitalized more often. The comparison of prevalence between the two algorithms and the general population for the three indicators showed that the cohort having one claim was very close to that with two or more, and statistically significant higher to that of people without ADHD.

CONCLUSION: This finding support that a single claim algorithm for ADHD can be used for case definition. More research is needed on the impact of potentially effective treatments in improving consequences of ADHD

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Int J Neuropsychopharmacol. 2022 Mar;25:215-25.

SELECTIVE EFFECTS OF METHYLPHENIDATE ON ATTENTION AND INHIBITION IN 22Q11.2 DELETION SYNDROME: RESULTS FROM A CLINICAL TRIAL.

Maeder J, Mancini V, Sandini C, et al.

BACKGROUND: Attention deficit and/or hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children with 22q11.2 deletion syndrome (22q11DS) and frequently persists into adulthood. Although medication with stimulant has been demonstrated to be highly effective in idiopathic ADHD, evidence in 22q11DS is still scarce. Previous studies have shown safety and effectiveness of methylphenidate (MPH) on core symptoms of ADHD as well as improvement of associated cognitive deficits. However, only a limited number of cognitive domains have been explored.

METHODS: Twenty-three participants with 22q11DS and attention difficulties, aged 8-24 years, entered a clinical trial aiming to specify the effects of MPH on clinical symptoms, cognition, and daily-life behavior. The effects of treatment were compared with/without medication in a within-subject design. The trial included both participants naÃ¨ve to the molecule and chronic users.

RESULTS: Benefit from the treatment was demonstrated through a decrease in core ADHD symptoms, specifically inattention symptoms, and improvement of cognitive measures of attention and inhibition. Conversely, no significant change was found for other executive functions (such as cognitive flexibility, working memory, initiation), learning, or memory. Moreover, no significant improvement on ecological measures of daily-life executive functioning was found, possibly because of the short treatment period. We replicated safety, and although very frequent, side effects were of mild intensity and comparable with previous findings.

CONCLUSIONS: This study extends the current knowledge on the effects of MPH in patients with 22q11DS. Treatment was found to be effective for core ADHD symptoms and cognitive measures of attention and inhibition

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Int J Sports Med. 2022 Jun;43:553-60.

PRESEASON SYMPTOM REPORTING AND COGNITION IN MIDDLE SCHOOL ATHLETES WITH PAST CONCUSSIONS.

Iverson GL, Berkner PD, Zafonte R, et al.

This study examined the association between past concussions and current preseason symptom reporting and cognitive performance in 9,257 youth ages 11-13. Participants completed neurocognitive testing prior to participating in a school sports between 2009 and 2019. We stratified the sample by gender and number of prior concussions and assessed group differences on the Post-Concussion Symptom Scale total score and the ImPACT cognitive composite scores. Those withâ‰¥2 prior concussions reported more symptoms than those with 0 concussions (d=0.43-0.46). Multiple regressions examining the contribution of concussion history and developmental/health history to symptom reporting showed the most significant predictors of symptoms scores were (in descending order): treatment for a psychiatric condition, treatment for headaches, history of learning disability (in boys only), history of attention-deficit/hyperactivity disorder, and age. Concussion history was the weakest statistically significant predictor in boys and not significant in girls. Cognitively, boys with 1 prior concussion had worse speed those with 0 concussions (d=0.11), and girls withâ‰¥2 prior concussions had worse verbal/visual memory than girls with 0 concussions (ds=0.38-0.39). In summary, youth withâ‰¥2 prior concussions reported more symptoms than those with no concussions. Boys with multiple concussions performed similarly on cognitive testing, while girls had worse memory scores

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Int J Environ Res Public Health. 2022;19.

CAREGIVERS' DIFFICULTY IN MANAGING SMARTPHONE USE OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING THE COVID-19 PANDEMIC: RELATIONSHIPS WITH CAREGIVER AND CHILDREN FACTORS.

Lee JI, Hsiao RC, Tsai CS, et al.

This study examined the difficulty encountered by caregivers of children with attention-deficit/hyperactivity disorder (ADHD) in managing childrenΓÇÖs smartphone use during the coro-navirus disease 2019 (COVID-19) pandemic and the caregiver-and children-related factors that influence this difficulty. In total, 252 caregivers of children with ADHD were recruited into this study. The caregivers completed a research questionnaire to provide data regarding the difficulty they encountered in managing the smartphone use of children during the COVID-19 pandemic, their general mental health and parenting styles, and the ADHD and oppositional defiant disorder (ODD) symptoms of the children they are caring for. The results indicated that almost 45% of the caregivers of children with ADHD sometimes or often found it difficult to manage the smartphone use of children with ADHD during the COVID-19 pandemic. For the caregivers, a short duration of education, poor general mental health, unaffectionate/uncaring and overprotective parenting styles, older children, and inattention and ODD symptoms were significantly associated with increased difficulty in managing their childrenΓÇÖs smartphone use during the COVID-19 pandemic. On the basis of the relevant factors identified in this study, an intervention should be developed to enhance the skills of caregivers of children with ADHD with respect to the management of childrenΓÇÖs smartphone use during the COVID-19 pandemic

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International Journal of Medical Toxicology and Forensic Medicine. 2022;12:35740.

THE INFLUENCE OF POSITIVE PARENTING TRAINING ON IMPROVING BEHAVIORAL FUNCTION AND IMPULSIVITY IN CHILDREN SUFFERING FROM ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jalilvand M, Bagheri F, Zahra N.

Background: Children with Attention-Deficit Hyperactivity Disorder (ADHD) have deficiencies in their executive functions and also impulsivity that can result in various social harms and criminal behaviors.

Methods: The research had a two-group semi-experimental design (case/control) with a pre-/ post-test. The statistical population consisted of all students' mothers aged between 7 and 12 years old suffering from ADHD. The studied samples included 30 parents matched based on age and randomly divided into the case and control groups with 15 people in each group and were examined from 2nd February to March 2020. Positive parenting training was performed for the case group in eight sessions of 90 minutes by observing all protocols. Both groups experienced pre- and post-test. We applied the BRIEF (parent form) and Canners (parent form) questionnaires to collect data. Data were analyzed by MANCOVA using SPSS v. 26 software at a significance level of 0.05.

Results: The studied samples were in the age range of 22-40 years (Mean-¦SD: case group: 32.93-¦6.04 years and control group: 34.13-¦5.47 years), 56% with education lower than diploma (0.60% and 46.7% for the case and control groups, respectively), and 44% had an official business (0.40% and 46.7%, respectively). Results showed significant differences in the variables of executive functions (inhibition, attention transfer, emotional control, initiation, working memory, planning, material organization, and control) and reducing impulsivity (cognitive problems-neglect, hyperactivity, opposition, and ADHD index) in the control and case groups (P<0.001).

Conclusion: Positive parenting training significantly affects improving executive functions and impulsivity in children aged between 7 and 12 years old suffering from ADHD. Accordingly, it is achievable to help modify their social behaviors and also decrease the amount of conflict and legal problems among these children by providing a codified positive parenting training program in their educational programs

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Ir J Psychol Med. 2022.

SERVICE USER SATISFACTION WITH CARE IN A SPECIALIST SERVICE FOR YOUNG PEOPLE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

McGrath J, Cawley B, McTiernan D, et al.

Objectives: Consumer satisfaction is considered one of the most important measures of service quality in child mental health; however, there is limited understanding of factors that influence satisfaction. The objective of this study was to investigate key factors influencing satisfaction with care (SWC) in ADMiRE, a specialist service for young people (YP) with attention deficit hyperactivity disorder (ADHD).
Methods: Parents/carers (n = 67) and YP > 9 years (n = 44) attending ADMiRE completed an anonymous Experience of Service Questionnaire (ESQ), a quantitative/qualitative measure of service user satisfaction. Parents/carers also completed symptom severity rating scales. Data were analysed to determine (i) overall SWC, (ii) the relationship between parent- and youth-reported SWC and (iii) the impact of symptom severity on SWC. Thematic analysis of qualitative ESQ data was completed.
Results: Parents/carers were significantly more satisfied than YP (p = 0.028). Symptom severity did not impact significantly on parent/carer satisfaction. YP with severe hyperactive/impulsive and inattentive ADHD symptoms were significantly less satisfied with care than those with less severe ADHD symptoms (p = 0.022 and p = 0.017 respectively). Factors related to the therapeutic alliance were identified as being particularly important to both parents/carers and YP.
Conclusions: This is the first Irish study that has investigated the impact of symptom severity on service user satisfaction in a child mental health service. The results highlight the different perspectives of YP and parents and provide novel insights into the impact of symptom severity on service user satisfaction. The importance of the therapeutic alliance should not be underestimated in future development of services

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J Am Acad Child Adolesc Psychiatry. 2022 May;61:597-98.

EDITORIAL: EVIDENCE CONCERNING DOSE-DEPENDENT EFFECTS OF STIMULANTS ON NEUROCOGNITIVE FUNCTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Rhodes SM.

The question of how stimulants affect cognitive function in children with attention-deficit/hyperactivity disorder (ADHD) is a challenging one that has been investigated across many studies. Part of the challenge lies in the difficulty of examining the range of cognitive functions that are now evidenced as areas of difficulty within a single study. A lack of studies examining the long-term effects of medication has also challenged advancement of knowledge in this area. When the available research is integrated, what is the conclusion regarding effects of stimulants on neurocognitive function?

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J Am Acad Child Adolesc Psychiatry. 2022 May;61:711-20.

UNDERSTANDING IRRITABILITY IN RELATION TO ANGER, AGGRESSION, AND INFORMANT IN A PEDIATRIC CLINICAL POPULATION.

Zik J, Deveney CM, Ellingson JM, et al.

OBJECTIVE: Despite its clinical relevance to pediatric mental health, the relationship of irritability with anger and aggression remains unclear. We aimed to quantify the relationships between well-validated, commonly used measurements of these constructs and informant effects in a clinically relevant population.
METHOD: A total of 195 children with primary diagnoses of attention-deficit/hyperactivity disorder, disruptive mood dysregulation disorder, or no major disorder and their parents rate irritability, anger, and aggression on measures of each construct. Construct and informant relationships were mapped via multi-trait, multi-method factor analysis.
RESULTS: Parent- and child-reported irritability and child-reported anger are highly associated (r = 0.89) but have some significant differences. Irritability overlaps with outward expression of anger but diverges from anger in anger suppression and control. Aggression has weaker associations with both irritability (r = 0.56) and anger (r = 0.49). Across measures, informant source explains a substantial portion of response variance.
CONCLUSION: Irritability, albeit distinct from aggression, is highly associated with anger, with notable overlap in child-reported outward expression of anger, providing empirical support for formulations of clinical

irritability as a proneness to express anger outwardly. Diagnostic and clinical intervention work on this facet of anger can likely translate to irritability. Further research on external validation of divergence of these constructs in anger suppression and control may guide future scale revisions. The proportion of response variance attributable to informant may be an under-recognized confound in clinical research and construct measurement

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J Atten Disord. 2022 Jul;26:1245-56.

THE PROCESSES UNDERLYING POSITIVE ILLUSORY BIAS IN ADHD: THE ROLE OF EXECUTIVE FUNCTIONS AND PRAGMATIC LANGUAGE SKILLS.

Crisci G, Cardillo R, Mammarella IC.

OBJECTIVE: Children with ADHD often show a positive illusory bias (PIB), reporting an extremely positive idea of their own competence, despite their difficulties. The mechanisms underlying this phenomenon are still poorly understood. In the present study, we examined social PIB and investigated the role of executive functions (EFs) and pragmatic language (PL).
METHOD: Forty-one children with ADHD and 42 typically-developing children matched on age, IQ, and receptive language were administered measures of social competence, EFs and PL. The parents were also asked to estimate their child's social competence.
RESULTS: There was evidence of social difficulties and PIB in children with ADHD. Only PL, not EFs, seemed to mediate the association between ADHD and PIB.
CONCLUSION: Our findings suggest that PL abilities should be considered in efforts to improve self-perception in children with ADHD

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J Atten Disord. 2022 Jun;26:1106-17.

EXAMINING BENCHMARKS FOR THE DAILY REPORT CARD INTERVENTION IN A THERAPEUTIC RECREATIONAL SETTING.

Rogers EE, Allan CC, Zoromski AK, et al.

OBJECTIVE: This study aimed to (1) examine benchmarks for the benefits of the Daily Report Card (DRC) within a therapeutic recreation setting, that is, the Summer Treatment Program (STP) and (2) explore differences in baseline characteristics and treatment outcomes among optimal and suboptimal responders. Benchmarks were examined for children's DRC target behaviors using standardized mean difference (SMD) effect sizes (ES) across 2-week periods of the STP.
METHOD: Participants were 38 children attending an STP.
RESULTS: Aside from teasing, all DRC targets showed improvement by the second 2-week period that was sustained through the third 2-week period. Optimal responders demonstrated greater improvement in parent-rated impairment and camp behaviors than suboptimal responders. Some baseline differences between responder groups were found.
CONCLUSION: This study provides the first benchmarks for change in DRC targets within a therapeutic recreational setting, offering guidelines for treatment expectations. Implications for clinical decision-making, treatment planning, and future research are discussed

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J Atten Disord. 2022 Jun;26:1097-105.

DOES IQ INFLUENCE ASSOCIATION BETWEEN WORKING MEMORY AND ADHD SYMPTOMS IN YOUNG ADULTS?

Soares PSM, de Oliveira PD, Wehrmeister FC, et al.

OBJECTIVE: This study examined the association between WM and ADHD symptoms in young adults and whether IQ-score influenced this association.
METHOD: Data from the 1993 Pelotas (Brazil) Birth Cohort Study were analyzed (N=2,845). Working memory and ADHD symptoms were collected at 22â€‰years. IQ was examined at age 18. Poisson regression with robust variance was used to assess the associations between working memory and ADHD symptoms. We also evaluated whether IQ modified associations between working memory and ADHD symptoms.

RESULTS: Working memory was negatively associated with Inattention symptoms of ADHD. The association between working memory and hyperactivity-impulsivity symptoms of ADHD varied by IQ.
CONCLUSIONS: This study provides new insights to theories about the relationship between WM and ADHD symptoms as well as the development of interventions aimed at improving the performance of WM in ADHD

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J Atten Disord. 2022 Jul;26:1167-86.
A Systematic Review of Longitudinal Studies Investigating the Association Between Early Life Maternal Depression and Offspring ADHD.
Tucker JRD, Hobson CW.
OBJECTIVE: The systematic review sought to understand the relationship between maternal depression and later ADHD in children.
METHOD: Three databases were used to identify the studies (Medline, Web of Science and PsychInfo) resulting in 1,223 studies being screened and 14 articles being included in the review.
RESULTS: The majority of studies (N = 11) reported a significant relationship between maternal depression (across both prenatal and postnatal periods) and ADHD symptoms in children. This relationship remained significant when temperament, or past ADHD symptoms were controlled for. Several methodological issues were identified including; overreliance on maternal report and parental ADHD not being accounted for in most studies.
CONCLUSION: The review adds to the literature regarding the temporal relationship between maternal depression and the development of ADHD in children, and thus supports the case for improving access to mental health services for mothers as a preventative strategy in the development of child psychopathology

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J Atten Disord. 2022 Jun;26:1130-38.
Prevalence of ADHD in Primary School Children, in Colombo District, Sri Lanka.
Nazeer N, Rohanachandra Y, Prathapan S.
OBJECTIVE: To determine prevalence of ADHD among primary school children in Colombo district, Sri Lanka.
METHODS: A descriptive cross-sectional study was conducted among 1,125 primary school children aged 6 to 10 years in Sinhala medium state schools in Colombo district. Prevalence was assessed with validated Sinhala version of Swanson, Nolan, Pelham-IV (SNAP-IV-S) scale where primary care givers and class teachers were the respondents and diagnosis was confirmed by a Consultant Child and Adolescent Psychiatrist.
RESULTS: The mean age of the sample was 7.9 years (SD=1.2) and largely males (n=603, 56.6%). Overall prevalence of ADHD was 6.5% (95% CI [5.1, 8.1]) with combined as the commonest subtype. Prevalence was higher among males (9.6%) than females (2.9%) with a sex ratio of 1:3.8 and was highest in the 7 to 8 year old age group (7.4%-7.5%).
CONCLUSION: School based screening enabling early detection of ADHD and timely referral is the need of the hour

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J Atten Disord. 2022 Jul;26:1257-68.
Parent ADHD Is Associated With Greater Parenting Distress in the First Year Postpartum.
Joseph HM, Khetarpal SK, Wilson MA, et al.
OBJECTIVE: Little is known about the experience of parenting infants when a mother or father has ADHD. This study examined cross-sectional predictors of parenting distress experienced by parents with and without ADHD who also have infants.
METHODS: Participants were 73 mother-father pairs (N = 146) of infants 6 to 10 months old. Half of the families included a parent with ADHD. Psychosocial predictors were tested using multilevel modeling.
RESULTS: Parent or partner ADHD, lower parent sleep quality, fewer social supports, and less infant surgency and effortful control were associated with greater parental distress. Infant negative affect and sleep were not associated.

CONCLUSIONS: Parents with ADHD and their partners experience greater parenting distress in the first year of their child's life than parents without ADHD. Addressing parent ADHD symptoms and co-occurring difficulties, including sleep disturbances, are potential targets for early interventions to maximize both parent and infant mental health outcomes

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J Atten Disord. 2022 Jul;26:1223-34.

IMPACT OF COVID-19 ON YOUTH WITH ADHD: PREDICTORS AND MODERATORS OF RESPONSE TO PANDEMIC RESTRICTIONS ON DAILY LIFE.

Rosenthal E, Franklin-Gillette S, Jung HJ, et al.

We examined COVID-19 symptoms and infection rates, disruptions to functioning, and moderators of pandemic response for 620 youth with ADHD and 614 individually matched controls (70% male; M(age)=12.4) participating in the Adolescent Brain and Cognitive Development study. There were no group differences in COVID-19 infection rate; however, youth with ADHD were more likely to exhibit COVID-19 symptoms (d=0.25), greater sleep problems (d=-0.52), fear and negative emotions to infection risk (d=-0.56), trouble with remote learning (d=-0.54), rule-breaking behavior related to COVID-19 restrictions (d=-0.23), family conflict (d=-0.13), and were less prepared for the next school year (d=0.38). Youth with ADHD were less responsive to protective environmental variables (e.g., parental monitoring, school engagement) during the pandemic and may need more specialized support with return to in-person schooling and daily activities

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J Autism Dev Disord. 2022 Jun;52:2379-87.

INVESTIGATING MOTOR PREPARATION IN AUTISM SPECTRUM DISORDER WITH AND WITHOUT ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Migò M, Guillory SB, McLaughlin CS, et al.

This study investigated motor preparation and action-consequence prediction using the lateralized readiness potential (LRP). Motor impairments are common in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), which commonly co-occur. Alterations in predictive processes may impact motor planning. Whether motor planning deficits are characteristic of ASD broadly or magnified in the context of co-morbid ADHD is unclear. ASD children with (ASD + ADHD; n = 12) and without (ASD - ADHD; n = 9) comorbid ADHD and typical controls (n = 29) performed voluntary motor actions that either did or did not result in auditory consequences. ASD - ADHD children demonstrated LRP enhancement when their action produced an effect while ASD + ADHD children had attenuated responses regardless of action-effect pairings. Findings suggest influence of ADHD comorbidity on motor preparation and prediction in ASD

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J Child Adolesc Psychiatr Nurs. 2022 May;35:164-70.

A PROGRAM TO IMPROVE THE ASSESSMENT OF A CHILD FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lukomski M, Caruso D, Thompson K, et al.

PROBLEM: Due to the number of children diagnosed with attention deficit hyperactivity disorder (ADHD), increased risk of these children having comorbidities and/or an adverse childhood experience and insufficient documentation of the Diagnostic and Statistical manual of Mental Disorders, fifth edition (DSM-5) criteria for an ADHD diagnosis, an ADHD evaluation program was developed for a child presenting for an initial ADHD evaluation.

METHODS: A quantitative design method evaluated provider's documentation by the percentage of DSM-5 criteria met before and after the implementation of the ADHD program. Descriptive statistics evaluated the system change by the percentage of providers who utilized the ADHD template and the use of the unspecified ADHD International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) code, F90.9 by the percentage of code use before and after implementation of the ADHD program.

FINDINGS: The two-tailed Mann-Whitney U test was significantly based on $p<0.001$. Providers met 100% of the DSM-5 criteria after implementation of the ADHD program in the electronic health record, compared to 50% before implementation.

CONCLUSIONS: The ADHD program increased the provider's documentation and consistency to the DSM-5 criteria, decreasing the use of the unspecified ADHD ICD-10 code, allowing the provider to develop a more successful plan of care for children between the ages of 5 and 18

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J Child Adolesc Psychopharmacol. 2022 May;32:200-14.

THE IMPACT OF PHARMACOTHERAPY OF CHILDHOOD-ONSET PSYCHIATRIC DISORDERS ON THE DEVELOPMENT OF SUBSTANCE USE DISORDERS.

Wilens TE, Woodward DW, Ko JD, et al.

Background and Objective: Child- and adolescent-onset psychopathology is known to increase the risk for developing substance use and substance use disorders (SUDs). While pharmacotherapy is effective in treating pediatric psychiatric disorders, the impact of medication on the ultimate risk to develop SUDs in these youth remains unclear.

Methods: We conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) systematic review of peer-reviewed literature published on PubMed through November 2021, examining pharmacological treatments of psychiatric disorders in adolescents and young adults and their effect on substance use, misuse, and use disorder development.

Results: Our search terms yielded 21 studies examining the impact of pharmacotherapy and later SUD in attention-deficit/hyperactivity disorder (ADHD), two studies on Major Depressive Disorder, and three studies on psychotic disorders. The majority of these studies reported reductions in SUD (N=14 sides) followed by no effects (N=10) and enhanced rates of SUD (N=2). Studies in ADHD also reported that earlier-onset and longer-duration treatment was associated with the largest risk reduction for later SUD.

Conclusions: Overall, pharmacological treatments for psychiatric disorders appear to mitigate the development of SUD, especially when treatment is initiated early and for longer durations. More studies on the development of SUD linked to the effects of psychotherapy alone and in combination with medication, medication initiation and duration, adequacy of treatment, non-ADHD disorders, and psychiatric comorbidity are necessary

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J Child Psychol Psychiatry. 2022 Jun;63:663-73.

PATTERNS OF OBJECTIVELY MEASURED MOTOR ACTIVITY AMONG INFANTS DEVELOPING ASD AND CONCERNS FOR ADHD.

Reetzke R, Iosif AM, Hatch B, et al.

BACKGROUND: Heightened motor activity is a hallmark of attention-deficit/hyperactivity disorder (ADHD), yet high activity levels are also often reported in young children with autism spectrum disorder (ASD). It is currently unclear whether increased motor activity represents a distinct versus shared early predictor of ASD and ADHD; no prior studies have directly examined this prospectively. We investigated differences in longitudinal patterns of objectively measured motor activity during early development.

METHODS: Participants included 113 infants at high and low risk for ASD or ADHD. Continuous motion-based activity was recorded using tri-axial accelerometers at 12, 18, 24, and 36 months of age. At 36 months, participants were categorized into one of three outcome groups: ASD (n=19), ADHD Concerns (n=17), and Typically Developing (TD; n=77). Group differences in trajectories of motor activity were examined in structured and semistructured contexts. Associations with behaviors relevant to ASD, ADHD, and general development were also examined.

RESULTS: In both structured and semistructured contexts, both the ASD and ADHD Concerns groups exhibited heightened activity relative to the TD group by 18 months; the ASD group exhibited higher activity than the ADHD Concerns group at 24-36 months in the structured context only. Attention/behavior regulation, nonverbal, and verbal development-but not social engagement-were differentially associated with objectively measured activity by outcome group across contexts.

CONCLUSIONS: Overactivity may be a shared, rather than distinct, precursor of atypical development in infants/toddlers developing ASD and concerns for ADHD, emerging as early as 18 months. Group differences in overactivity may be context-specific and associated with different underlying mechanisms

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J Dev Behav Pediatr. 2022 May;43:233-39.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PRACTICE PATTERNS: A SURVEY OF KENTUCKY PEDIATRIC PROVIDERS.

Trace ME, Feygin YB, Williams PG, et al.

OBJECTIVE: Kentucky ranks among the highest in the nation for attention-deficit/hyperactivity disorder (ADHD) prevalence in children aged 4 to 17 years. In 2011, the American Academy of Pediatrics (AAP) released a clinical practice guideline based on the DSM-IV. A guideline revision based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) was released in October 2019. In this study, we assess and describe pediatric providers' ADHD practices using the 2011 guideline and DSM-5 diagnostic criteria.

METHODS: This was a cross-sectional, survey-based descriptive study. Kentucky Chapter of the AAP (KY AAP) members were anonymously surveyed. The results were examined for trends in routine practice.

RESULTS: Fifty-eight general pediatricians and pediatric residents responded to the survey, yielding a 38% (58/154) response rate. Among respondents performing routine diagnosis of ADHD (N = 51), 73% (37/51) used DSM-5 criteria. Most providers usually or always initially assessed for coexisting behavioral conditions (96%; 49/51), developmental conditions (78%; 39/51), and adverse childhood experiences (73%; 37/51). Among respondents performing routine management of ADHD (N = 55), only 11% (6/55) of respondents indicated that they titrated stimulant medications every 3 to 7 days. After initiation of medication, 78% of providers scheduled a follow-up visit within 2 to 4 weeks. During subsequent visits, only half indicated discussing behavioral interventions, screening for coexisting conditions, and reviewing follow-up teacher-rated ADHD scales.

CONCLUSION: Pediatricians in the KY AAP adhere to the DSM-5 criteria for diagnosing ADHD. Pediatric providers' practices would benefit from education in improvements in pharmacotherapy titration, surveillance of coexisting conditions associated with ADHD, discussion of psychosocial interventions, and school support strategies

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J Nerv Ment Dis. 2022 Jun;210:462-67.

THE ASSOCIATION BETWEEN BINGE-WATCHING BEHAVIOR AND PSYCHOLOGICAL PROBLEMS AMONG ADOLESCENTS.

Özkent Y, Açıkel B.

This study aims to investigate the relationship between binge-watching addiction and family, emotional, conduct, cognitive and anger control problems, hyperactivity, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)-ADHD Index, DSM-IV-Inattention, and DSM-IV-Hyperactivity Impulsivity in a large sample of healthy Turkish adolescents. The association between binge-watching behavior addiction and mood disorders in healthy adolescents was examined in this cross-sectional study conducted in Turkey. Participants completed both measures, The Binge-Watching Addiction Questionnaire and The Conners-Wells' Adolescent Self-Report Scale. An online survey of 189 adolescents was conducted. One hundred fourteen subjects (60.3%) were categorized into the binge-watcher group. Results showed important positive associations between binge-watching behavior and emotional, conduct, cognitive problems, and DSM-IV-Inattention. The conducted analysis showed an important association between high frequency of binge-watching and emotional problems ($p < 0.001$), conduct problems ($p = 0.012$), cognitive problems ($p = 0.001$), and inattention ($p < 0.001$). These findings contributed to our comprehension of adolescents' psychological correlates of television viewing behavior. Further researches on the relationship between extreme binge-watching and psychiatric disorders of adolescents are recommended

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J Nippon Med Sch. 2022 May;89:190-95.

EFFECT OF CHILDHOOD DISEASE ON HOSPITAL PRESENTATION: A SURVEY OF PEDIATRICIANS.

Tajima H, Ogawa J, Nose I, et al.

BACKGROUND: Determining when caregivers should take their children to a hospital is crucial in ensuring the health and safety of children. Because children cannot make these decisions on their own, caregivers

bear the core responsibility for the wellness of their children. The aim of this study was to determine how disease, disability, and child behavior affect when and how often caregivers take their children to a hospital.
METHODS: A structured anonymous online survey was circulated to pediatricians in Japan. Pediatricians were queried about the characteristics of their patients, including reactivity to pain, expression of pain, behavior at the hospital, and the timing of presentation. Patients were school-aged children and included those with autism spectrum disorder, attention-deficit hyperactivity disorder, Down syndrome, mental retardation, epilepsy, premature birth, and allergies.
RESULTS: Sixty-eight of 80 pediatricians responded to the survey (85% response rate). The results indicated that caregivers of children with autism spectrum disorder, attention-deficit hyperactivity disorder, and mental retardation took them to the hospital later than was optimal. Conversely, children born prematurely and those with allergies were taken to hospitals even when symptoms were mild.
CONCLUSIONS: Caregivers make decisions on when to present to hospital on the basis of their child's expression of pain and behavior. Guidelines should be developed to assist caregivers in determining when to present for treatment at a hospital

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J Oral Rehabil. 2022 Jun;49:671-85.

PREVALENCE OF TOOTH GRINDING IN CHILDREN AND ADOLESCENTS WITH NEURODEVELOPMENTAL DISORDERS: A SYSTEMATIC REVIEW ANDÂ META-ANALYSIS.

Kammer PV, Moro JS, Soares JP, et al.

AIM: To conduct a systematic review and meta-analysis on the prevalence of tooth grinding and/or clenching (TGC) in children and adolescents with a neurodevelopmental disorder or other developmental condition.
METHODS: A search was performed in seven databases, two sources of grey literature and reference lists of included studies. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data. We used random-effects models with Freeman-Tukey double arcsine transformation for the meta-analyses.
RESULTS: After selection, 77 of the 2240 studies met inclusion criteria and were categorised by disability and type of TGC (reported, clinically observed and definitive). The pooled prevalence of reported TGC in individuals with attention-deficit hyperactivity disorder was 57.6% (95% CI [confidence interval]: 49.5-65.6), 50.4% (95% CI: 35.5-65.4) in individuals with autism spectrum disorder, 67% (95% CI: 59.2-74.8) in cerebral palsy and 68.2% (95% CI: 59.8-76.6) in Down syndrome. Pooled prevalence of clinically observed TGC was 57.5% (95% CI: 31.6-83.4) in autism spectrum disorder and 71.9% (95% CI: 52.4-91.4) in cerebral palsy. Individuals with attention-deficit hyperactivity disorder presented 39.8% (95% CI: 24-55.6) of definitive TGC.
CONCLUSION: Prevalence of reported, clinically observed, and definitive TGC varies according to disabilities, although due to high heterogeneity the result should be interpreted with caution. Variations exist mainly due to sampling bias and the use of non-validated methods to assess TGC. CRD42020212640

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J Pediatr Psychol. 2022 Mar;47:337-49.

HOW DO CHILD ADHD SYMPTOMS AND OPPOSITIONALITY IMPACT PARENT-CHILD INTERACTIONS WHEN CROSSING VIRTUAL ROADS?

O'Neal EE, Rahimian P, Jiang Y, et al.

OBJECTIVE: This study examined how parents and children interact when crossing virtual roads together. We examined (1) whether children's inattention/hyperactivity and oppositionality and children's failure to jointly perform the task interfered with parents' efforts to scaffold children's road-crossing skill and (2) whether experience with the joint road-crossing task impacted children's subsequent performance in a solo road-crossing task.
METHODS: Fifty-five 8- to 10-year-old children with and without attention-deficit/hyperactivity disorder and their parents first jointly crossed a lane of traffic in an immersive pedestrian simulator. Children then completed the same road-crossing task alone. Parents completed questionnaires about children's symptoms of inattention/hyperactivity and oppositionality.
RESULTS: Analyses of the joint road-crossing task showed that when parents and children crossed different gaps, parents suggested and opposed more gaps and were less likely to use a prospective gap

communication strategy (i.e., communicating about a crossable gap prior to its arrival). Crossing different gaps was also associated with increased expressions of negative affect among parents and children and an increase in collisions among children. Children's level of parent-reported oppositionality also predicted an increase in child defiance and parental redirection of child behavior. Analyses of children's subsequent crossing performance indicated that parents' use of a prospective gap communication strategy during the joint road-crossing task predicted selection of larger gaps during the solo crossing task.
CONCLUSIONS: Not crossing through the same gap and increased levels of child oppositionality interfered with the scaffolding process, potentially informing future parent-based intervention efforts for increasing children's road-crossing safety

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J Prim Care Community Health. 2022 Jan;13:21501319221089775.

DEVELOPMENT AND EARLY EXPERIENCE OF A PRIMARY CARE LEARNING COLLABORATIVE IN A LARGE HEALTH CARE SYSTEM.

Erickson R, Abu Dabrh AM, Chavez A, et al.

INTRODUCTION: Primary care clinicians are presented with hundreds of new clinical recommendations and guidelines. To consider practice change clinicians must identify relevant information and develop a contextual framework. Too much attention to information irrelevant to one's practice results in wasted resources. Too little results in care gaps. A small group of primary care clinicians in a large health system sought to address the problem of vetting new information and providing peer reviewed context. This was done by engaging colleagues across the system though a primary care learning collaborative.
METHODS: The collaborative was a grass roots initiative between community and academic-based clinicians. They invited all the system's primary care clinicians to participate. They selected new recommendations or guidelines and used surveys as the principal communication instrument. Surveys shared practice experience and also invited members to give narrative feedback regarding their acceptance of variation in care relate to the topic. A description of the collaborative along with its development, processes, and evolution are discussed. Process changes to address needs during the COVID-19 pandemic including expanded information sharing was necessary.
RESULTS: Collaborative membership reached across 5 states and included family medicine, internal medicine, and pediatrics. Members found involvement with the collaborative useful. Less variation in care was thought important for public health crises: the COVID pandemic and opioid epidemic. Greater practice variation was thought acceptable for adherence to multispecialty guidelines, such as diabetes, lipid management, and adult ADHD care. Process changes during the pandemic resulted in more communications between members to avoid practice gaps.
CONCLUSION: An internet-based learning collaborative in a health system had good engagement from its members. Using novel methods, it was able to provide members with feedback related to the importance of new practice recommendations as perceived by their peers. Greater standardization was thought necessary when adopting measures to address public health crisis, and less necessary when addressing multispecialty guidelines. By employing a learning collaborative, this group was able to keep members interested and engaged. During the first year of the COVID pandemic the collaborative also served as a vehicle to share timely information

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JAMA Network Open. 2022;5.

INDIVIDUAL AND COMBINED ASSOCIATION BETWEEN PRENATAL POLYSUBSTANCE EXPOSURE AND CHILDHOOD RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Garrison-Desany HM, Hong X, Maher BS, et al.

Importance: Polysubstance use among pregnant women has increased because of the opioid epidemic and the increasing legalization of cannabis along with persistent tobacco and alcohol consumption. Previous research on prenatal substance use and the child's risk of attention-deficit/hyperactivity disorder (ADHD) has mostly focused on single-substance exposures; simultaneous examination of multiple substance use and assessment of their synergistic health consequences is needed.

Objectives: To assess the consequences of the use of specific substances during pregnancy, investigate whether the interaction of multiple prenatal substance exposures is associated with increases in the risk of childhood ADHD, and estimate the aggregate burden of polysubstance exposure during gestation.
Design, Setting, and Participants: This cohort study analyzed data from the Boston Birth Cohort from 1998 to 2019. The sample of the present study comprised a multiethnic urban cohort of mother-child pairs who were predominantly low income. A total of 3138 children who were enrolled shortly after birth at Boston Medical Center were included and followed up from age 6 months to 21 years.
Exposures: Substance use during pregnancy was identified based on self-reported tobacco smoking, alcohol consumption, and use of cannabis, cocaine, or opioids in any trimester of pregnancy. Diagnostic codes for neonatal opioid withdrawal syndrome or neonatal abstinence syndrome from the International Classification of Diseases, Ninth Revision, and the International Classification of Diseases, Tenth Revision, were also used to identify opioid exposure during gestation.
Main Outcomes and Measures: ADHD diagnosis in the child's electronic medical record.
Results: Among 3138 children (1583 boys [50.4%]; median age, 12 years [IQR, 9-14 years]; median follow-up, 10 years [IQR, 7-12 years]) in the final analytic sample, 486 (15.5%) had an ADHD diagnosis and 2652 (84.5%) were neurotypical. The median postnatal follow-up duration was 12 years (IQR, 9-14 years). Among mothers, 46 women (1.5%) self-identified as Asian (non-Pacific Islander), 701 (22.3%) as Hispanic, 1838 (58.6%) as non-Hispanic Black, 227 (7.2%) as non-Hispanic White, and 326 (10.4%) as other races and/or ethnicities (including American Indian or Indigenous, Cape Verdean, Pacific Islander, multiracial, other, or unknown). A total of 759 women (24.2%) reported the use of at least 1 substance during pregnancy, with tobacco being the most frequently reported (580 women [18.5%]). Cox proportional hazards models revealed that opioid exposure (60 children) had the highest adjusted hazard ratio (HR) for ADHD (2.19; 95% CI, 1.10-4.37). After including main statistical effects of all individual substances in an elastic net regression model, the HR of opioids was reduced to 1.60, and evidence of a statistical interaction between opioids and both cannabis and alcohol was found, producing 1.42 and 1.15 times higher risk of ADHD, respectively. The interaction between opioids and smoking was also associated with a higher risk of ADHD (HR, 1.17).
Conclusions and Relevance: The findings of this study suggest that it is important to consider prenatal concurrent exposure to multiple substances and their possible interactions when counseling women regarding substance use during pregnancy, the future risk of ADHD for their children, and strategies for cessation and treatment programs

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J Adolesc Health. 2022.

REAL-WORLD CRASH CIRCUMSTANCES AMONG NEWLY LICENSED ADOLESCENT DRIVERS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Curry AE, Sartin EB, Metzger KB, et al.

Purpose: Adolescents with attention-deficit/hyperactivity disorder (ADHD) have 30%ΓÇô40% higher crash rates. However, we still do not understand which factors underlie heightened crash risk and if crash circumstances differ for drivers with ADHD. We compared prevalences of crash responsibility, driver actions, and crash types among adolescent and young adult drivers with and without ADHD who crashed within 48 months of licensure.
Methods: In this exploratory retrospective cohort study, we identified patients of Children's Hospital of Philadelphia's (CHOP) New Jersey (NJ) primary care locations who were born between 1987 and 2000, NJ residents, had their last CHOP visit age 12 years, and acquired a driver's license. We linked CHOP electronic health records to NJ's licensing and crash databases. ADHD diagnosis was based on International Classification of Diseases, Ninth Revision, Clinical Modification/International Classification of Diseases, Tenth Revision, Clinical Modification codes. Prevalence ratios were estimated using generalized estimating equation log-binomial regression.
Results: We identified 934 drivers with ADHD in 1,308 crashes and 5,158 drivers without ADHD in 6,676 crashes. Within 48 months postlicensure, drivers with ADHD were more likely to be at fault for their crash (prevalence ratio: 1.09 [1.05-1.14]) and noted as inattentive (1.15 [1.07-1.23]). -With the exception that drivers with ADHD were less likely to crash while making a left/U-turn, we did not find substantial differences in crash types by diagnosis. Analyses also suggest females with ADHD may have a higher risk of colliding with a nonmotor vehicle and crashing due to unsafe speed than females without ADHD.

Discussion: The results suggest crash circumstances do not widely differ for drivers with and without ADHD but highlight several factors that may be particularly challenging for young drivers with ADHD

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J Autism Dev Disord. 2022.

DEVELOPMENTAL CHANGES OF AUTISTIC SYMPTOMS, ADHD SYMPTOMS, AND ATTENTIONAL PERFORMANCE IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER.

Lin YJ, Chiu YN, Wu YY, et al.

This study followed up ADHD/autistic symptoms and attentional performance in children/adolescents with ASD and typically developing ones (TD) over 5-7years. The participants were stratified by age at baseline into child (< 12years) and adolescent (12-19years) groups. ADHD symptoms, especially hyperactivity, and attentional functions significantly improved during follow-up, more in children than in adolescents, in both ASD and TD. Significantly more omission errors and perseverations were noted in ASD than TD through the follow-up. Children with ASD had more improvement in reaction time while adolescents with ASD had less improvement in commission errors and detectability than TD. No correlation of attentional functions and ADHD symptoms in ASD implied different neural mechanisms of ADHD symptoms between ASD and ADHD

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J Autism Dev Disord. 2022 May;52:2149-55.

IMPACT OF SCHOOL CLOSURES DUE TO COVID-19 ON CHILDREN WITH NEURODEVELOPMENTAL DISORDERS IN JAPAN.

Kawaoka N, Ohashi K, Fukuhara S, et al.

In March 2020, many schools were closed to prevent the spread of COVID-19 in Japan, and it is predicted that many children, especially those with neurodevelopmental disorders (NDDs), will be affected emotionally and behaviorally. Here, we examined the impact of school closures due to COVID-19 on school-aged children with NDDs using the Child Behavior Checklist. Totally, data on 121 children diagnosed with autism spectrum disorder, attention-deficit hyperactivity disorder, and/or intellectual disorder were analyzed and it was found that externalizing and aggressive behavior increased in all NDDs, regardless of the type of diagnosis. A clear prospect is important for children with NDDs children to lead a stable life, and more generous supports for children with NDDs and their families are needed

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J Autism Dev Disord. 2022.

VALIDITY OF THE SNAP-IV FOR ADHD ASSESSMENT IN SOUTH AFRICAN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Zieff MR, Hoogenhout M, Eastman E, et al.

This study investigated the psychometric properties of the Swanson, Nolan, and Pelham ADHD Rating Scale (SNAP-IV) in a sample of South African children with neurodevelopmental disorders (n = 201), primarily Autism Spectrum Disorder and Intellectual Disability. We conducted a confirmatory factor analysis to inspect the two-factor structure of the SNAP-IV. We also calculated ordinal coefficient alpha to estimate internal consistency. Fit statistics for the two-factor model approached acceptable levels. The model fit improved slightly after removing an item related to spoken language. The subscales had acceptable internal consistencies. Findings partially support the use of the SNAP-IV in this group of children. However, there are limitations to its performance in this population likely related to the presence of neurodevelopmental disorders

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J Child Adolesc Psychopharmacol. 2022 Mar;32:80-88.

PSYCHOTROPIC DRUG PRESCRIPTION IN CHILDREN AND ADOLESCENTS: APPROVED MEDICATIONS IN EUROPEAN COUNTRIES AND THE UNITED STATES.

Smogur M, Onesanu A, Plessen KJ, et al.

Objectives: The decision to prescribe a medication and the choice of which one are often complex, particularly in the field of child and adolescent psychiatry where evidence is scarce. The aim of this review is

to provide a synthesis of psychotropic drugs approved in children and adolescents for psychiatric indications in several countries.
Methods: All psychopharmacological treatments used in child and adolescent psychiatry, approved by at least one regulatory agency from Switzerland, the United Kingdom, France, the European Union, or the United States, were considered. A comprehensive review of the summaries of product characteristics was performed.
Results: A total of 143 psychotropic drugs were included: 47 anxiolytics/hypnotics, 45 antidepressants, 37 antipsychotics, 10 medications for attention-deficit/hyperactivity disorder (ADHD), and 4 mood stabilizers. Only a few of these drugs were approved for use in children or adolescents (38%) at least for a single psychiatric diagnosis in at least one country. The therapeutic class with the lowest rate of approved status was antidepressants (20%), followed by mood stabilizers (25%), anxiolytics/hypnotics (28%), antipsychotics (57%), and medications for ADHD (100%). Important differences in approved diagnoses, ages, and doses were observed between regulatory agencies. Tables presenting drugs for approved diagnoses based on age and regulatory agencies are presented in this article. Drugs classified by regulatory agencies, with complete data on diagnoses, ages, doses, pharmaceutical forms, and particular restrictions, are presented as Supplementary Material.
Conclusion: This article provides an overview to prescribers with respect to the approved medications in children and adolescents in selected European countries and the United States

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J Child Psychol Psychiatry. 2022 May;63:544-52.

BEHAVIORAL, NEUROCOGNITIVE, POLYSOMNOGRAPHIC AND CARDIOMETABOLIC PROFILES ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA IN ADOLESCENTS WITH ADHD.

Puzino K, Bourchtein E, Calhoun SL, et al.

Background: A high comorbidity between attention-deficit/hyperactivity disorder (ADHD) and obstructive sleep apnea (OSA) as well as similar impairments across neurobehavioral outcomes has been described in children. However, there is a paucity of research examining the comorbidity of these two disorders in adolescents. This study examined the association of OSA with sleep, neurobehavioral, and cardiometabolic outcomes in adolescents with ADHD from the general population.
Methods: 421 adolescents (16.9 ± 2.3 years, 53.9% male) underwent 9-hr polysomnography, neurobehavioral, and physical evaluation. ADHD was ascertained by a parent-or-self-report of a lifetime diagnosis/treatment of ADHD. OSA was defined as an apnea hypopnea index of =2 events/hour. Groups of controls (n = 208), OSA-alone (n = 115), ADHD-alone (n = 54), and ADHD+OSA (n = 44) were studied. Multivariable-adjusted general linear models tested group differences in PSG parameters, neurobehavioral, and cardiometabolic outcomes after controlling for sex, race/ethnicity, age, and/or body mass index percentile.
Results: The ADHD+OSA group had significantly longer sleep onset latency, shorter total sleep time, lower sleep efficiency, and higher percent of stage 1 sleep, as compared with all other groups, however, these differences were diminished by excluding adolescents on psychoactive medication. The ADHD-alone group showed significantly higher periodic limb movements than controls. The ADHD+OSA and ADHD-alone groups did not significantly differ on any measure of neurocognitive or behavioral functioning. The ADHD+OSA and OSA-alone groups showed significantly worse cardiometabolic and inflammatory biomarkers when compared to controls or the ADHD-alone, but did not significantly differ between each other.
Conclusions: Adolescents with a diagnosis ADHD+OSA showed phenotypic risk factors for OSA (i.e., overweight/obesity, visceral adiposity, metabolic syndrome, and inflammation) but not worse neurobehavioral outcomes when compared with ADHD-alone. While comorbidity is possible, these data support that adolescents with a suspicion of ADHD should be screened for OSA, before a diagnosis is reached and psychoactive medication initiated

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J Clin Child Adolesc Psychol. 2022 Mar;51:211-18.

MULTISOURCE LONGITUDINAL NETWORK AND LATENT VARIABLE MODEL ANALYSES OF ADHD SYMPTOMS IN CHILDREN.

Preszler J, Burns GL, Becker SP, et al.

Objective: Multisource longitudinal network analysis was used to determine if between-child and within-child variance of attention-deficit/hyperactivity disorder (ADHD) symptoms provided unique findings of ADHD relative to latent variable model (LVM) analyses.

Method: Mothers and fathers of 802 Spanish first-grade children (54% boys) provided ratings of ADHD symptoms at two time points six weeks apart (assessment 1: 723 mothers and 603 fathers; assessment 2: 667 mothers and 584 fathers). Network and latent variable models were applied to the ratings.

Results: Inattention, hyperactivity, and mixed hyperactive/impulsive symptom communities occurred for the within- and between-children's symptom networks with the results being consistent across mothers and fathers, especially for the between-children's symptom networks. LVM analyses identified three factors with the same symptoms on each factor as in the symptom communities. These models also showed invariance across mothers and fathers as well as assessments.

Conclusions: Longitudinal networks provided several useful insights for ADHD, including centrality symptoms that differed across between- and within-child levels. However, many findings were also largely consistent with the LVM analyses. Future studies should use novel methods (e.g., intensive longitudinal measurement) and analytic tools to determine if more unique theoretical and clinical findings emerge when applying network analysis to longitudinally measured ADHD symptoms

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J Clin Child Adolesc Psychol. 2022 Mar;51:195-202.

SLUGGISH COGNITIVE TEMPO IN AUTISM SPECTRUM DISORDER, ADHD, AND THEIR COMORBIDITY: IMPLICATIONS FOR IMPAIRMENT.

McFayden T, Jarrett MA, White SW, et al.

Objective: Sluggish Cognitive Tempo (SCT), characterized by lethargy and daydreaming, has most commonly been studied in community samples and in youth with Attention-Deficit/Hyperactivity Disorder (ADHD). Despite shared neurodevelopmental symptoms with ADHD, few studies have investigated SCT in Autism Spectrum Disorders (ASD). The current study investigated SCT symptoms in youth with ASD, ADHD, and comorbid ASD+ADHD to explore the relations between SCT and global and social impairment.

Method: Caregivers of children and adolescents (n = 98; ages 6–17) diagnosed with ADHD (n = 46), ASD (n = 28), or ASD+ADHD (n = 24) completed measures of social impairment, SCT, and demographic variables.

Results: All three clinical groups demonstrated comparable levels of SCT. Diagnosis and SCT independently contributed to parent-rated social impairment, while SCT and IQ, but not diagnosis, contributed to clinician-rated global functioning. Specifically, having comorbid ASD+ADHD, but not an ASD or ADHD diagnosis alone, significantly predicted greater social impairment.

Conclusion: These results extend previous literature investigating SCT in ASD and provide evidence to suggest that SCT is associated with social and global impairment above and beyond the impairment associated with ADHD and/or ASD. These results may have implications for clinical assessment and treatment of ASD and ADHD

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J Clin Endocrinol Metab. 2022;107:E1434-E1443.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY: A NATIONAL STUDY OF 1.1 MILLION ISRAELI ADOLESCENTS.

Pinhas-Hamiel O, Bardugo A, Reichman B, et al.

Purpose: The incidences of obesity and attention-deficit/hyperactivity disorder (ADHD) have increased in parallel over recent decades. We assessed the association between obesity and ADHD in a national sample of adolescents.

Method: In a nationwide population-based study of 1 118 315 adolescents (57% males; mean age 17 years), risks of obesity were compared between individuals with severe and mild ADHD and those without ADHD. Diagnoses of ADHD were confirmed by specialists in either neurology or psychiatry. Adolescents requiring

regular and continuous treatment with stimulants with no improvement of symptoms under treatment were classified as having severe ADHD; data were available from 2004 to 2019. During 2015 to 2019, the diagnosis of ADHD was defined, and 65 118 (16.76%) of 388 543 adolescents with mild symptoms who required medications only for learning or who used stimulants irregularly were defined as having mild ADHD.
Results: The prevalence of severe and mild ADHD was 0.3% and 20.1%, respectively. Obesity was more prevalent among adolescents with severe ADHD than among those without ADHD (13.5% vs 7.5%). In the mild ADHD group 12.6% of males and 8.4% of females were diagnosed with obesity compared to 9.7% and 6.4%, respectively, in the non-ADHD group. The adjusted odds of severe ADHD for males and females with obesity were 1.77 (1.56-2.02) and 2.09 (1.63-2.66) times the odds for males and females with low-normal body mass index, respectively, and 1.42 (1.37-1.48) and 1.42 (1.34-1.50) for males and females with mild ADHD, respectively. The elevated risk persisted in several sensitivity analyses.
Conclusions: Both adolescents with severe and mild ADHD are at increased risk for obesity

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Journal of Clinical Medicine. 2022;11.

CAPTURING SUBTLE NEUROCOGNITIVE DIFFERENCES IN CHILDREN WITH AND WITHOUT TOURETTE SYNDROME THROUGH A FINE-GRAINED ANALYSIS OF DESIGN FLUENCY PROFILES.

Tessier M, Desmarais A, Leclerc JB, et al.

Background: Tourette syndrome (TS) can be accompanied by neurocognitive impairment. Only a few studies have focused on executive function assessment in TS using design fluency, providing preliminary results. This study aimed to characterize the detailed design fluency profile of children with TS compared with neurotypical children, while addressing the central concern of frequent comorbidities in studies on TS by considering tic severity and attention-deficit/hyperactivity disorder (ADHD) symptoms and diagnosis.
Methods: Sixty-one children aged between 6 and 15 years participated and were divided into a TS group (n = 28 (with ADHD n = 15)) and a control group (n = 33). Our objective was addressed by examining a wide range of measures of the Five-Point-Test, presumably sensitive to frontostriatal dysfunction. The total number of designs, repetitions, repetition ratio, unique designs, and numerical, spatial, and total strategies were examined for the total duration of the test (global measures) and at five equal time intervals (process measures).
Results: The TS group produced significantly fewer numerical strategies. Groups did not differ in other global or process measures. ADHD did not affect performance.
Conclusions: Children with TS do not inherently show general executive dysfunction but may present with subtle neurocognitive characteristics here revealed by comprehensive design fluency profiles

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J Consult Clin Psychol. 2022 May;90:367-80.

THE EFFECT OF STIMULANT MEDICATION ON THE LEARNING OF ACADEMIC CURRICULA IN CHILDREN WITH ADHD: A RANDOMIZED CROSSOVER STUDY.

Pelham WEI, Altszuler AR, Merrill BM, et al.

Objective: Evaluate whether stimulant medication improves acquisition of academic material in children with attention deficit hyperactivity disorder (ADHD) receiving small-group, content-area instruction in a classroom setting.
Method: Participants were 173 children between the ages of 7 and 12 years old (77% male, 86% Hispanic) who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD and were participating in a therapeutic summer camp. The design was a triple-masked, within-subject, AB/BA crossover trial. Children completed two consecutive phases of daily, 25-min instruction in both (a) subject-area content (science, social studies) and (b) vocabulary. Each phase was a standard instructional unit lasting for 3 weeks. Teachers and aides taught the material to small groups in a summer classroom setting. Each child was randomized to be medicated with daily osmotic-release oral system methylphenidate (OROS-MPH) during either the first or second of the instructional phases, receiving placebo during the other.
Results: Medication had large, salutary, statistically significant effects on children's academic seatwork productivity and classroom behavior on every single day of the instructional period. However, there was no detectable effect of medication on learning the material taught during instruction: Children learned the same

amount of subject-area and vocabulary content whether they were taking OROS-MPH or placebo during the instructional period.
Conclusions: Acute effects of OROS-MPH on daily academic seatwork productivity and classroom behavior did not translate into improved learning of new academic material taught via small-group, evidence-based instruction. (PsycInfo Database Record (c) 2022 APA, all rights reserved)
What is the public health significance of this article?—In this controlled study, there was no detectable impact of extended-release methylphenidate on the learning of units of academic material taught via small-group, evidence-based instruction. Methylphenidate improved seatwork productivity and classroom behavior, as in many previous studies, but these benefits did not translate into improved learning of academic material

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J Emot Behav Disord. 2022 Mar;30:3-15.

CHILDREN WHO RECEIVE SPECIAL EDUCATION SERVICES FOR ADHD: EARLY INDICATORS AND EVIDENCE OF DISPROPORTIONATE REPRESENTATION IN THE EARLY CHILDHOOD LONGITUDINAL STUDY (ECLS-K: 2011).

Rhinehart L, Iyer S, Haager D.

Approximately one in 10 children in the United States is diagnosed with attention-deficit/hyperactivity disorder (ADHD), a disability that can negatively affect academic achievement, yet relatively few children with ADHD are in special education. To better understand factors that determine which students with ADHD are in special education, we analyzed students in the Early Childhood Longitudinal Study, Kindergarten Class of 2010–2011 (ECLS-K: 2011). Using logistic regression, we looked to see which sociodemographic, academic, executive functioning, and behavioral skills, all measured in kindergarten, significantly influenced the odds a student would receive special education services for ADHD in fourth grade (N = 220). Results showed that higher conflict with teachers and lower working memory significantly increased these odds. Furthermore, even when controlling for academic and social skills, students who are girls, Hispanic/Latinx, and/or living in a home where a language other than English is spoken were less likely to receive special education services for ADHD. Findings suggest early identification of students with ADHD and special education needs is possible and that sociodemographic characteristics play a significant role in determining who receives special education services for ADHD. (PsycInfo Database Record (c) 2022 APA, all rights reserved)

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Journal of Infection. 2022.

ANTIBIOTIC EXPOSURE AND ADVERSE LONG-TERM HEALTH OUTCOMES IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Duong QA, Pittet LF, Curtis N, et al.

Background: Antibiotics are amongst the most commonly used drugs in children. In addition to inducing antibiotic resistance, antibiotic exposure has been associated with adverse long-term health outcomes.
Methods: A systematic search using PRISMA guidelines to identify original studies reporting associations between antibiotic exposure and adverse long-term health outcomes in children. Overall pooled estimates of the odds ratios (ORs) were obtained using random-effects models.
Results: We identified 160 observational studies investigating 21 outcomes in 22,103,129 children. Antibiotic exposure was associated with an increased risk of atopic dermatitis (OR 1.40, 95% confidence interval (CI) 1.30-1.52, p < 0.01), allergic symptoms (OR 1.93, 95%CI 1.66-2.26, p < 0.01), food allergies (OR 1.35, 95%CI 1.20-1.52, p < 0.01), allergic rhinoconjunctivitis (OR 1.66, 95%CI 1.51-1.83, p < 0.01), wheezing (OR 1.81, 95%CI 1.65-1.97, p < 0.01), asthma (OR 1.96, 95%CI 1.76-2.17, p < 0.01), increased weight gain or overweight (OR 1.18, 95%CI 1.11-1.26, p < 0.01), obesity (OR 1.21, 95%CI 1.05-1.40, p < 0.01), juvenile idiopathic arthritis (OR 1.74, 95%CI 1.21-2.52, p < 0.01), psoriasis (OR 1.75, 95%CI 1.44-2.11, p < 0.01), autism spectrum disorders (OR 1.19, 95%CI 1.04-1.36, p = 0.01) and neurodevelopment disorders (OR 1.29, 95%CI 1.09-1.53, p < 0.01). Dose-response effects and stronger effects with broad-spectrum antibiotic were often reported. Antibiotic exposure was not associated with an altered risk of allergic sensitisation, infantile colic, abdominal pain, inflammatory bowel disease, celiac disease, type 1 diabetes, fluorosis, and attention deficit hyperactivity disorder.

Conclusion: Although a causal association cannot be determined from these studies, the results support the meticulous application of sound antibiotic stewardship to avoid potential adverse long-term health outcomes

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J Ment Health Res Intellect Disabil. 2022 Apr;15:95-110.

RELATIONSHIP BETWEEN IQ AND INTERNALIZING AND EXTERNALIZING SYMPTOMS IN CHILDREN WITH AUTISM AND CHILDREN WITH ADHD.

Mayes SD, Baweja R, Waschbusch DA, et al.

Introduction: Findings regarding the relationship between IQ and comorbidity in autism and ADHD are inconsistent.

Methods: Mothers rated 1,436 children with autism and 1,056 with ADHD without autism (IQs 9–149, ages 2–17) on the Pediatric Behavior Scale.

Results: Children with IQs < 70 (vs. = 70) had less oppositional behavior, irritability, tantrums, conduct problems, generalized anxiety, and depression and more separation anxiety. Children with ADHD-Inattentive had less comorbidity than children with autism and children with ADHD-Combined. For autism, 80% had ADHD-Combined symptoms and 9% had ADHD-Inattentive symptoms. Most children with autism and with ADHD-Combined with IQs = 70 had oppositional defiant disorder, as did almost half with IQs < 70. For autism, 45% with IQs = 70 had generalized anxiety and 47% with IQs < 70 had separation anxiety.

Conclusions: Given high rates of comorbid symptoms in autism and ADHD, clinicians should be alert to and assess for psychiatric comorbidity

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J Neural Transm. 2022.

THERAPEUTIC DRUG MONITORING OF ATOMOXETINE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: A NATURALISTIC STUDY.

Ruppert K, Geffert C, Clement HW, et al.

The selective norepinephrine reuptake inhibitor atomoxetine is potentially among the first-line pharmacotherapy options for ADHD. Therapeutic drug monitoring (TDM) with the quantification and interpretation of atomoxetine serum concentrations is used to determine an individual dose followed by an optimal effectiveness and minimal side effects. The aim of this retrospective pharmacokinetic-pharmacodynamic analysis was to derive age-appropriate recommendations for the implementation of TDM to improve the efficacy and tolerability of atomoxetine in children and adolescents. Using the analytical method of high-performance liquid chromatography with UV detection, 94 serum concentrations of 74 patients between 6 and 21-áyears of age were determined. Therapeutic effectiveness and side effects were evaluated according to the categories low, moderate, and significant. As part of TDM, a time interval with maximum concentrations of 1-3 h after the administration of atomoxetine was determined for blood sampling. In this time interval, a significant correlation between the weight-normalized dose and the serum concentrations was found. The efficacy as well as the tolerability proved to be mainly moderate or significant. A preliminary therapeutic reference range was between 100 and 400 ng/ml. Naturalistic studies have limitations. Therefore, and due to a limited study population, the results have to be regarded as preliminary observations that must be confirmed in further studies. The preliminary therapeutic reference range for children and adolescents proved to be narrower than the reference range for adult patients. However, due to good efficacy and tolerability an exact reference range remained difficult to determine

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Journal of Personalized Medicine. 2022;12.

MULTIDISCIPLINARY CONSULTING TEAM FOR COMPLICATED CASES OF NEURODEVELOPMENTAL AND NEUROBEHAVIORAL DISORDERS: ASSESSING THE OPPORTUNITIES AND CHALLENGES OF INTEGRATING PHARMACOGENOMICS INTO A TEAM SETTING.

Gill PS, Elchynski AL, Porter-Gill PA, et al.

Neurodevelopmental disorders have steadily increased in incidence in the United States. Over the past decade, there have been significant changes in clinical diagnoses and treatments some of which are due to the increasing adoption of pharmacogenomics (PGx) by clinicians. In this pilot study, a multidisciplinary team

at the Arkansas ChildrenΓÇÖs Hospital North West consulted on 27 patients referred for difficult-to-manage neurodevelopmental and/or neurobehavioral disorders. The 27 patients were evaluated by the team using records review, team discussion, and pharmacogenetic testing. OneOme RightMed-« (Minneapolis, MN, USA) and the Arkansas Children's Hospital comprehensive PGx test were used for drug prescribing guidance. Of the 27 patientsΓÇÖ predicted phenotypes, the normal metabolizer was 11 (40.8%) for CYP2C19 and 16 (59.3%) for CYP2D6. For the neurodevelopmental disorders, the most common comorbid conditions included attention-deficit hyperactivity disorder (66.7%), anxiety disorder (59.3%), and autism (40.7%). Following the team assessment and PGx testing, 66.7% of the patients had actionable medication recommendations. This included continuing current therapy, suggesting an appropriate alternative medication, starting a new therapy, or adding adjunct therapy (based on their current medication use). Moreover, 25.9% of patients phenoconverted to a CYP2D6 poor metabolizer. This retrospective chart review pilot study highlights the value of a multidisciplinary treatment approach to deliver precision healthcare by improving physician clinical decisions and potentially impacting patient outcomes. It also shows the feasibility to implement PGx testing in neurodevelopmental/neurobehavioral disorders

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J Psychopathol Behav Assess. 2022.

CONSISTENTLY INCONSISTENT WORKING MEMORY PERFORMANCE AMONG CHILDREN WITH ADHD: EVIDENCE OF RESPONSE ACCURACY VARIABILITY (RAV).

Friedman LM, Rapport MD, Fabrikant-Abzug G.

Heterogeneity in cognitive performance, once regarded as noise, is now considered a causal mechanism or core deficit of ADHD and its related symptoms in most etiological models of the disorder. Previous research on cognitive performance variability has documented increased heterogeneity in response latencies using reaction time data. In contrast, variability in response accuracy remains understudied. The present study is the first to examine Response Accuracy Variability (RAV) among children with ADHD. Children with ADHD (N = 54) and typically developing children (N = 50) completed phonological working memory tasks with four set size conditions. RAV was calculated for each set size using the adjusted coefficient of variation (+Â). Results from a mixed model ANOVA indicated that children with ADHD evinced significantly greater variation in working memory performance relative to typically developing children when engaged in tasks within their cognitive capacity (i.e., set sizes 3 and 4), whereas all children exhibit similar, high levels of variability on tasks that exceeded their cognitive capacity (i.e., set sizes 5 and 6). Findings are aligned with the extant literature in documenting consistently inconsistent cognitive performance among children ADHD

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J Formos Med Assoc. 2022.

MULTIPLE TYPES OF HARASSMENT VICTIMIZATION IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDER: RELATED FACTORS AND EFFECTS ON MENTAL HEALTH PROBLEMS.

Liu TL, Wang PW, Hsiao RC, et al.

Background/Purpose: This study examined the prevalence and related factors of multiple (two or three) types of harassment victimization, including school bullying, cyberbullying, and teacher harassment, and their cumulative effects on depression, anxiety, self-esteem, and suicidality in adolescents with autism spectrum disorder (ASD) but without intellectual disability.

Methods: A total of 219 adolescents with ASD but without intellectual disability and their parents participated in this study. Their experiences of school bullying, cyberbullying, and teacher harassment were evaluated. The related factors of multiple types of harassment victimization, including demographic characteristics, socio-communicative skills, comorbid attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) symptoms, were examined. Moreover, the effects of multiple types of harassment victimization on depression, anxiety, self-esteem, and suicidality were examined. **Results**: In total, 20.54% of participants were victims of multiple types of harassment. Hyperactivity or impulsivity an
d ODD symptoms were positively associated with multiple types of harassment victimization. Adolescents with ASD who experienced multiple types of harassment victimization had higher severities of depression and anxiety and were more likely to have suicidality than nonvictims and those who experienced only one type of harassment victimization.

Conclusion: Experiencing more than one type of harassment victimization was significantly associated with the development of mental health problems in adolescents with ASD. ODD and hyperactivity/impulsivity symptoms predicted the risk of experiencing multiple types of harassment

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J Int Neuropsychol Soc. 2022 Apr;28:371-81.

SEX EFFECTS ON MIRROR OVERFLOW DURING FINGER TAPPING IN CHILDREN WITH ADHD.

Chen C, Rosch KS, Seymour KE, et al.

Objectives: The presence of excessive mirror overflow in children with Attention Deficit/Hyperactivity Disorder (ADHD) is discussed in numerous published reports. These reports, however, include a limited age range in their samples. The objective of this study is to examine the effects of diagnosis and sex on mirror overflow and standard deviation (SD) of tap time in children with and without ADHD across a larger age range (5–12 years) of children.

Methods: One-hundred and forty-eight children with ADHD and 112 age- and sex-matched typically developing (TD) children completed a finger sequencing task. Mirror overflow, SD of tap time, and mean tap time were measured using finger twitch transducers.

Results: Results reveal a significant diagnostic effect on mirror overflow such that boys and girls with ADHD demonstrate increased overflow compared to same-sex TD children. Boys with ADHD demonstrated more variable tap times compared to TD boys; no diagnostic effect was observed in the girls.

Conclusions: Boys with ADHD exhibit anomalous motor variability; girls with ADHD show similar levels of variability as TD girls. Boys and girls with ADHD exhibit similar levels of excessive mirror overflow. This lack of sex differences on mirror overflow is distinct from reports finding sex effects on overflow and could result from an examination of a broader age range than is included in prior reports. Adolescent data would provide a greater understanding of the trajectory of anomalous mirror overflow across development. Examination of functional and structural connectivity would expand the current understanding of the neurobiological foundation of motor overflow

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Laterality: Asymmetries of Body, Brain and Cognition. 2022 May;27:257-72.

OPPOSED ATTENTIONAL HEMI-BIAS ON A VISUOCONSTRUCTIVE TASK IN CHILDREN WITH SEVERE HYPERACTIVITY VERSUS SEVERE INATTENTION.

Braun CMJ, Sahakian T, Duval J, et al.

Twenty six empirical investigations have now established that children and adults with DSM-defined Attention deficit/Hyperactivity disorder (ADHD) of the Hyperactive type (ADHD-H) or, more commonly, Combined Hyperactive/Inattentive types (ADHD-C) manifest a small but significant visual attentional bias to the right side (left subclinical neglect), consistently suggesting the existence of a subtle right hemisphere dysfunction or hemispheric imbalance in hyperactive people. Only one research team has investigated and compared the DSM-defined Inattentive subtype (ADHD-I) to the Hyperactive subtype (ADHD-H), confirming that line bisection is biased to the right in ADHD-H and discovering that it is biased to the left in ADHD-I. We aimed to test whether a similar crossed double dissociation would extend to Rey's Complex Figure Copy Task (RCF-CT), a simple visuospatial-constructive task. Clinical files of 205 juvenile clients from 6 to 16 years of age from a neuropsychological private clinic specialized in ADHD were analysed. Extreme scores on the Connors-3 Hyperactivity vs Inattention Parent Rating scales associated, respectively, with significant rightward and significant leftward emplacement of the drawing on the page on the RCF-CT. These results replicate previous findings and extend the 'energetics' model of hemispheric specialization

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Med Phys. 2022 May;49:3171-84.

CONCEPTCNN: A NOVEL MULTI-FILTER CONVOLUTIONAL NEURAL NETWORK FOR THE PREDICTION OF NEURODEVELOPMENTAL DISORDERS USING BRAIN CONNECTOME.

Chen M, Li H, Fan H, et al.

BACKGROUND: Deep convolutional neural network (CNN) and its derivatives have recently shown great promise in the prediction of brain disorders using brain connectome data. Existing deep CNN methods using

single global row and column convolutional filters have limited ability to extract discriminative information from brain connectome for prediction tasks.
PURPOSE: This paper presents a novel deep Connectome-Inception CNN (ConCeptCNN) model, which is developed based on multiple convolutional filters. The proposed model is used to extract topological features from brain connectome data for neurological disorders classification and analysis.
METHODS: The ConCeptCNN uses multiple vector-shaped filters extract topological information from the brain connectome at different levels for complementary feature embeddings of brain connectome. The proposed model is validated using two datasets: the Neuro Bureau ADHD-200 dataset and the Cincinnati Early Prediction Study (CINEPS) dataset.
RESULTS: In a cross-validation experiment, the ConCeptCNN achieved a prediction accuracy of 78.7% for the detection of attention deficit hyperactivity disorder (ADHD) in adolescents and an accuracy of 81.6% for the prediction of cognitive deficits at 2 years corrected age in very preterm infants. In addition to the classification tasks, the ConCeptCNN identified several brain regions that are discriminative to neurodevelopmental disorders.
CONCLUSIONS: We compared the ConCeptCNN with several peer CNN methods. The results demonstrated that proposed model improves overall classification performance of neurodevelopmental disorders prediction tasks

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Mol Psychiatry. 2022 Jun;27:2742-50.

CORTICOLIMBIC DCC GENE CO-EXPRESSION NETWORKS AS PREDICTORS OF IMPULSIVITY IN CHILDREN.

Restrepo-Lozano JM, Pokhvisneva I, Wang Z, et al.

Inhibitory control deficits are prevalent in multiple neuropsychiatric conditions. The communication- as well as the connectivity- between corticolimbic regions of the brain are fundamental for eliciting inhibitory control behaviors, but early markers of vulnerability to this behavioral trait are yet to be discovered. The gradual maturation of the prefrontal cortex (PFC), in particular of the mesocortical dopamine innervation, mirrors the protracted development of inhibitory control; both are present early in life, but reach full maturation by early adulthood. Evidence suggests the involvement of the Netrin-1/DCC signaling pathway and its associated gene networks in corticolimbic development. Here we investigated whether an expression-based polygenic score (ePRS) based on corticolimbic-specific DCC gene co-expression networks associates with impulsivity-related phenotypes in community samples of children. We found that lower ePRS scores associate with higher measurements of impulsive choice in 6-year-old children tested in the Information Sampling Task and withÂ impulsive action in 6- and 10-year-old children tested in the Stop Signal Task. We also found the ePRS to be a better overall predictor of impulsivity when compared to a conventional PRS score comparable in size to the ePRS (4515 SNPs in our discovery cohort) andÂ derived from the latest GWAS for ADHD. We propose that the corticolimbic DCC-ePRS can serve as a novel type of marker for impulsivity-related phenotypes in children. By adopting a systems biology approach based on gene co-expression networks and genotype-gene expression (rather than genotype-disease) associations, these results further validate our methodology to construct polygenic scores linked to the overall biological function of tissue-specific gene networks

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Mol Psychiatry. 2022 Mar;27:1588-98.

POLYGENIC RISK FOR MENTAL DISORDER REVEALS DISTINCT ASSOCIATION PROFILES ACROSS SOCIAL BEHAVIOUR IN THE GENERAL POPULATION.

Schlag F, Allegrini AG, Buitelaar J, et al.

Many mental health conditions present a spectrum of social difficulties that overlaps with social behaviour in the general population including shared but little characterised genetic links. Here, we systematically investigate heterogeneity in shared genetic liabilities with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), bipolar disorder (BP), major depression (MD) and schizophrenia across a spectrum of different social symptoms. Longitudinally assessed low-prosociality and peer-problem scores in two UK population-based cohorts (4-17 years; parent- and teacher-reports; Avon Longitudinal Study of Parents and Children(ALSPAC): N 6,174; Twins Early Development Study(TEDS): N 7,112) were regressed

on polygenic risk scores for disorder, as informed by genome-wide summary statistics from large consortia, using negative binomial regression models. Across ALSPAC and TEDS, we replicated univariate polygenic associations between social behaviour and risk for ADHD, MD and schizophrenia. Modelling variation in univariate genetic effects jointly using random-effect meta-regression revealed evidence for polygenic links between social behaviour and ADHD, ASD, MD, and schizophrenia risk, but not BP. Differences in age, reporter and social trait captured 45-88% in univariate effect variation. Cross-disorder adjusted analyses demonstrated that age-related heterogeneity in univariate effects is shared across mental health conditions, while reporter- and social trait-specific heterogeneity captures disorder-specific profiles. In particular, ADHD, MD, and ASD polygenic risk were more strongly linked to peer problems than low prosociality, while schizophrenia was associated with low prosociality only. The identified association profiles suggest differences in the social genetic architecture across mental disorders when investigating polygenic overlap with population-based social symptoms spanning 13 years of child and adolescent development

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Mol Psychiatry. 2022 May;27:2425-38.

CONVERGENT SELECTIVE SIGNALING IMPAIRMENT EXPOSES THE PATHOGENICITY OF LATROPHILIN-3 MISSENSE VARIANTS LINKED TO INHERITABLE ADHD SUSCEPTIBILITY.

Moreno-Salinas AL, Holleran BJ, Ojeda-MuÃ±iz EY, et al.

Latrophilin-3 (Lphn3; also known as ADGRL3) is a member of the adhesion G Protein Coupled Receptor subfamily, which participates in the stabilization and maintenance of neuronal networks by mediating intercellular adhesion through heterophilic interactions with transmembrane ligands. Polymorphisms modifying the Lphn3 gene are associated with attention-deficit/hyperactivity disorder (ADHD) in children and its persistence into adulthood. How these genetic alterations affect receptor function remains unknown. Here, we conducted the functional validation of distinct ADHD-related Lphn3 variants bearing mutations in the receptor's adhesion motif-containing extracellular region. We found that all variants tested disrupted the ability of Lphn3 to stabilize intercellular adhesion in a manner that was distinct between ligands classes, but which did not depend on ligand-receptor interaction parameters, thus pointing to altered intrinsic receptor signaling properties. Using G protein signaling biosensors, we determined that Lphn3 couples to GÎ±i1, GÎ±i2, GÎ±s, GÎ±q, and GÎ±13. However, all ADHD-related receptor variants consistently lacked intrinsic as well as ligand-dependent GÎ±13 coupling efficiency while maintaining unaltered coupling to GÎ±i, GÎ±s, and GÎ±q. Consistent with these alterations, actin remodeling functions as well as actin-relevant RhoA signaling normally displayed by the constitutively active Lphn3 receptor were impeded by select receptor variants, thus supporting additional signaling defects. Taken together, our data point to GÎ±13 selective signaling impairments as representing a disease-relevant pathogenicity pathway that can be inherited through Lphn3 gene polymorphisms. This study highlights the intricate interplay between Lphn3 GPCR functions and the actin cytoskeleton in modulating neurodevelopmental cues related to ADHD etiology

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Mol Psychiatry. 2022 Jun;27:2731-41.

NEUROBIOLOGICAL, FAMILIAL AND GENETIC RISK FACTORS FOR DIMENSIONAL PSYCHOPATHOLOGY IN THE ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY.

Wainberg M, Jacobs GR, Voineskos AN, et al.

BACKGROUND: Adolescence is a key period for brain development and the emergence of psychopathology. The Adolescent Brain Cognitive Development (ABCD) study was created to study the biopsychosocial factors underlying healthy and pathological brain development during this period, and comprises the world's largest youth cohort with neuroimaging, family history and genetic data.

METHODS: We examined 9856 unrelated 9-to-10-year-old participants in the ABCD study drawn from 21 sites across the United States, of which 7662 had multimodal magnetic resonance imaging scans passing quality control, and 4447 were non-Hispanic white and used for polygenic risk score analyses. Using data available at baseline, we associated eight 'syndrome scale scores' from the Child Behavior Checklist-summarizing anxious/depressed symptoms, withdrawn/depressed symptoms, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior-with resting-state functional and structural brain magnetic resonance imaging measures; eight indicators of family

history of psychopathology; and polygenic risk scores for major depression, bipolar disorder, schizophrenia, attention deficit hyperactivity disorder (ADHD) and anorexia nervosa. As a sensitivity analysis, we excluded participants with clinically significant (>97th percentile) or borderline (93rd-97th percentile) scores for each dimension.
RESULTS: Most Child Behavior Checklist dimensions were associated with reduced functional connectivity within one or more of four large-scale brain networks-default mode, cingulo-parietal, dorsal attention, and retrosplenial-temporal. Several dimensions were also associated with increased functional connectivity between the default mode, dorsal attention, ventral attention and cingulo-opercular networks. Conversely, almost no global or regional brain structural measures were associated with any of the dimensions. Every family history indicator was associated with every dimension. Major depression polygenic risk was associated with six of the eight dimensions, whereas ADHD polygenic risk was exclusively associated with attention problems and externalizing behavior (rule-breaking and aggressive behavior). Bipolar disorder, schizophrenia and anorexia nervosa polygenic risk were not associated with any of the dimensions. Many associations remained statistically significant even after excluding participants with clinically significant or borderline psychopathology, suggesting that the same risk factors that contribute to clinically significant psychopathology also contribute to continuous variation within the clinically normal range.
CONCLUSIONS: This study codifies neurobiological, familial and genetic risk factors for dimensional psychopathology across a population-scale cohort of community-dwelling preadolescents. Future efforts are needed to understand how these multiple modalities of risk intersect to influence trajectories of psychopathology into late adolescence and adulthood

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Neuropediatrics. 2021;52.

PANIC ATTACKS AND ANXIETY DISORDER IN A CHILD WITH AUTISM SPECTRUM DISORDER AND ADHD TRIGGERED BY GAD65 AUTOIMMUNE ENCEPHALITIS.

De Vries H, Klaus D, Leister K, et al.

In this contribution, we present an 11-year-old girl previously known with a history of ADHD and Asperger's autism. Within few hours, the child became increasingly confused and agitated, and headaches and vomiting occurred. Reduced level of consciousness with sopor developed so that she was admitted to hospital. EEG showed generalized slow delta waves. Encephalitis was diagnosed by pleocytosis and protein elevation in the cerebrospinal fluid as well as the detection of GAD65-AK. Within a few days of methylprednisolone therapy, the patient recovered completely. In addition to the above-mentioned underlying psychiatric disorders, an anxiety disorder had been diagnosed 9 months before hospitalization. This was complicated by almost daily occurrence of panic attacks over the past weeks. After treatment with methylprednisolone, the symptoms of ADHD and autism disorder persisted, but since then there have been no panic attacks. The occurrence of subacute psychiatric symptoms is a typical finding of autoimmune encephalitis. Even in patients with an underlying psychiatric disease, new psychiatric symptoms can be caused by autoimmune encephalitis and thus be present independently of the underlying disease. Recognizing this is a major challenge for the treating physician. Autoimmune encephalitis with limbic encephalitis is a very rare disease in childhood. By presenting this case and taking a look at the literature on pediatric autoimmune encephalitis and psychiatric comorbidities, we would like to draw attention to this vulnerable patient group

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Neurosci Biobehav Rev. 2022 Jun;137:104662.

ASSOCIATIONS BETWEEN MENTAL AND PHYSICAL CONDITIONS IN CHILDREN AND ADOLESCENTS: AN UMBRELLA REVIEW.

Arrondo G, Solmi M, Dragioti E, et al.

We mapped the evidence on the type and strength of associations between a broad range of mental and physical conditions in children and adolescents, by carrying out an umbrella review, i.e., a quantitative synthesis of previous systematic reviews and meta-analyses. We also assessed to which extent the links between mental and physical conditions vary across disorders or, by contrast, are transdiagnostic. Based on a pre-established protocol, we retained 45 systematic reviews/meta-analyses, encompassing around 12.5 million of participants. In analyses limited to the most rigorous estimates, we found evidence for the following

associations: ADHD-asthma, ADHD-obesity, and depression-asthma. A transdiagnostic association was confirmed between asthma and anxiety/ASD/depression/bipolar disorder, between obesity and ADHD/ASD/depression, and between dermatitis and ASD/ADHD. We conclude that obesity and allergic conditions are likely to be associated with mental disorders in children and adolescents. Our results can help clinicians explore potential links between mental and physical conditions in children/adolescent and provide a road map for future studies aimed at shading light on the underlying factors

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Neurotoxicol Teratol. 2022 May;91:107078.

PRENATAL EXPOSURE TO BENZODIAZEPINES AND THE DEVELOPMENT OF THE OFFSPRING - A SYSTEMATIC REVIEW.

Jensen AG, Knudsen SS, Bech BH.

OBJECTIVE: To summarize the available literature on long-term-development of children exposed to benzodiazepines in utero, through a systematic review.

INFORMATION SOURCES: We conducted a systematic literature search of PubMed, PsycINFO and embase (1/9-2020 to 3/9-2020).

ELIGIBILITY CRITERIA: We included original studies with children older than one year prenatally exposed to BZ's and Z-hypnotics with outcomes regarding all psychological-, social-, motor- and neurodevelopmental disorders or disturbances of the children. Studies without a BZ-unexposed comparison group were excluded. Studies with only a single-dose exposure, conference abstracts, case reports and case series were excluded.

RISK OF BIAS: The intern validity of the included studies was assessed with the Newcastle Ottawa Scale tool (NOS).

INCLUDED STUDIES: 13 cohort studies were included in this systematic review.

SYNTHESIS OF RESULTS: The outcomes investigated were internalizing and externalizing problems, language, hearing and communication skills, neurological outcomes and motor function, behavioral and emotional problems, social skills, intellect and academic achievements, psychiatric diagnoses and overall development. We found some evidence of higher risk of developing internalizing problems, impaired gross motor skills, lower academic achievements and increased ADHD-traits among children exposed to benzodiazepines in utero.

CONCLUSION: Prenatal exposure to benzodiazepines were associated with 4 developmental outcomes indicating an impaired long-term-development of the offspring. However, results were contradicting, and it cannot be ruled out, that findings might be due to bias. Furthermore, it remains uncertain if the results are of clinical relevance and whether developmental problems persist in later childhood. This study revealed a clear need for further research in the subject

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Neurotoxicol Teratol. 2022 May;91:107089.

PRENATAL CANNABIS EXPOSURE PREDICTS ATTENTION PROBLEMS, WITHOUT CHANGES ON FMRI IN ADOLESCENTS.

Cioffredi LA, Anderson H, Loso H, et al.

OBJECTIVES: We hypothesized that prenatal cannabis exposure (PCE) would be associated with increased attention problems and altered neurocognition in young adolescents.

METHODS: Data were obtained from the Adolescent Brain Cognitive Development (ABCD study®), a cohort of approximately 12,000 children. Presence or absence of PCE after knowledge of pregnancy was measured by caregiver report. All participants with PCE (N = 224) were included and compared to two control groups; those matched on tobacco and alcohol exposure and those without prenatal tobacco or alcohol exposures. Outcomes were measured with the ABCD baseline assessment when participants were 9-10 years old and included attention, internalizing, externalizing and total problems scales on the Child Behavior Checklist (CBCL). Teacher reports were used when available. Mixed effects modeling assessed the association between PCE and outcomes controlling for parental psychopathology, prematurity and socioeconomic status. For participants with available data, patterns of brain activity during three fMRI tasks (the Stop Signal Task measuring response inhibition, the Monetary Incentive Delay (MID) task measuring reward processing and the EN-Back task measuring working memory) were analyzed using Permutation Analyses of the Linear Model.

RESULTS: Compared to both control groups, participants with PCE had significantly higher attention problems, externalizing, and total problem scores. PCE did not impact cognitive performance or patterns of brain activation during fMRI tasks.
CONCLUSIONS: There are long-term associations between PCE and early adolescent attention and behavioral problems. These are not reflected in cognitive performance or task fMRI measures, a finding that is consistent with reports that fewer than half of children with ADHD have any specific cognitive deficit (Nigg et al., 2005; Willcutt et al., 2005). The young age of the sample may also relate to this finding and future investigation of neurodevelopmental trajectories of youth with PCE is warranted

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Obes Facts. 2022;15:197-208.
ASSOCIATION BETWEEN MARGINALLY LOW BIRTH WEIGHT AND OBESITY-RELATED OUTCOMES AND INDIRECT EFFECTS VIA ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND ABNORMAL EATING.
Wei X, Hu J, Liu Y, et al.
Introduction: Evidence of the association between children born with marginally low birth weight (MLBW) and obesity-related outcomes was controversial, and our study aimed to examine the role of attention-deficit hyperactivity disorder (ADHD) and/or abnormal eating in these associations.
Methods: A retrospective cohort study consisting of 677 Chinese children was conducted. Obesity-related outcomes (body mass index [BMI], waist circumference [WC], skinfold thickness [SF], body fat, blood pressure, lipids, and blood glucose), behaviour problems (ADHD and eating behaviour) and birth weight were collected. Mediation analyses were used to explore whether ADHD and/or abnormal eating was an intermediary factor in the MLBW-OB relationship.
Results: Children with MLBW tended to have higher SF, triglycerides, fasting blood glucose, waistline, body fat, and abdominal obesity risks. Birth weight was negatively related to obesity-related outcomes, and the associations were mediated, partially, by the increased risk of ADHD or abnormal eating behaviour after adjustment for the BMI Z score. Furthermore, lower birth weight predicted higher WC indirectly through emotional overeating caused by ADHD (+¦: -0.10; 95% confidence interval: -0.19, -0.01).
Conclusion: Our study suggests the hypothetical role of ADHD and abnormal eating as underlying mechanisms in the association between MLBW and obesity-related outcomes, providing novel scientific evidence for childhood development interventions

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Paediatrics and Child Health (Canada). 2018;23:E102-E108.
BLOOD PRESSURE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.
Grisaru S, Yue M, Samuel SM, et al.
Objectives: Children with attention deficit/hyperactivity disorder (ADHD) are frequently treated with psycho-stimulant agents causing a modest but significant increase in blood pressure and heart rate. The objective of this study was to define blood pressure characteristics in children with ADHD treated with a variety of medications in a community setup.
Methods: Children registered at a large paediatric clinic in Calgary, AB with documented histories of ADHD were randomly contacted. Consenting participants had standardized office BP measurements, ambulatory blood pressure monitoring (ABPM) studies and were asked to complete the sleep disturbance scale for children (SDSC) questionnaire. Findings were compared with data from the Canadian Health Measures Survey (CMHS).
Results: Fifty-five children (47 males) aged 7 to 17 years (average 11.6 -¦ 2.5 years) with an average BMI z-score of -0.37 -¦ 1.22 completed the study. All children were medicated, the majority (82%), with various types of stimulant agents. Elevated office BP values were more prevalent than in the CMHS; >90th percentile in 5 (9.1%) and >95th percentile in 3 (5.5%). ABPM confirmed 'white coat hypertension' in 3 (5.5%), masked hypertension in 2 (3.6%) and nondipping in 28 (51%). The SDSC score suggested that 43 (78%) children had disturbed sleep. Logistic regression modelling indicated that nondipping correlated with disturbed sleep.

Conclusion: The 'white coat' phenomenon may be responsible for increased prevalence of elevated rest/office BP values in children with ADHD. Prevalent sleep 'non-dipping' in this population is associated with sleep disturbances but clinical significance of this finding requires further investigation

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Pediatr Res. 2022.

EMOTIONAL AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS OF PRETERM VS. FULL-TERM CHILDREN DURING COVID-19 PANDEMIC RESTRICTIONS.

Bailhache M, Monnier M, Moulin F, et al.

Background: Preterm children are at higher risk of developing mental health problems than full-term children. Deterioration of childrenΓÇÖs mental health was observed during COVID-19 pandemic restrictive measures. Our study compared emotional and attention-deficit/hyperactivity disorder (ADHD) symptoms during school closure between preterm and full-term children.

Methods: Data from two French birth cohortsΓÇöELFE and EPIPAGE-2 were used. In 2011, infants born 22 weeks gestation were recruited. Parents completed the Strengths and Difficulties Questionnaire when the children were 9 years old and experiencing school closure. Multivariate multinomial logistic regression models were used.

Results: Subjects included 4164 full-term and 1119 preterm children. In univariate analyses, compared to full-term children: extremely and very preterm children more frequently had abnormal and borderline ADHD scores (odds ratio [OR] 1.86, 95% confidence interval [CI] 1.50-2.30, OR 1.42, 95% CI 1.08-1.85, respectively) and abnormal emotional scores (OR 1.86, 95% CI 1.43-2.40); moderate to late preterm children more often had abnormal ADHD scores (OR 1.33, 95% CI 1.01-1.78). The associations did not remain when previous symptoms at 5 years old were considered.

Conclusions: School closure during lockdown did not appear to-áincrease the risk of mental health problems in preterm compared to full-term children. Impact statement: Preterm children are at higher risk of developing mental health problems than full-term children. Deterioration in children's mental health was observed during COVID-19 pandemic restrictions. However, whether preterm children were a particularly vulnerable subgroup during school closure is unclear. In univariate analyses, extremely and very preterm children more often had abnormal and borderline ADHD symptoms and abnormal emotional symptom scores than full-term children. The associations did not remain significantly associated when previous symptoms were considered. Preterm compared to full-term children more often suffer from ADHD and emotional symptoms, but school closure during lockdown did not appear to increase this risk

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Pediatr Res. 2022.

NEW INSIGHTS INTO PRECOCIOUS PUBERTY AND ADHD: A NATIONWIDE COHORT STUDY.

Pai LF, Wang DS, Hsu WF, et al.

Background: Attention deficit-hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children; however, studies delineating the association between ADHD and central precocious puberty are limited. This study aimed to understand whether children with ADHD are at a higher risk of central precocious puberty.

Methods: This population-based retrospective cohort study was conducted using the National Health Insurance Research Database of Taiwan to investigate the association between ADHD and the incidence of central precocious puberty between 2000–2015. We identified ADHD individuals treated with methylphenidate, atomoxetine or not. The control cohort consisted of individuals without ADHD. The outcome measure was central precocious puberty diagnosis.

Results: Among 290,148 children (mean age: 5.83 years), central precocious puberty incidence was 4.24 and 1.95 per 105 person-years in the ADHD and control groups, respectively. Children with ADHD treated with medication had a higher risk than those without ADHD. However, medication use did not affect the incidence of central precocious puberty among children with ADHD.

Conclusion: This study showed an association between ADHD and a higher risk of central precocious puberty. Early referral of children with ADHD to a pediatric endocrinologist for evaluation may facilitate correct diagnoses and early interventions. Impact: ADHD is associated with a higher risk of central precocious

puberty.This study provides relevant findings, as it is the first nationwide, population-based cohort study to investigate the association between ADHD and the risk of central precocious puberty with a 15-year follow-up.Early referral of children with ADHD to a pediatric endocrinologist for the evaluation of suspected precocious puberty could facilitate correct diagnosis.Early intervention treatment with gonadotropin-releasing hormone agonist might improve final height in children with central precocious puberty

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PLoS ONE. 2022;17.

SOCIAL GRADIENTS IN ADHD BY HOUSEHOLD INCOME AND MATERNAL EDUCATION EXPOSURE DURING EARLY CHILDHOOD: FINDINGS FROM BIRTH COHORT STUDIES ACROSS SIX COUNTRIES.

Spencer NJ, Ludvigsson J, Bai G, et al.

Objective: This study aimed to examine social gradients in ADHD during late childhood (age 9-11 years) using absolute and relative relationships with socioeconomic status exposure (household income, maternal education) during early childhood (<5 years) in seven cohorts from six industrialised countries (UK, Australia, Canada, The Netherlands, USA, Sweden).

Methods: Secondary analyses were conducted for each birth cohort. Risk ratios, pooled risk estimates, and absolute inequality, measured by the Slope Index of Inequality (SII), were estimated to quantify social gradients in ADHD during late childhood by household income and maternal education measured during early childhood. Estimates were adjusted for child sex, mother age at birth, mother ethnicity, and multiple births.

Findings: All cohorts demonstrated social gradients by household income and maternal education in early childhood, except for maternal education in Quebec. Pooled risk estimates, relating to 44,925 children, yielded expected gradients (income: low 1.83(CI 1.38,2.41), middle 1.42 (1.13,1.79), high (reference); maternal education: low 2.13(1.39,3.25), middle 1.42 (1.13,1.79)). Estimates of absolute inequality using SII showed that the largest differences in ADHD prevalence between the highest and lowest levels of maternal education were observed in Australia (4% lower) and Sweden (3% lower); for household income, the largest differences were observed in Quebec (6% lower) and Canada (all provinces: 5% lower).

Conclusion: Findings indicate that children in families with high household income or maternal education are less likely to have ADHD at age 9-11. Absolute inequality, in combination with relative inequality, provides a more complete account of the socioeconomic status and ADHD relationship in different high-income countries. While the study design precludes causal inference, the linear relation between early childhood social circumstances and later ADHD suggests a potential role for policies that promote high levels of education, especially among women, and adequate levels of household income over children's early years in reducing risk of later ADHD

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Psych J. 2022 Jun;11:419-27.

NEUROTHERAPEUTICS FOR ADHD: DO THEY WORK?

Rubia K.

This paper reflects on the use of neurotherapeutics for attention-deficit/hyperactivity disorder (ADHD). ADHD is the most imaged child psychiatric disorder, with over 3 decades of magnetic resonance imaging (MRI) research. Findings are relatively homogeneous compared to other psychiatric conditions with consistent evidence for differences, albeit small, relative to healthy controls in the structure and function of several frontal, parietotemporal, and striatal brain regions as well as their inter-regional structural and functional connections. The functional deficits have been targeted with modern neurotherapeutics, including neurofeedback (using most commonly electroencephalography and more recently functional near-infrared spectroscopy and functional MRI) and non-invasive brain stimulation (such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation, or external trigeminal nerve stimulation). Except for electroencephalography-neurofeedback, the majority of neurotherapeutic studies have been relatively small, with very heterogenous research protocols and outcome measures and-likely as a consequence-inconsistent findings. Furthermore, most brain stimulation studies have tested effects on cognitive functions rather than clinical symptoms. So far, findings have not been very promising. Future studies require

systematic testing of optimal protocols in large samples or homogenous subgroups to understand response prediction that could lead to individualized treatment

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Psychiatr Genet. 2022 Apr;32:80-86.

STIMULANT INTOLERANCE IN CHILDREN WITH ANGELMAN SYNDROME WITH HYPERACTIVITY: A CASE SERIES.

Keary CJ, Thom RP, McDougle CJ.

OBJECTIVES: Angelman syndrome is a neurogenetic disorder resulting from the loss of expression of the ubiquitin-protein ligase E3A gene on chromosome 15. Problematic behaviors including attention-deficit/hyperactivity disorder (ADHD) symptoms of hyperactivity, impulsivity and inattention are highly prevalent in Angelman syndrome. The efficacy, safety and tolerability of stimulant medications in children with Angelman syndrome for the treatment of ADHD symptoms have not been previously reported.

METHODS: We describe three boys with Angelman syndrome who were treated with open-label stimulant medications for ADHD symptoms.

RESULTS: Stimulant medications were highly intolerable, and treatment had to be discontinued after limited dosing in all three cases due to marked increases in hyperactivity and impulsivity along with worsened distractibility.

CONCLUSION: The findings of this study suggest that stimulant medications may be ineffective and poorly tolerated in children with Angelman syndrome

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Psychiatry Clin Neurosci. 2022;76:235-45.

ATYPICAL FUNCTIONAL CONNECTIVITY DURING REST AND TASK-RELATED DYNAMIC ALTERATION IN YOUNG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN ANALYSIS USING THE PHASE-LOCKING VALUE.

Chen IC, Chang CL, Chang MH, et al.

Aim: The study investigated the electroencephalography (EEG) functional connectivity (FC) profiles during rest and tasks of young children with attention deficit hyperactivity disorder (ADHD) and typical development (TD).

Methods: In total, 78 children (aged 5ΓÇô7 years) were enrolled in this study; 43 of them were diagnosed with ADHD and 35 exhibited TD. Four FC metrics, coherence, phase-locking value (PLV), pairwise phase consistency, and phase lag index, were computed for feature selection to discriminate ADHD from TD.

Results: The support vector machine classifier trained by phase-locking value (PLV) features yielded the best performance to differentiate the ADHD from the TD group and was used for further analysis. In comparing PLVs with the TD group at rest, the ADHD group exhibited significantly lower values on left intrahemispheric long interelectrode lower-alpha and beta as well as frontal interhemispheric beta frequency bands. However, the ADHD group showed higher values of central interhemispheric PLVs on the theta, higher-alpha, and beta bands. Regarding PLV alterations within resting and task conditions, left intrahemispheric long interelectrode beta PLVs declined from rest to task in the TD group, but the alterations did not differ in the ADHD group. Negative correlations were observed between frontal interhemispheric beta PLVs and the Disruptive Behavior Disorder Rating Scale as rated by teachers.

Conclusions: These results, which complement the findings of other sparse studies that have investigated task-related brain FC dynamics, particularly in young children with ADHD, can provide clinicians with significant and interpretable neural biomarkers for facilitating the diagnosis of ADHD

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Psychiatr Invest. 2022;19:213-19.

A 24-MONTH EFFECTS OF METHYLPHENIDATE USE ON GROWTH IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lee Y, Kong N, Koo S, et al.

Objective The primary objective of this study was to investigate the effect of methylphenidate (MPH) on height, weight, and body mass index (BMI) in drug-naive children and adolescents with attention deficit hyperactivity disorder (ADHD) over 24 months. The secondary objective was to investigate whether the age of MPH initiation and sex act as risk factors for growth retardation.

Methods A total of 82 patients with ADHD were included. Weight, height, and BMI were measured at baseline and every 6 months up to 24 months. Weight, height, and BMI data were converted to z-scores and analyzed using two-way repeated-measures ANOVA and multiple linear regression.
Results The z-score of height, weight and BMI decreased from the baseline values. The z-scores of height were at baseline 0.002; 6 months-0.100; 12 months-0.159; 18 months-0.159; 24 months-0.186. The z-scores of weight were at baseline 0.104; 6 months-0.155; 12 months-0.256; 18 months-0.278; 24 months-0.301. Here were no age and sex differences of height, weight, and BMI.
Conclusion The use of MPH was associated with attenuation of weight and height gain rates in children and adolescents with ADHD

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Psychiatry Res. 2022 Jun;312:114556.

CHILDHOOD-ONSET VERSUS ADOLESCENT-ONSET ANXIETY AND DEPRESSION: EPIDEMIOLOGICAL AND NEURODEVELOPMENTAL ASPECTS.

Doering S, Halldner L, Larsson H, et al.

Anxiety and depression are common in youth and are frequently accompanied by attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). However, it is unclear how common ADHD, ASD, and other neurodevelopmental disorders (NDDs, i.e., ADHD, ASD, developmental coordination disorder, learning disorder, and tic disorders) are in children versus adolescents with anxiety and depression. We aimed to delineate whether different anxiety/depression age-of-onset groups show distinguishable NDD patterns. The study was based on 4492 twins born in Sweden between 1998 and 2003 from the nation-wide population-based Child and Adolescent Twin Study in Sweden. Prevalence and odds ratios were calculated using screening measures of anxiety and depression at ages 9 and 15, and NDDs at age 9. Individuals with childhood-onset anxiety/depression had a substantially higher NDD prevalence compared to individuals with adolescent-onset anxiety/depression. Highest prevalence was found for individuals with anxiety/depression both in childhood and adolescence. In this group, individuals also had substantially higher odds of having at least one NDD (14.7, 95% CI 6.3 - 34.0) compared to individuals without anxiety/depression. This emphasizes the need to further investigate the etiology of childhood and adolescent anxiety/depression, as they most likely represent different constructs depending on age-of-onset, lending support for possibly different treatment approaches

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Psychiatry Res. 2022;311.

EFFECTS OF PHYSICAL EXERCISE ON ATTENTION DEFICIT AND OTHER MAJOR SYMPTOMS IN CHILDREN WITH ADHD: A META-ANALYSIS.

Sun W, Yu M, Zhou X.

Purpose: To explore the effects of physical exercise intervention on the cardinal symptoms, motor skills and executive function among children with attention deficit hyperactivity disorder (ADHD).
Methods: Literature searches for randomized controlled trials (RCTs) were performed in PubMed, The Cochrane Library, Web of Science, Embase, CNKI, CBM, VIP and Wanfang databases from the time of database construction to March 28, 2021. Screening was conducted based on inclusion and exclusion criteria. The Cochrane bias risk assessment tools were used to evaluate methodological quality. Relevant data were analyzed with RevMan5.3.5 software, and Stata16.0 was used for publication bias tests.
Results: A total of 15 RCTs with 734 subjects were included. The meta-analysis showed that physical exercise can improve the attention of ADHD children (standardized mean difference [SMD] = 0.60, 95% confidence interval [CI] [1.10, 0.11], p < 0.01), executive function (SMD = 1.22, 95% CI [0.61, 1.82], p < 0.01), and motor skills (SMD = 0.67, 95% CI [0.22, 1.12], p < 0.01). There were no significant effects on hyperactivity (SMD = 0.06, 95% CI [Γê Æ0.26, 0.37], p = 0.72), depression (SMD = 0.72, 95% CI [1.55, 0.11], p = 0.09), social problems (SMD = 0.27, 95% CI [0.64, 0.09], p = 0.14), or aggressive behavior (SMD=0.24, 95% CI [0.69, 0.21], p = 0.30). Intervention duration and frequency might be the source of heterogeneity.
Conclusion: Physical exercise can help alleviate the symptoms of ADHD in children. Specifically, it can improve attention, executive function, and motor skills

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Psychol Health. 2022 May;37:563-79.

CLINICAL APPLICATION OF MINDFULNESS-ORIENTED MEDITATION IN CHILDREN WITH ADHD: A PRELIMINARY STUDY ON SLEEP AND BEHAVIORAL PROBLEMS.

Zaccari V, Santonastaso O, Mandolesi L, et al.

OBJECTIVE: High incidence of sleep problems in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) has been described. Mindfulness meditation has emerged as a novel approach to sleep disturbances and insomnia remediation. This preliminary study tested the efficacy of Mindfulness-Oriented Meditation (MOM) training on sleep quality and behavioral problems in children with ADHD.

DESIGN: Twenty-five children with ADHD aged 7-11 years underwent two programs three times per week for eight-weeks: the MOM training (15 children) and an Active Control Condition (10 children). MAIN

OUTCOME MEASURES: Objective and subjective measures of sleep quality and behavioral measures were collected before and after the programs.

RESULTS: Positive effects on sleep and behavioral measures were found only in the MOM group.

CONCLUSION: Although they are preliminary, our results indicate that MOM training is a promising tool for ameliorating sleep quality and behavioral manifestations in ADHD

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Psychol Med. 2022 May;52:1356-64.

POLYGENIC RISK FOR ADHD AND ASD AND THEIR RELATION WITH COGNITIVE MEASURES IN SCHOOL CHILDREN.

Aguilar-Lacasaa S, Vilor-Tejedor N, Jansen PR, et al.

BACKGROUND: Attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are child-onset neurodevelopmental disorders frequently accompanied by cognitive difficulties. In the current study, we aim to examine the genetic overlap between ADHD and ASD and cognitive measures of working memory (WM) and attention performance among schoolchildren using a polygenic risk approach.

METHODS: A total of 1667 children from a population-based cohort aged 7-11 years with data available on genetics and cognition were included in the analyses. Polygenic risk scores (PRS) were calculated for ADHD and ASD using results from the largest GWAS to date (N = 55 374 and N = 46 351, respectively). The cognitive outcomes included verbal and numerical WM and the standard error of hit reaction time (HRTSE) as a measure of attention performance. These outcomes were repeatedly assessed over 1-year period using computerized version of the Attention Network Test and n-back task. Associations were estimated using linear mixed-effects models.

RESULTS: Higher polygenic risk for ADHD was associated with lower WM performance at baseline time but not over time. These findings remained significant after adjusting by multiple testing and excluding individuals with an ADHD diagnosis but were limited to boys. PRS for ASD was only nominally associated with an increased improvement on verbal WM over time, although this association did not survive multiple testing correction. No associations were observed for HRTSE.

CONCLUSIONS: Common genetic variants related to ADHD may contribute to worse WM performance among schoolchildren from the general population but not to the subsequent cognitive-developmental trajectory assessed over 1-year period

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Psychooncology. 2022 May;31:745-52.

SUICIDAL IDEATION AND EXECUTIVE FUNCTIONING IN PEDIATRIC CANCER.

Sharkey CM, Hardy KK, Gioia A, et al.

OBJECTIVE: Neurocognitive impairments and psychological distress are among the most common difficulties experienced by children treated for cancer. Elevated rates of suicidal ideation (SI) are documented among cancer survivors, and a link between neurocognitive deficits and SI is evident, yet the relationship between SI and pediatric cancer-related neurocognitive effects has not yet been studied.

PARTICIPANTS AND METHODS: Participants were 166 pediatric cancer patients (57.8% Brain Tumor, 31.3% leukemia, 10.8% other cancers) aged 6-23 (M = 11.57, SD = 3.82; 45.8% female) referred for neuropsychological surveillance. SI prevalence was measured by parent, teacher, or patient endorsement of self-harm related items on informant-report measures (e.g., the Child Behavior Checklist). Executive

functioning (Behavior Rating Inventory of Executive Function), ADHD symptoms (ADHD Rating Scale), and performance-based measures were compared between those with SI and those without.
RESULTS: 17.5% of pediatric cancer patients experienced SI, of which 44.7% had self-endorsement only, 58.5% parent-endorsement only, 20.6% teacher-endorsement only, and 24.1% had two endorsements. Those with SI had significantly greater impairments in global executive composite scores by both parent- and teacher-report (ps < 0.05). Parents of children with SI endorsed significantly more inattention symptoms (M = 6.10, SD = 15.48) than those without SI (M = 50.56, SD = 8.70; p < 0.01), but hyperactivity symptoms did not differ. Intellectual and executive function performance did not differ between those with and without SI (ps > 0.1).
CONCLUSIONS: An elevated number of children treated for cancer experience SI and related neurocognitive problems. Screening for SI and further assessment of the connection between executive functioning and SI in pediatric cancer populations is needed

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Res Child Adolesc Psychopathol. 2022 May;50:605-19.
COPING WITH COVID-19: LONGITUDINAL IMPACT OF THE PANDEMIC ON ADJUSTMENT AND LINKS WITH COPING FOR ADOLESCENTS WITH AND WITHOUT ADHD.
Dvorsky MR, Breaux R, Cusick CN, et al.
Understanding factors that foster resilience and buffer against the negative psychological impact of COVID-19 is critical to inform efforts to promote adjustment, reduce risk, and improve care, particularly for adolescents with neurodevelopmental disorders. This prospective longitudinal study addresses this gap by investigating the impact of the COVID-19 pandemic on adolescents' mental health and substance use, and by assessing specific positive coping strategies among adolescents with and without attention-deficit/hyperactivity disorder (ADHD). Using multi-group autoregressive cross-lagged path models, the present study explored the reciprocal influence of positive coping behaviors on multiple adjustment outcomes including mental health symptoms, substance use, stress, and worry. Participants included 238 adolescents (132 male participants; ages 15-17; 118 with ADHD). Parents provided ratings of adolescent routines, and adolescents provided ratings of coping behaviors and psychological adjustment in spring (May/June), summer (July/August), and fall (October/November) 2020. All models included the effects of adjustment at the prior timepoint as well as relevant covariates including adolescent race, ethnicity, sex, medication status, and family income. Adolescents with ADHD were at greater risk for experiencing increases in mental health symptoms and substance use throughout the pandemic, relative to adolescents without ADHD. The use of positive coping strategies and adolescent routines buffered against increases in substance use and mental health problems for adolescents with ADHD. These findings have important clinical and public policy relevance for parents, schools, and employers who may aim to prioritize keeping schedules as consistent as possible to promote healthy adjustment

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Res Child Adolesc Psychopathol. 2022 May;50:563-75.
BIRTH WEIGHT AND CHILDHOOD PSYCHOPATHOLOGY IN THE ABCD COHORT: ASSOCIATION IS STRONGEST FOR ATTENTION PROBLEMS AND IS MODERATED BY SEX.
Dooley N, Clarke M, Cotter D, et al.
Many studies have shown low birth weight is associated with psychopathology later in life, particularly attention-deficit/hyperactivity disorder (ADHD). The association is well-replicated, independent from a variety of potential familial confounds, and follows a dose-response curve (decreasing birth weight linked with increasing odds of disorder). However, the specificity of the association to attention problems is called into question by the extent of comorbidity in ADHD, and recent findings that the association is stronger for autism than ADHD. We test the relative dose-response strength of birth weight on multiple aspects of behavior to explore specificity of the effect to attention problems. We also test recent suggestions that the association between birth weight and attention problems is driven by males. Our sample consisted of 9,076 children aged 9-10 from the United States (Adolescent Brain Cognitive Development study). Outcomes included 9 problem-scales and the total problems scale from the Child Behavior Checklist (CBCL). Attention problems were the most strongly associated with birth weight after controlling for gestational age, potential familial confounds,

and multiple testing, supporting the outcome-specificity of this association. Contrary to recent registry-based findings, an association between birth weight and an autism scale was not observed. Sex moderated the effect of birth weight on total problems, attention problems and aggressive behavior such that these inverse associations were strongly driven by males. Our findings have strong implications for sex-specific prediction and etiological models of childhood psychopathology

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Res Child Adolesc Psychopathol. 2022 Jun;50:753-70.

CHILDHOOD ADHD AND EXECUTIVE FUNCTIONING: UNIQUE PREDICTIONS OF EARLY ADOLESCENT DEPRESSION.

Fenesy MC, Lee SS .

Given the increasing prevalence of adolescent depression, identification of its early predictors and elucidation of the mechanisms underlying its individual differences is imperative. Controlling for baseline executive functioning (EF), we tested separate ADHD dimensions (i.e., inattention, hyperactivity-impulsivity) as independent predictors of early adolescent depression, including temporally-ordered causal mediation by academic functioning and social problems, using structural equation modeling. At baseline, participants consisted of 216 children (67% male) ages 6-9 years old with (n=112) and without (n=104) ADHD who subsequently completed Wave 2 and 3 follow-ups approximately two and four years later, respectively. Predictors consisted of separate parent and teacher ratings of childhood ADHD and laboratory-based assessments of key EF domains. At Wave 2, parents and teachers completed normed rating scales of youth academic and social functioning; youth completed standardized assessments of academic achievement. At Wave 3, youth self-reported depression. Baseline inattention positively predicted early adolescent depression whereas childhood hyperactivity-impulsivity and EF did not. Neither academic nor social functioning significantly mediated predictions of depression from baseline ADHD and EF. We consider prediction of early adolescent depression from inattention, including directions for future intervention and prevention research

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Res Child Adolesc Psychopathol. 2022 Jun;50:721-35.

EXECUTIVE FUNCTIONING AND EMOTION REGULATION IN CHILDREN WITH AND WITHOUT ADHD.

Groves NB, Wells EL, Soto EF, et al.

Difficulties with emotion regulation affect the majority of youth with attention-deficit/hyperactivity disorder (ADHD) and predict greater functional impairment than ADHD symptoms alone. Deficits in executive functioning are also present for most children with ADHD, and have been linked with emotion regulation difficulties in both clinical and neurotypical populations throughout development. The current study was the first to assess all three core executive functions (working memory, inhibitory control, set shifting) simultaneously in a clinically-diverse sample of children with and without ADHD and common comorbidities and investigate the extent to which they uniquely predict emotion dysregulation. A sample of 151 children ages 8-13 years (M=10.36, SD=1.52; 52 girls; 70.2% White/Non-Hispanic) were assessed using a criterion battery of executive functioning tasks, teacher-reported ADHD symptoms, and parent-reported emotion regulation. Results of the bias-corrected, bootstrapped conditional effects path model revealed that better-developed working memory predicted better emotion regulation ($Î²$=0.23) and fewer ADHD symptoms ($Î²$=-0.21 to -0.37), that ADHD symptoms ($Î²$=-0.18 to -0.20) independently predicted emotion dysregulation, and that working memory exerted indirect effects on emotion regulation through both inattention and hyperactivity/impulsivity ($Î²$=0.04-0.07). Sensitivity analyses indicated that these effects were generally robust to control for age, sex, executive function interrelations, and inclusion/exclusion of children with co-occurring ASD. These findings underscore the importance of working memory (relative to inhibitory control and set shifting) and its relations with ADHD symptoms for understanding children's emotion regulation skills, and may help explain the limited efficacy of first-line ADHD treatments, which do not target working memory, for improving emotion regulation skills

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Res Child Adolesc Psychopathol. 2022 Jun;50:809-22.

LONGITUDINAL ASSOCIATION OF SLUGGISH COGNITIVE TEMPO WITH DEPRESSION IN ADOLESCENTS AND THE POSSIBLE ROLE OF PEER VICTIMIZATION.

Fredrick JW, Langberg JM, Becker SP.

It is unknown whether sluggish cognitive tempo (SCT) is prospectively associated with depression in adolescence, and possible processes linking SCT to depression remain unexamined. Using a longitudinal study with three timepoints over a two-year period, the current study tested the indirect effects of SCT on depression via peer victimization, specifically physical, relational, and verbal victimization. Participants were 302 adolescents (M(age) = 13.17 years; 44.7% female participants; 81.8% White; 52% with ADHD). In the fall of 8th grade, adolescents and parents completed measures of adolescents' SCT and ADHD symptoms. Adolescents completed a measure of peer victimization in spring of 8th grade and a measure of depressive symptoms in 10th grade. Models examining indirect effects were conducted with and without control of baseline ADHD and/or depressive symptoms. Across analyses, adolescent and parent ratings of SCT symptoms uniquely predicted greater depressive symptoms two years later when controlling for adolescent sex, study site, and either 8th grade depressive or ADHD symptoms. Further, adolescents' self-reported 8th grade SCT symptoms predicted 10th grade depressive symptoms via verbal victimization when controlling for 8th grade ADHD symptoms, but not in analyses incorporating 8th grade depressive symptoms. Findings underscore the predictive association of SCT on depressive symptoms, the possible role of adverse peer relationships as a mechanism linking SCT to depression, and the importance of considering ADHD and depressive symptoms in research on longitudinal correlates of SCT

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Res Child Adolesc Psychopathol. 2022 May;50:591-603.

METHYLPHENIDATE IMPROVES AUTONOMIC FUNCTIONING AMONG YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Morris SSJ, Musser ED, Tenenbaum RB, et al.

Psychostimulants are commonly prescribed medications for youth with attention-deficit/hyperactivity disorder (ADHD). Limited studies have evaluated how psychostimulants (e.g., methylphenidate [MPH]) impact autonomic nervous system (ANS) indexes among youth with ADHD. Understanding the effects of MPH on autonomic functioning is essential, given that youth with ADHD have been shown to experience atypical autonomic functioning (i.e., reduced activity across both sympathetic and parasympathetic branches) compared to typically developing youth. The current study investigated how a specific psychostimulant, Osmotic Release Oral System [OROS] MPH, impacts parasympathetic (indexed by respiratory sinus arrhythmia [RSA]) and sympathetic (indexed by electrodermal activity [EDA]) functioning among youth with ADHD via a within-subjects, double-masked, cross-over design. Two hundred fifty-six participants (157 youth with ADHD), ages 5 to 13 years, completed a two-minute resting baseline task while electrocardiograph and electrodermal data were obtained. Youth with ADHD completed the resting baseline task twice, 3Â weeks apart, once during active medication and once during placebo conditions (counterbalanced). Typically developing youth were assessed without medication or placebo. Youth with ADHD during the placebo condition exhibited reduced RSA and EDA compared to typically developing youth. In contrast, youth with ADHD during the medication condition did not differ significantly from typically developing youth with respect to either RSA nor EDA. As such, OROS MPH appears to normalize RSA and EDA levels among youth with ADHD to levels comparable to typically developing youth. Future studies including indexes of the ANS among youth with ADHD are urged to consider the impact of MPH

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Res Child Adolesc Psychopathol. 2022 Jun;50:737-51.

A SYSTEMATIC REVIEW AND META-ANALYSIS OF NARRATIVE LANGUAGE ABILITIES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jepsen IB, Hougaard E, Matthiesen ST, et al.

While children with ADHD are reported to have language problems, it is less clear if their ability to use language to tell a story (i.e., form a narrative) is impaired. Therefore, a systematic review and meta-analysis of studies examining the oral production of fictional stories in children with ADHD was conducted. Databases

were systematically searched in January 2019 and December 2020 (follow-up). Studies comparing children (≤ 18 years) with ADHD to a control group of typically developing children were included. The meta-analysis adhered to PRISMA guidelines and was preregistered with PROSPERO [CRD42019122040]. Sixteen studies were retained. Results indicated that compared to typically developing children, children with ADHD produced less coherent narratives (Hedges' g = 0.58 p < .001), gave more ambiguous references (Hedges' g = 0.52, p < .001), made more disruptive errors (Hedges' g = 0.41, p < .001), and produced language that was less syntactically complex (Hedges' g = 0.39, p < .05). Children with ADHD also produced less language overall (Hedges' g = 0.27, p < .05), although this result appeared to be an artefact of publication bias. Two studies investigated internal state language and both found children with ADHD to produce narratives with less internal state language. Children with ADHD did not produce less fluent narratives (Hedges' g = 0.23, p = .47), although a scarcity of studies [K = 4] preclude firm conclusions. In conclusion, children with ADHD were impaired in several areas of oral narrative production and screening for narrative language problems should be considered when assessing language and communicative abilities in children with ADHD

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Res Dev Disabil. 2022 Jul;126:104242.

DO COMORBID SYMPTOMS DISCRIMINATE BETWEEN AUTISM SPECTRUM DISORDER, ADHD AND NONVERBAL LEARNING DISABILITY?

Mammarella IC, Cardillo R, Semrud-Clikeman M.

Characterizing the functioning of individuals with neurodevelopmental disorders is crucial to their diagnosis. Research has found that children with different neurodevelopmental disorders, including autism spectrum disorders (ASD), attention deficit and hyperactivity disorder (ADHD), and nonverbal learning disability (NLD), may have comorbid symptoms of anxiety and depression, and problems with pragmatic language. The main aim of the present study was to identify any differences in the above-mentioned comorbid symptoms associated with these clinical profiles. A second aim was to establish how well signs of pragmatic language difficulties could discriminate between the three clinical profiles, in terms of their diagnostic power. For this purpose, 107 participants from 8 to 16 years old with a diagnosis of ASD, ADHD or NLD were compared with a group of typically-developing children. Self-reports on symptoms of anxiety and depression, and parents' reports on social and communication problems were analyzed. Our findings confirmed that symptoms of anxiety and depression, and problems with pragmatic language are associated with different neurodevelopmental disorders, but not in the same way. In terms of diagnostic power, we found that pragmatic language difficulties clearly discriminated children with ASD, ADHD or NLD from typically-developing children. Importantly, pragmatic language difficulties also discriminated adequately between ASD and NLD. Our findings are discussed in terms of the value of considering comorbid symptoms to obtain a more accurate diagnosis of neurodevelopmental disorders

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Res Dev Disabil. 2022 Jul;126:104238.

DEVELOPING AN ARABIC QUESTIONNAIRE TO ASSESS SENSORY PROCESSING DISORDERS AMONG PRESCHOOL EGYPTIAN CHILDREN.

Sobhy N, Afsah O, Baz H.

BACKGROUND: Sensory processing disorder (SPD) is a neurophysiologic disorder in which sensory input is poorly detected, modulated, interpreted and/or to which atypical responses occur. The objective of this study was to validate an Arabic questionnaire for identification of SPD among preschool Arabic-speaking children with Autism Spectrum Disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD).

METHODS: A newly constructed Arabic questionnaire for assessment of SPD was completed by parents of 100 Egyptian Arabic-speaking children including 40 typically-developing children (control group), 30 children with ASD, and 30 children with ADHD in the age range 3-6 years

RESULTS AND CONCLUSION: Sensory processing differences were detected between typically-developing children and children with ASD and ADHD. Significant differences were found in auditory processing, visual processing, oral sensory processing, olfactory processing, total scores and emotional/social response. The current study revealed non-significant differences between ASD and ADHD children as regards auditory, visual, touch, oral sensory, olfactory and total processing scores. On the other

hand, ASD children showed higher scores in proprioceptive processing and lower scores in emotional/social response than children with ADHD. The designed Arabic questionnaire is a valid and reliable assessment tool for identification of SPD in preschool Arabic-speaking children

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Res Dev Disabil. 2022 Jul;126:104244.

THE PERFORMANCE AND PREDICTORS OF CHINESE CHARACTER WRITING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hung YF, Chang CJ.

Writing difficulties are common in children with attention deficit hyperactivity disorder (ADHD). Preliminary evidence suggests that early character writing ability is fundamental for later writing composition and academic achievement. Critical factors of different character writing tasks in children with ADHD, however, remain unclear. This study aims to describe the performance and identify predictors of Chinese character writing in children with ADHD. Thirty Mandarin Chinese-speaking children with ADHD (7.16Â Â±Â 0.59 years) and thirty matched peers (7.21Â Â±Â 0.57 years) were recruited from northern Taiwan. They were evaluated with the Battery of Chinese Basic Literacy (BCBL); the Chinese version of the Test of Nonverbal Intelligence, fourth edition (C-TONI-4); the Chinese version of the Peabody Picture Vocabulary Test-Revised (C-PPVT-R); orthographic awareness test; character naming test; and the BruininksÂ Oseretsky Test of Motor Proficiency, second edition (BOT-2). The results showed that Mandarin Chinese-speaking children with ADHD scored lower than their typically developing peers on both dictation and copying subtests. After controlling for age, orthographic awareness and inattention were identified as important predictors of character dictation; while, manual dexterity was a critical predictor of character copying in children with ADHD. The results demonstrated that character writing problems may exist in Mandarin Chinese-speaking children with ADHD, and cognitive-linguistic and fine-motor skills have varying contributions to Chinese character writing tasks

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Rev Sci Instrum. 2022 May;93:054101.

INTEGRATION OF ELECTROENCEPHALOGRAM (EEG) AND MOTION TRACKING SENSORS FOR OBJECTIVE MEASURE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (MAHD) IN PRE-SCHOOLERS.

Bhattacharyya N, Singh S, Banerjee A, et al.

We developed an integrated device composed of a single-probe Electroencephalogram (EEG) and Charge Coupled Device (CCD) based motion sensors for objective measurement of Attention-deficit Hyperactivity Disorder (ADHD). While the measurement of attention-deficit hyperactivity disorder (MAHD) relies on the EEG signal for the assessment of attention during a given structured task, the CCD sensor depicts the movement pattern of the subjects engaged in a continuous performance task. A statistical analysis of attention and movement patterns was performed, and the accuracy of completed tasks was analyzed using indigenously developed software. The device with the embedded software is intended to improve certainty with criterion E. We used the EEG signal from a single-channel dry sensor placed on the frontal lobe of the head of the subjects (3-5 year old pre-schoolers). During the performance of the task power for delta and beta, EEG waves from the subjects are found to be correlated with relaxation and attention/cognitive load conditions. While the relaxation condition of the subject hints at hyperactivity, a more direct CCD-based motion sensor is used to track the physical movement of the subject engaged in a continuous performance task. We used our indigenously developed software for statistical analysis to derive a scale for the objective assessment of ADHD. We also compared our scale with clinical ADHD evaluations and found a significant correlation between the objective assessment of the ADHD subjects and the clinician's conventional evaluation. MAHD, the integrated device, is supposed to be an auxiliary tool to improve the accuracy of ADHD diagnosis by supporting greater criterion E certainty

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Rev Neurol. 2020;71:438-46.

THE EFFECTS OF PHARMACOLOGICAL TREATMENT WITH STIMULANTS ON CIRCADIAN ACTIVITY PATTERNS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sanabra M, et al.

Introduction. Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders in childhood. The nuclear symptoms of ADHD are treated with stimulant medication such as methylphenidate; however, there's a lot of controversy regarding its side effects.

Aims. To analyse the activity patterns in children with ADHD during a period of 24 hours for seven days, before and after taking pharmacological treatment with stimulants (methylphenidate) and observe the differences between the different presentations of ADHD (inattentive and combined subtype).

Patients and methods. A total of 30 children and adolescents (newly diagnosed with ADHD according to DSM-IV). Analyses were carried out through actigraphy, an instrument that allows us to monitor body movements by analysing movement patterns and differences between sleep and wakefulness.

Results. There were significant differences before and after treatment showing higher activity levels in patients with ADHD before treatment, and a decrease in this situation after taking pharmacological treatment. There are also differences between inattentive and combined subtype, showing the last group, higher activity levels.

Conclusions. The level of activation presented by ADHD subjects is higher before taking stimulant treatment, influencing circadian patterns, sleep and quality of life. Pharmacological treatments help to decrease the level of activation

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Sci Rep. 2022 Mar;12:4909.

META-ANALYTICAL TRANSDIAGNOSTIC NEURAL CORRELATES IN COMMON PEDIATRIC PSYCHIATRIC DISORDERS.

Dugra JR, Eickhoff SB, Potvin S.

In the last decades, neuroimaging studies have attempted to unveil the neurobiological markers underlying pediatric psychiatric disorders. Yet, the vast majority of neuroimaging studies still focus on a single nosological category, which limit our understanding of the shared/specific neural correlates between these disorders. Therefore, we aimed to investigate the transdiagnostic neural correlates through a novel and data-driven meta-analytical method. A data-driven meta-analysis was carried out which grouped similar experiments' topographic map together, irrespectively of nosological categories and task-characteristics. Then, activation likelihood estimation meta-analysis was performed on each group of experiments to extract spatially convergent brain regions. One hundred forty-seven experiments were retrieved (3124 cases compared to 3100 controls): 79 attention-deficit/hyperactivity disorder, 32 conduct/oppositional defiant disorder, 14 anxiety disorders, 22 major depressive disorders. Four significant groups of experiments were observed. Functional characterization suggested that these groups of aberrant brain regions may be implicated internally/externally directed processes, attentional control of affect, somato-motor and visual processes. Furthermore, despite that some differences in rates of studies involving major depressive disorders were noticed, nosological categories were evenly distributed between these four sets of regions. Our results may reflect transdiagnostic neural correlates of pediatric psychiatric disorders, but also underscore the importance of studying pediatric psychiatric disorders simultaneously rather than independently to examine differences between disorders

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Sensors (Basel). 2022 Apr;22.

DYNAMIC SEAT ASSESSMENT FOR ENABLED RESTLESSNESS OF CHILDREN WITH LEARNING DIFFICULTIES.

Stanià V, et al.

Children with Attention-Deficit/Hyperactivity Disorder (ADHD) face a range of learning difficulties in the school environment, thus several strategies have been developed to enhance or optimise their performance in school. One possible way is to actively enable appropriate restlessness using dynamic seats. In this paper, an assessment of the efficacy of a dynamic seat while solving school task is presented and compared to classic chair and therapy ball. To test the effectiveness of active seat, a study that examined task solving performance while observing the intensity of movement, in-seat behaviour and psychophysiological

responses (electrodermal activity, facial temperature) was designed. A total of 23 school-aged children participated in the study, 11 children with a combined type of ADHD and 12 children without disorders. Children with ADHD achieved the best results when sitting in the active seat, where the most intense movement and best in-seat behaviour was observed. At the same time, psychophysiological parameters indicate that when performing better at the task children with ADHD were not too challenged and were consequently less agitated. Results have suggested that for a better cognitive performance of children with ADHD, it is crucial to provide a comfortable and pleasant workspace that enables them the right amount of restlessness

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Soc Cogn Affect Neurosci. 2022 May;17:482-92.

THE LIMITS OF MOTIVATIONAL INFLUENCE IN ADHD: NO EVIDENCE FOR AN ALTERED REACTION TO NEGATIVE REINFORCEMENT.

Van DJ, Sonuga-Barke EJS, Moerkerke M, et al.

Functional magnetic resonance imaging studies have reported a diminished response in the brain's reward circuits to contingent cues predicting future monetary gain in adolescents with attention-deficit/hyperactivity disorder (ADHD). The situation with regard to monetary loss is less clear, despite recognition that both positive and negative consequences impact ADHD behaviour. Here, we employ a new Escape Monetary Loss Incentive task in an MRI scanner, which allows the differentiation of contingency and valence effects during loss avoidance, to examine ADHD-related alterations in monetary loss processing. There was no evidence of atypical processing of contingent or non-contingent monetary loss cues in A

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Sociol Health Illn. 2022 Mar;44:604-23.

MAPPING MENTAL HEALTH INEQUALITIES: THE INTERSECTING EFFECTS OF GENDER, RACE, CLASS, AND ETHNICITY ON ADHD DIAGNOSIS.

Bergey M, Chiri G, Freeman NLB, et al.

While the effects of social stratification by gender, race, class, and ethnicity on health inequalities are well-documented, our understanding of the intersecting consequences of these social dimensions on diagnosis remains limited. This is particularly the case in studies of mental health, where "paradoxical" patterns of stratification have been identified. Using a Bayesian multi-level random-effects Poisson model and a nationally representative random sample of 138,009 households from the National Survey of Children's Health, this study updates and extends the literature on mental health inequalities through an intersectional investigation of one of the most commonly diagnosed psychiatric conditions of childhood/adolescence: attention-deficit hyperactivity disorder (ADHD). Findings indicate that gender, race, class, and ethnicity combine in mutually constitutive ways to explain between-group variation in ADHD diagnosis. Observed effects underscore the importance and feasibility of an intersectional, multi-level modelling approach and data mapping technique to advance our understanding of social subgroups more/less likely to be diagnosed with mental health conditions

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Spec Care Dentist. 2022 May;42:252-56.

IMPACT OF AN ORAL HEALTH EDUCATION PROGRAM IN EGYPTIAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CROSS SECTIONAL STUDY.

Hanafy RM, Abdelmoniem SA.

AIM: This study was conducted to assess the oral health status in a group of Egyptian children, living with ADHD, before and after the implementation of an oral health education program.

METHODS: A total of 29 Egyptian children, aged 8-12 years old diagnosed with ADHD were enrolled in this study. Their oral health status was assessed using OHI-S. Oral health education program using audiovisual and verbal methods was addressed to the children and their caregivers. The children were advised to limit eating sugar to be once per week, and to brush their teeth twice a day. Modified Bass Technique of tooth brushing was demonstrated to the children using jaw model and toothbrush. A motivational visit was

performed for the children after 1 month. At the end of the 3 months program, oral health status of the children was reassessed.
RESULTS: The results showed that there was a significant increase in cases with "Good" scores after the oral health education program ($p < .001$), moreover, there was a significant decrease of OHI-S scores after the program ($p < .001$).
CONCLUSION: The oral health education program was efficient in achieving improvement in the oral health status of children with ADHD

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Syst Rev. 2022 Mar;11:49.
PREVALENCE OF NEURODEVELOPMENTAL DISORDERS AND THEIR IMPACT ON THE HEALTH AND SOCIAL WELL-BEING AMONG LOOKED AFTER CHILDREN (LAC): A SYSTEMATIC REVIEW PROTOCOL.
Heady N, Watkins A, John A, et al.
BACKGROUND: Looked after children (LAC) that are placed in either a foster, kinship, residential care setting or transition to adoption continue to develop debilitating disorders that significantly impact their overall health and social well-being. The prevalence of these disorders is often depicted under broad categories such as mental, behavioural or neurodevelopmental disorders (NDDs). Limited in research is the prevalence of what specific disorders fall under these broad categories. NDDs such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) which fall under an umbrella group in the expert field of genetics and neuropsychiatry will be explored. Unsupported, these disorders can lead to suboptimal health and social outcomes for both the child and family. In the general population, the prevalence of these NDDs and impacts on health and social well-being are relatively well documented, but for minority groups such as LAC, research is extremely limited. This review aims to estimate the prevalence of NDDs among LAC and explore how they might impact the health and social well-being of these vulnerable children. If feasible, the review will compare the prevalence rates to those children who are not looked after, to illuminate any differences or similarities between populations.
METHODS: PubMed, ASSIA, IBSS, Web of Science, PsychINFO, Scopus, Psych articles, Social Care Online, secondary, grey literature and government publications will be searched to identify any eligible studies. No restrictions will be placed on country, design or year of publication. Studies must provide primary data on the prevalence or incidence of NDDs for individuals < 25 years of age, supported by either a diagnostic code, standardised diagnostic assessment tool or survey response. The Joanna Briggs Institute (JBI) critical appraisal tools will be utilised to assess the quality and bias and the random-effects model used to estimate a pooled prevalence of NDDs.
DISCUSSION: Attaining an estimated prevalence of these NDDs and identifying any impacts on health and social well-being might inform key stakeholders in health, educational and social sectors with important information that might aid in the early identification and intervention to safeguard and meet the unique needs of these children.
SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD4201913103

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Therapeutic Drug Monitoring. 2022;44:340-44.
DETERMINATION OF GUANFACINE IN ORAL FLUID AND SERUM OF CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SHORT COMMUNICATION .
Wohkittel C, Scherf-Clavel O, Fekete S, et al.
Background: Guanfacine, a selective +¦2A-adrenoreceptor agonist, is a second-line medication for treating children and adolescents with attention-deficit/hyperkinetic disorder. The dosage administered as milligram per body weight to balance the potential benefits and risks of treatment. Therapeutic drug monitoring (TDM) is useful for identifying a patient's therapeutic window to optimize individual drug dosing and reduce the risk of adverse drug reactions. However, in children and adolescents, intravenous sample collection is especially stressful and thus remains a primary challenge, restricting the use of TDM. Therefore, evaluating alternative specimens to facilitate TDM is a worthwhile task. The aim of this study was to assess the feasibility of using oral fluid for TDM of guanfacine in children and adolescents.

Methods:In this article, 9 patients (median age 8.1 years; 6 boys and 3 girls) undergoing treatment with guanfacine were included. Simultaneously collected oral fluid and serum samples were deproteinized using methanol containing a stable isotope-labeled internal standard before the determination of guanfacine by liquid chromatography-tandem mass spectrometry. Pearson correlation and paired t test were used for statistical analysis.
Results:The mean serum guanfacine concentration was 3 times higher than that detected in oral fluid (7.47 ng/mL versus 2.36 ng/mL; t (8) = 5.94; P < 0.001). A strong positive linear correlation (r = 0.758, P = 0.018) was identified between oral fluid and serum concentrations. A strong but nonsignificant negative correlation (r = -0.574, P = 0.106) was detected between the oral fluid pH and oral fluid-to-serum concentration ratio.
Conclusions:The strong correlation between oral fluid and serum concentration and the probable small effect of oral fluid pH on oral fluid-to-serum concentration ratio supports guanfacine as a suitable candidate for TDM in oral fluid

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Transl Behav Med. 2022 May;12:714-20.

INFORMING WOMEN ABOUT THE RISKS OF EXPOSING BABIES TO TOBACCO SMOKE: OUTREACH AND EDUCATION EFFORTS USING FACEBOOK "BOOST POSTS".

Miller CA, Jung KS, Schwartz-Bloom RD, et al.

Maternal smoking is associated with a host of negative health outcomes, including an increased risk of children developing attention-deficit/hyperactivity disorder (ADHD). This study evaluated the efficacy of health messages disseminated through Facebook Ads focused on reducing tobacco smoke exposure during pregnancy. Two message versions were promoted via post advertisements on Facebook-a static infographic and a video containing an animated version of the infographic. The reach of and engagement with each message version was evaluated. Comments made to the posts were assessed using content analysis. The infographic reached approximately 60,000 people and the video reached about 16,000 people. The average costs were $10.00 and $40.00 per 1,000 people reached for the infographic- and video-based posts, respectively. While there was no engagement with the video, the infographic was liked (n = 157), given alternative likes (n = 59), shared (n = 171 to 341), and commented on (n = 221). About one-quarter of comments contained a personal narrative and mentions of health history related to ADHD and/or smoking. Comments were more often negative (than positive) (16.6% vs 3.9%) and expressed skepticism more often than message acceptance (21.5% vs 12.2%). Facebook users were more responsive to the infographic (compared to the video) and static posts were a preferred channel (i.e., higher engagement at a lower cost) to disseminate messages when using the boost post feature on Facebook for health education. Our review of the comments provided insights into message acceptance and guidance for future social media-based health message campaigns. However, it is not known whether and if so, how, these findings on message exposure would correlate with behavioral intentions or changes in behavior, such as intentions to quit smoking or smoking cessation

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Trials. 2022 May;23:434.

THE EFFECT OF ROSA CANINA L. AND A POLYHERBAL FORMULATION SYRUP IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A STUDY PROTOCOL FOR A MULTICENTER RANDOMIZED CONTROLLED TRIAL.

Golsorkhi H, Qorbani M, Kamalinejad M, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder in childhood and adolescence. A number of these patients do not respond to the current pharmacological treatments and there may also be drug side effects. This study aims to determine the efficacy and safety of two herbal medicine products, including Rosa canina L. (RC) and a polyherbal formulation (PHF) syrup, on the clinical manifestations of ADHD in children and adolescents.
METHODS: Ninety ADHD patients based on DSM-5 diagnostic criteria will be randomly assigned equally into three groups: (1) RC syrup + methylphenidate (MP), (2) PHF syrup + MP, and (3) placebo + MP according to the inclusion criteria (30 subjects in each group). The syrup dosage is 5cc every 8 h, and MP will have a stabilized dose for 8 weeks during the study. Moreover, Conner(')s questionnaires will be completed by the teacher and parents before the intervention and then every 4 weeks. Also, the Child

Symptom Inventory-fourth edition (CSI-4) and temperament questionnaires will be completed before the intervention and every 4 weeks until 2 months.
DISCUSSION: This trial is the first experiment to determine the effects of RC and PHF syrups on the clinical manifestations of ADHD in children and adolescents. Our findings provide new insight into the effect of these herbal products on the clinical manifestations of ADHD.
TRIAL REGISTRATION: Iranian Registry of Clinical Trials IRCT20190923044855N1 . Registered on 14 January 2020. The trial was registered at https://www.irct.ir/

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Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122:69-77.

MODERN APPLICATION POSSIBILITIES HOPANTHENIC ACID (PANTOCALCIN) IN TREATMENTDISEASES OF THE NERVOUS SYSTEM IN CHILDREN.

Nemkova SA.

The review analyzes the current possibilities of using hopanthenic acid (Pantocalcin) in the treatment of diseases of the nervous system in children (perinatal CNS lesions, developmental delays, cerebral palsy, ADHD, tics, enuresis, cognitive and neurotic disorders), taking into account modern standards and clinical recommendations. The results of numerous studies demonstrate that Pantocalcin is a highly effective and safe drug in the treatment of diseases of the nervous system in children with complex neurometabolic, neuroprotective, neurotrophic properties

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Review

Drugs for patients with epilepsy and excessive daytime sleepiness

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ABSTRACT

Excessive daytime sleepiness (EDS) and attentional deficits are often observed in people with epilepsy. They may be the consequence of seizures and subclinical discharges as well as of comorbid conditions as obstructive sleep apnea/hypopnea syndrome (OSAS), attention deficit hyperactivity disorder (ADHD), or other less frequent disorders. Excessive daytime sleepiness may also be caused or worsened by antiseizure medications (ASMs).

Several meta-analyses suggested that lamotrigine, lacosamide, and perhaps eslicarbazepine are less sedative than other traditional and new ASMs and, in patients prone to somnolence, might be preferred over ASMs with more sedative properties.

In patients with severe EDS and/or ADHD, advantages and risks of a treatment with a psychostimulant need to be considered. Methylphenidate, modafinil, armodafinil, pitolisant, and solriamfetol are authorized for use in ADHD and EDS in patients with narcolepsy and some of them also in OSAS. These agents are off-label for the treatment of EDS associated with epilepsy. They do not have proconvulsant effects, although there are several possible risks for patients with epilepsy. The risks of cardiovascular events and psychiatric symptoms should be carefully evaluated as such disorders can coexist with epilepsy and be triggered by these agents. Finally, combination of psychostimulants with ASMs may be associated with several pharmacokinetic drug–drug interactions.

1. Introduction

Somnolence and attention deficits are commonly reported by people with epilepsy and may have several underlying causes [1–3].

A subtle and often not perceived attention and executive dysfunction has been observed in 49% of adults with new-onset epilepsy before treatment [4], and it has been hypothesized that seizures themselves may impair vigilance and attention [5]. Focal seizures and subclinical discharges may cause functional impairment in several interconnected brain regions, including subcortical areas as the ascending reticular activating system (ARAS). This is a functional network involved in vigilance and composed by locus coeruleus, raphe nuclei, posterior tuberomammillary hypothalamus, and pedunculopontine tegmentum. Vigilance in wakefulness is maintained by ARAS through thalamic and extrathalamic projections to the cerebral cortex [6]. These pathways can be potentially disrupted by seizures or interictal discharges [5]. Resting-state functional magnetic resonance imaging (fMRI) has shown a decrease in the overall connectivity in patients with temporal lobe epilepsy, which was particularly evident between ARAS and the neocortex and was correlated with the number of seizures impairing consciousness [7].

Excessive daytime somnolence (EDS), characterized by persistent sleepiness during the day after apparently adequate or even prolonged nighttime sleep, resulting in irrepressible need for sleep and/or unintended lapses into drowsiness [8] is also the consequence of several sleep disorders that can be comorbid with epilepsy.

Obstructive sleep apnea/hypopnea syndrome (OSAS), is a disorder in which repeated episodes of obstructive apneas determine sleep disruption [9]. Epidemiologic studies estimated that this condition is very frequent: it affects 2 to 4 percent of middle-aged adults [10] and has a higher prevalence in patients with epilepsy [11–13]. A bidirectional mechanism between epilepsy and OSAS has been suggested [14]. On one hand, OSAS can lower seizure threshold through sleep fragmentation, oxygen desaturation and chronic sleep deprivation. On the other, epilepsy can promote sleep

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1525-5050/

apneas either by amplifying the sleep-induced breathing instability or as a consequence of antiseizure treatment. The continuous positive airway pressure (CPAP) device during the night is the treatment of choice, reduces EDS and improves quality-of-life in patients with moderate and severe OSAS [15]. Residual EDS, however, persists in 9–22% of patients treated with CPAP [16], and can be the consequence of irreversible brain damage, mainly to prefrontal cortex, due to chronic hypoxia. This damage could explain both the sleepiness and cognitive dysfunction observed in these patients.

In addition, medical or psychiatric disorders, substances or drugs including antiseizure medications (ASMs), insufficient sleep syndrome or rare diseases such as narcolepsy, idiopathic hypersomnia and Kleine-Levin syndrome can be associated with epilepsy and yield EDS [17].

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by disturbances of attention, impulsivity, and hyperactivity with an overall prevalence of about 5% in children and 2.5% in adults. Prevalence of ADHD in people with epilepsy is more than twice that of the general population, and symptoms of ADHD have been reported in up to 35% of patients with epilepsy [1].

There are several hints suggesting that ADHD and EDS share common pathophysiological mechanisms. Both conditions benefit from treatment with psychostimulants and symptoms of ADHD are frequently observed in patients with EDS, irrespective of the underlying disorder (i.e., narcolepsy, OSAS, restless leg syndrome, and periodic limb movements during sleep). It is reasonable that the fragmentation of sleep can predispose to develop ADHD symptoms [18]. There are also suggestions that hyperactivity in children with ADHD may be a strategy to avoid falling asleep because these subjects are in a hypoarousal state [18]. In one study, children with ADHD had inattention scores that correlated with the degree of EDS [19].

There is also evidence that noradrenergic and dopaminergic dysfunctions promote the disruption of high-level executive functions in ADHD and are implicated in the instability of sleep observed in patients with EDS [18,20,21].

A meta-analysis of 25 studies, has very recently shown that sleep quality is significantly worse in patients with epilepsy in respect to a control population while EDS (as measured trough Epworth sleepiness scale) was not significantly affected [22].

Excessive daytime sleepiness and attention deficits may interfere with several daily activities, increase the risk of accidents [23] and are associated with cognitive impairment, poor memory, and mood disorders that may themselves require treatment with psychostimulants [24].

In patients with epilepsy and severe EDS and/or ADHD, the effect of ASMs on somnolence and attention as well as the benefits and risks of the treatment with psychostimulant agents need to be taken into account in clinical practice. Pharmacokinetic and pharmacodynamic interactions between these two classes of drugs should also be considered.

Here, we address the relationship between ASMs and somnolence, and provide an overview of the pharmacology, efficacy and safety of psychostimulants. In addition, we address the interactions between ASMs and psychostimulant agents, and highlight the implications for use in clinical practice.

2. Somnolence as an adverse effect of antiseizure medications

Although all ASMs reduce neuronal excitability in the central nervous system, they have different sedative properties. Somnolence is one of the most common adverse events (AEs) associated with the traditional ASMs, while new ASMs are generally less burdened by detrimental sedative effects [25,26].

2.1. Assessment of rate of somnolence in randomized clinical trials of new antiseizure medications

We searched meta-analyses of the most frequently used ASMs [i.e., brivaracetam (BRV), cannabidiol (CBD), cenobamate (CBM), eslicarbazepine (ESL), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), perampanel (PER), pregabalin (PGB), rufinamide (RFN), topiramate (TPM), and zonisamide (ZNS)] to evaluate whether the AE "somnolence" was associated with the experimental drug in registrative RCTs of add-on treatment conducted in patients with drug-resistant focal seizures. These RCTs are relatively homogeneous and are available for all ASMs. Electronic search was performed through MEDLINE (accessed by PubMed: "antiepileptic drugs AND meta-analysis AND add on trial AND epilepsy"). In addition, we have searched all meta-analyses aimed to identify every treatment-emergent AE associated with the active drug across all available RCTs, including also studies where the drug was prescribed for indications other than the anti-seizure effects (Search performed "any ASM" AND meta-analysis AND adverse effect"). We searched also the network meta-analyses (NMAs) aimed at comparative evaluations of ASMs in whom the AE "somnolence" was assessed (PubMed: "Network meta-analysis AND antiepileptic drugs AND epilepsy"). Psychostimulants were selected among those drugs authorized for use in patients with EDS or ADHD.

Relevant references of the identified articles were also examined.

2.2. Results of the assessment of ASM-induced somnolence in clinical trials

By database searching, we identified 125 meta-analyses that assessed the safety and tolerability of ASMs. From the retrieved studies, for any of the above mentioned ASM, we selected only the most recent meta-analyses in whom the AE somnolence was evaluated. For 4 drugs (LCM, LEV, PER, PGB) there were also meta-analyses that specifically explored treatment tolerability across all the conditions for which the drug can be prescribed (see Table 1). In our search, we also identified 16 NMAs, and in 3 of these the item somnolence was analyzed (see Table 2).

Meta-analyses exploring AEs of ASMs showed that BRV, CBD, CBM, GBP, LEV, OXC, PER, PGB, RFN, TPM and ZNS, are significantly associated with somnolence, while LTG, and LCM are not and ESL is associated with somnolence at high and full doses. Results from the two NMAs further confirm these findings with the exception of ESL that resulted not associated with this adverse effect and add the information that LTG is significantly less sedative than GBP and PGB (Table 1). In one meta-analysis, the lack of association of several ASMs with somnolence was the consequence of the low number of RCTs (and patients) included [46].

3. Psychostimulants

Herein psychostimulants authorized for ADHD and EDS in patients with narcolepsy and OSAS are shortly described. These agents are often prescribed "off label" in other conditions associated with EDS and can be used in patients with epilepsy and EDS.

3.1. Mechanism of action

Methylphenidate (MPH) is structurally related to amphetamine and is used for ADHD and narcolepsy since the mid-twentieth cen-

Table 1
The treatment emergent adverse event "somnolence" in meta-analyses of randomized clinical add on trials of antiseizure medications.

Antiseizure medication	Clinical condition and experimental design	Number of RCTs included	Total number of patients included in each meta-analysis	Main findings on the adverse event "somnolence" versus placebo
Brivaracetam [27]	Drug-resistant focal epilepsy (adults). Double-blind, add on, parallel.	6	2.434	Significantly associated (all doses pooled)
Cannabidiol [28]	Drug-resistant patients with Lennox–Gastaut and Dravet syndrome. Double-blind, add on, parallel.	4	550	Significantly associated
Cenobamate [29]	Drug-resistant focal epilepsy (adults). Double-blind, add on, parallel.	2	659	Significantly associated (any dose)
Eslicarbazepine acetate [30]	Drug-resistant focal epilepsy (adults). Double-blind, add on, parallel	5	1.799	Significantly associated (High dose and all doses)
Gabapentin [31]	Drug-resistant focal epilepsy (adults). Double-blind, add on, parallel.	12	2–607	Significantly associated
Lacosamide [32]	Drug-resistant focal epilepsy (adults). Double-blind, add on, parallel.	3	1.311	Significantly associated
Lacosamide [33]	Drug-resistant focal epilepsy and patients with various diseases (adults). Double blind, add on in patients with epilepsy, parallel.	10	3.148	Not significantly associated (any dose)
Lamotrigine [34]	Drug-resistant focal epilepsy (children and adults) Double blind, cross over or parallel.	5 parallel 8 cross-over	1.806	Not significantly associated
Levetiracetam* [35]	Drug-resistant focal epilepsy (children) Double-blind vs placebo and retrospective open studies.	31 (18 prospective and 13 restrospective)	1.763	Significantly associated (all doses pooled)
Levetiracetam [36]	Drug-resistant focal epilepsy and various diseases (any age) All double blind studies.	25	2.832	Significantly associated (all doses pooled)
Oxcarbazepine [37]	Drug-resistant focal epilepsy (any age) Double-blind, add-on, parallel.	6	1.593	Significantly associated
Perampanel [38]	Drug-resistant focal epilepsy and Parkinson disease (adults). Add on (epilepsy), double-blind, parallel.	9	3.947	Significantly associated at the dose of 8 mg/day.
Pregabalin [39]	Drug-resistant focal epilepsy (adults) Double-blind, add-on, parallel.	6	2.009	Significantly associated
Pregabalin [40]	Drug-resistant epilepsy and various diseases (adults). Double-blind, add-on (patients with epilepsy), parallel.	38	11.918	Significantly associated
Rufinamide [41]	Drug-resistant focal epilepsy (any age) Double-blind, add-on, parallel.	6	1.759	Significantly associated
Topiramate [42]	Drug-resistant focal epilepsy (adults) Double-blind, add on, parallel.		1.401	Significantly associated
Zonisamide [43]	Drug-resistant epilepsy Double blind, add on, parallel.	8	1.636	Significantly associated

Abbreviations: AE = adverse event, RCT = randomized controlled trial.
Meta-analyses included are those that have evaluated the adverse effect "somnolence/drowsiness" *Meta-analysis and pooled analysis.
For levetiracetam and pregabalin were available meta-analyses of RCTs for drug-resistant epilepsy and meta-analyses including RCTs from all conditions.

tury [1]. MPH reduces dopamine (DA) and norepinephrine (NE) reuptake in the neuron through inhibition of presynaptic transporters. It also increases activity of a transporter that carries monoamines into presynaptic neuron vesicles and decreases metabolism of extra-vesicular DA. All these actions result in increased extracellular availability of DA and NE. In addition, MPH is agonist of 5HT1A serotonin and α2 adrenergic receptors [47,48].

Modafinil (a mixture of R- and S-enantiomers) is a psychostimulant whose precise mechanism of action is not entirely known; this agent binds to the transporter of DA and inhibits the reuptake of DA without affecting DA receptors [49]. Armodafinil is the R-enantiomer of modafinil and shows similar pharmacological properties in animal and *in vitro* studies [50].

Solriamfetol is the newest psychostimulant drug; it inhibits the transporters of DA and NE without significant effects on other targets, and increases extracellular concentrations of DA and NE in the striatum and prefrontal cortex [51].

Pitolisant has a completely different mechanism of action being a selective, high-affinity competitive antagonist and an inverse agonist of the histamine H3 receptor subtype. Through blockade of histamine auto-receptors, pitolisant enhances the activity of brain histaminergic neurons [52,53].

3.2. Pharmacokinetic

All these drugs are rapidly absorbed and have a linear pharmacokinetic; the absorption of MPH, modafinil, armodafinil, and solriamfetol is delayed by concomitant food administration, without change in bioavailability.

MPH undergoes extensive hepatic metabolism with only a small amount of drug excreted in the urine (methylphenidate, SPC). Likewise, modafinil and armodafinil are metabolized to inactive metabolites in the liver, mainly by CYP 3A4, with a small proportion of drugs being eliminated unchanged [49,50]. Solriamfetol is primarily excreted in the urine as unchanged drug; hepatic impairment and concomitant drugs are therefore not expected to affect its pharmacokinetics [54].

Pitolisant is metabolized to inactive metabolites by the hepatic oxidative enzymes CYP3A4 and 2D6. Inactive metabolites are excreted as glycine and glucuronide conjugates [55].

Table 2
. Network meta-analyses conducted on ASMs in whom the item "somnolence" has been analyzed.

Study	Study aim, antiseizure medications assessed, and included population	Main findings on the adverse event "somnolence" versus placebo	Comparative findings for the adverse event "somnolence"
[43]	Network meta-analysis of 8 RCTs aimed to assess AEs of 3 ASMs (eslicabazepine, lacosamide, oxcarbazepine) in drug-resistant patients with epilepsy: 1858 randomized to active drug and 874 to placebo.	Somnolence significantly associated with high doses of oxcarbazepine and not with eslicarbazepine or lacosamide (any dose).	Somnolence not assessed in the indirect comparisons.
[44]	Network meta-analysis of 90 RCTs aimed to assess comparative efficacy and tolerability (three selected AEs: somnolence, dizziness and fatigue) of 17 ASMs (brivaracetam, carisbamate, eslicarbazepine, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, retigabine, tiagabine, topiramate, vigabatrin, and zonisamide) in adults with drug-resistant epilepsy: 27.638 patients.	Brivaracetam, carisbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, perampanel, rufinamide, retigabine, topiramate, and zonisamide significantly associated with somnolence.	Lamotrigine was statistically
		Eslicarbazepine, lacosamide, lamotrigine, tiagabine, not associated (vigabatrin not assessed for this adverse effect)	Better than gabapentin and pregabalin. Tiagabine was better than gabapentin and pregabalin.
[45]	Network meta-analysis of 32 RCTs aimed to assess efficacy and tolerability (two selected AEs: somnolence and dizziness) of 11 ASMs (eslicarbazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, retigabine, tiagabine, topiramate, zonisamide) in adults with drug-resistant epilepsy: 5048 patients randomized to active drugs and 2610 to placebo.	Perampanel, topiramate and pregabalin significantly associated with somnolence.	No ASM was significantly worse or better than any other
		Eslicarbazepine, levetiracetam, gabapentin, oxcarbazepine, retigabine, tiagabine, zonisamide not associated (only few studies included for gabapentin, retigabine, and tiagabine) Lamotrigine not included in the analysis of somnolence*	

All drugs have a low protein binding with the exception of pitolisant.

3.3. Efficacy

MPH has been approved in 1953 and is currently indicated for ADHD and narcolepsy. Many studies have assessed efficacy of MPH in subjects with these diseases [1,56]. There are also several open-label and few controlled studies, often of short duration and with small sample sizes, performed in epileptic patients with ADHD symptoms, mainly of pediatric age [1]. In general, these studies demonstrated that MPH improves attention, hyperactivity, and impulsivity also in people with ADHD/epilepsy comorbidity. A positive evaluation of efficacy and safety of MPH in children with ADHD and epilepsy has been reported in a consensus paper [57].

Randomized, placebo-controlled trials have been more recently performed with the new psychostimulants, specifically called "wake promoting agents". These studies demonstrated the efficacy of modafinil, armodafinil, pitolisant, and solriamefetol in the treatment of EDS in patients with narcolepsy [49,50,58,59]. Efficacy on residual EDS in patients with OSAS and treated with CPAP or refusing this treatment has been demonstrated for modafinil [60,61], pitolisant [62,63], and solriamfetol [64,65]. Up to now, no clinical studies with these drugs have been performed in patients with epilepsy, with the exception of pitolisant. This molecule has been investigated for the treatment of seizures in patients with drug-resistant epilepsy in an exploratory phase 2 trial, but results were inconclusive [66].

3.4. Effect on seizures

Seizures are well-recognized adverse reactions of central nervous system stimulants [67], with recreational drugs (cocaine, amphetamine, methamphetamine, heroin, and phencyclidine) being the most often implicated substances [68,69]. In experimental models, amphetamine displayed the potential to both increase and decrease the risk of seizures [70]. Likewise, modafinil showed both anticonvulsant and convulsant effects in animal models of seizures [71].

However, the treatment with different "wake promoting agents" (MPH, modafinil, armodafinil) has not been associated with higher incidence of seizures in clinical studies and post-marketing surveillance of patients without epilepsy [72], even when taken in overdose [73,74]. In a recent review, MPH has been considered safe for the treatment of epilepsy-related attention deficits [1].

The new agents pitolisant and solriamfetol were not associated with seizures in regulatory clinical studies [52,75].

The possible anti-seizure effect of pitolisant has been studied in an early phase II study in photosensitive epilepsy. Patients with generalized photoparoxysmal discharges showed a statistically significant and dose-dependent suppression of the response to intermittent photic stimulation in the EEG after single doses of 20, 40, and 60 mg of pitolisant [76]. However, a clinical, phase II study aimed to demonstrate the anti-seizure effect of pitolisant in focal drug-resistant epilepsy gave inconclusive results, possibly due to the low number of patients recruited [66].

4. Special aspects concerning safety of psychostimulants in patients with epilepsy

4.1. Psychiatric adverse effects

Psychostimulants may exacerbate behavioral disturbances and their use has been associated with rare cases of psychotic and/or mood symptoms also in patients without a prior psychiatric history. For this reason, these agents should be used with special attention in patients with epilepsy that are at higher risk of psychiatric disturbances [77]. Clinical studies suggested that schizophrenia-like psychoses are between 6 and 12 times more fre-

quent in patients with epilepsy than in the general population, with prevalence rates of 7–10% [78].

MPH has been associated with psychoses at supra-therapeutic doses [1]. Psychiatric symptoms have been reported in clinical trials and post-marketing experience of modafinil [79], armodafinil [50], pitolisant [55], and solriamfetol [58]. Among these AEs, agitation, aggression, suicidal ideation, and psychomotor hyperactivity were the most frequently observed. Mania and psychosis have been described with modafinil, armodafinil, and pitolisant [58]. Up to now, similar cases have not been reported with solriamfetol [58]. It should be however considered that this drug has been administered to a limited number of patients and patients with a history of concurrent psychosis or bipolar disorders were excluded from clinical trials.

4.2. Cardiovascular adverse effects

Cardiovascular diseases [80,81] and sudden death [82] are more frequent in patients with epilepsy than in general population. The main risk factors for sudden death in epilepsy include uncontrolled tonic-clonic seizures [82] and underlying structural cardiac diseases; ASMs that can alter cardiac electrophysiology can also have a role in some cases [83]. Cardiovascular diseases are more often caused or aggravated by enzyme-inducing ASMs that have atherogenic effects [84].

All psychostimulants, with the exception of pitolisant, may determine a modest increase in blood pressure and heart rate that require monitoring during treatment and avoidance of drugs that may cause severe hypertension. Cases of sudden death after MPH use have been reported in children with structural cardiac abnormalities or other serious heart problems [1]. One epidemiological study suggested an increase in stroke incidence among modafinil-treated patients compared to those not treated with this drug [85]. Use of modafinil in Europe has not been allowed for the treatment of EDS in patients with OSAS because in this population the risk/benefit balance has not been considered favorable in terms of potential cardiovascular and cerebrovascular complications [58]. Of note, pitolisant, which does not increase blood pressure [63], may prolong QT interval at supra-therapeutic doses [53].

In patients with epilepsy, especially those at high risk of cardiovascular diseases, the administration of these agents should be considered with caution and their effects on the cardiovascular system should be monitored.

4.3. Idiosyncratic adverse effects

Among the ASMs, carbamazepine (CBZ), ESL, LTG, OXC, phenytoin (PHT), phenobarbital (PB), primidone (PRI), and zonisamide (ZNS) are associated with rash and more serious idiosyncratic cutaneous reactions [86].

In post-marketing experience, modafinil and armodafinil have been associated with rare cases of serious and life-threatening rash reactions, including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms, both in adults and children. The incidence of rash leading to discontinuation of modafinil was 0.8% in clinical trials with pediatric patients [49]. Cutaneous adverse effects with MPH have been very rarely observed [48].

Starting treatment with modafinil or armodafinil in people with epilepsy and prior idiosyncratic reactions induced by ASMs should be assessed carefully: the history of idiosyncratic effects is, indeed, a predisposing factor for similar complications with other drugs [86].

5. Potential drug–drug interactions between psychostimulants and antiseizure medications

MPH is not metabolized by cytochromes to a clinically relevant extent, and inducers or inhibitors of these enzymes are not expected to alter MPH pharmacokinetics. Conversely, MPH is a weak inhibitor of several CYP enzymes. All clinical studies aimed to assess potential DDIs between MPH and ASMs failed to show any significant change of ASMs plasma concentration after MPH administration [87,88]. Few case reports have, however, documented that the combination of MPH with specific ASMs (i.e., CBZ, PHT) can increase the levels of ASMs and lead to toxic adverse effects [89,90].

Modafinil and armodafinil are substrates and induce several cytochromes with the largest effects on CYP3A in the gastrointestinal tract. Consequently, co-administration of ASMs that are potent inducers of CYP activity, such as CBZ and PB, can reduce the plasma levels of these "wake promoting agents"; conversely, all ASMs metabolized by CYP3A4 may potentially have their metabolism induced. Modafinil has also the property to inhibit CYP2C19 and, possibly, CYP2C9 and therefore decrease the clearance of PHT and diazepam [49]. *In vitro* studies showed that modafinil and armodafinil are substrates of P-glycoprotein (P-gp) [49].

The metabolism of pitolisant can be induced and this drug has inducing properties on several P450 cytochromes (CYP3A4, CYP1A2, and CYP2B6); clinically relevant interactions with UGTs, CYP2C and P-gp substrates are also hypothesized. ASMs that are strong CYP3A4 enzyme inducers (CBZ, PHT, and PB) potentially decrease pitolisant levels. Although predicted by *in vitro* studies, however, clinical studies failed to confirm these findings in healthy volunteers receiving therapeutic doses of pitolisant [58].

Finally, *in vitro* studies indicated that clinically significant drug–drug interactions involving CYPs and transporters are not expected with solriamfetol [58,75].

In conclusion, combination of modafinil, armodafinil, and pitolisant with ASMs that are strong enzyme inducers might require drug monitoring and dosage adjustments. MPH, modafinil, and armodafinil are weak inhibitors of some CYP enzymes and may increase levels of PB and PHT. Solriamfetol does not seem to be associated with any clinically relevant interactions with other medications.

For details on indication, pharmacokinetic, drug–drug interactions and most important safety concerns of psychostimulants see Table 3.

6. Other agents used for treatment of excessive daytime somnolence

Although several agents are used for treatment of cataplexia and EDS, the hallmark symptoms of type 1 narcolepsy [58,59], only sodium oxybate, has been specifically approved for use in this condition [91] and will be briefly discussed. This agent is a central nervous system depressant that reduce fragmented nighttime sleep thus improving sleep architecture and, through this indirect mechanism, reduces EDS in patients with narcolepsy [91]. It is rapidly absorbed after oral administration and eliminated with a half-life of less than 1 hour by biotransformation to carbon dioxide, which is subsequently eliminated by expiration. In vitro studies indicate that this agent does not significantly inhibit the activities of several human isoenzymes [91].

Its positive effect on EDS, has been recently demonstrated by a recent meta-analysis of 15 placebo-controlled studies performed on about 2000 narcolepsy patients [92] and a few clinical cases suggest its safety in patients with generalized epilepsies [93].

Table 3
Characteristics of wake promoting agents and implications for use in patients with epilepsy.

Psychostimulant agent	Indication	Drug dose	Pharmacokinetics	Potential drug-drug interactions with antiseizure medications	Main safety concerns in patients with epilepsy
Methylphenidate	ADHD in children > 6 years	ADHD: up to 60 mg BID	Tmax (IRF) = 1–3 h (delayed by high-fat meal).	Weak inhibitor of several cytochromes. It may potentially increase levels of phenobarbital, phenytoin, oxcarbazepine, topiramate and rufinamide.	Demonstrated lack of proconvulsant effects in patients with epilepsy.
	up to the age of 65 (FDA and EMA)		HL = approximately 3 h.		Associated with psychoses at supratherapeutic doses.
			Protein binding = approximately15%.		Cardiac effects: tachycardia and palpitations.
			Not metabolized by cytochromes.		
Modafinil	Excessive daytime sleepiness associated with narcolepsy (FDA and EMA) and OSA and shift work disorder (FDA) in adults	Narcolepsy, OSA or shift work disorder: up to 400 mg (once day or BID)	Tmax = 2–4 h (delayed by food).	Inducer of several cytochromes (especially CYP3A) and inhibitor of CYP2C19.	Associated with mania and psychosis.
			HL = approximately 15 h.	Carbamazepine and phenobarbital potentially decrease modafinil plasma levels.	Modest increase in blood pressure and heart rate in RCTs.
			Protein binding = 60%.	Carbamazepine, midazolam, perampanel and zonisamide may potentially have their metabolism induced by modafinil.	Associated with life-threatening rushes.
			Substrate of several cytochromes. Substrate of P-glycoprotein.	Phenytoin and diazepam may potentially have their metabolism inhibited	
Armodafinil	Excessive daytime sleepiness associated with narcolepsy, OSA and shift work disorder (FDA) in adults	OSA and Narcolepsy: up to 250 mg once day.	Tmax = 2 h (delayed by food).	See modafinil	Associated with mania and psychosis.
		Shift work disorder: 150 mg once day	HL = approximately 15 hours.		Modest increase in blood pressure and heart rate in RCTs.
			Protein binding = 60%.		Associated with life-threatening rushes.
			Amide hydrolysis and CYP3A4/5 metabolism.		
Pitolisant	Excessive daytime sleepiness associated with narcolepsy in adults (FDA and EMA)	Narcolepsy: between 4.5 and 36 mg once day	Tmax = 3 h.	Its metabolism can be induced by strong enzyme inducers like carbamazepine, phenytoin, and phenobarbital.	Possible anticonvulsant effect.
			HL = 10–12 h.	It can potentially induce metabolism of several ASMs that are CYP3A4 substrates.	Associated with mania and psychosis.
			Protein binding > 90%.		Prolong the QTc interval at supra-therapeutic doses.
			Substrate of CYP3A4 and CYP2D6.		
Solriamfetol	Excessive daytime sleepiness associated with narcolepsy and OSA in adults (FDA and EMA)	Narcolepsy or OSA: up to 150 mg once day	Tmax = 2 h (delayed by approximately 1 h by food). HL = 7.1 h.	No clinically significant drug-drug interactions involving CYPs and transporters are expected.	Not associated with serious psychiatric symptoms. Modest increase in blood pressure and heart rate in RCTs.
			Protein binding = 13–19%. Excreted unchanged by kidneys.		

Abbreviations: ADHD = Attention-Deficit Hyperactivity Disorder, ASM = antiseizure medication, BID = bis in die, CYP = cytochrome P450, EMA = European Medicines Agency, FDA = Food and Drug Administration, HL = half-life, IRF = immediate release formulation, OSA = Obstructive Sleep Apnoea, RCT = randomized controlled trial, Tmax = time to peak plasma concentrations. References are in the text.

7. Conclusions

Excessive daytime sleepiness is often observed in patients with epilepsy and may heavily interfere with their daily activities.

Concerning the assessment of sedative effects of ASMs, there are factors that limit results of our analysis. We should consider that the adverse effect "somnolence", which correspond to a subjective feeling, may be overestimated in RCTs and it is not clear the relation between this AE, and EDS. In addition, there are several factors that limit the validity of the assessment of somnolence both in RCTs and in clinical practice. First, because of its subjective nature, somnolence is influenced by patient and clinician expectations

and concomitant disturbances. For example, although "treatment emergent somnolence" was one of the most frequently observed AEs in a meta-analysis of 79 RCTs, a correlation was found both between patients treated with the active ASM and those treated with placebo, stemming for a strong effect due to the expectations of patients and investigators [94]. The perception of somnolence in a patient can be influenced by a variety of factors, like depression, age, quality of sleep, OSAS, seizure frequency, and number of concomitant ASMs [95].

A limit of our analysis is that in clinical trials, EDS is assessed with a single question while the Epworth Sleepiness Scale is a more reliable method for measuring persistent EDS in adults [3] and is used in the majority of studies specifically assessing EDS [22]. Neurophysiological tests as the multiple sleep latency test are more objective. So far, however all studies performed with this technique recruited small and selected populations of patients [3], with limited external validity. This limit also apply to studies looking at the effect of drugs on the sleep structure among subjects with epilepsy and treated with ASMs [96].

Bearing in mind these limits, the currently available evidence from our analysis shows that LTG, LCM and, with a lower degree also ESL, have lower sedative effects than all other new generation ASMs. Interestingly, LTG has been associated with insomnia in some clinical series [97].

Excessive daytime sleepiness that persists with unacceptable consequences, even after switching to a less sedative ASM, may require concomitant administration of a "wake promoting agent".

These psychostimulants are, however, authorized for use only in specific indications (ADHD, narcolepsy, and OSAS) and are off-label in epilepsy. None of these agents worsen seizures and pitolisant may have anti-seizure effects in photosensitive seizures.

We propose that, in patients with epilepsy and EDS, the treatment with a "wake promoting agent" should be mainly based on safety considerations. All psychostimulants have similar negative cardiovascular effects with the exception of pitolisant, which however may increase QT interval at high doses. Psychiatric adverse effects and drug–drug interactions are more often observed with modafinil/armodafinil and are possibly induced also by MPH, while solriamfetol is not expected to induce neither clinically significant pharmacokinetic interactions nor psychiatric AEs.

Further studies are required to evaluate the clinical impact of EDS and the effects of psychostimulants in people with epilepsy. So far, several studies have shown that MPH is relatively safe and effective. Additional clinical studies are warranted in the next years to provide more robust evidence about the effectiveness of MPH and explore the safety and efficacy of the new "wake promoting agents" in people with epilepsy and EDS and/or ADHD symptoms.

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Declaration of Competing Interest

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Article

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The Processes Underlying Positive Illusory Bias in ADHD: The Role of Executive Functions and Pragmatic Language Skills

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Abstract

Objective: Children with ADHD often show a positive illusory bias (PIB), reporting an extremely positive idea of their own competence, despite their difficulties. The mechanisms underlying this phenomenon are still poorly understood. In the present study, we examined social PIB and investigated the role of executive functions (EFs) and pragmatic language (PL). **Method:** Forty-one children with ADHD and 42 typically-developing children matched on age, IQ, and receptive language were administered measures of social competence, EFs and PL. The parents were also asked to estimate their child's social competence. **Results:** There was evidence of social difficulties and PIB in children with ADHD. Only PL, not EFs, seemed to mediate the association between ADHD and PIB. **Conclusion:** Our findings suggest that PL abilities should be considered in efforts to improve self-perception in children with ADHD. *(J. of Att. Dis. 2022; 26(9) 1245-1256)*

Keywords

ADHD, executive function, positive illusory bias, pragmatic language

ADHD is a neurobiological developmental disorder characterized by a persistent pattern of inattention and/or hyperactivity/impulsivity severe enough to interfere with a child's normal psychological development (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM 5, American Psychiatric Association [APA], 2013). The disorder is often associated with social and relational difficulties (Staikova et al., 2013). Children with ADHD are rejected by their peers and the quality of their relationships is not adequate for their age (Carpenter Rich et al., 2009). They are described as immature, and as having difficulty creating and maintaining friendships (Hoza et al., 2004). Despite such social difficulties being emphasized by parents, teachers, and even classmates, children with ADHD seem to underestimate their problems. This tendency in children with ADHD to overestimate their capabilities vis-à-vis external criteria is called positive illusory bias (PIB) (Capodieci et al., 2019; Hoza et al., 2002; Owens et al., 2007). PIB is generally measured as the discrepancy between a child's self-rated competence and how it is judged by others, such as parents or teachers. Previous studies have criticized the use of discrepancy scores from both the theoretical and the statistical perspective. From the theoretical perspective, some authors have suggested that a positive discrepancy between ADHD children's self-ratings of their competence and parents' and teachers' ratings could be associated with negative parental or teacher attributions (Evangelista et al., 2008; Hoza et al., 2002, 2004; Owens & Hoza, 2003). Other studies identified the same overestimation of abilities in ADHD by comparing children's self-ratings with their objective performance in academic and social tasks (Chan & Martinussen, 2016; McQuade et al., 2017; Ohan & Johnston, 2002; Owens & Hoza, 2003). These findings are consistent with the hypothesis that PIB is a genuine overestimation of ability, not just a reflection of negative parental attribution. From the statistical perspective, some authors have criticized the use of discrepancy scores (Swanson et al., 2012), judging alternative approaches (e.g., standardized residual or standardized discrepancy scores) more appropriate and informative. Others have claimed that alternative approaches also have statistical limitations, such as a low reliability (Owens et al.,

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2007), as well as being far from easy to interpret from a clinical standpoint (Martin et al., 2019).

PIB has been studied mainly in children with ADHD aged from 7 to 13 years, because it is in this age range that they overestimate their academic, behavioral, and social competence the most (Capodieci et al., 2019; Crisci et al., 2018; Golden, 2009; Hoza et al., 2002, 2004; Linnea et al., 2012; Martin et al., 2019; McQuade et al., 2011, 2017). It is nonetheless worth noting that the only study that included a sample of children with ADHD over a wide age range (from 6 to 15 years) found that age was not significantly associated with PIB. The discrepancy between children's and self and parents' competence ratings tended to decrease with age, but the difference proved insignificant (Volz-Sidiropoulou et al., 2016). PIB in children with ADHD seems to be particularly evident in social and academic aspects (Volz-Sidiropoulou et al., 2016), probably because these are the domains in which they encounter the most difficulties (Hoza et al., 2004). Previous studies focused rather exclusively on the self-perception of children with ADHD in the academic and cognitive fields (Owens et al., 2007; Prevatt et al., 2012), whereas few investigated social relationships and how well children with ADHD are accepted in their social sphere, with conflicting results. Some findings (Bourchtein et al., 2017; Linnea et al., 2012) suggested that only a small subset (around 30%) of youth with ADHD exhibit an overall PIB, but it seems to be stable over time in the social sphere (Linnea et al., 2012). Other authors (Emeh et al., 2018; McQuade et al., 2017; Swanson et al., 2012) found that children with ADHD overestimated their social competence and this was associated with specific cognitive impairments. PIB in the social sphere therefore warrants more attention, also because of its possible implications in terms of a less prosocial behavior (Linnea et al., 2012), or weaker response to treatment in children with ADHD (Hoza et al., 2010).

A phenomenon similar to PIB has been described in the typically-developing (TD) population as well (Alicke & Govorun, 2005), but PIB in children with ADHD takes on specific features. In TD children, a moderate degree of positive illusion of competence is interpreted as an adaptive mechanism, because it can help to motivate children when they engage in challenging tasks (Owens et al., 2007). Children with ADHD tend instead to perform less well and to give up on challenging tasks, despite their illusory positive self-perception (Hoza et al., 2001). Another difference between the PIB of TD children and of those with ADHD lies in that the discrepancy between their self-perception and external measures is larger in the latter (Owens & Hoza, 2003).

Although it is still not clear what causes PIB, at least three main hypotheses have been advanced: cognitive immaturity (Milich, 1994); ignorance of incompetence (Hoza et al., 2002); and neuropsychological deficits (Owens & Hoza, 2003). As regards the first hypothesis, some authors have made the point that younger children with typical development tend to overestimate their abilities and their performance more than older adolescents, and these positive beliefs help them to persist when faced with difficult tasks (Owens et al., 2007). Children with ADHD are described as behaviorally and cognitively immature, and that is why cognitive immaturity has been suggested as an explanation for their PIB (Milich, 1994). Children with ADHD are not very persistent in performing challenging tasks, however, even though their PIB seems to resemble the optimism of young children (Hoza et al., 2001). This evidence detracts from the credibility of cognitive immaturity as the best explanation for PIB (Owens et al., 2007). Moving on to the second hypothesis, incompetence in a given domain can make people poor judges of their own or others' competence therein (Dunning et al., 2003). In other words, the ignorance of incompetence hypothesis suggests that children with ADHD are unaware that the difficulties they encounter are due to their own incompetence. Evangelista et al. (2008) discredited this hypothesis, however, when they found that children with ADHD were accurate in assessing other children's competence in several situations, even though their own performance was weak. Finally, several studies have shown that executive functions (EFs) are needed to assess and judge one's own and other people's competence and behavior (Bivona et al., 2008). Impaired EFs could therefore be associated with a lesser awareness of competence, and with a form of PIB in several clinical populations (Ownsworth et al., 2002; Shad et al., 2006). To give an example, a specific relation between EF deficits and a lack of insight has been demonstrated in patients with brain injuries, especially frontal damage (Ownsworth et al., 2002), and with schizophrenia (Shad et al., 2006). Such patients were found unable to monitor and adjust their own behavior, and they tended to overestimate their abilities. EFs are higher-level cognitive processes that enable us to plan, organize, focus attention, and carry out multiple tasks. According to Miyake et al. (2000), EFs can be divided into three distinct, but interacting processes. Inhibition refers to the ability to deliberately inhibit dominant or automatic responses. Shifting refers to an attention-switching process or the flexibility needed to disengage from an irrelevant task and then actively engage in a relevant task. Updating refers to the monitoring and coding of information, and the replacing of older or irrelevant information with newer or more relevant information in the working memory system. EF impairments have been extensively described in children with ADHD (Barkley, 1997, 2011; Sergeant et al., 2002), but the little research conducted on the relation between EFs and PIB has produced contradictory results. McQuade et al. (2011) found that EF processes partially mediated the relation between ADHD symptoms and PIB in social domains. The same authors

(McQuade et al., 2017) reported that children in the PIB group (including those with ADHD and TD children with a social PIB) were significantly more impaired on EF tasks than children in the no-bias group. Chan and Martinussen (2016) identified EFs as being connected to PIB only in the academic field. Golden (2009) likewise found that EFs were not related to self-perception discrepancy scores in the social domain, but only in the scholastic domain.

Another important aspect that has rarely been considered is the role of language in PIB (Graham et al., 2020). PIB is relatively close to the concept of perspective taking, the ability to understand and process a situation from another person's point of view (Selman, 1971). Perspective taking is needed to accurately assess a situation, one's own skills, and others' opinions, thoughts, and perspective. It is essential to children's proper social development (Selman, 2003). Several studies support the existence of a close link between language and perspective taking (Farrant et al., 2006), leading to speculation that language impairments—particularly in pragmatic aspects—could have a role in the development of social PIB. We specifically refer to pragmatic language abilities because they concern the social use of language, the aspect of language that governs how phonology and syntax are used in social contexts (Russell, 2007). Pragmatic language (PL) skills have both verbal and non-verbal aspects, such as initiating and ending a conversation, assumptions about the social context, facial expressions, and tone of voice (Adams, 2002). These aspects have been investigated in children with ADHD in relation to their social difficulties. PL deficits seem to affect academic functioning and performance (Troia, 2011), peer relationships (Leonard et al., 2011), and general adjustment (Landa, 2005). It is important to emphasize that PL deficits can occur irrespective of general language problems of the kind seen, for instance, in social communication disorder (DSM 5, APA, 2013). Previous studies (Leonard et al., 2011; Staikova et al., 2013) found that children with ADHD have PL impairments, especially in prosody, turn taking, and semantic aspects. Despite the evident link between language impairments and behavioral problems observable in ADHD, as well as in conduct disorder and oppositional defiant disorder (Dockrell et al., 2011), only one study to our knowledge (Graham et al., 2020) has investigated how oral language competence influences PIB in children with behavioral problems. This study showed that children with behavioral problems differ significantly in expressive and receptive language from TD children, but no evidence of PIB emerged. The relationship between PL and social PIB should be further investigated, taking this theoretical point of view into account (Graham et al., 2020). That is why PL was included among the aspects to consider in our efforts to shed light on the variables related to social PIB. In the present study, we also examine receptive language to make sure that any differences in receptive language between our ADHD and TD groups could not have affected our findings regarding their PL skills.

The Present Study

As mentioned earlier, previous studies found that children with ADHD tended to overestimate their abilities compared with their parents' or teachers' opinions of them. This overestimation makes them more susceptible to failure, because they are unable to recognize the need to improve their social attitude, to acknowledge negative feedback about their performance, and to change their approach to the completion of a task (Milich & Okazaki, 1991). In addition, PIB makes children with this clinical diagnosis less responsive to treatment, because an awareness of one's own impairments is an important prerequisite for changing one's own behavior (Mikami, 2010).

Regarding the theoretical explanations of the PIB phenomenon, there has been little empirical support for the hypotheses of cognitive immaturity or ignorance of incompetence to explain this behavior. The hypothesis of neuropsychological deficits is also in need of further confirmation. The idea that neuropsychological deficits—in EFs, in particular—mediate the association between ADHD and social PIB has generated contradictory results (Chan & Martinussen, 2016; Golden, 2009; McQuade et al., 2011, 2017). Meanwhile, despite the known fundamental role of PL abilities in perspective taking and understanding other people's opinions and thoughts, no studies to our knowledge have considered PL impairments in relation to PIB (Graham et al., 2020).

The present study was designed to seek empirical evidence of social PIB, and to clarify the specific role of EF abilities and PL impairments. For this purpose, specific tests measuring social skills and tapping EFs and PL were used to compare the performance of two groups, one of children with ADHD, the other of TD children. We tested a sample of children with a clinical diagnosis of ADHD, matched for chronological age, intelligence level, and receptive language with a sample of TD children. All the children were between 8 and 15 years old. According to previous studies (Hoza et al., 2010; Volz-Sidiropoulou et al., 2016), social PIB is atypical in TD children in this age range, and the differences between children with ADHD and those with a typical development are greater. Our three main goals were: (a) to identify weak social skills in children with ADHD, and confirm the presence of PIB in this group; (b) to investigate specific impairments in EFs and PL abilities in children with ADHD, comparing their performance with TD children; and (c) to run mediation analyses to clarify the role of EF impairments and PL deficits in PIB.

Based on previous studies, we expected the children with ADHD to be weak in terms of social competence

Table 1. Characteristics of the ADHD and Typical Development (TD) Groups: Means (*M*), Standard Deviations (*SD*), and Results of ANOVAs.

	ADHD ($n=41$)	TD ($n=42$)	ANOVAs		
	M (*SD*)	*M* (*SD*)	$F(1, 81)$	p	Adjusted R^2
Age (years)	10.9 (2.2)	11.1 (2.2)	0.013	.91	.01
IQ	107.56 (11.4)	108.38 (11.97)	0.10	.75	.01
TROG-2	101.54 (9.62)	102.67 (10.30)	0.27	.61	.001
CPRS-R:S					
Oppositional	65.63 (11.38)	49.17 (10.45)	47.18	<.001	.36
Cognitive problems/inattention	73.10 (11.55)	50.90 (9.13)	94.56	<.001	.53
Hyperactivity	65.78 (13.10)	48.83 (8.55)	48.95	<.001	.37
ADHD	75.75 (10.03)	51.95 (10.46)	111.9	<.001	.57

Note. ADHD = group with attention deficit and hyperactivity disorder; TD = control group with typical development; IQ = intelligence quotient; TROG-2 = Test of Reception of Grammar-2; CPRS-R:S = Conners' Parent Rating Scales-Revised: Short form.

(Carpenter Rich et al., 2009; Hoza et al., 2010), and to overestimate their social skills (Capodieci et al., 2019; Hoza et al., 2002; Owens et al., 2007). We also expected these children to be impaired in terms of EFs (Barkley, 2011; Sergeant et al., 2002) and PL (Staikova et al., 2013). Finally, based on the assumption that PIB is caused by an EF impairment (Bivona et al., 2008), we might expect this impairment to mediate the relation between ADHD status and the presence of social PIB. On the other hand, on the grounds of previous research identifying PL deficits in children with ADHD (Staikova et al., 2013), and a link between pragmatic aspects and social perspective taking (Selman, 2003), we might also expect PL abilities to mediate this same relation between ADHD and PIB, after controlling for receptive language abilities. To our knowledge, this is the first attempt to test this particular association.

Method

Participants

The total sample included 83 children, 64 males and 19 females, between 8 and 15 years of age ($M=10.53$, $SD=2.23$). Children with a clinical diagnosis of ADHD ($N=41$ age range from 8.5 to 15 years) were enrolled at specialized centers for neurodevelopmental disorders, hospitals, or clinics. The TD children (TD, $N=42$, age range from 8.8 to 14.2 years) serving as controls were recruited through local community contacts or at local schools in northeastern Italy. All participants were native Italian speakers, and none had any visual or hearing impairments, or any other diagnosed neurological conditions.

Children with ADHD had a diagnosis of ADHD according to the criteria of the DSM 5 (APA, 2013), previously established either by private practitioners (child psychiatrists or psychologists) or at the child neuropsychiatry department of the hospital to which they referred. Their diagnosis included a complete assessment reported in their medical records, to which the present authors had access with the consent of the children's caregivers. Confirmation of the diagnosis of ADHD required *T*-scores of 65 or higher for inattention and/or hyperactivity on the Conners' Parent Rating Scale (CPRS-R:S, Conners, 1997), as well as meeting the DSM 5 (APA, 2013) criteria. For all participants, our exclusion criteria were: a history or concurrent diagnosis of autism spectrum disorder, a history of neurological problems, ongoing use of medication, or a certified intelligence quotient (IQ) below 85. The two groups were matched on chronological age ($F[1, 81]=0.01$, $p=.91$, Adjusted $R^2=.01$), and IQ ($F[1, 81]=0.10$, $p=.75$, Adjusted $R^2=.01$). Participants' level of intelligence was confirmed by administering the block design and vocabulary subtests from the WISC-IV (Wechsler, 2003). The TROG-2 (Test for Reception of Grammar-Version 2, Bishop, 2009) revealed no differences in receptive language between the two groups ($F[1, 81]=0.27$, $p=.61$, Adjusted $R^2=.001$). Among the children with a clinical diagnosis of ADHD, 19 had prevalent inattention symptoms, and 22 had combined inattention and hyperactivity symptoms. The ADHD group scored significantly higher on all the Conners' indexes: oppositional ($F[1, 81]=47.18$, $p<.001$, Adjusted $R^2=.36$); cognitive problems/inattention ($F[1, 81]=94.56$, $p<.001$, Adjusted $R^2=.53$); hyperactivity ($F[1, 81]=48.95$, $p<.001$, Adjusted $R^2=.37$); and ADHD index ($F[1, 81]=111.9$, $p<.001$, Adjusted $R^2=.57$). The participants' characteristics are summarized in Table 1.

Materials

Social competence

Interpersonal competence scale (ICS). This questionnaire assessing interpersonal skills (see also Crisci et al., 2018) was administered to both the parents and the children to identify any discrepancies between their impressions of the

child's social abilities (Cairns et al., 1995). The scale consists of 18 items covering: three main factors, aggression, popularity, and academic skills; and three secondary factors, friendliness, appearance, and internalizing difficulties. Each item is rated from 1 to 7 on a continuum between two polarities, one positive, and the other negative (e.g., from never aggressive to always aggressive), expressing the child's usual behavior. The total interpersonal competence score is derived from the mean of the five subscale scores (aggression, popularity, academic skills, friendliness, appearance), reversing the score for aggression (Cronbach's alpha: aggression factor = .82, popularity factor = .81, academic skills factor = .71, friendliness factor = .71, appearance factor = .67, and overall scale score = .84).

Executive functions

Inhibition (NEPSY II). This subtest assesses the ability to inhibit automated responses in favor of novel responses, and to switch between automatic and inhibitory types of response (Korkman et al., 2007). The children were shown a series of black and white shapes or arrows, and the task included two conditions: (a) inhibition, in which participants had to name the opposite shapes (or arrow directions) as rapidly and accurately as possible; and (b) shifting, in which they had to label either the correct or opposite shapes (or arrow directions) depending on their color. Test-retest reliability for different age groups ranges from .79 to .82 for the inhibition condition, and from .75 to .93 for the switching condition (Brooks et al., 2009).

Verbal and visuospatial updating. Verbal and visuospatial updating tasks were devised using different types of stimuli, verbal in one and visuospatial in the other (see Crisci et al., 2021). Both tests were administered using a laptop computer with a 15-inch LCD screen, programed with the E-Prime software (Schneider et al., 2007). The children were asked to recall the last verbal stimulus or the last positions of a visual stimulus belonging to *target categories* previously shown on the screen. The verbal updating task consists of 8-word lists, containing from 6 to 12 words. After listening to a word list, participants had to remember the last word they had heard that belonged to a given semantic category shown on the screen. Every list included: "target," words belonging to one of the semantic categories; and "distractors," words belonging to another category. The test consisted of four levels of increasing difficulty (from two to five words, to increase the memory span required), with two lists for each level of difficulty. At the beginning of each list, the target semantic categories appeared on the computer screen, and remained visible until a new list was presented. Immediately (1000 ms) after the categories appeared, the words were presented verbally, one at a time with an interval of 1000 ms.

The visuospatial updating task was much the same, but consisted of visuo-spatial stimuli. The task involved 8 sets of shapes, each containing 6 to 12 shapes. Participants were asked to recall the last position of a target shape seen on the computer screen. Each set included these "targets" (the position of the shape to be remembered) and "distractors" (the positions of the other figures shown). Here again, there were four levels of difficulty (as in the verbal updating test), with two to five shape positions to remember, and two trials for each level of difficulty. The target shapes were initially presented in the center of the screen (for 600 ms), then they appeared below a 4×4 grid in which each shape in a given set (targets and distractors) was presented in a randomized position, with an interval of 1000 ms between one shape and the next. After a set of shapes had been presented, participants used the mouse to indicate the positions of the target shapes. The proportion of correct responses was taken into account for both tasks (Cronbach alpha: .71 verbal updating and .76 visuospatial updating).

Pragmatic language abilities

Children's Communication Checklist, second edition (CCC-2). The CCC-2 is a 70-item questionnaire designed to assess children's skills in various areas of language, including pragmatics (Bishop, 2003). The CCC-2 provides standard scores for 10 scales: speech, syntax, semantics, coherence, inappropriate initiation, stereotyped language, use of context, non-verbal communication, social relations, and interests. For the present study we used four of these scales (inappropriate initiation, stereotyped language, use of context, and non-verbal communication) to compute a pragmatic language (PL) index (see also, Bignell & Cain, 2007; Leonard et al., 2011; Staikova et al., 2013), focusing on verbal and nonverbal pragmatic skills. Internal consistency, or Cronbach's reliability coefficients ranged from .94 to .96 across age groups (Bishop, 2003).

Procedure

The study was approved by the ethics committee at the University of Padua. Written consent was obtained from children's parents before they took part in the study. Participants were tested in a quiet room during two individual sessions lasting about 40 minutes. Tasks were administered in a counterbalanced order. Instructions were given for each task, and participants practiced with each task before starting the experiment. At the same time, parents completed a rating scale to assess their children's communication abilities.

Results

Data Analyses

The statistical analyses were conducted using R (R Core Team, 2019). One-way ANOVAs were run for each subtest to examine differences between the groups. A positive

Table 2. Mean Scores (*M*), Standard Deviations (*SD*), and Results of ANOVAs for the ADHD and TD Groups.

	ADHD ($n=41$)	TD ($n=42$)	ANOVAs		
	M (*SD*)	*M* (*SD*)	*F*(1, 81)	*p*	Adjusted R^2
Social competence					
ICS_SCP	4.34 (.51)	5.06 (0.5)	41.67	<.001	.33
ICS_SCC	4.47 (.63)	4.72 (0.6)	3.39	.07	.03
PIB index	−0.13 (.80)	.34 (0.56)	9.47	.003	.09
Executive functions					
Inhib	6.85 (2.49)	8.60 (2.45)	10.33	.002	.10
Shift	6.55 (2.57)	8.83 (2.42)	17.17	<.001	.17
UPv	0.60 (.12)	0.70 (0.12)	15.09	<.001	.15
UPvs	0.65 (.29)	0.69 (0.17)	0.66	.42	.004
EF index	−0.44 (.88)	0.46 (0.86)	21.92	<.001	.21
Pragmatic language abilities					
Inappropriate initiation	6.22 (1.89)	9.43 (2.95)	34.66	<.001	.29
Stereotyped language	8. 07 (3.06)	9.17 (2.79)	2.89	.09	.02
Use of context	6.20 (3.03)	9.17 (3.33)	18.05	<.001	.17
Non-verbal communication	7.51 (3.35)	8.90 (3.41)	3.52	.06	.03
PL index	−0.41 (.84)	0.40 (0.98)	16.46	<.001	.16

Note. ICS_SC = total interpersonal competence on the Interpersonal Competence Scale according to parents (P) and children (C); PIB index = positive illusory bias index; Inhib = inhibition (NEPSY II); Shift = shifting (NEPSY II); UPv = verbal updating; UPvs = visuospatial updating; EF index = executive functioning index; PL index = pragmatic language index.

illusory bias index (PIB index) was then computed as the discrepancy between the adult's report and the child's social abilities on the ICS. Positive scores indicate an underestimation of a child's social acceptance, or negative illusory bias (NIB), and negative scores indicate an overestimation of a child's social abilities (PIB) (McQuade et al., 2017). Latent variables (the EF index and PL index) were computed using the *psych* statistical package (Revelle, 2019), then mediation analyses were run with *lavaan* (Rosseel, 2012) to examine the mediation effect of the EF and PL indexes on the relationship between ADHD status and the PIB index. We assumed that a model with a smaller Akaike information criterion (AIC) better describes the relationship between the variables (Bentler, 1990; Schermelleh-Engel et al., 2003).

Social competence. Table 2 sums up the descriptive statistics for the two groups (ADHD and TD) on the general scale of the ICS, for both the parents' reports and the children's self-reports. Concerning the parents' reports, a main effect of group emerged for the aggressiveness scale ($F[1, 81]=12.81$, $p<.001$, Adjusted $R^2=.13$), the popularity scale ($F[1, 81]=6.13$, $p=.015$, Adjusted $R^2=.06$), the academic skills scale ($F[1, 81]=30.59$, $p<.001$, Adjusted $R^2=.27$), and the appearance scale ($F[1, 81]=3.84$, $p=.05$, Adjusted $R^2=.03$). In other words, when compared with TD children, those with ADHD were described by their parents as more aggressive, less popular, with weaker academic skills, and less general competence. Significant differences between the two groups also emerged for overall scores on the ICS ($F[1, 81]=41.68$, $p<.001$, Adjusted $R^2=.33$), again indicating that the group with ADHD was weaker than the TD group in terms of interpersonal competence. No significant effect of group emerged for the two secondary factors: friendliness ($F[1, 81]=2.26$, $p=.14$, Adjusted $R^2=.02$) or internalizing difficulties ($F[1, 81]=0.16$, $p=.69$, Adjusted $R^2=.01$). When the self-report version of the ICS was examined, there was no significant effect of group on any of the subscales considered. Compared with TD children, those with ADHD showed no significant differences in self-reported aggressiveness ($F[1, 81]=2.57$, $p=.11$, Adjusted $R^2=.02$), popularity ($F[1, 81]=0.28$, $p=.60$, Adjusted $R^2<.001$), academic skills ($F[1, 81]=2.91$, $p=.09$, Adjusted $R^2=.02$), friendliness ($F[1, 81]=0.007$, $p=.93$, Adjusted $R^2=.01$), competence ($F[1, 81]=0.46$, $p=.50$, Adjusted $R^2=.006$), or internalizing difficulties ($F[1, 81]=2.26$, $p=.14$, Adjusted $R^2=.02$). No main effect of group came to light for the overall score on the ICS ($F[1, 81]=3.37$, $p=.07$, Adjusted $R^2=.03$).

Positive illusory bias (PIB). Table 2 summarizes the descriptive statistics for the two groups as concerns their scores on the PIB index, computed as the discrepancy between the adults' reports of the children's social acceptance on the ICS and the children's self-reports (Cairns et al., 1995), in terms of NIB and PIB, as explained above. A main effect of group emerged ($F[1, 81]=9.47$, $p=.003$, Adjusted $R^2=.09$): the children with ADHD showed evidence of PIB, the TD children did not.

Executive functions. Table 2 shows descriptive statistics for the performance of the two groups (ADHD and TD) in the EF tasks. In the inhibition task, there was a main effect of group for both the conditions investigated, inhibition ($F[1, 81]=10.33$, $p=.002$, Adjusted $R^2=.10$) and shifting ($F[1, 81]=17.17$, $p<.001$, Adjusted $R^2=.17$), in which the children with ADHD performed significantly worse than the TD children. There was also a main effect of group in the verbal updating task ($F[1, 81]=15.09$, $p<.001$, Adjusted $R^2=.15$), again with the ADHD group performing worse than the TD group, no significant differences came to light between the groups in the visuospatial updating task ($F[1, 81]=0.66$, $p=.42$, Adjusted $R^2=.004$). A main effect of group emerged for the EF index ($F[1, 81]=21.92$, $p<.001$, Adjusted $R^2=.21$), the children with ADHD again performing significantly worse than the TD children.

Pragmatic language abilities. There was a main effect of group for inappropriate initiation ($F[1, 81]=34.66$, $p<.001$, Adjusted $R^2=.29$), and use of context ($F[1, 81]=18.05$, $p<.001$, Adjusted $R^2=.17$). Children in the ADHD group were more often described by their parents as impaired in appropriate initiation and use of context than children in the TD group. No significant effect of group emerged for stereotyped language ($F[1, 81]=2.89$, $p=.09$, Adjusted $R^2=.02$) or non-verbal communication skills ($F[1, 81]=3.52$, $p=.06$, Adjusted $R^2=.03$). Table 2 shows the descriptive statistics for the two groups (ADHD and TD) on the pragmatic language subscales used to compute the PL index. The main effect of group ($F[1, 81]=16.46$, $p<.001$, Adjusted $R^2=.16$) emerged for the PL index, in which the ADHD performed significantly worse than the TD group.

Mediation analyses. Two mediation analyses were performed to examine the hypothesis that EF and PL aspects (computed as latent variables) mediated the relationship between ADHD and PIB, with group as the independent variable.

Figure 1A shows that group was significantly associated with PIB ($\beta=.46$, $SE=0.15$, $p=.002$). Group was also significantly associated with the EF index ($\beta=.90$, $SE=0.19$, $p<.001$), whereas the EF index was not associated with PIB ($\beta=-.08$, $SE=0.09$, $p=.38$). These paths do not support the first mediation hypothesis (Figure 1A). On the other hand, group was also significantly associated with the PL index ($\beta=.82$, $SE=0.20$, $p<.001$), and the PL index emerged as significantly associated with PIB (fully mediated: $\beta=.24$, $SE=0.08$, $p=.01$; partially mediated: $\beta=.17$, $SE=0.08$, $p=.03$). These paths support the second mediation hypothesis (Figure 1B). When we compared a fully-mediated and a partially-mediated model, the better model with the lower AIC was the partially-mediated one (AIC[fully-mediated]=398.07, AIC[partially-mediated]=396.03). The partially-mediated model explained 32% of the variance with a total coefficient of determination (TCD) of 0.21 (Bollen, 1989; Jöreskog & Sörbom, 1996).

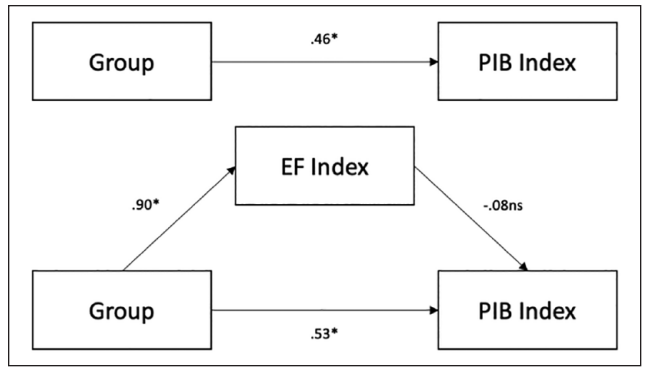

Figure 1. (A) Mediation model between group and PIB index using the EF index as a partial mediator. *Note.* Group: 0 = ADHD; 1 = TD; PIB index = positive illusory bias index; EF index = executive function index. (B) Mediation model between group (0 = ADHD; 1 = TD) and PIB index using the PL index as a full and partial mediator. *Note.* Group: 0 = ADHD; 1 = TD; PIB index = positive illusory bias index; PL index = pragmatic language index.

Discussion

Using a mediation model approach, this study aimed to shed further light on how EFs and PL relate to PIB (Hoza et al., 2002) in children with ADHD, focusing specifically on identifying their weaknesses in social skills and any evidence of PIB. For this purpose, children with ADHD were compared with TD children on their EFs and PL abilities. To better understand whether specific neuropsychological characteristics or PL abilities affect children's self-perception, we tested the association between impairments in EF and/or PL and PIB regarding social competence. The children in our ADHD group had previously been diagnosed at centers specializing in neurodevelopmental disorders. Their diagnoses were confirmed by administering the CPRS-R:S (Conners, 1997), and their intelligence and receptive language abilities were assessed to ensure that the ADHD and TD groups did not differ in these dimensions.

Concerning our first goal, our results generally confirm that children with ADHD tend to have a PIB. Parents of the children in the ADHD and TD groups described the former as more aggressive, less popular, with weaker academic skills, and a lower degree of interpersonal competence than the latter. The children with ADHD, on the other hand, reported no difference in their perception of their own abilities when compared with TD children. These results are consistent with previous studies showing a significant PIB in most children with ADHD, regarding not only their academic and cognitive abilities, but also their social

competence (Hoza et al., 2002; Linnea et al., 2012; Owens & Hoza, 2003). TD children tend to have less confidence in their social skills, describing themselves as less capable than their parents' ratings would suggest; in short, they experience what is called negative illusory bias (NIB, McQuade et al., 2017).

A second goal of our study was to test our two groups' EFs and PL. EFs such as inhibition, shifting, and verbal or visuospatial updating (Miyake et al., 2000) are often impaired in children with ADHD (Barkley, 2011; Sergeant et al., 2002). This was largely the case in our sample, too, with the ADHD group performing less well than the TD children in terms of inhibition, shifting, and verbal updating. Somewhat surprisingly, we found no differences between the ADHD and TD groups on the visuospatial updating tasks. Previous studies had found children with ADHD impaired in visuospatial working memory (Kasper et al., 2012; Martinussen et al., 2005)—though it is worth noting that working memory and updating are similar, but distinct processes (Bledowski et al., 2009; Nee et al., 2013; Oberauer et al., 2003). Most importantly, variability across tasks is one of the most common outcomes when assessing children with ADHD (Castellanos & Tannock, 2002) and a core factor in this variability seems to be motivation (Sonuga-Barke et al., 2010). Children with ADHD may perform better when a task is cognitively challenging, but not excessively so (Silvetti et al., 2013). This may have been the case of our visuospatial updating task, and would explain why our ADHD group performed better than we expected. Further studies are needed to investigate children's perception of this task in more depth, and to replicate our findings. Previous studies also suggested that children with ADHD have pragmatic language problems (Staikova et al., 2013). We found that the parents of children with ADHD described their children's PL abilities as weak, specifically as concerns understanding when to start a conversation, and adapting their language to a given context. It is worth noting that the PL difficulties described by the parents of children with ADHD in our study were clearly apparent, although the ADHD and TD groups were matched on their receptive language abilities. These PL deficits do not seem to be linked to the core symptoms of ADHD (attentional problems, hyperactivity, or impulsivity), and interventions showing benefits on the core and typical symptoms of the disorder have little effect in improving PL abilities or social skills (Hoza et al., 2004).

Finally, the third aim of our study was to identify the variables associated with social PIB by performing mediation analyses. Based on previously-proposed explanations for the phenomenon of PIB, we examined neuropsychological impairments, and specifically EF deficits, in our sample. EFs seem to be necessary to assess and judge one's own and others' competence, so neuropsychological difficulties could be responsible for PIB (Shad et al., 2006). We also considered an alternative hypothesis attributing a role to PL skills, considered fundamental to the social use of language (Russell, 2007). Previous studies suggested that PL is needed for social perspective taking (Russell, 2007; Selman, 1971), which demands an accurate assessment of one's own skills and of others' opinions and thoughts. We thus hypothesized that both EFs and PL abilities might be involved in social PIB. Although specific EF impairments emerged in our group with ADHD, EF processes did not seem to mediate the relation between ADHD and social PIB. As concluded in previous studies, EF probably mediates PIB not in the social domain, but only in the academic and achievement domains (Chan & Martinussen, 2016; Golden, 2009). It is worth noting that previous research sometimes found a significant relation between EF and social PIB (McQuade et al., 2011, 2017), probably due to the procedure used to regroup children based on level of social bias, rather than on their diagnosis. Despite the significant association between EF and social PIB, the authors concluded that ADHD symptoms did not significantly moderate the effect of EF impairment on social bias (McQuade et al., 2017). We found evidence instead to support PL partially mediating the presence of PIB: in this case, although the association between the groups and PIB was limited in absolute terms, based on the PL index, it nonetheless differed from zero when the mediator was introduced.

To our knowledge, this is the first study to test the specific relation between ADHD, PL, and PIB, after accounting for receptive language skills (which did not differ between our ADHD and TD groups). To the best of our knowledge, only one study considered the role of oral language competence in PIB among children with behavioral problems (Graham et al., 2020), with inconclusive results. Arguably, our findings suggest the importance of PL when it comes to paying attention to other people' perspectives, and understanding them (Selman, 2003). Previous studies showed a relation between PL and social perspective taking (Cardillo et al., 2021; Farrant et al., 2006). This hypothesis is also supported by findings in children with another type of neurodevelopmental disorder: Geurts et al. (2010) pointed out that PL deficits in children with autism spectrum disorder arise from their inability to take another's perspective during communicative interactions, and described a similar situation in children with ADHD. Cardillo et al. (2021) tested the mediating role of theory of mind and EFs on PL in children with autism spectrum disorder, and found that only theory of mind contributed to the association found between group (autism spectrum disorder vs. TD) and PL. Our study confirms that PL can be seen as the social part of language, the ability to take the other party's perspective into account, and to provide the right amount of information to obtain suggestions from other people. PL could thus contribute to explaining differences

between children with ADHD and TD children in terms of social PIB.

Although this study provides new insight on the factors relevant to the development of PIB, it has several limitations. First of all, we only administered a limited set of EF tasks. The tasks we used were chosen because they reflect our theoretical background (Miyake et al., 2000), but other measures and EFs could be considered in further studies. Second, our measure of PL was based on parental reporting scales; no objective measures were administered to our children. The literature shows that children with ADHD reveal important PL problems, whatever the assessment method used (Staikova et al., 2013), but further studies should compare the mediating role of PL measured in different ways (i.e., parental reports vs. objective measures) and its effect on PIB. Third, we were unfortunately unable to run a power analysis because the number of participants with a clinical diagnosis was based on a delicate balance that needed to be struck between the amount of time clinicians and families could be available. The children included in the study also had to meet very restrictive inclusion and exclusion criteria. In addition, our experimental design prevented us from testing for the effect of age or gender in the mediation model, given the limited power due to the relatively small sample size, once all the variables had been taken into account. Although previous studies found that both children and adolescents with ADHD overestimate their abilities (Volz-Sidiropoulou et al., 2016), further research could include a sample of children with ADHD over a wider age range to empirically test the relation with EF and PL impairments, also considering the role of age and gender. Finally, alternative hypotheses could be tested to ascertain whether other variables affect PIB. In the present study we considered two possibilities, that is, the mediating role of EFs and PL abilities in the development of PIB. Future research could consider the self-protection hypothesis (Hoza et al., 2010). To be more specific, the relation between PIB and internalizing problems and loneliness should be tested, as some studies suggest that PIB could have a protective role (Hoza et al., 2010). PIB could also mask internalizing symptom severity in children with ADHD (Martin et al., 2019) or be explained by higher self-esteem (Hoza et al., 2002). Future research could consider the role of negative parental attributions and parental style as well, as some authors found greater parental warmth associated with less PIB among children with ADHD (Emeh & Mikami, 2014).

Even with the above-mentioned limitations, our study has some important clinical implications. It is important to tailor interventions specifically on social PIB for children with ADHD because an inaccurate self-perception seems to predict worse long-term outcomes (Owens & Hoza, 2003). Children with ADHD who experience PIB may not respond well to treatment, resulting in negative consequences in adolescence and adulthood (Owens et al., 2007). This is probably because an accurate self-perception is essential to enable change in behavior (McQuade et al., 2017). Judging from the results of the present study, PL should be included among the social skills forming the object of treatments, and could be helpful in improving social perspective taking and realistic self-concept in children and adolescents with ADHD. This could prompt new recommendations for improving clinical approaches, as existing interventions for ADHD seem to have little effect in improving social skills and social perspective taking (Hoza et al., 2004; Staikova et al., 2013).

Overall, our findings partially confirm previous results. The parents of our sample of children with ADHD rated their children as impaired in terms of their social abilities, whereas their children saw no such difference between themselves and TD children, thus confirming their social PIB. Impairments were also confirmed in these children' EFs and PL, especially as regards turn taking and adapting their language to a given context. Only PL abilities seemed to partially mediate the relation between our ADHD and TD groups and PIB, however.

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Review article

Associations between mental and physical conditions in children and adolescents: An umbrella review

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ABSTRACT

We mapped the evidence on the type and strength of associations between a broad range of mental and physical conditions in children and adolescents, by carrying out an umbrella review, i.e., a quantitative synthesis of previous systematic reviews and meta-analyses. We also assessed to which extent the links between mental and physical conditions vary across disorders or, by contrast, are transdiagnostic. Based on a pre-established protocol, we retained 45 systematic reviews/meta-analyses, encompassing around 12.5 million of participants. In analyses limited to the most rigorous estimates, we found evidence for the following associations: ADHD-asthma, ADHD-obesity, and depression-asthma. A transdiagnostic association was confirmed between asthma and anxiety/ASD/depression/bipolar disorder, between obesity and ADHD/ASD/depression, and between dermatitis and ASD/ADHD. We conclude that obesity and allergic conditions are likely to be associated with mental disorders in children and adolescents. Our results can help clinicians explore potential links between mental and physical

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conditions in children/adolescent and provide a road map for future studies aimed at shading light on the underlying factors.

1. Introduction

Increasingly studies point to significant associations between mental and physical conditions, but evidence remains inconclusive (Qureshi and Mehler, 2013). This putative link is likely underpinned by multiple factors. Either, physical conditions may contribute to mental disorders (e.g., hypothyroidism underlying depression) (Hage and Azar, 2012). Alternatively, mental disorders may increase the risk of physical conditions (e.g., increased risk of sexually transmitted infections in bipolar disorder) (Chen et al., 2019). Then again, mental and physical disorders may share common risk factors, including early trauma, chronic stress, inflammation, and socioeconomic factors (e.g., low income and poor educational attainment) (Druss and Walker, 2011). With a global peak age at onset of any mental disorders of 14.5 years and 63% of mental disorders occurring prior to age 25 (Solmi et al., 2021b), and with associated physical health burden being frequently observed in children and adolescents, prevention and early intervention in young people has the potential to synergistically maximise the benefit for both mental and physical health (Fusar-Poli et al., 2021).

There has been a large number of individual studies (Patten et al., 2009) and systematic reviews/meta-analyses (Cortese et al., 2018) on the association between specific mental disorders and specific physical conditions. For some associations, e.g., attention-deficit/hyperactivity disorder (ADHD)-obesity, evidence from primary studies and even from meta-analyses is mixed (Cortese et al., 2018; Nigg et al., 2016).

Umbrella reviews aim to summarise data from systematic reviews and/or meta-analysis following a systematic evidence synthesis approach. Umbrella reviews may also entail the repetition of the statistical pooling of relevant effect sizes from available meta-analyses (Fusar-Poli and Radua, 2018). As such, the quality of an umbrella review depends on the coverage of the literature and quality of the previous systematic reviews/meta-analyses. A possible limitation of umbrella reviews is related to the risk of pooling multiple times the same data, although this issue can be minimised by checking the data from the primary studies included in the umbrella review. Finally, and similarly to what occurs in a typical meta-analysis, the results of an umbrella review should be considered in the light of the heterogeneity across populations or outcome assessments in the systematic reviews/meta-analyses retained for the umbrella review.

These potential limitations need to be weighed against the arguable advantages of umbrella reviews, namely the fact that they: 1) provide the most comprehensive quantitative overview on a specific topic or ranges of topics; 2- collate all the previous literature appraisals and individual studies and, hence, can comprehensively point to guideline-relevant, robust and consistent, high-quality evidence as well as relevant gaps, guiding future avenues of research on specific topics.

A quantitative synthesis of the literature across mental disorders and physical conditions, highlighting the strength of the evidence for each association, is currently lacking. Furthermore, whereas transdiagnostic research is gaining traction in psychiatry (Fusar-Poli, 2019; Fusar-Poli et al., 2019), it is unclear to which extent the links between mental and physical conditions vary across disorders or, by contrast, are transdiagnostic.

To fill these gaps, we conducted an umbrella review of systematic reviews (SRs) and/or meta-analyses (MAs) to assess the credibility of the associations between individual mental disorders and physical conditions, and ascertain if specific mental disorders are selectively associated with specific physical conditions or if there are transdiagnostic, across-spectra, or diagnostic spectrum-specific associations. We aimed to create the largest and most comprehensive quantitative atlas on the associations between mental and physical problems in order to summarise relevant areas of available evidence and to highlight missing meta-analytic data in the field of psychiatric morbidity. Given the magnitude of the work, its purpose is not to elucidate mechanisms, but to provide the best quantitative synthesis that will guide future work on mechanisms. Gaining in-depth quantitative insights into the associations between mental and physical conditions has important implications for the understanding of the pathophysiology of these conditions, the clinical management of patients with both mental and physical disorders, and for preventive efforts (Fazel et al., 2021; Qureshi and Mehler, 2013). Here, we focus specifically on the associations between mental and physical disorders in children/adolescents, although the current report is part of a larger research project that also aims to investigate similar associations in adults. These two sections (children/adolescents and adults) are not reported together for conciseness, and also because there are specificities in terms of type and risk of mental and physical conditions in children/adolescents as opposed to adults.

2. Methods

We followed the PRISMA 2020 and MOOSE recommendations (Liberati et al., 2009; Moher et al., 2015; Page et al., 2021; Stroup et al., 2000), and published the protocol (Cortese et al., 2020).

2.1. Data sources and searches

We searched PubMed, OVID, and Web of Knowledge databases (details in eTables 1–4) with no language/date/type of publication restrictions, up to January 1st, 2021. We also hand-searched references of relevant SRs/MAs.

The search syntax had the following structure: *("term for physical disorder"$_1$ OR "term for physical disorder"$_2$ … OR "term for physical disorder"$_n$) AND ("term for mental disorder"$_1$ OR "term for mental disorder"$_2$ … OR "term for mental disorder"$_n$) AND ("term for SR/MA"$_1$ OR "term for SR/MA"$_2$ … OR "term for SR/MA"$_n$) AND ("term for children/adelescent"$_1$ OR "term for children/adelescent"$_2$ … OR term for "children/adolescent"$_n$);* and its creation was supervised by an expert librarian from the University of Southampton. Details on the search are reported in eTables 1–4.

2.2. Types of studies to be included

We included SRs, with or without MAs, of observational studies (case-control, cohort, cross-sectional studies) reporting on the association between mental disorders and physical conditions. The list of mental disorders is reported in eTable 5. The list of physical disorders, based on Correll et al. (2015), and expanded with the advice of a paediatrician (MR-G), included a broad range of physical disorders (eTable 6). Eligibility criteria for SRs/MAs are provided in *eMethods* 1.

2.3. Conditions being studied

Eligible mental disorders were those defined based on standardised criteria, codes in electronic records, clinical diagnosis in medical files, self-reported diagnosis, or a score above a threshold on a validated scale/questionnaire. Hence, diagnostic procedures had to be categorical, dividing the samples among those with and without the disorder. Conversely, studies using continuous measures of symptomatology without a dichotomisation were excluded. While all these definitions of mental disorders were accepted, those clearly following DSM or ICD criteria were deemed to be more reliable. We considered that a gold-standard diagnosis had been carried out when articles specifically

indicated that a clinical diagnosis following the mentioned criteria had been performed, or when a classification in a medical file followed DSM or ICD codes. Any categorical definition of physical conditions was accepted.

2.4. Participants

At least one of the conditions (i.e., mental or physical) had to occur in childhood or adolescence (mean/median/mid-range < 18 years).

2.5. Outcome selection

Per protocol, the primary outcome included the unadjusted or adjusted odds ratio (OR) or other ESs (i.e., risk ratios and hazard ratios) of physical-mental disorder associations, provided in the article or calculated based on the raw data reported in the article. In longitudinal studies, we selected the outcome at the first follow-up. Whenever the same outcome was reported across multiple reviews, it was extracted from the largest MA/SR in order to avoid double-counting it.

2.6. Data screening and extraction

Two authors conducted screening and data extraction independently; conflicts were resolved by consensus, or with a third author. Individual studies' and pooled ESs were obtained from included MAs, or SRs. We first extracted data on the characteristics of the SR/MAs included in our umbrella review, and then, when needed (i.e., data not reported at the SR/MA level) relevant data from the primary studies.

We extracted the country/ies the primary study was conducted in and excluded any effect sizes with overlapping databases for the same association. Whenever two reports were based on the same database when calculating an association, we kept the largest study. Methodology and tools employed for the diagnosis of the mental disorder were also extracted. Importantly, we extracted data that allowed us to calculate the unadjusted odds ratio (our primary effect measure) even if it was not present at the SR or MA level. Likewise, we extracted the adjusted measure of association. Data were obtained from the largest SR/MA whenever possible, from other SR/MAs, or if they were not present in any of these, they were obtained from the primary papers. We also assessed, using the Newcastle-Ottawa scale (NOS) (Wells et al., 2000), the bias of any primary study that had not been appraised at the SR/MA level. Whenever the calculation of the unadjusted OR obtained from the data in the primary study did not match the one reported in the SR/MA, and/or it was unclear how the measures of association had been obtained, we retained the ones reported in the SR/MA as we deemed that they were derived following contact with the authors of the primary study. The same procedure was followed if a primary study was not accessible or was in any language other than English, Spanish, French, German or Italian (languages the authors are fluent in). Hence, authors of primary papers were not contacted, relying instead on the extractions carried out in the SRs/MAs.

We systematically checked whether each primary study fulfilled our inclusion criteria, and extracted data that allowed us to calculate the unadjusted ES even if it was not reported at the SR/MA level, as well as the maximally adjusted ES (i.e., statistically adjusted for the largest number of variables). We also assessed, using the Newcastle-Ottawa scale (NOS) (Wells et al., 2000), the risk of bias of any primary study that had not been appraised at the SR/MA level. Extracting information from primary articles is not a common procedure in umbrella reviews (Fusar-Poli and Radua, 2018), but we deemed that it provided additional information on the primary studies that could not be found at the SR/MA level.

The risk of bias of the included SRs/MAs was rated with the AMSTAR-2 (Shea et al., 2017).

2.7. Data synthesis

For each association, we conducted a random-effects meta-analysis (DerSimonian and Laird, 1986), with ESs obtained from the largest available MA and any relevant additional ES found in the primary studies included in the remaining SRs/MAs. Databases used, as reported in the primary studies, were taken into account in order to only include one outcome per database in each meta-analytic computation, and hence, minimising the risk of combining non-independent data. The combination of non-independent data may skew the results of a meta-analysis and overstate the confidence in the results. In this umbrella review, pooling the same data multiple times for the same analysis might have occurred for two main reasons: 1-Two different SR/MAs on the same association may have pooled different versions of the same study (e.g., a conference proceeding in one SR/MA and the full article in the other SR/MA), or two different studies using the same database; 2-A single SR/MA combined non-independent data within the same analysis. While the former would not affect the estimates provided in the different meta-analyses, it could affect our meta-analytic result. The latter case would affect both our results and the estimate of the original meta-analysis. In our study, we aimed to be stringent in this regard and err on the safe side. For every combination of mental and physical disorders, we only pooled the effect size that was derived from the study with the largest number of participants with mental disorder among those studies using the same cohort or database.

I^2 and Q were computed to estimate the presence of significant heterogeneity and the proportion of total variability due to between-study heterogeneity, respectively. Egger's test was used to estimate publication bias. Publication bias plus ES being larger than that of the largest study in each association indicated small study effects (Dragioti et al., 2019). The 95% prediction intervals for the ESs were computed to estimate the possible range in which the ESs of future studies were anticipated to fall (Riley et al., 2011). We finally measured excess significance bias by assessing whether the observed number of studies with nominally statistically significant results was different from the expected number of studies with statistically significant results. For excess significance bias, a p-value ≤ 0.10 was considered statistically significant (Ioannidis and Trikalinos, 2007; Ioannidis, 2013). Analyses were carried out using STATA 17.0 (StataCorp. 2017. Stata Statistical Software: Release 17. College Station, TX) and R (version 4.0.3).

Since the distinction between adjusted and unadjusted is more blurred than it would appear, as studies presenting "unadjusted" ES typically match participants during recruitment based on a number of factors, in the primary analysis we included adjusted ESs when unadjusted ESs were not available after systematically checking the primary studies included in each retained SR/MA. The hierarchy of selection of outcomes for the primary analysis was as follows: 1-unadjusted OR, 2-adjusted OR, 3-Other types of unadjusted risk measures (i.e., hazard ratio or relative risk), 4-adjusted hazard ratios. No transformations were carried out when combining ORs, HR and RR into the same analysis, as frequencies of disorders for which HRs were reported was low or ESs were small. The underlying rationale was that the gains in the robustness of the estimates from including additional effect sizes outweighed the bias derived from combining multiple statistical metrics that are not equal but tend to converge when the mentioned factors occur. However, it must be noted that this combination was only carried out when it was impossible to obtain or calculate ORs from the data reported at the SR/MA or primary article level.

A secondary analysis, combining adjusted ORs derived from studies using gold-standard diagnoses, was considered as particularly rigorous. Sensitivity analyses focused on: 1) unadjusted ESs only; 2) maximally adjusted ESs only; 3) studies using formal (i.e., based on DSM or ICD) diagnoses only; 5) studies with a low risk of bias (consistent with previous studies (Brady et al., 2017; Rønnstad et al., 2018), we used a threshold of $< 66\%$ of the total score of the individual tool used to assess study quality to judge a study as at high risk of bias (see *eMethods 1* for

details); 6) overweight (age and sex-adjusted BMI ≥85th percentile) rather than obesity used in the primary analysis of studies reporting on association with increased weight. In an additional sensitivity analysis, we removed studies for which the OR had been calculated in the retained SRs/MAs through a conversion from continuous measures. We had also planned a-priori to carry out a sensitivity analysis on drug-naïve participants, however there were insufficient data to pursue this analysis. While performing the project, we came to the conclusion that it was not feasible to carry out a sensitivity analysis taking into account the temporality of the associations due to several reasons. 1-Most studies were either cross-sectional (and evaluated the presence of the two disorders at a given time point) or evaluated the presence of one or both disorders over long time periods (in many cases over the entire life), with both designs hindering the possibility of evaluating temporality. 2-Additionally, while some disorders are pervasive and/or have an unclear onset time (e.g., type I diabetes or ADHD), others have a clearer time demarcation (e.g. cancer or PTSD), and other disorders may run over long periods of time (high BMI, depression). Moreover, some disorders mostly occur in childhood, while others are typical of adulthood. Importantly, different combinations of these characteristics would require different designs to evaluate temporality. 3-This information was not available in most cases at the SR/MA level in a reliable form.

2.8. Classification of the level of evidence

Following our protocol, we stratified available evidence (Fusar-Poli and Radua, 2018; Tsilidis et al., 2015) as follows: Class I, convincing (number of cases >1000, $p < 10^{-6}$, I^2 <50%, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias); class II, highly suggestive (number of cases >1000, $p < 10^{-6}$, largest study with a statistically significant effect, and class I criteria not met); class III, suggestive (number of cases >1000, $p < 10^{-3}$, and class I-II criteria not met); class IV, weak ($p < 0.05$ and class I-III criteria not met); and non-significant ($p > 0.05$).

Table 1
Definition and operationalization of TRANSD criteria.

Criterion	Definition	Operationalization
T	Transparent definition of disorders	Analysis focuses on studies defining disorders according to gold-standard definitions only
R	Reporting of the primary outcome of the study, as well as the study design and the definition of the transdiagnostic construct in the abstract and main text (criterion R)	Criterion R was met through the inclusion criteria adopted by the current study
A	necessity of Appraising the conceptual transdiagnostic framework/approach as "across diagnoses and within spectrum" or "across diagnostic spectra"	Analysis focuses on relationships across all disorders and spectra
N	for Numerating the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated	Diagnostic categories are included in supplementary material, eTable 7
S	Necessity of Showing the degree of improvement or non-inferiority of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses	A transdiagnostic class of evidence of at least III, and not inferior to the lowest class of evidence for the corresponding disorder-specific associations is required
D	Demonstrate the generalisability of the transdiagnostic construct through external validation studies	Associations had to be confirmed in more than one study in eligible meta-analyses

2.9. Transdiagnostic analysis

We used the TRANSD-iagnostic criteria (Table 1), to assess to which extent the associations between mental disorders and physical conditions were disorder-specific or transdiagnostic (Arango et al., 2021; Fusar-Poli, 2019; Fusar-Poli et al., 2019). Diagnostic spectra were defined according to the ICD-11 diagnostic blocks (eTable 7). For the TRANSD analyses, we used studies adopting only gold-standard (i.e., formal) diagnoses.

Additions/amendments to the pre-registered protocol are reported in eMethods 1, alongside additional methodological details.

3. Results

The screening of 26,711 records led to the final inclusion of 45 SRs/MAs (Fig. 1, eResults, eTables 8–10), which included close to of 12.5 million individuals (1.5 million with physical conditions and 500,000 with mental disorders, respectively). Out of 341 records the full-text of which was assessed for eligibility, 290 reports were excluded (eTable 9) as they did not: 1) evaluate risk (78 articles); 2) include primary studies in children/adolescents (59 articles); 3) include eligible mental or physical conditions (35 articles in both cases). Six additional records were obtained from the list of references of included articles and umbrella reviews. See eTables 11–14 for details on the included SR/MAs, and eMethods for the methodology to estimate sample counts in our study. Using the AMSTAR-2 tool (eTable 15 and eFig. 2), nine MAs were deemed of overall high or moderate quality, and 36 of low or critically low quality. Relevant summary ESs found in each MA for each association are presented in eTable 16. The retained SRs/MAs included a median of 15 studies (interquartile range: 11–27). Most SRs/MAs reported ORs, implemented a random effects model when pooling data, and carried out an appraisal evaluation of the risk of bias. Eighteen SRs/MAs conducted the search between 2017 and 2021. Twenty-four SRs/

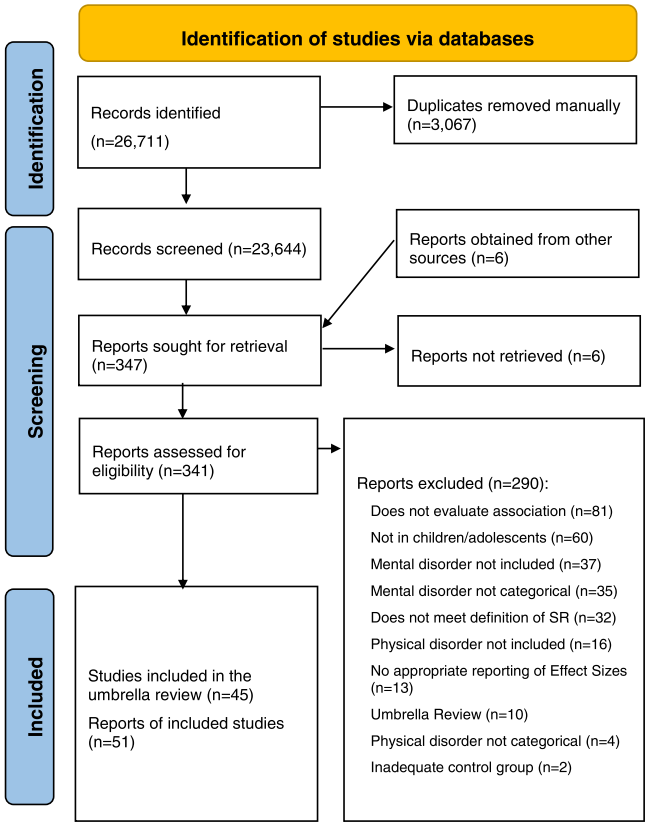

Fig. 1. Study selection flowchart.

MAs only included studies in which both disorders occurred in childhood and/or adolescence. In three SRs/MAs, only the physical disorder had to occur in individuals under the age of 18. The remaining SRs/MAs accepted any age of diagnosis or measurement of the association and varying definitions of the mental and physical disorders. An evaluation of the risk of bias was implemented in 37 SRs/MAs. The most frequently chosen tool was the NOS, which was used in 54% of those SRs/MAs performing a quality appraisal (in some cases with modifications). It must be noted that the total number of included participants that we present is this report is derived from summing samples included in the primary studies and inevitably an approximation. However, the total number does not count studies for which we were unable to extract the sample sizes. Conversely, if two studies used the same database for different mental-physical combinations of outcomes, the individuals would be included in this count more than once.

3.1. Outcomes

Criteria from a number of included SR/MAs differed from those in our umbrella review. For example, SR/MAs might have pooled together studies on children and on adults or have included conditions that were not relevant to the umbrella review. Overall, 363 outcomes reported in the primary studies and included in the retained SRs/MAs were excluded (eTables 17 and 18), as determined when evaluating the descriptive tables of the SRs/MAs or the primary studies themselves. The most frequent reasons for outcome exclusion were that they referred to adults (109 outcomes), were based on overlapping databases (75 outcomes), did not have a control group or it was inadequate (68 outcomes), or used an inadequate measure for diagnosis (50 outcomes). Six hundred twenty-one outcomes, deriving from 290 samples in 276 primary studies from all continents, were retained in the umbrella review (eTables 19–21). The larger number of outcomes in relation to that of samples derives from the fact that many studies evaluated the risk of multiple mental-physical associations in the same sample. Moreover, some primary studies reported on multiple samples.

Sixty-four percent of the primary studies were considered to be at a low risk of bias. Median and interquartile ranges for sample sizes were 752 (196−6836) for the total sample, 121 (46−591) for the number of individuals with a mental disorder, and 154 (42−683) for the number of individuals with a physical disorder. Almost all studies reported ORs. Only 5 HRs or RR were included in the main analyses. For the majority of these, the frequency of the events was low (under 10%) making the reported ES arguably equal to ORs (Cummings, 2009). In three cases were frequency could be expected to be higher, ES were under 2, and hence the expected OR would be only slightly higher.

3.2. Association between mental disorders and physical conditions

While searches were created to retrieve any SR/MA evaluating combinations between broad lists of physical and mental disorders, the included outcomes evaluated the association between ten mental disorders and 18 physical disorders (Table 2).

There were data in SR/MAs for 42 combinations of mental and physical disorders for the main analysis. The median number of outcomes included in the re-analyses (and interquartile range: IQR) was 6 (IQR=2.25–9.75). The median number of participants was 44,335 (IQR=8687–444,452), whereas the median number of cases with the physical disorder was 6805 (IQR=879–16,593). The pooled effect sizes ranged between 0.68 and 7.74, with 30 effects (71%) laying between an equivalent OR of 1 and 2. Pooled effects were significant in 31 analyses (74%). The percentage of heterogeneity due to true variation was important: eleven studies had either low (<25%) or moderate (25–50%), while twelve had substantial (50–75%) and 15 very substantial heterogeneity (>75%). The prediction interval (the estimate of the interval in which a future observation will fall in 95% of the occasions) was significant for six out of 31 effects (19%) with more than 2 outcomes, whereas five of them showed evidence of small study effects/publication bias (16%). Excess significance bias was found for three out of 38 effects (8%). In 18 (47%) effects, E was larger than O, indicating that an excess of significant findings was not pertinent and in eight effects (21%) there was no evidence of excess significance bias. This test could not be estimated for nine effects (24%). Regarding the class of evidence, two associations showed convincing evidence, ten highly suggestive evidence, six had convincing evidence and for thirteen there was weak evidence on their association.

There were data in SR/MAs for 22 combinations of mental and physical disorders for the analysis including adjusted effect sizes obtained with a gold-standard diagnosis. The median number of outcomes included in this set of analysis was 2 (IQR=1–4). The median number of participants was 31,132 (IQR=5142–247,672), whereas the median number of cases with the physical disorder was 3367 (IQR=992–15,405). The pooled effect sizes ranged between 0.22 and 3.04, with 16 effects laying between an equivalent OR of 1 and 2. Pooled effects were significant in 12 analyses, although 4 derived from single studies where no meta-analysis was carried out. Heterogeneity was lower than for the main analyses: eight studies had either low (<25%) or moderate (25–50%), while two had substantial (50–75%) and four very substantial heterogeneity (>75%). The prediction interval was significant for 2 out of 9 effects with more than 2 outcomes, whereas none of them showed evidence of small study effects/publication bias. There was no excess significance bias for the 14 effects (0%). In six (42%) effects, E was larger than O, indicating that an excess of significant findings was not pertinent and in four effects (29%) there was no evidence of excess significance bias. Also, this test could not be estimated for four effects (29%). Regarding the class of evidence, two associations showed convincing evidence, one highly suggestive evidence, one convincing evidence and for four there was weak evidence on their association.

Results of the primary (unadjusted-if-possible ES) and secondary analysis based on adjusted ES only with gold standard diagnoses can be found in Tables 2 and 3, respectively.

Sensitivity analyses are shown in eTables 22–28. We summarise here the results by groups of mental disorders.

Neurodevelopmental/disruptive disorders (21 SRs/MAs): In the primary analysis, there was convincing (class I) or highly suggestive (class II) evidence for an association of ASD with rhinitis (OR=1.66; CI-=1.49, 1.85), obesity (OR=1.90; CI=1.51, 2.39), and food allergy (OR=2.65; CI=1.97, 3.56), of ADHD with rhinitis (OR=1.58; CI=1.32, 1.90), obesity (OR=1.32; CI=1.18, 1.47; with evidence of excess significance bias), and dermatitis (OR=1.41; CI=1.31, 1.51; with evidence of small study effects/publication bias), and of disruptive behaviour with dermatitis (OR=1.54; CI=1.31, 1.80). ADHD-obesity was the association based on the largest evidence (43 primary studies; 1,390,311 individuals). In the sensitivity analysis focusing on adjusted ESs only, with gold standard diagnoses, there was convincing or highly suggestive evidence for an association of ADHD with asthma (OR=1.47; CI=1.38, 1.57) and obesity (OR=1.81; CI=1.40, 2.33). The other sensitivity analyses were, in general, quite consistent with the primary analysis.

Mood disorders (20 SRs/MAs): When considering unadjusted-if-possible ORs, there was convincing or highly suggestive evidence for an association between depressive disorders and cancer (OR=1.40; CI=1.21, 1.61), obesity (OR=1.53; CI=1.39, 1.70; with evidence of small study effects/publication bias) and rhinitis (OR=1.87; CI=1.47, 2.38), as well as between bipolar disorder and asthma (OR=1.87; CI=1.47, 2.38). Evidence for the largest association (obesity-depression) was based on 57 primary studies (159,767 participants). In the sensitivity analysis considering adjusted ES with gold-standard diagnoses, the association depression-asthma was rated as convincing (OR=1.63; CI=1.35, 1.97). All other associations were considered suggestive or weak. The other sensitivity analyses were in general in line with the primary analysis, except for the association depression-cancer that was downgraded to suggestive or weak. Importantly, out of 45 SR/MAs only

Table 2
Associations between psychiatric and physical outcomes by class of evidence (unadjusted-if-possible ES), listed by group of disorders and, within group, by class level.

Author, year	Mental	Physical	k	n/N	eOR (95% CI)	p	PI sign	I^2 (%)	SSE	ESB	LS sign	Class	AMSTAR-2
Miyazaki, 2015	ASD	Rhinitis	5	2592/ 9685	1.66 (1.49, 1.85)	5.6×10^{-20}	Yes	0.0	No	No	Yes	I	Low
Xie, 2019	Disruptive Behaviour	Dermatitis	6	12,925/ 92,733	1.54 (1.31, 1.80)	1.7×10^{-7}	Yes	28.6	No	No	Yes	I	Low
Miyazaki, 2017, van der Schans, 2017 MA, van der Schans, 2017 SR, Schmitt, 2010, Xie, 2019	ADHD	Dermatitis	22	435,477/ 1,190,930	1.41 (1.31, 1.51)	1.9×10^{-21}	Yes	65.8	Yes	NP	Yes	II	Moderate, low, low, crit low, low
Cortese, 2016, Li and Xie, 2020, Nigg, 2016	ADHD	Obesity	43	74,476/ 1390,311	1.32 (1.18, 1.47)	5.3×10^{-7}	No	83.6	No	Yes	Yes	II	High, moderate, crit low
Miyazaki, 2017, van der Schans, 2017 MA, van der Schans, 2017 SR	ADHD	Rhinitis	8	15,197/ 83,438	1.58 (1.32, 1.90)	7.3×10^{-7}	No	79.2	No	NP	Yes	II	Moderate, low, low
Li, 2020, Miyazaki, 2015, Wang, 2020	ASD	Food allergy	16	16,593/ 419,752	2.64 (1.97, 3.55)	1.2×10^{-10}	No	84.3	No	NP	Yes	II	Low, low, crit low
Kahathuduwa, 2019, Li and Xie, 2020, Zheng, 2017	ASD	Obesity	21	32,525/ 420,382	1.90 (1.51, 2.39)	3.7×10^{-8}	No	93.7	No	No	Yes	II	Moderate, moderate, crit low
Salem, 2018	ADHD	Headache	8	4480/ 19,419	1.58 (1.23, 2.03)	3.6×10^{-4}	No	67.7	No	No	Yes	III	Moderate
Miyazaki, 2015, Xie, 2019	ASD	Dermatitis	8	418,161/ 900,854	1.85 (1.35, 2.55)	1.4×10^{-4}	No	92.2	No	NP	Yes	III	Low, low
McElhanon, 2014	ASD	Diarrhoea	12	554/ 37,303	3.67 (1.83, 7.35)	2.4×10^{-4}	No	86.8	No	NA	Yes	IV	Crit low
Cortese, 2018, Kaas, 2020, Miyazaki, 2017, van der Schans, 2017 MA	ADHD	Asthma	29	572,114/ 482,2797	1.55 (1.17, 2.06)	0.002	No	99.7	No	NP	Yes	IV	High, low, crit low, low
Miyazaki, 2017	ADHD	Conjunctivitis	3	9564/ 41,908	1.69 (1.04, 2.75)	0.035	No	92.5	No	NP	Yes	IV	Crit low
McElhanon, 2014	ASD	Abdominal Pain	8	196/ 608	2.45 (1.18, 5.07)	0.016	No	69.7	No	NA	No	IV	Crit low
Kaas, 2020, Miyazaki, 2015, Zheng, 2016	ASD	Asthma	18	34,292/ 202,656	1.36 (1.13,1.65)	0.002	No	88.0	Yes	Yes	No	IV	Low, low, low
McElhanon, 2014	ASD	Constipation	9	161/ 608	3.87 (2.23, 6.71)	1.5×10^{-6}	No	63.8	No	NA	Yes	IV	Crit low
McElhanon, 2014	ASD	General gastrointestinal problems	9	353/ 1008	4.50 (1.76, 11.55)	0.002	No	93.4	No	NA	No	IV	Crit low
Nujic, 2020	Disruptive behaviour	Obesity	2	6926/ 43,442	1.71 (1.01, 2.90)	0.047	NA	69.8	NA	NA	Yes	IV	Moderate
Christie, 2017	Intellectual disability	Bacterial meningitis	5	526/ 1139	7.74 (2.85, 21.02)	5.8×10^{-5}	Yes	0.0	No	NP	Yes	IV	Low
Miyazaki, 2017	ADHD	Food allergy	3	506/ 8613	1.15 (0.89, 1.48)	0.279	No	0.00	No	NP	No	NS	Moderate
Maiano, 2016	Intellectual disability	Obesity	2	2775/ 21,256	1.25 (0.71, 2.21)	0.437	NA	34.4	NA	NP	No	NS	Low
Wu, 2016	BD	Asthma	2	49,568/ 129,741	2.17 (1.85, 2.54)	7.3×10^{-22}	NA	0.0	NA	NA	Yes	II	Crit low
Secinti, 2017	Depression	Cancer	14	10,289/ 13,503	1.40 (1.21,1.61)	6.9×10^{-6}	Yes	16.3	No	NP	Yes	II	Low
Luppino, 2010, Mannan, 2016, Moradi, 2020, Quek, 2017, Rao, 2019, Rao, 2020, Sutaria, 2019, Villagrasa Blasco, 2020	Depression	Obesity	57	23,547/ 159,767	1.53 (1.39, 1.70)	1.3×10^{-16}	No	57.7	Yes	NP	Yes	II	Low, moderate, low, low, crit low, crit low, low, crit low
Lu, 2018	Depression	Rhinitis	2	1876/ 8911	1.87 (1.47, 2.38)	3.0×10^{-7}	NA	0.0	NA	No	Yes	II	Crit low
Brady, 2017, Lu, 2012, Lu, 2018, Secinti, 2017	Depression	Asthma	15	6805/ 45,228	2.09 (1.63, 2.67)	5.1×10^{-9}	No	84.0	No	Yes	No	III	Crit low, crit low, crit low, low
Ronnstad, 2018, Xie, 2019	Depression	Dermatitis	8	47,320/ 452,475	1.34 (1.17, 1.53)	9.2×10^{-6}	No	73.8	No	NA	Yes	III	Crit low, low
Secinti, 2017	Depression	Congenital heart disease	2	388/ 577	1.63 (0.39, 6.78)	0.498	NA	76.5	NA	NP	Yes	NS	Low
Brady, 2017, Secinti, 2017	Depression	Diabetes	7	2645/ 482,591	1.54 (0.99, 2.41)	0.057	No	78.8	No	NP	Yes	NS	Crit low, low
Brady, 2017	BD	Diabetes	1			–	–	–	–	–	–	SS	Crit low

(*continued on next page*)

Table 2 (*continued*)

Author, year	Mental	Physical	k	n/N	eOR (95% CI)	p	PI sign	I^2 (%)	SSE	ESB	LS sign	Class	AMSTAR-2
				1989/ 471,685	1.67 (0.53, 5.2)								
Secinti, 2017	Depression	Epilepsy	1	334/ 457	0.68 (0.23, 1.99)	–	–	–	–	–	–	SS	Low
Secinti, 2017	Depression	Rheumatoid arthritis	1	334/ 457	1.61 (0.57, 4.56)	–	–	–	–		–	SS	Low
Lu, 2012, Secinti, 2017	Anxiety	Asthma	6	3231/ 12,991	1.66 (1.36, 2.03)	6.3×10^{-7}	No	65.0	No	NP	Yes	II	Crit low, low
Brady, 2017, Secinti, 2017	Anxiety	Diabetes	4	2101/ 481,709	1.70 (1.37, 2.12)	1.6×10^{-6}	Yes	3.9	No	NP	Yes	III	Crit low, low
Secinti, 2017	Anxiety	Cancer	10	8574/ 10,310	1.62 (1.24, 2.13)	4.7×10^{-4}	No	58.1	Yes	NP	Yes	III	Low
Secinti, 2017	Anxiety	Congenital heart disease	2	879/ 919	2.58 (1.45, 4.60)	0.001	NA	0.0	NA	NA	Yes	IV	Low
Xie, 2019	Anxiety	Dermatitis	7	10,797/ 80,894	1.34 (1.07, 1.68)	0.011	No	26.1	No	NP	Yes	IV	Low
Moradi, 2020	Anxiety	Obesity	6	8438/ 57,692	1.06 (0.83, 1.35)	0.627	No	61.0	No	No	Yes	NS	Low
Secinti, 2017	Anxiety	Epilepsy	1	257/ 391	0.7 (0.3, 1.4)	–	–	–	–	–	–	SS	Low
Jiang, 2020	Psychosis	Infection	3	256,106/ 2,281,723	1.45 (1.17, 1.79)	0.001	No	89.8	No	No	Yes	IV	Crit low
Xie, 2019	Sleep disorders	Dermatitis	6	702/ 1711	2.90 (1.59, 5.29)	0.001	No	84.7	No	NA	Yes	IV	Low
Jiang, 2020	Psychosis	Infection (CNS)	5	9164/ 688,277	1.68 (0.94, 2.98)	0.077	No	71.6	Yes	No	No	NS	Crit low
Brady, 2017, Galling, 2016	Schizophrenia	Diabetes	2	2489/ 483,605	1.99 (0.36, 11.02)	0.431	NA	69.1	NA	NP	No	NS	Crit low, moderate

Abbreviations: Class – class of evidence, CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, I2 – heterogeneity, k – number of effects per association, LS – largest study with significant effect, n – number of cases per association (those with the physical disorder), N – total number of individuals in cohort per association, NP=not pertinent, because the estimated E (Expected) is larger than the O (Observed), and there is no evidence of excess statistical significance based on the assumption made for the plausible effect size, OR – odds ratio, PI – prediction interval, SSE – small study effects, sign. – significant, SS – single study in which case cells with statistical values calculated from meta-analysis are left empty.

two (Cortese et al., 2016; Nigg et al., 2016) took into account medication in their final analyses, while a third one had planned to use it but was unable to carry out the analyses due to lack of reliable data in the primary papers (Cortese et al., 2018). Indeed, this shows that information in this regard is typically hard to extract even from primary articles. Hence, it was decided not to pursue this analysis due to insufficient data.

Anxiety disorders (10 SRs/MAs): There was highly suggestive evidence for an association of anxiety disorders with asthma (OR=1.66; CI=1.36, 2.03; with 6 studies and 12,991 individuals), which was generally confirmed in most sensitivity analyses, but was downgraded to weak in the sensitivity analysis focused on adjusted ES with gold standard diagnoses.

Other disorders (4 SRs/MAs): All associations regarding other mental disorders (psychosis/schizophrenia and sleep disorders) were weak or non-significant.

3.3. Transdiagnostic analysis

We were able to test if there was a transdiagnostic association for four physical disorders (obesity, asthma, dermatitis and rhinitis), as for these there was evidence of association with more than one mental disorder when only gold-standard diagnoses were considered. There was evidence for a transdiagnostic association for all of them except for rhinitis (Table 4). Considering adjusted ESs only and limiting results to class I and II, we found evidence for a transdiagnostic association only for asthma (Table 4).

4. Discussion

We report the most comprehensive transdiagnostic quantitative evidence synthesis on the associations between mental-physical disorder pairs in children/adolescents, grading the credibility of the evidence. Previous MAs provided inconclusive evidence and have generally been restricted to specific pairs of mental-physical conditions (e.g., ASD and food allergy (Wang et al., 2021)), small sets of disorders (e.g., depression and anxiety with obesity (Wang et al., 2019)) or just one mental or physical condition (e.g., mental disorders and dermatitis (Xie et al., 2019)) in children and adolescents. By contrast, our umbrella review included a broad set of mental and physical conditions, using the same criteria to rate the strength of the evidence for each association.

When considering unadjusted ES (when possible; otherwise, adjusted ES) and any method to diagnose mental disorders, we found convincing evidence for the association of ASD with rhinitis, disruptive behaviour disorder with dermatitis, and highly suggestive evidence for ADHD with rhinitis, dermatitis, and obesity, ASD with food allergy and obesity, anxiety with asthma, bipolar disorder with asthma, and depression with cancer, obesity, and rhinitis. We found evidence of transdiagnostic associations for asthma, dermatitis and obesity.

The results of our primary analysis in children and adolescent extend previous research, including a large-scale analysis based on ~5.9 million adults in Denmark showing that the majority of mental disorders were associated with an increased risk of a subsequent physical condition, with significant association across 76 of 90 mental-physical disorder pairs (Momen et al., 2020). Our analyses complement and extend these results showing that a number of specific associations start being significant in childhood/adolescence. Our findings are also based on more comprehensive and diverse evidence from different study designs and provide a more international perspective. Unlike the Danish study, we did not find any instance in which the presence of a mental disorder decreased the risk of physical conditions. This difference may be accounted for either by developmental effects - protective role manifesting later across the lifespan or premature death in mentally ill individuals prior to the emergence of the medical condition - or by the fact that available SRs/MAs focused mainly on increased risk of physical conditions.

The temporality of the significant associations detected in our

Table 3
Sensitivity analysis including only adjusted ES from studies using gold-standard diagnoses, listed by group of disorders and, within group, by class level.

Author, year	Mental	Physical	k	n/ N	eOR (95% CI)	p	PI sign	I^2 (%)	SSE	ESB	LS sign	Class	AMSTAR-2
Cortese, 2018, Kaas, 2020	ADHD	Asthma	8	12,577/ 77,300	1.47 (1.38, 1.57)	9.3×10^{-33}	Yes	12.8	No	NP	Yes	I	High, low
Cortese, 2016, Li and Xie 2020	ADHD	Obesity	5	19,511/ 499,744	1.81 (1.40, 2.33)	4.2×10^{-7}	No	25.4	No	NP	Yes	II	High, critically low
Miyazaki, 2017, Schmitt, 2010, van der Schans, 2017 MA, Xie, 2019	ADHD	Dermatitis	7	392,925/ 802,099	1.30 (1.14, 1.47)	4.3×10^{-5}	No	43.50	No	No	Yes	III	Moderate, critically low, low, low
Li and Liu, 2020, Wang, 2021	ASD	Food allergy	3	3718/ 83,961	1.60 (1.19, 2.15)	0.001	No	34.2	No	No	Yes	IV	Low, low
Zheng, 2017	ASD	Obesity	2	16,348/ 299,244	3.04 (1.14, 8.10)	0.026	NA	99.2	NA	NA	Yes	IV	Critically low
Miyazaki, 2017	ADHD	Conjunctivitis	2	1065/ 4193	1.41 (0.50, 3.99)	0.520	NA	63.8	NA	NP	No	NS	Moderate
Miyazaki, 2017	ADHD	Food allergy	3	506/ 8613	0.99 (0.75, 1.31)	0.943	No	0.0	No	NP	No	NS	Moderate
Miyazaki, 2017, van der Schans, 2017 MA	ADHD	Rhinitis	5	12,234/ 45,391	1.30 (0.98, 1.72)	0.073	No	88.8	No	No	Yes	NS	Moderate, low
Kaas, 2020	ASD	Asthma	4	12,487/ 53,039	1.10 (0.74, 1.64)	0.632	No	94.9	No	NP	No	NS	Low
Miyazaki, 2017	ADHD	Drug allergy	1	84/ 4113	1.15 (0.62, 2.11)	–	–	–	–	–	–	SS	Moderate
Salem, 2018	ADHD	Headache	1	139/ 1308	2.43 (0.86, 6.85)	–	–	–	–	–	–	SS	Moderate
Miyazaki, 2017	ADHD	Urticaria	1	6/ 80	0.22 (0.03, 2.10)	–	–	–	–	–	–	SS	Moderate
Xie, 2019	ASD	Dermatitis	1	387,262/ 774,524	1.36 (1.26, 1.46)	–	–	–	–	–	–	SS	Low
Miyazaki, 2015	ASD	Rhinitis	1	2336/ 7990	1.70 (1.51, 1.91)	–	–	–	–	–	–	SS	Low
Brady, 2017, Lu, 2012	Depression	Asthma	4	3016/ 16,874	1.63 (1.35, 1.97)	5.1×10^{-7}	Yes	0.0	No	NP	Yes	I	Critically low, critically low
Mannan, 2016, Moradi, 2020, Rao, 2020, Sutaria, 2019	Depression	Obesity	9	1354/ 9393	1.46 (1.06, 2.02)	0.020	No	41.2	No	NA	Yes	IV	Moderate, low, critically low, low
Wu, 2016	BD	Asthma	1	46,443/ 92,955	1.82 (1.25, 2.65)	–	–	–	–	–	–	SS	Critically low
Lu, 2018	Depression	Rhinitis	1	1673/ 8365	1.59 (1.02, 2.50)	–	–	–	–	–	–	SS	Critically low
Miyazaki, 2017	Anxiety	Asthma	2	968/ 2609	1.61 (1.18, 2.20)	0.003	NA	0.0	NA	No	Yes	IV	Moderate
Secinti, 2017	Anxiety	Epilepsy	1	257/ 391	0.70 (0.00, 1.40)	–	–	–	–	–	–	SS	Low
Jiang, 2020	Psychosis	Infection	2	248,592/ 2,230,259	1.37 (0.85, 2.21)	0.200	NA	87.5	NA	NA	Yes	NS	Critically low
Jiang, 2020	Psychosis	Infection (CNS)	2	4738/ 662,016	2.09 (0.34, 12.83)	0.425	NA	70.9	NA	NA	No	NS	Critically low

Abbreviations: Class – class of evidence, CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, I2 – heterogeneity, k – number of effects per association, LS – largest study with significant effect, n – number of cases per association (those with the physical disorder), N – total number of individuals in cohort per association, NP=not pertinent, because the estimated E (Expected) is larger than the O (Observed), and there is no evidence of excess statistical significance based on the assumption made for the plausible effect size, OR – odds ratio, PI – prediction interval, SSE – small study effects, sign. – significant, SS single study, NA – not available.

Table 4
Evidence for transdiagnostic associations.

	TR	AN	S	D	TRANSD
Unadjusted effect sizes if possible					
Physical disorder	Mental disorders (ICD-11 code), Class	Number of mental disorders (spectra)	Pooled class; equivalent Odds Ratio (95% CI); number of individual studies, cases	Number of individual studies reporting significant associations, ≥ 2 within each mental disorder	Criteria met or not
Asthma	Anxiety (6B0), III ASD (6A02), IV B (6A6) II Depression (6A7), III	4 (3)	II; 1.64 (1.35; 1.99); 25; 409,402	16, yes	Yes
Obesity	ADHD (6A05), III ASD (6A02), IV Depression (6A7), I	4 (2)	II; 1.54 (1.35; 1.75); 61; 333,274	25, yes	Yes
Dermatitis	ADHD (6A05), II ASD (6A02), IV	2 (1)	II; 1.44 (1.31; 1.58); 16; 407,121	9, yes	Yes
Rhinitis	ADHD (6A05), IV ASD (6A02), II	2 (1)	II; 1.52 (1.30; 1.77); 8; 1405	4, no	No
Adjusted effect sizes					
Physical disorder	Mental disorders (ICD-11 code), Class	Number of mental disorders (spectra)	Pooled class; equivalent Odds Ratio (95% CI); number of individual studies, cases	Number of individual studies reporting significant associations, ≥ 2 within each mental disorder	Criteria met or not
Asthma	ADHD (6A02), I Anxiety (6B0), IV Depression (6A7), I	3 (3)	I; 1.50 (1.43; 1.57); 14; 16,561	8, no	Yes*
Obesity	ADHD (6A05), II ASD (6A02), IV Depression (6A7), IV	3 (2)	III; 1.76 (1.35; 2.29); 16; 808,381	8, yes	Yes

umbrella review is complex. In our protocol we planned subgroup analyses including cross-sectional and prospective studies only, respectively. However, when carefully analyzing each of the retained SRs/MAs, we could not disentangle temporality or causality. Thus, the significant associations that we detected may be explained by several, non-mutually exclusive factors.

First, it is possible that that the links between physical and mental disorders are underpinned by shared genetic factors. For instance, for depression, in a recent population-based cohort study comprising 16,687 singletons, a higher liability to major depression was associated with increased asthma risk (Liu et al., 2020). As for ADHD, a large genome-wide association meta-analysis (20,183 individuals diagnosed with ADHD and 35,191 controls) found a small albeit significant genetic correlation between asthma and ADHD (Demontis et al., 2019). However, we are not aware of any genome-wide study assessing genetic associations of physical conditions across several mental disorders. Our results point to the need of conducting such studies. Second, mental and physical disorders might share non-purely genetic factors, i.e., factors related to the environment that may eventually include indirect genetic effects. In this regard, a meta-umbrella review summarising 1180 associations between putative risk or protective factors and mental disorders found convincing or highly suggestive evidence for a number of non-purely genetic factors and a broad set of mental conditions (Arango et al., 2021). Of note, the most robust non-purely genetic risk factors identified for childhood conditions (e.g., maternal pre-pregnancy obesity, maternal smoking during pregnancy, maternal overweight pre/during pregnancy for ADHD, and maternal overweight pre/during pregnancy for ASD) may increase the risk also for physical dysfunctions in the child/adolescent. Common genetic and non-purely genetic factors, as well as their interplay and epigenetic factor, may lead to shared pathophysiologic pathways for mental and physical conditions. These pathways may include immunological dysfunctions. Indeed, pro-inflammatory changes have been reported in children/adolescents with mental disorders, like depression (D'Acunto et al., 2019), anxiety (Khandaker et al., 2016), and ADHD (Chang et al., 2021). Such inflammatory alterations may contribute to behavioural/emotional symptoms. For instance, hyper-secretion of pro-inflammatory cytokines from allergic reactions passing through the blood-brain barrier may affect the prefrontal cortex, contributing to the clinical symptomatology of ADHD (Strom et al., 2016). Fourth, it is also possible that mental disorders increase the risk of psychological stress, which in turn would contribute to immunological dysfunctions (Ohno, 2017). Fifth, the pharmacological treatment of physical disorders may contribute to psychiatric symptoms (e.g., corticosteroid contributing to disruptive behaviours) (Warrington and Bostwick, 2006). Sixth, the pharmacological treatment of mental disorders may contribute to physical conditions (e.g., antipsychotics, mood stabilisers or certain antidepressants contributing to overweight/obesity, dyslipidemia and diabetes) (Correll et al., 2015; Firth et al., 2019). Seventh, physical dysfunctions might increase the risk of mental disorders (e.g. cancer contributing to depression). Of note, we did not find convincing evidence of increased risk of medical conditions in children due to dysregulated behaviours related to mental conditions, such as sexual infections caused by inappropriate/risky behaviours related to mental conditions (e.g. ADHD), although primary individual studies support this link in older individuals (Chen et al., 2018).

Notably, when focusing on more rigorous adjusted ES, gold standard diagnoses of mental disorder, we found convincing/highly suggestive evidence for less associations, also due to fewer such data, yet still involving conditions characterised by immunologic dysfunctions (asthma-ADHD and asthma-depression and highly suggestive evidence for ADHD-obesity).

Our results might have important clinical and public health implications in terms of screening programs. This is particularly relevant in light of the well documented disparity in the screening and management of physical conditions in individuals with vs. those without mental disorders (Solmi et al., 2021a, 2020). However, we urge caution in interpreting our results as evidence supporting the need for a systematic, universal screening of physical conditions in children with mental disorders, as this would require evidence of cause-effect relationships as well as pragmatic randomised controlled trials of universal screening showing effectiveness in the real world.

Our results should be considered in the light of several limitations. We relied on evidence provided in available SR/MAs to find significant associations. Robust evidence on other associations may be offered by primary studies that have not been included in meta-analyses yet, and key information might not be reported at the SR/MA level. Relatedly, the quality of the included SR/MAs was deemed high for two meta-

analyses only (Cortese et al., 2018, 2016). However, we note that this assessment is based on judgments that, inevitably, have a subjective component, and are also influenced by the reporting of the SR/MA, rather than exclusively by its quality.

While it could be argued that redoing a systematic search and data extraction of primary articles would be ideal, such a task at the scale of our work was clearly not be feasible. Nevertheless, it must be highlighted that our work used a mixed approach, as we relied heavily on primary articles obtained from the SRs/MAs. SRs/MAs helped to identify a list of potential articles, but then key data were checked or completed with the primary article whenever possible. A major advantage of our methodology is related to a relevant risk in umbrella reviews, namely the danger of double-counting participants or studies and, therefore, overstating the confidence in the pooled effect sizes. We took great care in minimising this risk by checking the database used in each included primary article and eliminating any effect sizes that could violate such a requirement for independence.

As previously mentioned, we were unable to disentangle the direction of the association between physical and mental conditions. Similarly, we were not able to study in depth other factors that could be influencing the results of the different pooled effects, such as the effect of combining epidemiological or clinical disorders, the fact that patients may also present with more than one co-occurring physical and mental condition, and the effect of medications (both for mental and physical disorders) in contributing to the associations. All these effects were not analyzed both due to limitations in the retained SRs/MAs and primary studies and the broadness and scope of our project. However, the results of our work now provide a roadmap to move forward in the field of evidence synthesis in developmental psychiatry, forming a strong base from which to develop and update future meta-analyses. Indeed, we explicitly planned the present work as the first step of a larger project aiming to complete, update or improve the meta-analytic evidence on relationships between mental and physical disorders. These future studies can be carried out in a much focused and in-depth way while standing on the shoulders of our present results.

In conclusion, there is converging evidence that physical conditions involving (auto)immunological and/or inflammatory processes may be related to mental disorders. Since at least half of mental disorders emerge in childhood and adolescence (Solmi et al., 2021b), these results should guide future research in the field, aimed at gaining insight into the temporal and causal links between mental and physical conditions as well as specific factors linking the two in order to devise effective preventive and intervention strategies.

CRediT authorship contribution statement

CC and SC conceptualized the study; GA, MS, AFC, AC, PF-P, HL, CC and SC designed the protocol; GA, LE, MR-G, AMC-L, SM, SW and SC carried out the Screening, data extraction and risk of bias evaluation; GA, MS, ED and SC performed and interpreted the statistical analyses; GA and SC drafted the initial version of the article and coordinated and supervised the overall project; all authors critically revised the manuscript and approved its final version. GA and SC had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

Authors in the current umbrella review have also authored SR/MAs included. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, Canadian AADHD Alliance Resource (CADDRA), British Association of Psychopharmacology (BAP) and from Healthcare Convention for educational activity on ADHD. MS has received honoraria/has been a consultant for Angelini, Lundbeck. CC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Cardio Diagnostics, Compass, Damitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Relmada, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. He has provided expert testimony for Bristol- Myers Squibb, Janssen and Otsuka. He served on a Data Safety-Monitoring Board for Lundbeck, Relmada, ROVI and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of Cardio Diagnostics, Holmusk and LB Pharma. AC has received research grants, educational and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. All other authors declare no competing interests.

Data Availability

Please contact the corresponding author if you would like to request any data that are not included in the Article or the Appendix.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104662.

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Clinical application of mindfulness-oriented meditation in children with ADHD: a preliminary study on sleep and behavioral problems

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ABSTRACT

Objective: High incidence of sleep problems in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) has been described. Mindfulness meditation has emerged as a novel approach to sleep disturbances and insomnia remediation. This preliminary study tested the efficacy of Mindfulness-Oriented Meditation (MOM) training on sleep quality and behavioral problems in children with ADHD.

Design: Twenty-five children with ADHD aged 7-11 years underwent two programs three times per week for eight-weeks: the MOM training (15 children) and an Active Control Condition (10 children).

Main Outcome Measures: Objective and subjective measures of sleep quality and behavioral measures were collected before and after the programs.

Results: Positive effects on sleep and behavioral measures were found only in the MOM group.

Conclusion: Although they are preliminary, our results indicate that MOM training is a promising tool for ameliorating sleep quality and behavioral manifestations in ADHD.

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. It is usually first diagnosed in childhood and

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often lasts into adulthood. The prevalence of ADHD in the population is 3-7% (Rowland et al., 2015) with about 5% of children (American Psychiatric Association (APA), 2013) and 4% of adults showing ADHD (Kessler et al., 2006). According to the DSM-5 (APA, 2013), the essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. Manifestations of the disorder interfere with, or reduce the quality of, social, academic, or occupational functioning (Singh et al., 2015). Sleep problems are frequently seen in ADHD, with a prevalence ranging between 25 and 55% (Hodgkins et al., 2013; Hvolby et al., 2008; Owens, 2005; Sung et al., 2008). Several studies have documented high incidence of sleep onset insomnia (van der Heijden et al., 2006), difficulty initiating and maintaining sleep (Owens, 2005), night awakenings, delayed sleep, bedtime resistance, fear of the darkness and/or sleeping alone, parasomnias, nocturnal enuresis, loud snoring (Gomes et al., 2014; Lecendreux & Cortese, 2007; Nakatani et al., 2013; Owens, 2008, Owens et al., 2009; Sciberras et al., 2011; Yoon et al., 2012), delayed sleep phase and increased nocturnal activity (Gruber et al., 2000; Owens et al., 2009).

Sleep problems in children and adolescents with ADHD have been studied with objective (polysomnography and actigraphy) and subjective measures (parental or self-rated questionnaires and diaries). In recent years, actigraphy has become a major assessment tool, especially in sleep research, sleep medicine, and proved to be a reliable (Martin & Hakim, 2011), valid (Morgenthaler et al., 2007) and cost-effective (Sadeh, 2011) instrument. Actigraphy is a non-invasive method for objectively recording motor activity and sleep parameters by means of an electronic device worn on the body. The actigraphy allows activity information to be obtained either in an experimental or in a natural setting for a prolonged and continuous period. A first meta-analysis by Cortese et al. (2009) summarized results of studies using both actigraphy and subjective measures in a total pooled sample of 722 children with ADHD versus 638 typically developing controls. As for objective parameters, four actigraphy studies reported longer mean sleep onset latency and shorter true sleep time in non-medicated children with ADHD than those in controls. One of these studies (Hvolby et al., 2008) showed that mean actigraphy sleep onset latency was longer in children with ADHD than in community controls and children with psychiatric conditions. A further study (Moreau et al., 2014) confirmed worse sleep measures derived from actigraphy (as sleep onset latency, sleep efficiency, and total sleep time) in children with ADHD than those in controls. However, a more recent meta-analysis of actigraphy measures (De Crescenzo et al., 2016) reached different results. Investigating twenty-four studies comprising 2179 children with ADHD versus controls, children with ADHD showed similar sleep duration, and a moderately altered sleep pattern (De Crescenzo et al., 2016).

With regards to subjective measures, the meta-analysis by Cortese et al. (2009) indicated children with ADHD had significantly higher bedtime resistance, longer sleep onset latency and more night awakenings, more difficulty with morning awakenings, more sleep disordered breathing and daytime sleepiness than controls. By parental reports of sleep, Moreau et al. (2014) confirmed more severe sleep disturbances in children with ADHD than those in controls.

In sum, the results that exist on sleep patterns in ADHD, especially those derived from actigraphy, are controversial. Furthermore, at our knowledge, there are no data

on sleep in ADHD that have been derived by combining objective and subjective measures with parent- and self-reported questionnaires.

The presence of psychiatric comorbidities and the use of psychostimulants complicate the picture of sleep problems in ADHD. It is debated whether sleep problems are specific of ADHD (Ringli et al., 2013; Yoon et al., 2012), originated from psychiatric comorbidities in ADHD (Brand & Kirov, 2011; Jan et al., 2011; Lecendreux & Cortese, 2007; Owens et al., 2009; Stein et al., 2012), or they are adverse effects resulting from stimulant therapy (Corkum et al., 1999; Cortese et al., 2013; Owens et al., 2009; Rothenberger & Rothenberger, 2013; Stein et al., 2012; Tsai & Huang, 2010).

Moreau et al. (2014) found no evidence to suggest that those children with ADHD who were treated with a psychostimulant medication experienced more sleep disturbances than untreated children did. However, the presence of psychiatric comorbidity was strongly associated with sleep disturbances (Moreau et al., 2014). The meta-analysis by De Crescenzo et al. (2014) reached different conclusions on psychostimulant medication: results from eight studies comprising 393 children and adolescents with ADHD documented that methylphenidate reduced total sleep time and mean activity.

Mindfulness meditation has emerged as a new approach for sleep disturbances (for a meta-analytic review, see Gong et al., 2016) and for insomnia remediation (e.g. the Mindfulness-Based Therapy for Insomnia by Ong et al., 2008, 2009; Ong & Sholtes, 2010; Ong et al., 2014, 2018). Mindfulness is defined as 'the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience' (Kabat-Zinn, 2003). It is especially indicated for sleep-related problems because it reduces the hyperarousal and negative emotional states (e.g. anxiety and worry) that are frequently reported by individuals experiencing sleep disorders (Harvey, 2002; Riemann et al., 2010).

With its focus on attention, mindfulness meditation is a form of training that is gaining empirical support as a complementary intervention for young adults (Aadil et al., 2017; Cairncross & Miller, 2020) and children and adolescents with ADHD (see the meta-analyses and systematic reviews by Evans et al., 2018; Zoogman et al., 2015; Felver et al., 2016; Carsley et al., 2018). A central mechanism of mindfulness meditation is attention control (Hölzel et al., 2011; Malinowski, 2013), which comes from paying attention on present-moment experiences (thoughts, emotions, body sensations). Existing evidence has proved that mindfulness interventions significantly increase attention and reduce hyperactivity/impulsivity in individuals with ADHD (Cairncross & Miller, 2020). For example, the meta-analysis and review in children and adolescents with ADHD (Zhang et al., 2018) found that meditation-based interventions were significantly more effective than the control conditions on symptoms of ADHD by increasing attention process, self-control, and emotional regulation. A more recent meta-analysis (Xue et al., 2019) confirmed that mindfulness-based interventions are effective on the reduction of ADHD symptoms irrespective of the informant and that the effect is larger on inattention than hyperactivity/impulsivity. It seemed to be a result of mindfulness-based practice, with its emphasis on the one's occurring experience in the present moment, the improvement of attentional regulation.

The present study aimed at examining the preliminary efficacy of a mindfulness-oriented meditation (MOM) program with regards to objective and

subjective measures of sleep and behavioural measures in a small but homogeneous age-group of children with ADHD. The MOM program was based on a mindfulness-meditation program that was recently proposed by Fabbro and Muratori (2012) and already used with children (Crescentini et al., 2016). It consisted of three sessions a week for eight weeks, in which the duration of the sessions increased gradually over time.

In this preliminary study, 32 children with ADHD aged 7–11 years were randomly assigned to the MOM group (MOM G), which underwent eight weeks of mindfulness training or joined the Active Control Condition group (ACC G), which entered an eight-week emotional awareness and recognition program. Participants were assessed at baseline (T0) and post-program (T1) for objective (actigraphy) and subjective measures (questionnaires completed by parents) of sleep quality and behavioral measures associated with ADHD. Accounting for the potential effects of confounding variables in interpreting results of MOM program, children with ADHD with psychiatric comorbidity and under psychostimulant therapy were excluded from the study.

Materials and methods

Participants

Thirty-five children with ADHD aged 7–11 years were recruited from a waiting list for a multimodal treatment at the Child and Adolescent Psychiatry Unit of the Bambino Gesù Children's Hospital (Italy). The diagnosis of ADHD was made according to the DSM-5 criteria (APA, 2013) and was based on developmental history and an extensive clinical examination. A semi-structured interview, K-SADS-PL (Kaufman et al., 1997), was also administered by an expert clinician to obtain information from children and parents, separately, about current and past psychopathological disorders. Global functioning was assessed with the Children's Global Assessment Scale (C-GAS; Shaffer et al., 1983). The children with ADHD were characterized as follows: 30 fulfilled the diagnostic criteria for ADHD Combined presentation, 2 had ADHD Hyperactive-Impulsive presentation and 3 had ADHD Inattentive presentation. IQ was measured by using the Wechsler Intelligence Scale for Children-IV (WISC-IV, Italian edition, Orsini et al., 2012) or Coloured Progressive Matrices (Raven, 2010). Children with ADHD who were included in the study met the following criteria: a) a primary diagnosis of ADHD; b) age range between 7 and 11 years; c) IQ $\geq$ 85.

The exclusion criteria were as follows: a) IQ $<$ 84; b) the presence of neurological and neurosensory deficits; c) the presence of comorbid psychopathological disorders and/or autism spectrum disorder; d) past or present drug treatment, or behavioral therapy, and educational program.

Procedure

All participants and their parents gave written informed consent after receiving a comprehensive description of the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethical committee of the Bambino Gesù Children's Hospital (Process Number 1162/2016). After completing

baseline measures, three children declined to participate to the study. Thirty-two participants (23 males; 9 females) were randomly assigned to MOM G or to the ACC G based on simple random allocation by using computer-generated random number sequence administered by clinical staff not involved in the research.

The MOM G was composed of 16 children (3 females) who underwent eight-week mindfulness meditation training. The ACC G was composed of 16 children (6 females) who participated in eight-week emotional awareness and recognition program.

Sleep and behavioral evaluation was conducted twice within four weeks before trainings (T0) and within two weeks after treatments (T1) by child developmental psychologists who were blind to the interventions. Before the training began, one participant in the MOM-G and six in the AAC G dropped out. At baseline (T0), MOM G and ACC G did not differ in chronological age [$t(23) = -0.21$, $p = 0.83$; CA MOM G: $M = 8.9$, $SD = 1.3$; CA ACC G: $M = 9$, $SD = 1.2$], IQ [$t(23) = 1.34$; $p = 0.19$; IQ MOM G: 109.9, $SD = 11.1$; IQ ACC G: 104.4, $SD = 8.2$] and for C-GAS scores [$t(23) = -0.1$; $p = 0.3$; C-GAS MOM G: $M = 53.4$, $SD = 2.6$; C-GAS ACC G: $M = 53.5$, $SD = 1.8$].

Programs

The MOM program was an eight-week intervention inspired by previous eight-week MOM interventions for clinical and non-clinical adult and children populations (Campanella et al., 2014; Crescentini et al., 2014, 2015, 2016; Fabbro & Muratori, 2012), which were in turn based on the Mindfulness Based Stress Reduction protocol (MBSR; e.g. Kabat-Zinn, 1990, 2003). The MOM training was conducted by qualified mindfulness meditation instructors with several years of experience in educational settings. The training consisted of three sessions per week, for a total of eight weeks and, consistent with earlier mindfulness meditation programs for children (e.g. Flook et al., 2010), the duration of the sessions increased gradually over the weeks, starting from 6 min and rising to 30 min. Even as the sessions progressively lengthened, the structure remained the same. Each session was divided into three meditation exercises that focused on three types of activities: (I) mindfulness of breathing, (II) mindfulness of body parts, (III) and mindfulness of thoughts. After the three types of meditation activities, there was a short debriefing phase (see Crescentini et al., 2016 for some example of meditation exercises). Specifically, the three types of meditation activities were verbally presented and proposed as 'games' that were meant to promote awareness of breath, body parts, and thoughts. In each of the sessions, children were first required to concentrate on breath, then to focus their attention on various body parts and finally were encouraged to observe the stream of their thoughts. During the eight weeks of MOM training, children were given homework ('Meditation Diaries') and instructed to write their meditation experiences in everyday life. Parents were not engaged in mindfulness exercises with their children neither at the hospital nor at home to prevent the interference of this confounding variable in outcomes between MOM and ACC groups.

The ACC program was led by the same trainers as in the MOM training. The ACC program was designed to be structurally equivalent to the MOM training (see Crescentini et al., 2016) and it was organized into three meetings per week for eight weeks. The duration of the sessions followed the same progression as in the MOM

training: for the first two weeks, the ACC lasted less than 10 minutes at each meeting, rising to 30 minutes at the end of the program.

The activities of the AAC G consisted of listening to and commenting on chapters of the book 'Six Pixies in My Heart' ('Sei folletti nel mio cuore', Corallo, 2011) to discover various emotions that can be experienced in many situations and to consider and be aware of their own emotions. The book is about a sensitive child who decided not to express his emotions to avoid being called 'sensitive' by his schoolmates. However, at the end of the book, the child learns the importance of feeling positive and negative emotions in his heart. During the sessions, the trainers asked the children to discuss the stories, and the emotions that they had felt. As in the MOM training, during the eight weeks of the AAC program children were given homework ('Diaries') and instructed to write down the situations in which they were aware of their emotions. As in the MOM training, parents were not engaged in the program with their children neither at the hospital nor at home.

The ACC program shared several elements with MOM training, including timing and setting, group work, interaction between children and trainers, and the assignment of homework, but was designed in order not to be related to the training of mindfulness.

Both the programs were provided at the Child and Adolescent Psychiatry Unit of the Bambino Gesù Children's Hospital (Italy). The children in each group were monitored by their parents at home to verify that they did their homework (wrote their diaries). The structure of the sessions and activities of both training were described in detail in a manual aimed at allowing for replication (Crescentini & Menghini, 2019).

Sleep measures

Participants were asked to wear wActisleep Bt actigraph (Actigraph Inc., Pensacola, FL) on the non-dominant wrist for one week both before and after the training (recording epoch length = 1 min).

Mean behavioral outcomes over the recorded nights were automatically calculated using the Actilife software (version 6, Actigraph Inc., Pensacola, FL) and then individual nights of sleep were recorded by an expert somnologist (G.C.) who compared the results from the scoring algorithm with the data reported on sleep logs.

Although participants were asked to wear the actigraphy for one week, only a minority of children did so and we considered in the analyses the maximum number of nights in which everyone correctly reported actigraphic data, which were three nights. Trying to control for the variability (Berger et al., 2008), the three days of the week in which monitoring occurred was kept constant in our study. Although it is highly recommended a 'sufficiently long' period of recording wrist actigraphy to study sleep, nonetheless a few monitored nights could assure a sufficiently accurate measure of sleep patterns (Littner et al., 2003). In the same vein, the American Academy of Sleep Medicine also recommends that actigraphic studies should be conducted for a minimum of three consecutive 24-hour periods (Smith et al., 2018). The following actigraphy measures were considered: Sleep Latency (SL), Total Sleep Time (TST), Wake After Sleep Onset (WASO), Number (nAW) and Duration of Awakenings (durAW), Motility (MI), Sleep Fragmentation (SF) and Sleep Efficiency (SE).

In order to achieve a more reliable measure of sleep (excluding possible night-to-night fluctuations), actigraphy measures across the three nights were averaged and a single index of sleep for each measure was considered at both T0 and at T1.

The Sleep Disturbance Scale for Children (SDSC; Bruni et al., 1996) is a 26-item-questionnaire to investigate the occurrence of sleep disorders during the previous 6 months. The SDSC is completed by parents according to Likert scale of 0-5 levels (higher numerical values reflect a higher frequency of occurrence of symptoms). The SDSC contains six subscales representing the most common areas of sleep disorders in childhood and adolescence: Disorders of Initiating and Maintaining Sleep (DIMS); Sleep Breathing Disorders (SBD); Disorders of Arousal (DA) like sleepwalking, sleep terrors, nightmares; Sleep-Wake Transition Disorders (SWTD) as hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesia, bruxism; Disorders of Excessive Somnolence (DOES); Sleep Hyperhidrosis (SHY). The SDSC provides T-score for each subscale and the total score. T-scores cut off for relevance is ≥70 (very elevated) while T-scores from 60 to 69 are considered borderline, high average or elevated.

Behavioral measures

The Child Behavior Checklist for Ages 6-18 (CBCL 6-18; Achenbach & Rescorla, 2001) is a widely used paper and pencil questionnaire completed by parents for identifying behavioral and emotional problems in children and adolescents. According to the normative data, raw scores are converted in T-scores. In the present study, only symptoms of ADHD, derived from Attention Problems and Attention Deficit/Hyperactivity Problems subscales, were analyzed.

The Conners' Parent Rating Scales Long Version Revised (CPRS-R:L; Conners, 2007) is composed by behavior rating scales that are completed by parents and commonly used to assess behaviors related to ADHD in children. According to the normative data, raw scores are converted in T-scores. In the present study, the two global index subscales for ADHD of CPRS-R:L were considered: the Conners' Global Index (CGI) for the Restless-Impulsive subscale (CGI Restless-Impulsive) and for the Total (CGI Total).

For CBCL 6–18 and CPRS-R:L subscales, T-scores cut off for relevance is ≥70 (clinical) while T-scores from 60 to 69 are considered borderline.

Results

Sleep measures

Regarding actigraphy (Table 1), a repeated measures MANOVA was conducted on the eight actigraphy measures as dependent variables (SL, TST, WASO, nAW, durAW, MI, SF, SE) with Group (MOM, ACC) and Time (T0, T1) as the independent factors. The groups did not differ [$F(1,23) = 0.53$, $p = 0.47$, $\eta p^2 = 0.02$] after the programs for the considered actigraphy measures. Neither the Group x Time [$F(1,23) = 2.5$, $p = 0.13$, $\eta p^2 = 0.09$] nor the Group x Time x Actigraphy Measures interaction [$F(7,161) = 1.33$, $p = 0.24$, $\eta p^2 = 0.05$] was significant.

Table 1. Scores obtained by children with ADHD on Actigraphy measures.

Time	Group	SL M (SD)	TST M (SD)	WASO M (SD)	nAW M (SD)	durAW M (SD)	MI M (SD)	SF M (SD)	SE M (SD)
T0	MOM G	5.53 (6.94)	498.43 (26.34)	59.00 (24.57)	20.50 (7.73)	2.82 (0.50)	14.32 (4.09)	25.36 (8.56)	88.73 (4.32)
	ACC G	0.03 (0.11)	484.11 (50.91)	49.50 (26.08)	18.67 (5.12)	2.63 (0.70)	11.71 (1.97)	23.91 (5.98)	90.59 (5.39)
T1	MOM G	14.28 (14.12)	487.16 (45.56)	62.17 (29.20)	19.07 (7.71)	3.55 (1.28)	15.17 (4.79)	30.08 (6.67)	86.74 (5.47)
	ACC G	5.90 (7.17)	484.45 (33.26)	77.67 (22.18)	23.67 (5.22)	3.46 (1.11)	16.74 (2.54)	30.77 (7.06)	85.38 (4.09)

Note. MOM G = Mindfulness-Oriented Meditation Group; ACC G = Active Control Condition Group; T0 = baseline; T1 = post-program; SL = Sleep Latency; TST = Total Sleep Time; WASO = Wake After Sleep Onset; nAW = Number of Awakenings; durAW = Duration of Awakenings; MI = Motility; SF = Sleep Fragmentation; SE = Sleep Efficiency.

A repeated measures MANOVA was run for the seven subscales of the SDSC (Table 2) as dependent variables (DIMS, SBD, DA, SWTD, DOES, SHY and TOTAL-SDSC) with Group (MOM, ACC) and Time (T0, T1) as the independent factors. No significant effect for Group was found [$F(1,23) = 2.06$, $p = 0.17$, $\eta p^2 = 0.08$]. However, Group x Subscale interaction [$F(6,138) = 2.95$, $p = 0.0097$, $\eta p^2 = 0.114$] and Group x Time x Subscale interaction [$F(6,138) = 2.67$, $p = 0.018$, $\eta p^2 = 0.104$] was significant.

The post hoc analysis (Fisher's Least Significant Difference - LSD - Test) of the effect of Group x Time x Subscale indicated that groups did not differ at T0 in DIMS subscale ($p = 0.85$), but differed at T1 ($p = 0.022$): only scores in the MOM G decreased from T0 to T1 in initiating and maintaining sleep. In SBD subscale, groups did not differ either at T0 ($p = 0.07$) nor or at T1 ($p = 0.85$) in breathing problems. However, in DA scale groups differed at T0 ($p = 0.004$) and at T1 ($p = 0.016$) with less disorders of arousal for MOM G than for ACC G. Concerning DOES subscale, groups differed at T0 ($p = 0.03$), with MOM G showing higher scores than ACC G (even if in the normal range), but not at T1 ($p = 0.16$).

No other differences between Groups at T0 nor at T1 were found for SWTD (T0: $p = 0.66$; T1: $p = 0.31$), SHY (T0: $p = 0.52$; T1: $p = 0.7$) subscales and TOTAL-SDSC (T0: $p = 0.93$; T1: $p = 0.07$).

A chi-square test for association with the risk difference (RD) and 95% confidence intervals (95% CI) was also conducted to compare the frequency of children with very elevated scores (T-score ≥70) at the end of the treatment (T1) in the MOM G vs. ACC G for subscales of the SDSC.

Results showed that in DIMS subscale the number of children in the MOM G presenting very elevated scores was significantly smaller than those of ACC G (RD = −0.5, 95% CI: −0.81, −0.19; $p = 0.0022$). As shown in Table 2, at T0 the MOM G obtained average borderline scores (T-scores from 60 to 69) in three scales of SDSC (i.e. DIMS, DA and TOTAL-SDSC), while at T1 the average scores fell within the normal range (T-scores ≤59) in any scale considered. Conversely, except for SBD subscale, the ACC G continued to show borderline or very elevated scores in the SDSC also at the end of the intervention (T1).

Behavioral measures

With regards to the behavioral questionnaires completed by parents, a repeated measures MANOVA was run for the four measures considered as dependent variables

Table 2. Scores obtained by children with ADHD on the Sleep Disturbance Scale for Children.

Time	Group	DIMS M (SD)	SBD M (SD)	DA M (SD)	SWTD M (SD)	DOES M (SD)	SHY M (SD)	TOTAL-SDSC M (SD)
T0	MOM G	61.33[a] (10.73)	55.53 (10.68)	66.87[a] (22.55)	52.80 (11.86)	53.33 (15.38)	57.47 (15.27)	61.53[a] (12.57)
	ACC G	60.20[a] (17.29)	66.30[a] (15.97)	84.40[b] (17.25)	55.40 (9.66)	40.40 (4.30)	53.70 (9.32)	61.00[a] (15.08)
T1	MOM G	55.20 (7.65)	49.20 (6.22)	53.87 (13.08)	55.13 (10.12)	58.73 (16.71)	59.00 (17.57)	59.13 (12.69)
	ACC G	69.00[a] (15.04)	51.40 (8.38)	68.40[a] (18.51)	61.20[a] (14.79)	61.60[a] (13.94)	61.30[a] (14.10)	70.10[b] (17.80)

Note. MOM G = Mindfulness-Oriented Meditation Group; ACC G = Active Control Condition Group; T0 = baseline; T1 = post-program; DIMS = Disorders of Initiating and Maintaining Sleep; SBD = Sleep Breathing Disorders; DA = Disorders of Arousal; SWTD = Sleep-Wake Transition Disorders; DOES = Disorders of Excessive Somnolence; SHY = Sleep Hyperhidrosis. Total-SDSC = Total score Sleep Disturbance Scale for Children; SD = Standard Deviation;.
[a]= borderline score (T-score from 60 to 69);.
[b]= very elevated score (T-score ≥70).

(Attention Problems and Attention Deficit/Hyperactivity Problems subscales for CBCL 6-18; CGI Restless-Impulsive and CGI Total subscales for CPRS-R:L) with Group (MOM, ACC) and Time (T0, T1) as the independent factors. A Group effect was found [$F(1,23) = 7.9$, $p = 0.0097$, $\eta p^2 = 0.26$), with lower scores for MOM G than ACC G. A subscale effect was also found [$F(3,69) = 4.97$, $p = 0.0035$, $\eta p^2 = 0.18$], with lower scores on Attention Deficit/Hyperactivity Problems subscale of CBCL 6-18 than on Attention Problems subscale of CBCL 6-18 ($p = 0.023$) and than on CGI Restless-Impulsive subscale of CPRS-R:L ($p = 0.001$). Significant Group x Time effect [$F(1,23) = 5.5$, $p = 0.028$, $\eta p2 = 0.19$], and Group x Subscale effect [$F(3,69) = 3.24$, $p = 0.027$, $\eta p^2 = 0.12$] were also found. Post-hoc analyses of Group x Time effect documented that MOM G significantly reduced scores at T1 ($p = 0.014$), and that groups significantly differed at T1 ($p = 0.0008$), but not at T0 ($p = 0.25$). Post-hoc analyses of Group x Subscale effect showed in MOM G no significant difference in scores among subscales (Attention Deficit/Hyperactivity Problems of CBCL *vs.* Attention Problems of CBCL, $p = 0.43$; CGI Restless-Impulsive of CPRS-R:L *vs.* CGI Total of CPRS-R:L, $p = 0.08$). However, in ACC G scores of Attention Deficit/Hyperactivity Problems of CBCL 6-18 were lower than those of Attention Problems of CBCL ($p = 0.008$), of those of CGI Restless-Impulsive of CPRS-R:L ($p = 0.0003$), and of those CGI Total subscale ($p = 0.0007$).

Chi-square test for association with the risk difference (RD) and 95% confidence intervals (95% CI) was also conducted to compare the frequency of children with clinical scores (T-score ≥70) at the end of the treatment (T1) in the MOM G vs. ACC G for behavioral measures. Results showed that the number of children in MOM G having, on average, clinical scores was significantly smaller than those of ACC G in Attention Problems subscale of CBCL 6-18 (RD = −0.53, 95% CI: 0-.86, −0.19; $p = 0.0089$), CGI Restless-Impulsive subscale of CPRS-R:L (RD = −0.46, 95% CI: −0.81, −0.12; $p = 0.0221$), and CGI Total of CPRS-R:L (RD = −0.6, 95% CI: −0.92, −0.27; $p = 0.0031$). At T0 (Table 3), the MOM G and ACC G had, on average, clinical scores (mean T-score ≥70) in three subscales of behavioral questionnaires (Attention Problems subscale of CBCL 6-18, CGI Restless-Impulsive subscale of CPRS-R:L, and CGI Total of CPRS-R:L). At T1, MOM G did not show, on average, any clinical score in the behavioral questionnaires (mean T-score ≥70), while ACC G achieved clinical scores in each subscale.

Discussion

In this study, we tested the preliminary efficacy of a mindfulness training on sleep quality and behavioral measures in children with ADHD. To that end, an evaluation before and after a mindfulness-oriented meditation training and an active control intervention based on emotional awareness and recognition was conducted in two groups of children with ADHD.

MOM training had positive effects on sleep measures, as evidenced by parental perception of sleep quality. Indeed, results from the parental questionnaire SDSC showed that the scores in initiating and maintaining sleep (DIMS subscale) improved significantly at T1 compared with T0 in the MOM G but not in the ACC G. The analysis on frequency at post-program, confirmed that in the MOM group the number of children with difficulties in initiating and maintaining sleep (T scores ≥70) was lower compared with ACC G. In the MOM G, also the average score of the other subscales of SDSC fell within the normal range at T1, while in the ACC G the average score continued to fall in the borderline or in the very elevated range, with the except of breathing problems (SDB). Conversely, the groups did not differ at post-program for objective sleep parameters as measured by actigraphy.

With regards to behavioural measures, only the MOM G had significantly lower T scores at T1 than at T0. At post-program, analyses on frequency confirmed that the number of children in the MOM G having clinical scores was significantly lower than that of ACC G in three subscales (i.e. Attention Problems subscale of the CBCL 6-18, the CGI Restless-Impulsive subscale and the CGI Total of the CPRS-R:L). In the MOM G, also the average score of three out of four behavioural measures decreased from a clinical level at T0 to a borderline range at T1 (see Table 3), while in the ACC G the average score of each behavioural measure continued to fall in the clinical range at T1 (T scores ≥70).

The effect of MOM training on subjective measures of sleep quality (i.e. parental questionnaire) but not on objective ones (i.e. actigraphy) was in line with previous studies. Indeed, parental perception of sleep problems in children with ADHD has not always been supported by objective measures of sleep, such as actigraphy and polysomnography (Choi et al., 2010; Cohen-Zion & Ancoli-Israel, 2004; Corkum et al., 2001; Hvolby et al., 2008; Lim et al., 2008; Owens, 2005; Owens et al., 2009; Wiggs et al., 2005; Yoon et al., 2012). Parental sensitivity to behavioral problems at bedtime may explain discrepancies with results obtained by objective measures of sleep (Hvolby et al., 2008; Owens et al., 2009; Yoon et al., 2012). Objective measures may not garner a complete picture of children's sleep since captured single night's measurement or averaged parameters over several nights, while subjective reports may emphasize particularly problematic nights. Moreover, considering the effects of mindful trainings, positive influences on sleep were primarily detected by subjective measures in clinical disorders, as in patients with fibromyalgia, multiple sclerosis and chronic diseases (Amutio et al., 2018; Cavalera et al., 2019; Greeson et al., 2018; Zou et al., 2018) and changes were identified by objective measures, as EEG measures of sleep, only in expert mindfulness meditators (see for example Dentico et al., 2016, 2018; Ferrarelli et al., 2013). In particular, studies documented that when expert meditators were involved, strong changes in sleep architecture (i.e. increases of deep sleep stages)

Table 3. Scores obtained by children with ADHD on Parental Behavioral Questionnaires.

Time	Group	Attention Problems CBCL 6-18 M (SD)	Attention Deficit/ Hyperactivity Problems CBCL 6-18 M (SD)	CGI Restless-Impulsive CPRS-R:L M (SD)	CGI Total CPRS-R:L M (SD)
T0	MOM G	70.06[b] (11.69)	66.67[a] (8.17)	73.47[b] (14.29)	70.4[b] (14.83)
	ACC G	74.4[b] (8.75)	69[a] (4.88)	76.9[b] (9.42)	76.7[b] (9.92)
T1	MOM G	65.47[a] (7.51)	66[a] (6.88)	63.93[a] (10.12)	60.53[a] (9.88)
	ACC G	77.4[b] (8.04)	70.9[b] (6.69)	79.6[b] (11.17)	78.8[b] (13.2)

Note. MOM G = Mindfulness-Oriented Meditation Group; ACC G = Active Control Condition Group; T0 = baseline; T1 = post-program; CBCL 6-18 = Child Behavior Checklist for Ages 6-18; CPRS-R:L = Conners' Parent Rating Scales Long Version Revised; CGI = Conners' Global Index; SD = Standard Deviation.
[a]= borderline score (T-score from 60 to 69).
[b]= clinical score (T-score ≥70).

and signs of synaptic plasticity (i.e. increased low-frequency oscillatory activity peaking in theta-alpha range) were detected (Dentico et al., 2016; 2018). The relatively brief MOM training (eight weeks) in meditation-naïve children could also explain the lack of objective changes in sleep of our participants.

With regards to behavioral aspects, the present results are in line with other studies showing the efficacy of mindfulness-based intervention on ADHD core symptoms (for a review see Aadil et al., 2017; Cairncross & Miller, 2020), as hyperactivity and impulsivity measured by parental questionnaires (Zylowska et al., 2008). In particular, the meta-analysis conducted by Zoogman et al. (2015) documented a small to moderate effect size for mindfulness trainings in ameliorating attention problems, internalizing and externalizing behavioral problems and sleep disorders in clinical and non-clinical groups of children. The effect size of clinical groups was in the moderate range and equal to nearly three times the magnitude of non-clinical groups, suggesting that mindfulness may be particularly beneficial for clinical populations. Moreover, the meta-analysis (Zoogman et al., 2015) indicated that mindfulness most robustly addressed symptoms of psychopathology, with nearly twice the effect size of other outcomes.

Our study had limitations. As a preliminary study, the number of participants was limited, but the results are encouraging in designing clinical trial on MOM with large groups. Moreover, children were not equally distributed in the two programs as six children dropped out from the ACC G and only one child from the MOM G. Recruiting more participants, children could be more equally distributed with regards to demographics.

Another limitation was that substantial findings on sleep and behavioral difficulties were derived from parent reports and parents would/should be aware of the intervention condition to which their child was assigned. Future studies that directly evaluate children are needed to validate and support sleep and behavioral findings from parental reports. Including multiple informants, such as teachers, will also allow for better behavioral assessment of children with ADHD.

Another potential source of bias in our study was the small number of nights children with ADHD have worn the actigraphy, especially if we consider the high variability in children's behavior. Further studies should consider more nights of

actigraphy data to confirm our negative results on the actigraphy ability to get a picture of sleep disturbance in children with ADHD.

An increasing number of research in pediatric populations is indicating that emotional problems have important moderating effects on the relationship between ADHD symptoms and sleep problems (see, for example, Tong et al., 2018). Future research should also better investigate the relationship between sleep disturbances and ADHD by comparing children with ADHD with and without comorbidities on sleep measures.

In both programs, the parents were involved only in monitoring the execution of homework. Given the positive results of the literature, that includes parents in mindfulness program, further studies should involve parents in MOM training and control condition as well.

In conclusion, inattention and/or hyperactivity-impulsivity interfere with functioning and with general well-being of children with ADHD (Singh et al., 2015). Sleep problems have a direct negative impact on the nature and severity of daytime symptoms as well as on children's quality of life (Hvolby et al., 2008; Sung et al., 2008). Therefore, developing effective strategies to improve sleep problems in ADHD represents a considerable challenge for the clinician (Barrett et al., 2013; Cortese et al., 2013). Our results, although they are preliminary, suggest that mindfulness meditation practices may promote specific positive changes in sleep indices and behavioral measures in children with ADHD.

Overall, our results are encouraging, but a more in-depth study on the use of mindfulness meditation is warranted in a larger cohort to give weight to this form of mental training in sleep and behaviors and to reduce the burden of ADHD' symptoms on health-related quality of life in children and their families.

Data availability statement

The data that support the findings of this study are openly available in OSF Registries at http://doi.org/10.17605/OSF.IO/G2BDZ, reference number (https://osf.io/82rhc/).

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Do comorbid symptoms discriminate between autism spectrum disorder, ADHD and nonverbal learning disability?

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ABSTRACT

Characterizing the functioning of individuals with neurodevelopmental disorders is crucial to their diagnosis. Research has found that children with different neurodevelopmental disorders, including autism spectrum disorders (ASD), attention deficit and hyperactivity disorder (ADHD), and nonverbal learning disability (NLD), may have comorbid symptoms of anxiety and depression, and problems with pragmatic language. The main aim of the present study was to identify any differences in the above-mentioned comorbid symptoms associated with these clinical profiles. A second aim was to establish how well signs of pragmatic language difficulties could discriminate between the three clinical profiles, in terms of their diagnostic power. For this purpose, 107 participants from 8 to 16 years old with a diagnosis of ASD, ADHD or NLD were compared with a group of typically-developing children. Self-reports on symptoms of anxiety and depression, and parents' reports on social and communication problems were analyzed. Our findings confirmed that symptoms of anxiety and depression, and problems with pragmatic language are associated with different neurodevelopmental disorders, but not in the same way. In terms of diagnostic power, we found that pragmatic language difficulties clearly discriminated children with ASD, ADHD or NLD from typically-developing children. Importantly, pragmatic language difficulties also discriminated adequately between ASD and NLD. Our findings are discussed in terms of the value of considering comorbid symptoms to obtain a more accurate diagnosis of neurodevelopmental disorders.

1. Introduction

There is an ongoing debate on the fluidity of the boundaries between many neurodevelopmental disorder "categories", and many symptoms attributed to one disorder may occur, on varying levels of severity, in many others (Annaz, Karmiloff-Smith, & Thomas, 2008; Thomas et al., 2009). For instance, several neurodevelopmental disorders show comorbid symptoms of anxiety, depression (Jang et al., 2013; Meyer, Mundy, Van Hecke, & Durocher, 2006; Van Steensel, Bögels, & de Bruin, 2013) and difficulties with pragmatic language (e.g., Landa, 2005). In the present study, we focus on three neurodevelopmental disorders: autism spectrum disorders (ASD), attention deficit and hyperactivity disorder (ADHD) and nonverbal learning disability (NLD), in an effort to better understand cross-disorder differences. Symptoms of anxiety and depression, and pragmatic language deficits have previously been identified in all three disorders (Mammarella et al., 2016; Simonoff et al., 2008). It is worth noting, however, that considering the developmental

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population, there are reports of 7.1% of children aged 3–17 years having anxiety issues, and 3.2% having depression (Ghandour et al., 2019). According to the World Health Organization (WHO, 2021), it is estimated that 3.6% of 10- to 14-year-olds and 4.6% of 15- to 19-year-olds experience an anxiety disorder. Depression is estimated to occur among 1.1% of adolescents aged 10–14 years, and 2.8% of those aged 15–19. Different prevalence rates of anxiety and depression have been estimated in young people with neurodevelopmental disorders.

Individuals with ASD are characterized by varying degrees of impairment in communication and reciprocal social interaction as well as stereotyped interests and behaviors (American Psychiatric Association, APA, 2013). Along with these core features, comorbid symptoms of anxiety have been found to occur at high rates in this population (Gillott, Furniss, & Walter, 2001; White, Oswald, Ollendick, & Scahill, 2009). In their meta-analysis, Van Steensel, Bögels and Perrin (2011) found 39.6% of children and adolescents with ASD had at least one comorbid anxiety disorder. The most frequent diagnoses included specific phobias (29.8%), and social anxiety disorder (16.6%). The picture is less clear for symptoms of depression. Overlap in symptoms between depression and ASD (e.g. flat or depressed affect, reduced motivation, social withdrawal and reduced desire to communicate with others) may make it hard to tell whether signs of depression are due to the primary diagnosis of ASD or to an actual comorbidity of depressive symptoms (Magnuson & Constantino, 2011). The reported prevalence rates for major depressive episodes in individuals with ASD have ranged from 1.5% (Simonoff et al., 2008) to 10% (Leyfer et al., 2006), with the two studies describing high rates of subclinical depressive symptoms (10.4% and 14%, respectively).

ADHD is a disorder characterized by persistent patterns of inattention, hyperactivity and impulsivity. Comorbid symptoms have been extensively studied (Wåhlstedt, Thorell, & Bohlin, 2009). ADHD is often found to be highly comorbid with both internalizing (13–51%) and externalizing disorders (43–93%) symptoms, suggesting that the disorder without comorbidity is the exception rather than the rule (Biederman, Newcorn, & Sprich, 1991; Jensen et al., 2001). Previous studies estimated that approximately 25–50% of children with ADHD have a comorbid anxiety disorder or comorbid symptoms of anxiety (Bishop, Mulraney, Rinehart, & Sciberras, 2019; Jarrett & Ollendick, 2008). Children with ADHD also have more unipolar depressive disorders, or subthreshold depressive symptoms than might be expected (Blackman, Ostrander, & Herman, 2005; Busch et al., 2002). In their meta-analysis, Meinzer, Pettit, and Viswesvaran (2014) reported a medium-sized association between ADHD and depressive symptoms ($r = 0.22$, from 29 studies) with a marked heterogeneity across studies.

The third neurodevelopmental disorder considered in the present study is nonverbal learning disability (NLD), which is characterized by visuospatial processing deficits, but an average verbal intelligence (Cornoldi, Mammarella, & Fine, 2016; Mammarella, Cardillo, & Zoccante, 2019). Children with NLD struggle in visuo-constructive and visuospatial working memory tasks, and these impairments may be associated with academic, motor, and even socio-relational problems. Although a remarkable effort has been made by researchers in recent years to better define the characteristics of NLD (Fine, Semrud-Clikeman, Bledsoe, & Musielak, 2013; Fisher, Reyes-Portillo, Riddle, & Litwin, 2021; Mammarella & Cornoldi, 2014), it is still not recognized by the international classification systems (DSM-5, APA, 2013; ICD-10, World Health Organization, WHO, 1992; ICD-11, World Health Organization, WHO, 2019). Only a few studies have been published on comorbid symptoms of anxiety and depression in NLD (Semrud-Clikeman, Walkowiak, Wilkinson, & Minne, 20101; Mammarella et al., 2016). Most of the research on NLD to date aimed to demonstrate how the children affected differ from other clinical groups, and any presence of comorbidities would have complicated the interpretation of their results (Mammarella, 2021). Among previous studies on NLD that considered comorbidity with anxiety and depressive symptoms, Semrud-Clikeman et al. (2010) examined groups of children with NLD, ASD or ADHD, comparing them with typically-developing children. They found no differences between the NLD group and the other two groups in terms of anxiety and depressive symptoms, while all three groups had more depressive symptoms than typically-developing controls. In addition, Mammarella et al. (2016) compared children with NLD, specific learning disorder of reading, and typically-developing controls, assessing them on different types of anxiety and depressive symptoms. They found that children with NLD or specific learning disorder of reading experienced more general and social anxiety than controls. Children with NLD also revealed more severe separation and school anxiety than those with specific learning disorder of reading or typically-developing controls. In contrast, no difference on depressive symptoms was found between NLD and typically-developing controls in children aged 8–11 years old.

The pragmatics of language represent the ability to use language effectively in interactions with other people and peers (Milligan, Astington, & Dack, 2007; O′Neill, 2014). Children with difficulties in this language domain may be impaired in several aspects of communication, showing signs of: a use of excessively formal language, verbosity, unusual or odd-sounding prosody, difficulties with following the rules of conversation, using social communication and understanding implicit, nonliteral or ambiguous meanings (Lam & Ho, 2014; Martin & McDonald, 2003). Communication failures are more common in children who struggle with pragmatic language, and this can have a crucial impact on their socio-emotional development (Roselló, et al., 2017). This type of deficit has been widely reported in ASD without intellectual disability, and can become apparent from a limited engagement in turn taking, for instance, or restricted speech acts, trouble with starting or following conversations, difficulty with taking another's perspective and with structuring narratives (e.g., Landa, 2000; Tager-Flusberg, Paul, & Lord, 2005; Young, Diehl, Morris, Hyman, & Bennetto, 2005). Baron-Cohen (1988) suggested that pragmatic language belongs to the sphere of social skills, and that the problems individuals with ASD have in these areas relate to their difficulty with understanding other people's state of mind. According to other researchers (Noens & van Berckelaer-Onnes, 2005; Norbury & Bishop, 2002), a possible explanation for the difficulties with pragmatic language seen in individuals with ASD is weak central coherence. This theory posits that such individuals have a tendency to interpret words in isolation and have problems integrating information from multiple sources. On the other hand, Cardillo, Mammarella, Demurie, Giofrè, and Roeyers (2021) recently suggested that theory of mind (meaning the ability to consider other people's perspective, intentions and beliefs) contributes significantly to mediating differences in the pragmatic language skills between children with ASD and typically-developing children.

Social difficulties in ADHD seem to be associated with weaknesses in the pragmatics of language (Bruce, Thernlund, & Nettelbladt, 2006). When Camarata and Gibson (1999) examined ADHD symptoms in relation to pragmatic language skills, they showed that both inattention and hyperactivity/impulsivity can interfere with verbal and nonverbal aspects of communication. Executive function deficits in planning, organizing and monitoring have also been claimed to account for pragmatic language difficulties in children with ADHD (Purvis & Tannock, 1997). Some studies compared groups of children with ASD and ADHD. Bishop and Baird (2001) found that not only children with ADHD have more pragmatic language deficits and social difficulties than typically-developing children, but their pragmatic language skills differed only slightly from those of children with ASD. Geurts et al. (2004), (see also Geurts and Embrechts (2008)) showed that children with ADHD were less impaired than those with ASD on stereotyped language and non-verbal communication.

Pragmatic language deficits have also been described in NLD (Rourke, 1989; Solodow et al., 2006). While a greater consensus has been reached regarding the neuropsychological profile of children with NLD, which is characterized by visuospatial processing deficits, the involvement of social and pragmatic language deficits in NLD are still debated and there is little empirical evidence available as yet (see Fisher et al., 2021 for a review). When Cardillo, Garcia, Mammarella and Cornoldi (2018) compared children with specific learning disorder of reading and children with NLD, they found the NLD children had a better profile in terms of pragmatic language, while they struggled to understand perceptual metaphors presented with pictorial materials. This finding is in line with previous reports that children with NLD find it hard to understand and process visuospatial materials (Humphries, Cardy, Worling, & Peets, 2004; Mammarella et al., 2009; Mammarella, Meneghetti, Pazzaglia, & Cornoldi, 2015; Worling, Humphries, & Tannock, 1999).

The present study, thus, considered comorbid symptoms of anxiety and depression, and pragmatic language difficulties in a cross-disorder comparison with two specific aims. The first was to identify similarities and differences between those comorbid symptoms in individuals with ASD, ADHD and NLD. Second, to establish how well signs of pragmatic language difficulties could discriminate between the three clinical profiles, in terms of their diagnostic power, we calculated the area under the curve (AUC) of the ROC curve (Robin et al., 2011). The AUC indicates the performance of a continuous variable when used as a binary classifier for two groups at a time, and it is especially relevant in diagnostic settings. Although previous studies revealed pragmatic language deficits in the three clinical groups considered (e.g., Cardillo, Basso Garcia, Mammarella, & Cornoldi, 2018; Geurts et al., 2004; Noens & van Berckelaer-Onnes, 2005), this kind of statistical analysis may be useful for establishing whether these deficits can distinguish cases of ASD, ADHD and NLD from typically-developing children, or differentiate children with ASD from those with other neuro-developmental disorders.

Based on previous research findings, we did not expect to find differences in symptoms of anxiety and depression between children with ASD, ADHD and NLD. Instead, we expected to find greater pragmatic language deficits in ASD and ADHD than in NLD. As for the AUC, we hypothesized that pragmatic language skills would distinguish cases of NLD from typical development less well than it would

Table 1
Characteristics of the groups with: typical development (TD); autism spectrum disorders without intellectual disability (ASD), nonverbal learning disability (NLD), and attention deficit hyperactivity disorder (ADHD).

Measures	TD (N = 35) M (SD)	ASD (N = 25) M (SD)	ADHD (N = 28) M (SD)	NLD (N = 19) M (SD)	Group significance
Gender (M:F)	30:5	24:1	26:2	14:5	N.S.
Age (months)	143.54 (25.95)	146.94 (35.49)	136.46 (28.34)	146.95 (33.35)	N.S.
Wechsler Intelligence Scales – IV[a]					
FSIQ	109.66 (12.24)	106.88 (15.30)	106.61 (16.26)	99.21 (13.37)	N.S.
Autism Diagnostic Interview - Revised					
ADI-R A	4.03 (3.26)	15.8 (6.30)	4.46 (3.39)	5.53 (3.03)	ASD > TD, NLD, ADHD
ADI-R B	2.97 (2.23)	11.12 (4.27)	4.36 (3.49)	4.37 (2.69)	ASD > TD, NLD, ADHD
ADI-R C	0.77 (0.94)	6.08 (3.57)	1.25 (1.35)	1.74 (2.49)	ASD > TD, NLD, ADHD
Conners' Parent Rating Scale – Revised					
Oppositional	48.09 (7.93)	56.8 (13.70)	61.32 (13.66)	61.74 (14.64)	ASD, NLD, ADHD > TD
Cognitive Problems	46.51 (5.15)	61.52 (14.38)	71.93 (11.56)	61.32 (15.13)	ADHD > ASD, NLD, TD ASD, NLD > TD
Hyperactivity/Impulsivity	46.6 (7.95)	59.00 (15.85)	64.64 (12.56)	55.79 (16.56)	ADHD > NLD, TD ASD, NLD > TD
ADHD	47.54 (5.30)	63.32 (14.22)	73.43 (10.79)	63.11 (13.90)	ADHD > ASD, NLD, TD ASD, NLD > TD

Note.
[a] Standard scores on the Wechsler Intelligence Scale for Children - Fourth Edition (for participants aged 8–16 years) or Wechsler Adult Intelligence Scale - Fourth Edition (for participants from 16 years onwards). FSIQ = Full-Scale Intelligence Quotient; ADI-R = Autism Diagnostic Interview-Revised (Rutter, Le Couteur, & Lord, 2005): A = Reciprocal Social Interaction, B = Language/Communication, C = Repetitive Behavior/Interests; high scores on the ADI-R reflect more severe autistic symptoms.

for ASD or ADHD.

2. Method

2.1. Participants

The sample included 107 participants, 94 males and 13 females. Four groups of children were identified for the purposes of this study: ASD without intellectual disability (ID) ($N = 25$), NLD ($N = 19$), ADHD ($N = 28$), and typically-developing (TD) controls ($N = 35$). The four groups did not differ statistically in terms of chronological age [F (3, 103) = 0.684, $p = .56$, *adjusted* $R^2 = .01$] (participants' ages ranged between 8 and 16 years) or gender distribution [χ^2 ($df = 3$) = 5.93, $p = .115$, Cramer-V = 0.236)]. A standard score of 80 or above on the Full Scale Intelligence Quotient (FSIQ) from the Wechsler Intelligence Scale for Children – IV (WISC IV; Wechsler, 2003) was required for participation in the study. A summary of the participants' characteristics is shown in Table 1. A detailed description of the screening measures employed, and of the results summarized in Table 1, is provided in the Supplementary materials. All children were recruited via local community contacts, at centers specializing in the diagnosis of neurodevelopmental disorders, or at local schools (for the TD children).

The participants with ASD who had already received an independent clinical diagnosis of high-functioning autism or Asperger syndrome according to DSM-IV-TR (American Psychiatric Association, APA, 2000) or ICD-10 (WHO, 1992) criteria were included. Their diagnosis was also confirmed using the ADI-R (ADI-R; Rutter et al., 2005). Only participants with scores above the cut-off on the three modules of the interview, including stereotyped behaviors, were considered. Participants also had to have at least two symptoms of each of the three criteria required by the DSM-IV-TR (APA, 2000) for a diagnosis of ASD.

Children with ADHD previously diagnosed either by private practitioners (child psychiatrists or psychologists) or at the Child Neuropsychiatry Department of the hospital to which they referred had to meet the DSM-IV-TR or DSM 5 (APA, 2000, 2013) criteria for a diagnosis of ADHD. Conners' Parent Rating Scale (Conners, 2007) was used to confirm their diagnosis.

Children in the NLD group had been previously diagnosed either by private practitioners (child psychiatrists or psychologists) or at the Child Neuropsychiatry Department of the hospital to which they were referred. All clinical diagnoses previously made by practitioners were confirmed by consensus of two authors of this manuscript (R.C., and I.C.M.). Rey's complex figure test (Rey, 1968) was used to confirm the diagnosis of NLD. The diagnostic procedure was consistent with the latest recommendations (Cornoldi et al., 2016; Mammarella & Cornoldi, 2014).

The TD controls had no history of psychiatric, neurological or neurodevelopmental disorders. They were healthy children of normal intelligence recruited at various schools. All participants were native Italian speakers, and none had any visual or hearing impairments, or any other diagnosed neurological conditions. The main exclusion criterion was a concomitant diagnosis of two of the disorders considered (ASD, ADHD and NLD). None of the participants in the NLD, ADHD or TD groups met the criteria for autism using the ADI–R (Rutter et al., 2005). Similarly, none of the participants with ASD, NLD or TD met the criteria for ADHD using Conners' Parent Rating Scale (Conners, 2007). Individuals with ASD without ID, NLD or ADHD who showed anxiety or depression symptoms were not excluded. The study was approved by the research ethics committee at the University of Padova, Italy. All participants' parents signed an informed consent form.

2.2. Materials

2.2.1. RCMAS-2

The Revised Children's Manifest Anxiety Scale - Second Edition (RCMAS - 2; Reynolds & Richmond, 2012) is a self-report questionnaire used to assess the source and level of general anxiety in children and adolescents from 6 to 19 years old. The questionnaire consists of a total of 49 items with a yes/no response format. Higher scores indicate higher levels of general anxiety. Responses contribute to a total anxiety score (Cronbach's $\alpha = 0.92$) and four separate subscales measuring physiological anxiety, worries, social anxiety, and defensiveness, with good levels of internal consistency (Cronbach's α respectively.75;0.86;0.80 and.79). The assessment can be completed in 10–15 min.

2.2.2. SAFA-D

The Self Administrated Psychiatric Scales for Children and Adolescents - Depression (SAFA-D; Cianchetti & Sannio Fancello, 2001) is a self-report questionnaire for the assessment of depression symptoms in people aged from 8 to 18 years. The scale has two separate versions for age 8–10 and age 11–18 years, consisting of 48 and 56 items, respectively. Each version includes eight different subscales assessing Total depression, Depressed mood, Anhedonia and disinterest, Touchy mood, Sense of inadequacy, Insecurity, Guilt, and Hopelessness. The SAFA-D has a three-level response format (*"true", "false", "half way between"*). Higher scores indicate more severe depressive symptoms. The authors reported good levels of internal consistency (Cronbach's α ranged from.89 to.94).

2.2.3. CCC-2

The CCC-2 (Bishop, 2013) is a questionnaire completed by a caregiver, developed to assess communication problems in children aged from 4 years to 16 years and 11 months. The CCC-2 consists of 70 items grouped in 10 scales: (A) speech; (B) syntax; (C) semantics; (D) coherence; (E) inappropriate initiation; (F) stereotyped language; (G) use of context; (H) nonverbal communication; (I) social relationships; and (J) interests. Scales A, B, C, & D assess articulation and phonology, language structure, vocabulary and discourse; scales E, F, G & H address pragmatic aspects of communication; and scales I and J assess behaviors commonly impaired in

children with ASD. In the present study only the scales from E to J were administered in order to focus on the two dimensions mainly related to the aims of our research. Each item is assigned a score ranging from 0 (“*less than once a week [or never]*”) to 3 (“*several times [more than twice] a day [or always]*”). Lower scores indicate more severe communication impairments. The internal consistency values (Cronbach’s α ranged from.80 to.70) indicate that the item ratings are grouped consistently within each scale, with the only exception of the Interests subscale, for which Cronbach’s α was.66.

2.2.4. Data analyses

Data analyses were conducted using R (R Studio Team, 2015). The data were fitted with a linear regression model using the “lm” function. The fixed effect of Group (with 4 levels: ASD, NLD, ADHD, TD) was tested for each task. Bonferroni’s correction was used for multiple comparisons, when appropriate.

We also calculated the Area Under the Curve (AUC) of the ROC curve (Robin et al., 2011) for the pragmatic language measures to see their discriminatory value, in the sense of their diagnostic power. Specifically, AUC were computed for: Pragmatic language total score (considering the mean scores for subscales E, F, G, H of the CCC-2) and the Social relations-Interests total score (considering the mean scores for scales I and J of the CCC-2), to see how well each parameter could distinguish between the diagnostic groups. The AUC indicates the performance of a continuous variable when used as a binary classifier for two groups, and it is especially useful in diagnostic settings. We calculated it using the “auc” function of the “pROC” package in R, which uses the trapezoidal rule (as generally done to calculate an AUC). The advantages of the AUC over the *Cohen’s d* are that: 1) it directly expresses diagnostic power rather than a less interpretable standardized difference; and 2) it is robust against any normality violation because it is essentially a non-parametric indicator. In the present study, the AUC were estimated comparing the TD group with each clinical group, and comparing the clinical groups with one another. The AUC can range from 0 to 1.0, with values of 1.0 for a perfect diagnostic test, and 0.5 or less for a useless test. According to the classification proposed by Zhu, Zeng, and Wang (2010), AUC = 0.70, can be taken as a cut-off when considering the diagnostic power of a measure, even though it would still be of limited use as a diagnostic classifier (i.e., it would only be able to

Table 2
Means and standard deviations (SD) by group*:* typical development (TD); autism spectrum disorders without intellectual disability (ASD), nonverbal learning disability (NLD), and attention deficit hyperactivity disorder (ADHD).

		TD M (SD)	ASD M (SD)	ADHD M (SD)	NLD M (SD)	*F* (3, 103)	*p*	*adjusted* R^2	*Group Significance*[a]
RCMAS-2	Total score	48.43 (7.90)	51.56 (11.23)	49.25 (11.37)	51.42 (13.17)	.58	.63	.012	ns
	Physiological anxiety	50.09 (11.71)	52.44 (10.32)	52.82 (11.08)	53.58 (11.68)	.53	.66	.014	ns
	Worry	48.77 (8.93)	50.92 (12.10)	46.75 (11.11)	50.05 (12.20)	.72	.54	.008	ns
	Social anxiety	46.71 (8.65)	50.84 (10.55)	49.04 (11.13)	50.68 (13.49)	.93	.43	.002	ns
	Defensiveness	47.09 (8.95)	48.76 (9.53)	45.79 (8.94)	51.05 (11.31)	1.30	.28	.008	ns
SAFA-D	Total score	52.40 (7.72)	58.00 (11.06)	56.68 (12.40)	54.58 (8.94)	1.75	.16	.021	ns
	Depressed mood	48.46 (6.69)	53.92 (10.23)	52.25 (9.29)	51.05 (9.79)	2.03	.11	.028	ns
	Anhedonia and disinterest	47.14 (6.32)	56.76 (11.41)	57.29 (12.64)	48.42 (7.43)	8.45	**< 0.001**	.174	b, c, d, e
	Touchy mood	51.46 (10.19)	56.60 (10.42)	54.04 (10.54)	55.26 (10.61)	1.31	.28	.009	ns
	Sense of inadequacy	50.97 (9.05)	54.20 (11.48)	54.29 (10.63)	51.05 (10.49)	.88	.45	.003	ns
	Insecurity	53.29 (10.27)	51.16 (10.82)	51.39 (10.63)	50.63 (10.02)	.36	.78	.018	ns
	Guilt	46.17 (8.06)	45.44 (9.87)	52.04 (12.37)	48.42 (9.11)	2.50	.06	.04	ns
	Hopelessness	49.51 (5.77)	54.44 (12.31)	56.21 (15.80)	49.42 (8.76)	2.59	**.05**	.043	d, e
CCC-2	Initiation	10.09 (3.80)	5.52 (1.96)	5.69 (2.11)	5.95 (3.10)	17.88	**< 0.001**	.32	b, d, g
	Scripted language	10.74 (3.05)	5.60 (2.57)	6.79 (2.85)	7.95 (3.89)	15.94	**< 0.001**	.30	b, c, d, g
	Context	9.97 (3.26)	3.60 (3.42)	4.43 (2.41)	6.21 (4.06)	23.57	**< 0.001**	.39	b, c, d, g
	Nonverbal communication	9.83 (2.89)	4.60 (2.75)	5.61 (2.30)	7.47 (3.75)	19.18	**< 0.001**	.34	b, c, d, e, g
	Social relations	9.94 (3.36)	3.80 (2.71)	3.89 (2.92)	5.89 (3.80)	25.66	**< 0.001**	.41	b, c, d, e, g
	Interests	9.20 (3.79)	4.20 (2.31)	5.54 (2.04)	5.37 (2.73)	17.33	**< 0.001**	.32	b, d, g

Note. [a]Only significant pairwise comparisons are shown. b. ASD ‡ TD; c. ASD ‡ NLD; d. ADHD ‡ TD; e. ADHD ‡ NLD; f. ADHD ‡ ASD; g. NLD ‡ TD.

identify around 70% of true-positive cases correctly, while wrongly identifying around 30% of false-positive cases). AUC values from 0.80 to 0.90 could be considered as good, and values higher than 0.90 as excellent (Zhu et al., 2010).

3. Results

Table 2 summarizes the descriptive statistics for the participants' performance by group.

3.1. RCMAS-2

No fixed effect of group emerged for the Total score [$F(3, 103) = 0.58$, $p = .63$; *adjusted* $R^2 = .012$], or for the Physiological Anxiety scale [$F(3, 103) = 0.53$, $p = .66$; *adjusted* $R^2 = .014$], the Worry scale [$F(3, 103) = 0.72$, $p = .54$; *adjusted* $R^2 = .008$], the Social anxiety scale [$F(3, 103) = 0.93$, $p = .43$; *adjusted* $R^2 = .002$], or the Defensiveness scale [$F(3, 103) = 1.30$, $p = .28$; *adjusted* $R^2 = .008$].

3.2. SAFA-D

No fixed effect of group emerged for the Total score [$F(3, 103) = 1.75$, $p = .16$; *adjusted* $R^2 = .021$], or for the Depressed mood scale [$F(3, 103) = 2.03$, $p = .11$; *adjusted* $R^2 = .028$], the Touchy mood scale [$F(3, 103) = 1.31$, $p = .28$; *adjusted* $R^2 = .009$]; the Sense of inadequacy scale [$F(3, 103) = 0.88$, $p = .45$; *adjusted* $R^2 = .003$], or the Insecurity scale [$F(3, 103) = 0.36$, $p = .78$; *adjusted* $R^2 = .018$]. A trend towards a main effect of Group was found for the Guilt scale [$F(3, 103) = 2.50$, $p = .06$; *adjusted* $R^2 = .041$], showing higher scores for the ADHD than for the TD ($p = .022$) or ASD ($p = .018$) groups. A fixed effect of Group emerged for the Anhedonia and disinterest scale [$F(3, 103) = 8.45$, $p < .001$; *adjusted* $R^2 = .174$], showing higher scores for the ADHD and ASD groups, than for the NLD ($p = .003$ and $p = .006$ respectively) and TD ($p < .001$ and $p < .001$ respectively) groups. A significant effect of Group was also found for the Hopelessness scale [$F(3, 103) = 2.59$, $p = .05$; *adjusted* $R^2 = .043$], showing higher scores for the ADHD group than for the TD ($p = .02$) or NLD ($p = .04$) groups.

3.3. CCC-2

A significant main effect of Group was found for the Initiation scale [$F(3, 103) = 17.88$, $p < .001$; *adjusted* $R^2 = .32$]. The ASD, NLD and ADHD groups all had worse scores than the TD group ($p_s<0.001$). A fixed effect of Group was also found for the Scripted language [$F(3, 103) = 15.94$, $p < .001$; *adjusted* $R^2 = .30$] and Context [$F(3, 103) = 23.57$, $p < .001$; *adjusted* $R^2 = .39$] scales, showing a worse performance in the three clinical groups than in the TD group ($p_s < .002$), and a worse performance in the ASD group than in the NLD group ($p = .013$ and $p = .010$ respectively). We also found a significant effect of Group for the Nonverbal communication [$F(3, 103) = 19.18$, $p < .001$; *adjusted* $R^2 = .34$], and Social Relations [$F(3, 103) = 25.66$, $p < .001$; *adjusted* $R^2 = .41$] scales, indicating a worse

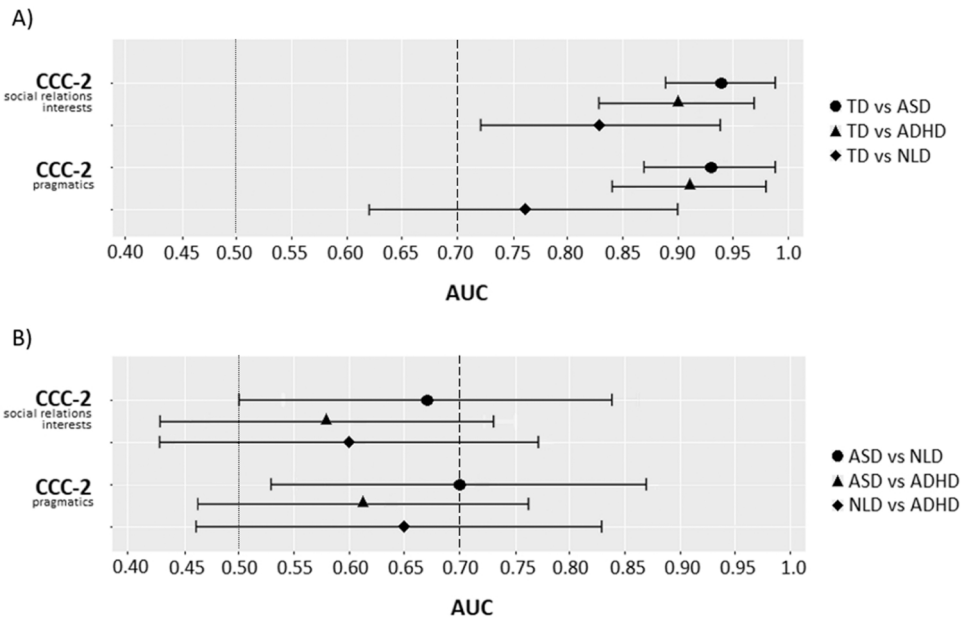

Fig. 1. Values of the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve, computed by comparing pairs of the groups on the following measures: CCC-2 for pragmatics of language, and for the total scores for Social relations and Interests. Comparisons between the TD group and the clinical groups in panel A; comparisons between the clinical groups in panel B. Error bars represent 95% confidence intervals. AUC = 0.50 is the chance level. AUC = 0.70 is the cut-off according to the classification proposed by Zhu et al. (2010).

performance in the ASD, NLD and ADHD groups than in the TD group (p_s <0.005), and a worse performance in the ASD and ADHD groups than in the NLD group (p_s <0.04). As for the Interest scale, there was a fixed effect of Group [$F(3, 103) = 17.33$, $p < .001$; *adjusted* $R^2 = .32$], with lower scores for the ASD, NLD and ADHD groups than for the TD group (p_s <0.001).

3.4. Receiver operating characteristic (ROC) curve analysis

Fig. 1 summarizes the results emerging from an analysis of the AUC computed by comparing pairs of groups on the pragmatic language measures. The results showed that these measures were useful not only in distinguishing the clinical groups from the TD group, but also in discriminating between some of the clinical groups (see Fig. 1). The AUC for the Pragmatic language and the Social relations and Interests indexes of the CCC-2 revealed an excellent predictive power in discriminating between the TD group and the ASD group (AUC =0.93 and AUC =0.94 respectively), and between the TD group and the ADHD group (AUCs =0.91). The Pragmatics of language index of the CCC-2 revealed a weaker, but still sufficient predictive power in discriminating between the TD group and the NLD group (AUC =0.76), and between the ASD group and the NLD group (AUC =0.70). The AUC for the Social relations and Interests index of the CCC-2, revealed a good power in discriminating the TD group from the NLD group (AUC =0.83).

4. Discussion

The present study examined the similarities and differences between children with ASD, ADHD and NLD in terms of their comorbid symptoms of anxiety and depression, and difficulties with pragmatic language. The AUC of the ROC curves were calculated to ascertain how discriminatory comorbid symptoms of pragmatic language difficulties might be, in terms of their diagnostic power. Studying comorbidities in neurodevelopmental disorders may help us to better understand the specificities of each disorder, and subtle differences that might lead to apparent associations across conditions. In this cross-disorders comparison, we also included children with NLD. As previously mentioned, NLD is still not recognized as a distinct clinical entity, and there is little empirical evidence regarding its symptoms in comorbidity (Mammarella, 2021). Social and pragmatic language deficits have been described in children with NLD (Rourke, 1989; Solodow et al., 2006), but findings are not always consistent (Cardillo et al., 2018; Semrud-Clikeman, Fine, & Bledsoe, 2014). The present study thus aimed to shed further light on this topic.

As expected, we found no differences in the clinical groups' anxiety symptoms. Contrary to our expectations, cross-disorder differences in depressive symptoms varied depending on the subscales of the self-report measure. In the Anhedonia and disinterest scale, the ASD and ADHD groups both scored higher than the NLD or TD groups. On the Guilt scale, children with ADHD showed barely significant differences compared with the ASD and TD groups. This latter result is consistent with findings that adolescents with ADHD self-report more negative affect in their close relationships with peers, teachers and parents than participants with specific learning disorders or no diagnosed disorder (Al-Yagon, 2016). Children with ADHD also scored higher than TD children on the Hopelessness scale, in agreement with previous studies suggesting that negative self-assessments were associated with parents' reports of a worse social functioning in adolescents with ADHD (Becker, Langberg, Evans, Girio-Herrera, & Vaughn, 2015).

Regarding pragmatic language skills, our results show that parents rated their children with ASD, ADHD or NLD as having more difficulties than TD children on all the subscales. In contrast, children with NLD were rated by their parents on the Nonverbal communication and Social relations subscales as having fewer difficulties than children with ASD or ADHD. This finding is supported by the AUC of the ROC curves. In terms of diagnostic power, the Social relations/Interests and the Pragmatic language scales both discriminated the clinical groups from the TD controls. However, while difficulties with pragmatic language showed an excellent predictive power in discriminating TD from ASD or ADHD, this parameter was less powerful in discriminating TD from NLD. In the comparison between the three clinical groups, the Pragmatic language scale reached the cut-off that sufficed to discriminate between the ASD and NLD groups, again showing that pragmatic language is less impaired in children with NLD than in those with ASD. Taken together, our findings show that pragmatic language is less impaired in NLD than in ASD or ADHD. Importantly, this difference may be useful in distinguishing between cases of ASD and children with NLD. It is worth noting that this latter diagnostic power reached the cut-off, but it can be considered a limited diagnostic classifier according to the classification proposed by Zhu et al. (2010). This finding nonetheless adds to what we know about the characteristics of the neurodevelopmental disorders considered in this study. As in previous studies (Bishop & Baird, 2001; Geurts et al., 2004), pragmatic language skills seemed to be similarly impaired in children with ASD or ADHD. For NLD, our findings revealed cross-disorder differences, especially vis-à-vis ASD. Other studies (Mammarella et al., 2019; Semrud-Clikeman et al., 2010) had clearly revealed neuropsychological differences between ASD, ADHD and NLD, and only NLD seemed to involve visuospatial processing deficits. We could argue that, together with the neuropsychological profile, pragmatic language skills could also be used to discriminate between these profiles.

Although interesting findings emerged from this study, it had some limitations that need to be mentioned. Firstly, we did not collect details of the children's symptoms from multiple informants. Symptoms of anxiety and depression were derived from self-report scales, while parents' scales were used for pragmatic language skills. Further research should confirm our findings by collecting information from different sources (teachers, parents, children). A second limitation of the study concerns the limited sizes of our clinical samples, especially in the NLD group. As this disorder is still not recognized by the international classification systems, it is likely that children with NLD go undiagnosed or receive a diagnosis that erroneously emphasizes isolated features associated with this disorder (e.g., difficulties with mathematics, motor coordination or social relationships), thereby missing the whole picture, and underestimating deficits in visuospatial processing (Cornoldi et al., 2016; Mammarella, 2020). It is worth noting that, in selecting our groups, we excluded children with a comorbidity for two of the three disorders (ASD, ADHD and NLD) as this enabled us to bring out any difference associated with a given clinical profile. On the other hand, this means that our sample may not be entirely representative of the

whole population of children with ASD or ADHD or NLD, many of whom may have comorbid conditions. Finally, it should be noted that our participants were predominantly males. Although most of neurodevelopmental disorders are overrepresented in boys in the population as well, the small number of females in our clinical groups does not allow us to generalize our findings to the females with these disorders. Future research should consider this limitation, in order to explore possible gender differences in the comorbid symptoms associated with the three clinical profiles.

Overall, our findings contribute to a better understanding of the associated symptoms in children with ASD, ADHD or NLD and point to the importance of cross-disorder comparisons. This could help to improve the diagnosis of these disorders. Our cross-disorder comparison confirmed that symptoms of anxiety and depression, and pragmatic language problems can be involved in several neurodevelopmental disorders, but with subtle differences. As concerns their diagnostic power, we found that impairments in social relations and pragmatic language could strongly discriminate cases of ASD and ADHD from TD children, while they were less powerful in distinguishing between cases of NLD and TD children. Importantly, signs of difficulties with pragmatic language adequately discriminated between the ASD and NLD groups. Overall, our study added further supports to the hypothesis that NLD can be considered as a diagnostic entity distinct from other neurodevelopmental disorders.

CRediT authorship contribution statement

Irene C. Mammarella: Conceptualization, Writing – original draft. **Ramona Cardillo:** Data curation, Formal analysis, Writing – review & editing. **Margaret Semrud-Clikeman:** Methodology, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ridd.2022.104242.

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Caso contributivo

SINDROME DELLO SPETTRO AUTISTICO E MACROCEFALIA: LA SINDROME DI COWDEN

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MACROCEPHALY AND AUTISM SPECTRUM DISORDER: A CASE OF COWDEN SYNDROME

Key words *Autism, Macrocephaly, Cowden syndrome, PTEN gene mutation*

Summary
The paper reports the story of a 4-year-old boy presenting with macrocephaly and autism spectrum disorder. Genetic testing for an overgrowth syndrome revealed the presence of a heterozygous mutation in the PTEN gene, responsible for Cowden syndrome. The clinical case is an example of the need to investigate all cases of autism spectrum syndrome that may present an underlying genetic mutation, with important care implications that may derive from it.

Caso clinico - Un bambino di 4 anni giunge alla nostra attenzione per macrocefalia e disturbo dello spettro autistico. È nato a termine da taglio cesareo da gravidanza decorsa con diabete gestazionale. Alla nascita tutti i parametri auxologici risultavano superiori al 97° percentile (circonferenza cranica 38 cm) ma con il passare dei mesi, mentre peso e altezza si allocavano tra il 75°-90° centile, la circonferenza cranica presentava un *trend* in aumento, molto al di sopra del 97° centile *(Figura 1)*.
Dal punto di vista dello sviluppo psicomotorio il bimbo raggiungeva la deambulazione autonoma a 18 mesi. A 14 mesi, bilingue, pronunciava solo poche parole in arabo (mamma, papà, ciao...) con progressiva tendenza a parlare sempre meno. Con l'inserimento alla scuola dell'infanzia emergeva una spiccata tendenza all'iperattività.
A circa 3 anni e mezzo viene preso in carico dalla Neuropsichiatria infantile che formula diagnosi di sindrome dello spettro autistico e lo invia presso il nostro Centro per ulteriore valutazione in merito alla macrocefalia.
Alla visita congiunta con la genetista confermiamo un quadro di macrocefalia (CC 57,5 cm, > del 97° percentile) con restanti parametri auxologici adeguati, un *habitus* caratteristico con forma del volto allungata, fronte bombata, rime palpebrali *downslanting* con ipertelorismo (distanza intercantale 3 cm, distanza interpupillare 5,5 cm), labbro superiore sottile, mento a punta, padiglioni auricolari normoposti, angolati, ruotati, non macroglossia, non macchie cutanee. Alla visita oculistica riscontro di pseudopapilledema da drusen papillari. La RM encefalo conferma la macrocefalia, in assenza di anomalie intracraniche. Ecografia addome ed ecocardiogramma nella norma, età ossea corrispondente all'età anagrafica. Vengono escluse, attraverso la ricerca di aminoacidi urinari, plasmatici e acidi organici urinari, eventuali patologie metaboliche.
Viene eseguito pannello genetico per geni responsabili delle sindromi da iperaccrescimento, in particolare per le sindromi di Sotos, Weaver, Malan. Il risultato dell'analisi genetica mostra una variante nonsenso c.1003C>T p.(Arg335*) nel gene *PTEN* in eterozigosi, che consente di porre diagnosi di sindrome di Cowden. Al fine di stabilire se *de novo* o familiare, è stata in seguito eseguita la ricerca della medesima variante nei genitori del bambino con rilievo della stessa nel padre.
Il padre presenta una circonferenza cranica di 64 cm (> 97° percentile) e non presenta problematiche di rilievo. Perfettamente adeguato in merito al profilo intellettivo ed emotivo. Apprezzabili al volto del padre lesioni cutanee sospette per trichilemmomi. È in corso la valutazione della mutazione per gli altri due fratelli del nostro caso che non presentano problematiche di rilievo.

Discussione - La sindrome di Cowden (SdC) è una condizione autosomica dominante causata, in oltre l'80% dei casi, da una mutazione del gene *PTEN (Box 1, disponibile online)*. Nel 10-50% dei casi un genitore è affetto, di conseguenza la formulazione di tale diagnosi implica l'estensione dello screening tumorale anche ai suoi familiari, apparentemente asintomatici e privi di macrocrania. In letteratura, sono descritti casi di intere famiglie con singoli componenti che presentavano fenotipi lievi (solo la macrocefalia o un lieve ritardo mentale che aveva beneficiato di una terapia comportamentale) a cui era stata fatta diagnosi di macrocefalia familiare e che arrivarono alla diagnosi solo dopo uno screening genetico familiare allargato.
La malattia si caratterizzata per la presenza di amartomi multipli in diversi tessuti e per un elevato rischio di sviluppare neoplasie benigne e maligne della tiroide (68% per le patologie benigne dal 3 al 38% per le maligne), endometrio (fino al 28%) e a seguire seno (81-85% nel sesso femminile), reni, colon-retto e cute. I soggetti affetti presentano in genere macrocefalia, dolicocefalia e nel 10-17% dei casi si riscontrano alterazioni comportamentali (es. disturbo dello spettro autistico). Altra rara manifestazione della sindrome, descritta in pochi casi in letteratura, sono i drusen papillari che sono stati riscontrati nel nostro caso.
In circa il 90% dei casi, le prime manifestazioni cliniche si rendono evidenti tra la seconda e la terza decade di vita (penetranza età-dipendente) e sono di tipo cutaneo con lesioni muco-cutanee patognomoniche quali trichilemmomi o piccole papule facciali papillomatose o cheratosi acrale. Il rischio neoplastico è precoce con lo sviluppo di neoplasie già a partire dalla terza decade di vita.
La diagnosi di SdC è essenzialmente genetica, malgrado dal Consorzio Internazionale per la Cowden (ICC) siano stati definiti dei criteri successivamente revisionati *(Tabella I, disponibile online)* con applicazione nella popolazione adulta, poco in quella pediatrica per i pochi sintomi presenti nell'infanzia.
La SdC è una condizione clinica largamente sottodiagnosticata in quanto, pur riconoscendo una causa genetica, determina manifestazioni cliniche tipiche (specie quelle cutanee) solo a

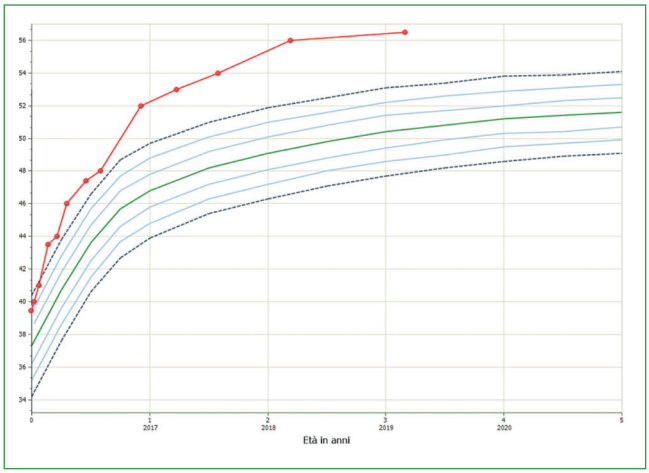

Figura. *Variazione della circonferenza cranica in relazione all'età.*

partire dalla seconda decade di vita. Spesso infatti, come nel nostro caso, si tendono a prendere in considerazione prima altre sindromi.
Nel caso descritto, seppur avevamo un quadro iniziale di iperaccrescimento, successivamente l'unico valore auxologico che tendeva ad aumentare era la circonferenza cranica. Questo dato però appariva coerente con l'autismo del bimbo. Infatti è noto che questo determina una disregolazione della crescita in generale e quindi una disregolazione della crescita neuronale (assenza di decremento del numero di neuroni) tale da determinare una macrocefalia.
La SdC rientra in una di quelle forme di iperaccrescimento segmentario tale da non interessare tutti i parametri auxologici ma solo la circonferenza cranica.
In queste situazioni la diagnosi differenziale non va posta con le condizioni che prevedono un iperaccrescimento ma con quelle che prevedono una macrocefalia anatomica *(Tabella)*.
Il caso descritto è istruttivo per diversi aspetti. L'assenza di alterazioni a carico di peso e altezza, l'associazione tra autismo o altri disturbi dell'apprendimento e macrocefalia deve sicuramente farci prendere in considerazione anche la SdC.

CAUSE DI MACROCEFALIA ANATOMICA

Forma familiare benigna
Associata ad anomalia neurologica (autismo, ritardo del linguaggio)
Cromosomopatie
Sindrome dell'X-fragile
Sindromica
Con gigantismo: sindrome di Sotos, sindrome di Weaver, sindrome di Malan
Senza gigantismo: acondroplasia, sindrome di Beckwith-Widemann
Sindromi neurocutanee
Sclerosi tuberosa
Neurofibromatosi tipo I
Ipomelanosi di Ito
Sindrome di Sturge-Weber
Sindrome di Cowden
Sindrome di Bannayan-Riley-Ruvalcaba
Sindrome di Klippel-Trenaunay-Weber

Tabella

Dobbiamo però ricordarci che in circa un quarto dei pazienti con disturbo dello spettro autistico è anche presente macrocefalia e a questo punto, quando presenti, dovranno essere valorizzati i dismorfismi soprattutto facciali. La diagnosi precoce è fondamentale poiché ne influenza la prognosi. Consente infatti di stabilire una corretta tempistica per la sorveglianza organo-specifica, evitando di arrivare alla diagnosi tardivamente, con aumentato rischio che vi sia già in atto una trasformazione neoplastica. Inoltre permette di individuare precocemente altri membri della famiglia che possono avere la mutazione patogenetica ma non avere manifestazioni cliniche e beneficiare quindi di uno screening tumorale precoce.
È inoltre utile sottolineare, come ci insegna il caso descritto, che di fronte a un bambino con una sindrome dello spettro autistico l'ambito della valutazione genetica debba essere sempre preso in considerazione, come riportato in sintesi nelle motivazioni nel *Box (disponibile online)*.

Due casi che parlano dei disturbi dello spettro autistico e delle condizioni genetiche che possono essere associate, a partire dalla familiarità. Si sottolinea, come testimoniato dalla storia del secondo caso, l'importanza di una diagnosi precoce con appositi strumenti validati (vedi Appunti di Neuropsichiatria, pag. 313) al fine di una tempestiva presa in carico con intervento intensivo, che è in grado di modificare le traiettorie neuro-evolutive di questi bambini speciali.

DIAGNOSI PRECOCE DEI DISTURBI DELLO SPETTRO AUTISTICO: ESPERIENZA CLINICA E RUOLO DEI TEST GENETICI

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Autistic spectrum disorders (ASD) and genetic test

Key words *Autistic spectrum disorder, Genetic tests*

The case of an infant diagnosed with Autistic Spectrum Disorders (ASD) associated to a maternal segregated micro duplication (Xp21.2 region involving IL1RAPL1 and NR0B1 genes) is described. The role of the genetic test in approaching the diagnosis and the therapy of ASD is discussed.

Introduzione

Il disturbo dello spettro autistico (DSA) è un'anomalia dello sviluppo neurologico a base biologica caratterizzato da deficit persistenti nella comunicazione e nell'interazione sociale e modelli di comportamento, interessi e attività limitati e ripetitivi. La gestione del bimbo con DSA deve essere individualizzata in base all'età e alle sue esigenze specifiche e richiede un approccio multidisciplinare che faccia leva sui suoi punti di forza per affrontare le sue debolezze.

Caso clinico

Bambina nata da seconda gravidanza a termine (38+6 settimane di gestazione), da taglio cesareo (madre pre-cesarizzata). Alla nascita i suoi parametri antropometrici sono nella norma (pesa 3040 g, è lunga 49 cm e la sua circonferenza cranica è di 34 cm), presenta un buon adattamento alla vita extrauterina. Ha un gentilizio positivo per sindrome di Down, la madre è affetta da ipotiroidismo in trattamento sostitutivo. Nel corso del follow-up attuato dal pediatra di famiglia vengono rilevati segni suggestivi di potenziale disturbo dello spettro autistico dall'età di 8 mesi, permettendo al neuropsichiatra di porre diagnosi già a 11 mesi e di intraprendere in modo tempestivo una terapia logopedica e psicomotoria a carattere intensivo. La bambina ha iniziato a deambulare con base allargata all'età di 19 mesi, di contro però non ha smesso di attuare stereotipie gestuali e sensomotorie (tirarsi i capelli, dondolarsi). Ha mostrato notevole sensibilità ai rumori, manifestando momenti di fissazione dello sguardo nel vuoto e mancata attenzione all'ambiente. Se inizialmente non agganciava lo sguardo della madre e non esprimeva richieste relative ai suoi bisogni primari, dopo assidua riabilitazione la piccola ha mostrato un miglioramento della comunicazione deittica ma non del linguaggio verbale, ha migliorato il contatto relazionale con familiari ed estranei e iniziato a farsi comprendere, ha cominciato inoltre a rispondere al richiamo per nome. Svezzata a 5 mesi, ha inizialmente rifiutato il cibo solido, poi non ha mostrato selettività alimentari.

Valutata dal genetista, è stata sottoposta insieme ai genitori a studio tramite SNP-*array* che ha evidenziato una micro-duplicazione della regione Xp21.2 (29,725,833-30,328,646) a segregazione materna, estesa circa 603 kb, che include i geni OMIM *(Online Mendelian Inheritance in Man) Disease Causing*, in parte il gene *IL1RAPL1* e il gene *NR0B1*. Abbiamo impiegato i siti UCSC Genome Browsers e Decipher per identificare l'eventuale patogenicità nota della micro-duplicazione identificata. Filtrando i risultati forniti dal *database* per i criteri "microduplicazioni" (escluse delezioni) e per il sesso femminile abbiamo ottenuto 63 case report con simile mutazione. Escludendo i casi con microduplicazione all'esterno della regione contenente la nostra, rimangono (dei 63 precedentemente identificati) solo 2 casi: uno con disabilità intellettiva ed epilessia, l'altro con malformazione cardiaca congenita. In questi due casi uno riguarda un'anomalia del neurosviluppo, ma l'origine parentale della mutazione è paterna (nel nostro caso invece è materna). Il *database* impiegato ha attribuito alla mutazione identificata nella nostra bambina e ai due casi precedentemente descritti con microduplicazione sovrappolinibile al nostro un significato probabilmente benigno o incerto. Ripetendo l'operazione di ricerca per la mutazione identificata e filtrando per sesso maschile il significato della microduplicazione invece è patologico: associato a disturbi del neurosviluppo. Deduciamo dunque che la medesima mutazione sortisce un effetto fenotipico differente in base al sesso.

Discussione

Molti dei casi di DSA sono associati a patologie a base genetica e rappresentano la categoria a esordio più precoce e peggiore *outcome*. I test più appropriati per il bambino con DSA possono variare in base alle caratteristiche cliniche (es. in base a dismorfismi e storia familiare). La *flow-chart* di approccio ai disturbi del neurosviluppo proposta dalla *American Accademy of Pediatrics* prevede in prima istanza un inquadramento anamnestico e clinico nonché una consulenza metabolica. In base alle condizioni del bambino si può scegliere se eseguire subito indagini strumentali di secondo livello (incluso l'*imaging* cerebrale). Di concerto alla valutazione del genetista, i test genetici standard includono il *micro-array* cromosomico e analisi del DNA per X-fragile (sesso maschile) e sindrome di Rett (sesso femminile), indipendentemente dal fatto che il bambino abbia o meno caratteristiche dismorfiche. Lo studio del cariotipo è giustificato se si sospetta una traslocazione bilanciata (ad esempio in caso di storia di poliabortività) in considerazione del fatto che il *micro-array* non rileva traslocazioni bilanciate (per quanto siano rare). In caso di negatività dei precedenti esami un ulteriore *step* potrebbe essere rappresentato dall'analisi dei pannelli per neurosviluppo o dall'esoma. L'identificazione di una diagnosi genetica può prevenire complicazioni mediche associate per il bambino, fornire infor-

mazioni specifiche sul rischio di recidiva per i membri della famiglia e impedire ulteriori ricerche di diagnosi e trattamenti complementari e alternativi. Può anche fornire sollievo emotivo ai *caregiver* e può essere cruciale per l'alleanza terapeutica. Tuttavia, non bisogna dimenticare il ruolo delle varianti a significato incerto che possono essere individuate nel corso dello studio e non rappresentare un vantaggio per il percorso diagnostico-terapeutico.

Conclusioni

Il trattamento per il DSA deve essere individualizzato e la diagnosi precoce e il trattamento intensivo hanno il potenziale per influenzare, in particolare per quanto riguarda il comportamento, le abilità funzionali e la comunicazione. Sebbene non esista una cura, il quadro può subire un miglioramento nel tempo e in una piccola minoranza non causare disabilità: per tale motivo nessun caso può subire un ritardo diagnostico.

DISTURBO DELLO SPETTRO AUTISTICO: LA FAMIGLIA PRIMA DI TUTTO

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Familial autistic spectrum disorder (ASD)

Key words *Autistic spectrum disorder, Genetic tests*

Two Senegalese children (brother and sister) affected by ASD are described. The Author stress the incresed risk to be affected by ASD in children of immigrant mothers.

Bimbo di 5 anni nato in Senegal, in Italia da 7 mesi. Viene inviato dalla curante all'attenzione della Neuropsichiatria perché rispetto ai coetanei dimostra un netto ritardo negli apprendimenti e nello sviluppo del linguaggio.

Alla valutazione neuropsicologica mostra scarse capacità attentive, imitative e di interazione sociale. Il contatto visivo e l'attenzione condivisa sono molto poco frequenti, il linguaggio è spesso ecolalico e scorretto e dal punto di vista motorio manifesta goffaggine. Si fa diagnosi di ritardo cognitivo in bambino con disturbo dello spettro autistico (DSA).

Viene preso in carico e inizia un percorso intensivo di interventi volti al miglioramento della comunicazione sociale e dei comportamenti con la collaborazione della famiglia e con un sostegno scolastico ben strutturato. Alle successive valutazioni dalla pediatra di famiglia emerge un notevole progresso nel bimbo. Un anno dopo, la mamma porta al bilancio dei 18 mesi la secondogenita.

Le risposte all'M-CHAT-R, strumento di screening per i disturbi dello spettro autistico, indirizzano anche nel suo caso verso un DSA. Pertanto, valorizzando la familiarità, viene inviata a una valutazione specialistica che confermerà la diagnosi di autismo.

I disturbi dello spettro autistico sono un gruppo di disordini del neurosviluppo su base genetica piuttosto frequenti (prevalenza di 1:68) che si manifestano nella prima infanzia. Le aree prevalentemente interessate dal disturbo pervasivo sono quelle relative alla comunicazione sociale, al linguaggio, alla interazione sociale reciproca e al gioco funzionale e simbolico.

L'autismo si struttura con il tempo e va gradualmente a compromettere lo sviluppo del cervello, quindi è necessario intervenire quanto prima sul modello dell'approccio terapeutico *Early Start Denver Model*, rivolto ai bimbi fra i 18 e i 30 mesi.

È interessante sottolineare l'origine senegalese dei due fratelli; numerosi studi hanno infatti riconosciuto un aumento del rischio di sviluppo dei DSA nei figli di madri immigrate, soprattutto provenienti da Paesi in via di sviluppo. La diagnosi in questi casi risulta più complessa e tardiva a causa della barriera linguistica.

Il caso dei due fratellini ci ricorda di valorizzare sempre la familiarità nei DSA, per poter fare diagnosi precoce. Sottolinea inoltre i vantaggi della presa in carico con intervento intensivo, approccio che è in grado di dare una vera svolta alla vita dei pazienti con diagnosi di autismo.

IL GRAFFIO

"Matti" da morire

Le cosiddette malattie non comunicabili (MNC) (come i tumori, le malattie croniche degenerative, la malattia mentale nelle sue tante sfaccettature, le dipendenze e certamente anche la malnutrizione intesa in senso qualitativo oltre che come difetto o eccesso assoluto di introito di nutrienti) affliggono più di un terzo degli adolescenti degli Stati dell'Unione Europea e ne mortificano le aspettative e la qualità di vita: con costi materiali, ma anche morali e di prospettiva, inimmaginabilmente elevati per l'intera società (European Chronic Disease Alliance. Towards an EU strategic framework for the prevention of Non-Communicable Diseases (NCDs). May, 2019. https://easl.eu/wp-content/ uploads/2019/05/ Final-NCD-Paper-full-version.pdf accessed Jan 18, 2022). Estrapolando i dati del Global Burden of Diseases Injuries, and Risk Factors 2019 (GBD 2019) (Armocida B, et al. Lancet Child Adolescent Health. doi: 10.1016/S2352-4642(22)00073-6) è stato calcolato che, nei Paesi dell'Unione Europea, le MNC danno conto del 35% della mortalità e dell'85% degli anni vissuti con disabilità dei giovani della fascia di età compresa tra 10 e 24 anni. Intendiamoci: le cose sembrano per molti versi migliorare e la mortalità per MNC si è ridotta globalmente di circa il 40% negli ultimi trent'anni. Ma, a fronte di questo miglioramento complessivo, pesa sui bambini e sugli adolescenti il progressivo e significativo aumento della mortalità per malattia mentale e quello degli anni vissuti con disabilità a questa correlati. Una vera e apparentemente inarrestabile catastrofe. Già drammaticamente evidente anche prima che su tutto questo si abbattesse la pandemia da Covid-19: alla quale ora ci affrettiamo a dare tutte le colpe, senza la capacità (l'interesse?) e l'onestà di approfondire, comprendere e prevenire le cause del disastro che avevamo già da tempo sotto gli occhi. Le cose non vanno di certo meglio negli USA dove, a fronte del pesante aumento dei disturbi mentali in bambini e adolescenti (40% ne soddisfano i criteri diagnostici prima dei 18 anni di età e sta crescendo il numero dei casi anche tra i più piccoli) registrato anche lì ancor prima della pandemia di Covid-19 (Bitsko RH, et al. Mental Health Surveillance among Children-United States, 2013-2019. https://www.cdc.gov/mmwr/volumes/71/su/su7102a1.htm?s_cid=su7102a1_w), l'Accademia Americana di Pediatria (AAP), l'Accademia Americana di Psichiatria del Bambino e dell'Adolescente (AACAP) e l'Associazione degli Ospedali Pediatrici (CHA) hanno dichiarato lo "stato nazionale di emergenza" (sic!) (AAP, AACAP, CHA declare national emergency in children's mental health | AAP News | American Academy of Pediatrics. Accessed January 31, 2022). Anche perché, di tutti i bambini e gli adolescenti con disturbo mentale, solo una piccolissima minoranza viene effettivamente presa in carico dal punto di vista terapeutico (circa il 10% e ancora di meno se si tratta di bambini e adolescenti neri e latino americani). Vabbè, lo so, non è la prima volta che ne parliamo. E forse dovremmo finirla di fermarci a contare i morti e a... contarcela. Lì nel mezzo infatti, con la possibilità di dire la nostra, di intercettare i fattori di rischio (ad esempio quelli familiari, come la povertà educativa e a volte la violenza, o quelli sociali come il razzismo agito in tutte le sue più subdole forme) e il loro impatto erosivo sul cervello del bambino (badate bene... di quel bambino lì), ci siamo anche noi pediatri. E dovrebbero esserci (sì, è un appello!), appassionati, colti, consapevoli e motivati (come tanti di fatto sono), anche i nostri amici neuropsichiatri: con altro ruolo certo, ma solidali con noi anche nel momento del disaccordo, anche quando l'agire professionale appare poco gratificante e in qualche modo distante dalle aspettative che ognuno si era dato. A evitare fraintendimenti e frustrazioni rispetto alla vocazione che motiva ogni singolo, si tratta intanto, ne sono convinto, di cominciare a separare la formazione e le carriere di neuropediatri e psichiatri del bambino, come succede in tante parti del mondo e come propongono non pochi neuropsichiatri italiani con alta valenza professionale e accademica. Ma sono altrettanto convinto che anche questo non basterà se non ci impegneremo tutti insieme, e noi pediatri per primi, a riconoscerci con umiltà nel compito e nell'identità di semplici operatori di salute dell'età evolutiva. Se non sapremo condividere, con passione e onestà, la consapevolezza di dover attualizzare la nostra professionalità all'emergenza che è stata dichiarata e che tutti abbiamo sotto gli occhi. Il che significa, inevitabilmente, cambiare almeno un po', tutti e tutti insieme, il nostro modo di stare al mondo.

Alessandro Ventura

"Matti" da morire

Caro Professor Ventura,
leggiamo con spirito dialettico le sue considerazioni (Graffio di aprile: 2022;41(4):217) e volentieri ci confrontiamo. Vogliamo rassicurarla: i neuropsichiatri dell'infanzia e dell'adolescenza sono presenti. Celebriamo quest'anno i 50 anni della nostra Società Scientifica (Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza - SINPIA) e circa i 70 dalla nascita della disciplina e ci siamo, appassionati e in prima linea, da ben prima che la pandemia disvelasse e aggravasse scenari a noi già noti da anni e da tempo segnalati alle Autorità e all'opinione pubblica. Ci siamo insieme a tutti gli operatori che con noi lavorano in quelle *équipe* multidisciplinari e multiprofessionali che sono la forza e la ricchezza dei nostri Servizi sparsi nelle realtà ospedaliere, territoriali, negli Istituti di ricerca e nelle Università in tutto il territorio nazionale.

La prevalenza raddoppiata dei disturbi neuropsichici di cui tanto si parla non è fenomeno attribuibile solo alla pandemia, ma è espressione di un *trend* già presente nei 10 anni precedenti che l'emergenza e le sue restrizioni hanno purtroppo drammaticamente peggiorato, colpendo in modo particolare i bambini e gli adolescenti che già presentavano vulnerabilità. La crescita esponenziale delle richieste non è avvenuta solo per i disturbi psichiatrici né solo in adolescenza. Riguarda tutti i disturbi del neurosviluppo, trasversalmente a tutte le fasce dell'età evolutiva e va affrontata di conseguenza, con uno sguardo di sistema, ben radicato nelle nuove conoscenze offerte dalle Neuroscienze, e nella messa punto di modelli clinici e organizzativi in grado di adattarsi rapidamente al cambiamento dei bisogni senza cadere in facili riduzionismi.

Il cervello è per sua definizione un sistema complesso e con la consapevolezza della complessità va affrontato lo studio e la cura del suo funzionamento e dei suoi disturbi. Ed è di questa complessità che la Neuropsichiatria dell'infanzia e dell'adolescenza rivendica di farsi carico, nell'affrontare la diagnosi e la cura di un sintomo o di un disturbo sapendo che questo non può che impattare anche su altre funzioni e altri sistemi che sono tra l'altro in continuo cambiamento visto che parliamo di un soggetto in via di sviluppo.

Consapevoli che questo processo di sviluppo, adattamento, cambiamento avviene in un ambiente (famiglia, scuola, contesti di vita) che gioca esso stesso un ruolo fondamentale che permette di plasmare, modificare, riorganizzare le traiettorie evolutive delle funzioni adattive emergenti (sensoriale, motoria, cognitiva, comunicativa, emotivo relazionale ecc.). Senza contare che il modello di cura della Neuropsichiatria infantile è *family-centered* perché senza coinvolgimento attivo e partecipativo della famiglia ogni tipo di cura è destinato a fallire.

La ricerca ha ormai ampiamente dimostrato come i disturbi del neurosviluppo vedano il coinvolgimento di fattori di rischio comuni e di componenti genetiche, neurobiologiche e ambientali trasversali ed età specifiche[1], includendo a pieno titolo, oltre ai disturbi ampiamente noti come autismo, disabilità intellettiva, disturbi specifici di linguaggio e apprendimento, tutti i disturbi psichiatrici dell'infanzia e dell'adolescenza, inclusa la schizofrenia, nonché i disturbi neurologici. Perfino l'epilessia, spesso considerata malattia esempio di "neurologica pura", in età evolutiva dovrebbe essere considerata, nella maggior parte dei casi, un disturbo del neurosviluppo[2].

Ricerche recenti hanno evidenziato come sia proprio questa base comune a determinare la frequentissima coesistenza di più disturbi e la trasformazione degli stessi nel tempo, e come un approccio frammentato o schematico possa essere solo riduttivo e avere conseguenze molto gravi in termini di appropriatezza delle risposte, di cura e prognosi a lungo termine[3].

La frammentazione, che semplifica quello che è per sua natura complesso, rappresenta purtroppo una risposta frequente anche nel nostro Paese, nonostante l'unitarietà della disciplina e dei Servizi. Una quota rilevante di disturbi neurologici a esordio prescolare-scolare sono presi in carico da pediatri-neuropediatri senza comprenderne a fondo l'intima connessione ed embricazione sia con la maturazione psicoaffettiva e della personalità, direttamente connessa con il disturbo di base, spesso genetico, sia con l'interazione ambientale, a sua volta negativamente influenzata dalla solo parziale comprensione e presa in carico della complessità. D'altra parte disturbi psicoaffettivi e comporta-mentali vengono letti e presi in carico solo in ambito psicologico o psichiatrico senza comprenderne la base neurobiologica, e senza attuare una appropriata valutazione delle componenti costituzionali/individuali, genetiche e delle abilità strumentali del soggetto. È invece ormai ben noto come disturbi psicoaffettivi, comportamentali e psichiatrici che si manifestano più avanti negli anni siano il risultato dell'impatto di un disturbo precoce del neurosviluppo, che agisce sulla plasticità genetica-funzionale durante le finestre evolutive, interferendo con lo sviluppo di funzioni determinanti per una adeguata vita di relazione.

Non è offrendo un insieme di valutazioni separate e culturalmente e professionalmente diverse tra loro che si può aiutare un bambino o un ragazzo con un sé fragile e frammentato per diversi motivi a raggiungere l'equilibrio per lui possibile. Né è così che si risolve il drammatico problema della carenza di risorse e del mancato investimento nei Servizi che hanno il compito istituzionale di garantire risposte appropriate e basate sulle evidenze. Proprio l'ulteriore frammentazione indotta da valutazioni e prese in carico settoriali e dalla moltiplicazione di servizi per singole aree di bisogno è alla base del fallimento degli interventi e favorisce un progressivo incremento del disagio e delle problematiche psichiatriche, neurologiche e neuropsicologiche nel tempo, nonché un maggior consumo di risorse.

L'individuazione tempestiva delle condizioni di rischio e dei sintomi precoci dovrebbe essere compito condiviso con i pediatri di famiglia; una diagnosi esaustiva, la valutazione della più probabile traiettoria evolutiva non solo del sintomo ma dell'insieme del neurosviluppo negli anni, la presa in carico nel tempo e il monitoraggio costante degli esiti possono essere garantiti unicamente da Servizi in grado di leggere i sintomi più

manifesti nella loro complessità, e la costante bidirezionale influenza tra quelli neurologici e psichici. Servizi di Neuropsichiatria dell'infanzia e dell'adolescenza multiprofessionali integrati, in grado di leggere tutta la complessità del quadro clinico del soggetto e del suo ambiente a partire da un modello basato culturalmente su una visione olistica del neurosviluppo. Se alcune strategie diagnostico-terapeutiche possono dover necessitare del supporto di una consulenza superspecialistica, la medesima non può verificarsi che all'interno di una valutazione e presa in carico neuropsichiatrica infantile unitaria.

Preme sottolineare peraltro come la risposta ai disturbi comportamentali e psichiatrici non risulti migliore negli USA, dove le figure del neurologo pediatra e dello psichiatra infantile sono separate: per quanto le risposte italiane siano carenti, disomogenee e vadano potenziate, la prevalenza trattata nei servizi di NPIA è dalle due alle quattro volte superiore rispetto agli Stati Uniti. Analogamente, va evidenziato come l'*escalation* delle richieste per tutti i disturbi del neurosviluppo sia trasversale a tutti i Paesi, e si evidenzi maggiormente proprio quando il modello neuropsichiatrico integrato si scinde in presa in carico neurologica - psichiatrica - sociale in assenza di integrazione culturale e organizzativa tra loro.

Infine, certamente l'impatto sempre più prepotentemente negativo delle diseguaglianze economiche, sociali, e culturali, a loro volta aggravate da eventi ulteriormente destabilizzanti come pandemie, guerre ecc., insieme all'indifferenza, alla negazione, all'incomprensione, all'ostilità e allo stigma, come ben da Lei ricordato, ha una valenza dirompente nell'incremento dei disturbi neuro-psichiatrici. La coscienza di ciò dovrebbe appartenere a tutti noi indipendentemente dal ruolo professionale e sociale, e dovrebbe includere la consapevolezza che è proprio nelle situazioni di maggiore fragilità e vulnerabilità sociale che una valutazione mono-oculare iniziale, che si muove sulla base del sintomo più apparente verso approfondimenti neurologici, psicologici o psichiatrici separati, rischia di condizionare in maniera particolarmente negativa la traiettoria evolutiva del bambino.

Il modello italiano, che mantiene integrate da sempre in una prospettiva evolutiva (trasversale e longitudinale) componenti neurologiche, psichiatriche e neuropsicologiche, è certamente unico al mondo e può sembrare datato, ma è in realtà assolutamente innovativo, avvalorato dalle Neuroscienze più attuali e ampiamente invidiato in altri Paesi proprio per questa capacità di mantenere specificità nella consapevolezza della complessità

La risposta al problema che Lei pone non è frammentare, semplificare e ridurre, che andrebbe in senso contrario rispetto alla comprensione della natura del problema, a tutti i contributi della ricerca e alle nuove conoscenze sui sistemi complessi, migliorando solo in apparenza la gestione e "mettendoci un cerotto"[4]. Servono risorse e risposte di sistema, integrate e coordinate, a partire da standard chiari e adeguati a quanto previsto dai ivelli essenziali di assistenza (LEA), nell'ambito di un cambiamento culturale profondo che apra all'innovazione e al futuro, perché tutti i bambini e ragazzi con disturbi del neurosviluppo e le loro famiglie vedano finalmente riconosciuto il diritto a cure appropriate e tempestive e vedano garantito il loro massimo potenziale di sviluppo.

È per tutti questi motivi che, come Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza, nell'ambito della Settimana europea di sensibilizzazione sulla salute mentale e delle attività per il 50° anniversario SINPIA, abbiamo scelto di lanciare la Giornata Nazionale per la promozione del Neurosviluppo per mercoledì 11 maggio 2022.

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Grazie, grazie di cuore al Presidente della SINPIA, ai suoi past president, ai suoi consiglieri per l'interesse e la sensibilità dimostrata all'appello che avevo lanciato nel recente Graffio "Matti da morire" (Medico e Bambino 2022;41(4): 217. doi: 10.53126/MEB41217). Dove, tra l'altro, avevo richiamato l'attenzione di tutti gli operatori di salute dell'età evolutiva (pediatri e neuropsichiatri per primi) sulla necessità e sull'urgenza di un cambio di passo a fronte della incalzante e pervasiva epidemia di disturbi psichiatrici e del neurosviluppo nei bambini e negli adolescenti.

Certamente (come tutti i pediatri di buona volontà) non posso che condividere l'importanza e l'irrinunciabilità di un approccio olistico ai problemi del neurosviluppo, in cui si intersechino produttivamente le competenze sul cervello e sui sentimenti del bambino e, più in generale, sui suoi bisogni di salute, sulle possibili patologie e sulle loro determinanti individuali e sociali. E benissimo quindi se si ritiene che la formazione e l'opera del NPI non debbano frammentarsi e debbano continuare a essere sostenute (come è ovvio che sia) dalla conoscenza e dalla consapevolezza della complessità e della inscindibile relazione tra neuro e psico nella fisiopatologia del neurosviluppo. Ci mancherebbe! Ma sarebbero guai (guai per i bambini... si intende) se l'affermazione e il per-

seguimento di questa infrangibile unitarietà culturale e professionale rimanessero l'unica risposta alla concreta necessità di cambiare qualcosa nella realtà reale dell'assistenza: anche e soprattutto in quella delle citate équipe multidisciplinari e multiprofessionali che, viene scritto, "sono la ricchezza dei nostri Servizi... ospedalieri, territoriali... universitari...". È proprio in queste realtà, è proprio sul campo, dove si sente di più il bisogno del cambio di passo da tanti invocato (e che, ripeto, non riguarda solo i NPI). Cambio di passo che di certo non può prescindere dall'adeguamento quantitativo delle risorse professionali ai nuovi bisogni (nel rispetto anche, dico io, delle diverse vocazioni di ognuno: a questo proposito perché non prevedere un tronco comune e poi due orientamenti diversi nella formazione e nelle carriere dei NPI?). Ma ancor prima caratterizzato, da parte dei singoli operatori, da un diverso atteggiamento, da una diversa disponibilità personale, da una rinnovata consapevolezza dell'importanza e della non delegabilità del proprio ruolo nella pianificazione e nella effettiva realizzazione di un intervento terapeutico tempestivo e per questo efficace. È questo il cambio di passo che anche personalmente, pur lontano dal campo ormai da un po' (sono un past più a buon titolo di ogni altro...), mi sono preso la libertà di invocare a nome di tanti colleghi: che, nella quotidiana fatica di dare un senso al proprio lavoro, si attendono magari di sentire condivisa la propria sofferenza piuttosto che di dover scontrarsi con l'insofferenza per la tipologia dei problemi da affrontare. Troppo spesso il campo fa vivere (ai pediatri come ai NPI, certo) una realtà fatta da difficoltà di consulenze, da frammentazione del progetto di intervento, da assenza di un riferimento che tenga le redini della complessità (appunto!) del problema, da deleghe piuttosto che da assunzione di responsabilità, da solitudine piuttosto che da certezza della condivisione. Da frustrazione, anche: come nel caso (e qui parlo sicuramente a nome di tanti bravi pediatri) dei ritardi (quando non proprio della mancanza) nella presa in carico dei bambini con disturbi del neurosviluppo, in particolare di quelli con disturbo dello spettro autistico che, proprio grazie alla sensibilità che i NPI ci hanno trasmesso, sappiamo ora intercettare sempre più tempestivamente. Sembra a volte che proprio in quelli che dovrebbero effettivamente rappresentare "la ricchezza dei nostri Servizi" si realizzi più spesso (briglie della burocrazia? prevalere e abuso della perversa logica istituzionale di basagliana memoria? dispersione delle responsabilità in nome della fantomatica "rete"?) un esiziale rallentamento piuttosto che la dovuta accelerazione e specializzazione delle cure dovute al bambino. Ma è vero! La realtà è sempre più complessa di quanto possa apparire nella interpretazione e nel vissuto di ognuno. Ed è senz'altro un bene che il dibattito aperto ormai da molti anni sulle pagine di Medico e Bambino sull'emergenza psichiatrica nel bambino e nell'adolescente sia stato rilanciato ora, su queste stesse pagine e con tanta autorevolezza, proprio dalla presidenza e dal consiglio direttivo della SINPIA che già da tempo, in altre sedi e in altri modi, aveva segnalato l'allarme. Ma non basta. C'è bisogno che ancora di più ognuno di noi (pediatra, neuropsichiatra, operatore dell'età evolutiva più in generale) si senta ora impegnato a dare al dibattito il suo contributo di riflessioni ed esperienze. Prospettando anche soluzioni concrete (concrete, mi raccomando, e non solo fatte da modelli organizzativi teoricamente più belli che altrove, ma che non impongano a ognuno di adeguarsi ai bisogni reali, di cambiare il passo, di cambiare almeno un po', appunto, il proprio modo di stare al mondo). Sono sicuro che tra i tanti pediatri e neuropsichiatri che non ambiscono ad altro che a far bene il proprio mestiere nessuno rinuncerà a far sentire la propria voce.

Alessandro Ventura

ERRATA CORRIGE

Nella versione cartacea del Graffio di aprile sono state invertite le percentuali riguardanti la mortalità e la disabilità in cui sono coinvolte le malattie non comunicabili.

La frase:

"[...] è stato calcolato che, nei Paesi dell'Unione Europea, le MNC danno conto dell'85% della mortalità e del 35% degli anni vissuti con disabilità dei giovani della fascia di età compresa tra 10 e 24 anni."

diventa quindi:

"[...] è stato calcolato che, nei Paesi dell'Unione Europea, le MNC danno conto del 35% della mortalità e dell'85% degli anni vissuti con disabilità dei giovani della fascia di età compresa tra 10 e 24 anni."

Ci scusiamo molto per l'errore.

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