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ARTICLE

Causal Relationship between Attention-Deficit Hyperactivity Disorder and Autism Spectrum Disorder: A Two-Sample Mendelian Randomization

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Abstract

Aims/Background Despite the exponential increase in the incidence rate of Autism spectrum disorder (ASD), effective therapies for the disorder are still limited. According to vast clinical observations, the pathogeneses of ASD and Attention-deficit hyperactivity disorder (ADHD) share a great deal of similarities. This serves as a prompt to investigate, in this study, whether patients with ADHD are at a higher risk for ASD, which is significant for disease prevention.

Methods Data concerning ADHD as the exposure variable and ASD as the outcome variable were collected from the publicly available Integrative Epidemiology Unit Open GWAS project (IEU GWAS) database. After screening the instrumental variables (IVs), statistical analysis was performed using the TwoSampleMR package of version R4.3.1, and sensitivity testing was conducted to evaluate the stability and reliability of the results.

Results After screening the Single nucleotide polymorphisms (SNPs) through the calculation of *F*-value and Mendelian randomization (MR) Pleiotropy RESidual Sum and Outlier test (MR-PRESSO), seven SNPs that satisfied the three major assumptions of Mendelian randomization were selected as IVs and could be used in place of ADHD in exploring the aforementioned causal relationship. The Odds ratio (OR) for the random-effect Inverse-variance weighted (IVW) method was 1.31 (95% Confidence interval [CI]: 1.14–1.52; $p = 0.0001$). A similar trend was observed for the Weighted median estimator (WME) method, with an OR of 1.37 (wider 95% CI: 1.15–1.64; $p = 0.0005$).

Conclusion This study includes the pooled data on ADHD and ASD from the IEU GWAS public database, and there is sufficient evidence that patients with ADHD have a higher risk of ASD.

Key words: Autism spectrum disorder; Attention-deficit hyperactivity disorder; Mendelian randomization; Single nucleotide polymorphism; Genome-wide association study

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Introduction

Autism spectrum disorder (ASD) is a disorder that often develops since infancy, and the affected individuals have three main symptoms: social impairment, narrow interests, and stereotyped behaviors. Pediatric patients with ASD often experience poor development and mental retardation (Lord et al, 2018; Salmerón-Medina et al, 2022). Clinically, it is common for such patients to suffer from neurological disorders, such as epilepsy (Kwon et al, 2022). ASD can be caused by chromosomal aberration owing to the old age of parents, genetic mutations, and nutrient

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deficiencies (Usui et al, 2023; Wang et al, 2020). At present, no specific effective therapy is available for ASD, and the pathogenesis remains unclear. Multiple factors during pregnancy can influence the incidence rate of ASD in children, including physical and mental health status during perinatal and postpartum periods, as well as complications during pregnancy (Doi et al, 2022; Zhen Lim et al, 2023). Previous studies have documented that neuroinflammation, gut dysbiosis, genetics, and immunity can lead to ASD (Taniya et al, 2022; Hughes et al, 2023; Wang et al, 2023). Gut microbiota regulates brain signals through various pathways including neurotransmitters, which in turn influence the brain functions and behaviors. The dysregulation of signaling pathways that underlie neuronal activities has been shown to play a key role in ASD (Jourdon et al, 2023). Gamma-aminobutyric acid (GABA) plays a critical role in the central nervous system. A reduction of the level of GABA causes a disruption to the excitation-inhibition balance in the brain, thus resulting in the symptoms of ASD (Paulsen et al, 2022). The incidence rate of ASD has increased exponentially in recent years, and the prevalence rate of ASD in boys is 3.8 times higher than that in girls (Maenner et al, 2023); therefore, it is necessary to study the pathogenesis and treatment of ASD.

Attention-deficit hyperactivity disorder (ADHD), which is also known as hyperactivity disorder, is a childhood neurodevelopmental disorder with three main symptoms: difficulty concentrating with a short attention span, hyperactivity, and impulsivity. Many pediatric patients with ADHD often suffer from learning difficulties owing to the difficulty in concentrating. In adulthood, they also face relevant difficulties while working, resulting in family burden. In most cases, the symptoms of ADHD diminish with age, but the aforementioned difficulty persists (Wong, 2023). Despite a high incidence rate, there has been a low consultation rate related to ADHD in clinical practice. Therefore, our current understanding regarding the development of ADHD is relatively poor, and the pathogenesis of the disorder remains largely unknown. The development of ADHD in children is associated with several maternal factors during pregnancy and labor, including gestational age, mode of delivery, and physical and mental health status during pregnancy (Ahlqvist et al, 2024; Kian et al, 2022). Furthermore, gestational diabetes can significantly increase the risk of ADHD in offspring (Rodolaki et al, 2023). Moreover, preterm infants are considered to have a higher risk of ADHD and have a more severe disease condition after the onset of disease (Song, 2023). The gut microbiota plays a crucial role in influencing the development of ADHD from the immune, endocrine, metabolic, and neurological aspects, and there have been cases of improvement in ADHD-related symptoms after fecal microbiota transplantation (Hooi et al, 2022).

Mendelian randomization (MR) is an approach that uses the loci of Single nucleotide polymorphisms (SNPs) as the genetic instrumental variables (IVs) to simulate the effect of an exposure variable on an outcome variable to explore the causal relationship between the exposure variable and the outcome variable. Through the use of genetic IVs, MR precludes the effects of temporal, reverse, and confounding factors. The utilization of MR requires the satisfaction of three major assumptions: (1) the assumption of association where the genetic IVs, SNPs, need to be strongly associated with the exposure variable; (2) the assumption of independence where

the genetic IVs, SNPs, must not be associated with any confounding factors; (3) the assumption of exclusivity where the genetic variants must not be directly associated with the outcome variable. ASD and ADHD are often present simultaneously, and recent studies have established that gut dysbiosis, neuroinflammation, genetic mutations, and compromised immunity can lead to ASD and ADHD (Granadillo et al, 2020; Han et al, 2021; Kwak et al, 2023). Furthermore, research has revealed that prenatal exposure to toxic metals or alterations in maternal essential element levels during pregnancy are potential risk factors for neurodevelopmental disorders (Modabbernia et al, 2017). Specifically, it has been suggested that the pathogeneses of both ADHD and ASD might share an overlapping set of neurochemical and neurodevelopmental pathways (Skogheim et al, 2021). Whether there is a correlation between ASD and ADHD remains to be elucidated. Therefore, we conducted an MR study, in which ADHD was regarded as the exposure variable and ASD as the outcome factor to evaluate the causal relationship between ADHD and ASD. Although a previous study has indirectly suggested a possible connection between ASD and ADHD (Antshel and Russo, 2019), it has not directly elucidated whether an association exists between them. Hence, this research employed the MR method to explore the relationship between ADHD and ASD, directly depicting the causal link between ADHD and ASD for the first time.

Methods

Research Design and Data Sources

This study utilized the two-sample MR to study the causal relationship between ADHD and ASD. Microsoft Visio 2021 (Microsoft Corporation, Albuquerque, NM, USA) was used to draw the flowchart. The flow chart detailing the fulfilment of the three major assumptions of MR analysis and the cognitive process of this study is presented in Fig. 1.

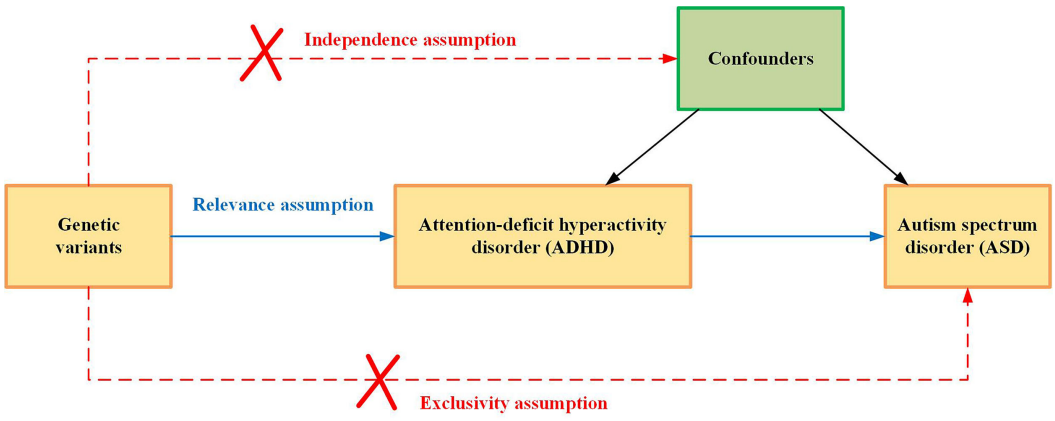

Fig. 1. A schematic summary of the study design. ASD, Autism spectrum disorder; ADHD, Attention-deficit hyperactivity disorder.

To minimize the geographical and ethnic biases, the participants included in this study were mostly of European ancestry. The pooled data of ADHD from

Table 1. Studies included in Mendelian randomization analyses.

Trait	Author (year)	Sample size	Sex	Number of SNPs	Ancestry	GWAS ID
ADHD	Demontis et al (2019)	55,374	Males and females	8,047,420	Worldwide (mostly European)	ieu-a-1183
ASD	Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium (2017)	46,351	Males and females	9,112,386	Worldwide (mostly European)	ieu-a-1185

ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder; GWAS ID, Genome-wide association study identification; SNPs, Single nucleotide polymorphisms; MRC, Medical Research Council.

the Psychiatric Genomics Consortium (PGC) were selected from the Integrative Epidemiology Unit Open GWAS project (IEU GWAS) database (https://gwas.mrcieu.ac.uk/datasets/) to serve as the exposure variable. The data contained 20,183 ADHD cases and 35,191 controls. The subjects of ADHD were mostly Europeans, with minor portions of Chinese and North Americans. This study involved three replication analyses, including: (1) analysis of a cohort of diagnosed ADHD; (2) analysis of a self-reported ADHD sample; and (3) a meta-analysis of quantitative measures of ADHD symptoms in the population. The data of ASD from the Lundbeck Foundation Initiative for Integrative Psychiatric Research, part of the PGC (iPSYCH-PGC) were also selected from the IEU GWAS database to serve as the outcome variable. The data were derived from the Medical Research Council (MRC) of the Centre for Neuropsychiatric Genetics and Genomics at Cardiff University, Wales. Most of the participants with ASD are of European ancestry. All the ASD cases were aged over 3 years old and eligible for the Autism Diagnostic Interview-Revised (Lord et al, 1994) or the Autism Diagnostic Observation Schedule (Lord et al, 2000). The detailed information is presented in Table 1. The exposure and outcome variables were selected from different organizations to avoid the collection of overlapping samples. Ethical approval and informed consent were not required as the data were obtained from published studies.

Selection of IVs

The selection of genetic IVs should be conducted to fulfil the three major assumptions of MR analysis. Therefore, we first set the *p*-value and the conditions for linkage disequilibrium ($p < 5 \times 10^{-8}$, $r^2 < 0.01$, kb = 10,000). After eliminating the SNPs that did not satisfy the conditions, the remaining SNPs were used as the IVs in place of ADHD for further screening. The *F*-value was calculated for each of the SNPs that remained after screening. An *F*-value of >10 indicates no weak instrument bias. Hence, the SNPs with an *F*-value of >10 were retained, whereas the SNPs with an *F*-value of ≤ 10 were excluded. Eventually, the remain-

ing SNPs were strongly associated with ADHD and could be used as the IVs in place of ADHD for further data analysis.

Statistical Analysis

MR Analysis

Statistical analysis was performed using the TwoSampleMR (version 0.6.6) package and MR Pleiotropy RESidual Sum and Outlier test (MR-PRESSO) (version 1.0) of version R4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The MR approach consists of five data analysis methods, namely Inverse-variance weighted (IVW), Weighted median estimator (WME), MR-Egger regression, Simple mode, and Weighted mode. The IVW method is the most robust approach in MR analysis. In MR analysis, the results of the IVW method are frequently regarded as reliable outcomes. The prerequisite for its application is that all IVs are effective. The inverse of the variance of the IV estimate for each SNP is employed as the weight for weighted computation. The intercept term is not taken into account. Ultimately, the weighted mean of the IV estimates of all SNPs is obtained. On the other hand, the use of the WME method in an MR analysis provides valid results when the number of valid SNPs is small. The use of MR-Egger method provides a valid evaluation of the causal effect when all SNPs are invalid IVs. The simple mode does not consider the magnitude of the IV's effect estimate, taking only the median as the estimate of the causal effect. When there is greater uncertainty in the validity of IVs, it can provide a relatively conservative estimate. The weighted mode plays an important role in accurately estimating causal effects, integrating multi-source information, and performing statistical inference.

Sensitivity Analysis

MR Pleiotropy RESidual Sum and Outlier test (MR-PRESSO) comprises three components: (1) detecting horizontal pleiotropy; (2) correcting for pleiotropy by eliminating the detected outliers (genetic variants with horizontal pleiotropy); and (3) comparing the disparities in causal associations before and after correction. MR-PRESSO employs the effect of the same genetic variant in the outcome to regress against the effect of the exposure. The slope of the regression line indicates the association between the exposure and outcome. Possible outliers are detected by comparing the distance (sum of squared residuals) between effect size of all genetic variants and the regression line with the expected distance under the assumption of no horizontal pleiotropy. Further, MR-PRESSO removes the detected outliers and recalculates the causal association between exposure and outcome. In conclusion, the results obtained by MR-PRESSO are less influenced by outliers (if present) in the genetic instrument.

In MR, when evaluating horizontal pleiotropy through MR-Egger method, the magnitude and direction of horizontal pleiotropy are appraised by utilizing the intercept term. The specific computational steps are as follows: Firstly, the association effect (βX) of each genetic variant with the exposure factor and the association effect (βY) with the outcome variable are estimated. Then, regression analysis with βY as the dependent variable and βX as the independent variable is conducted to

obtain the regression coefficient and intercept term. The regression coefficient represents the estimated value of the causal effect, while the intercept term reflects the degree of horizontal pleiotropy. In MR analysis, a *p*-value for horizontal pleiotropy of >0.05 implies the absence of horizontal pleiotropy. The test for heterogeneity is used to test for the differences between each pair of IVs. This study adopted Cochran's Q test. A *p*-value of <0.05 suggests heterogeneity, whereas >0.05 suggests no heterogeneity. After eliminating the SNPs one by one through the leave-one-out method, the remaining SNPs were analyzed using the MR analysis to identify whether individual SNPs had a substantial effect on the final results.

In the present study, the Bonferroni correction was employed to adjust for multiple comparisons, thereby enhancing the robustness of the findings. Within the context of MR analysis, the simultaneous examination of multiple exposure variables in relation to outcome variables is a common practice. The absence of correction for multiple testing can lead to an increased likelihood of committing a type I error, which is the erroneous rejection of a true null hypothesis. The Bonferroni correction mitigates this risk by adjusting the significance level to control the overall type I error rate. The underlying principle of this correction is to divide the total significance level by the number of tests conducted, thereby increasing the stringency of the significance level for each individual test.

Results

Selection of Genetic IVs

The screening of genetic IVs was conducted based on the selection criteria described above. Eventually, the loci of 12 SNPs with genome-wide significance were selected to serve as the IVs in place of ADHD. From among the 12 SNPs, one palindromic SNP (rs11591402) was identified and excluded from subsequent data analysis. The remaining 11 SNPs were subjected to the MR-PRESSO method. Eventually, four potential outliers (rs1222063, rs281324, rs4916723, rs9677504) were identified and excluded. After performing the screening, seven SNPs remained. The *F*-value was calculated for each of the seven SNPs, and all the *F*-values fall within the range from 30.56 to 52.71, suggesting that the remaining SNPs are strongly associated with ADHD.

MR Analysis

In the PGC, the genetically predicted ADHD has a higher risk of ASD (IVW: Odds ratio [OR] = 1.31, 95% Confidence interval [CI]: 1.14–1.52, $p = 0.0001$, Fig. 2). A similar trend was observed for the WME approach but with a wider CI (OR = 1.37, 95% CI: 1.15–1.64, $p = 0.0005$). The OR for the MR-Egger method was 1.05 (95% CI: 0.56–2.00; $p = 0.87$). The OR for the simple mode method was 1.43 (95% CI: 0.99–2.08, $p = 0.06$). The OR for the weighted mode method was 1.43 (95% CI: 0.96–2.13, $p = 0.08$). Scatter plot (Fig. 3) and forest plot (Fig. 4) were employed to generate a more intuitive and visual representation of the study result.

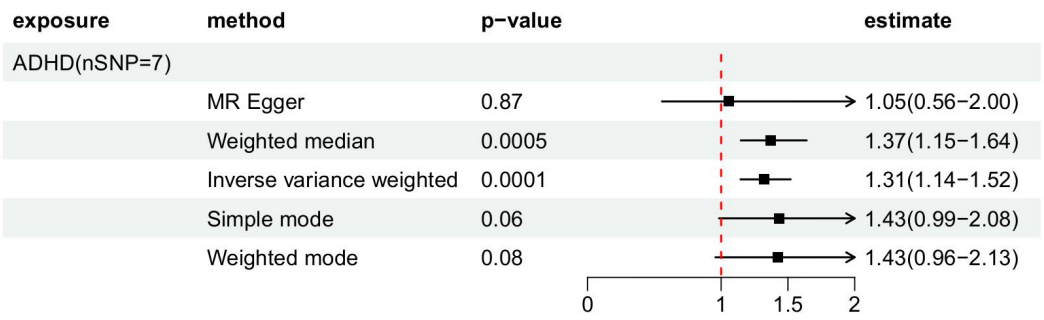

Fig. 2. Causal relationships between ADHD and ASD using MR. nSNP, Number of SNPs used in MR; OR, Odds radio; 95% CI, 95% Confidence interval; MR, Mendelian randomization.

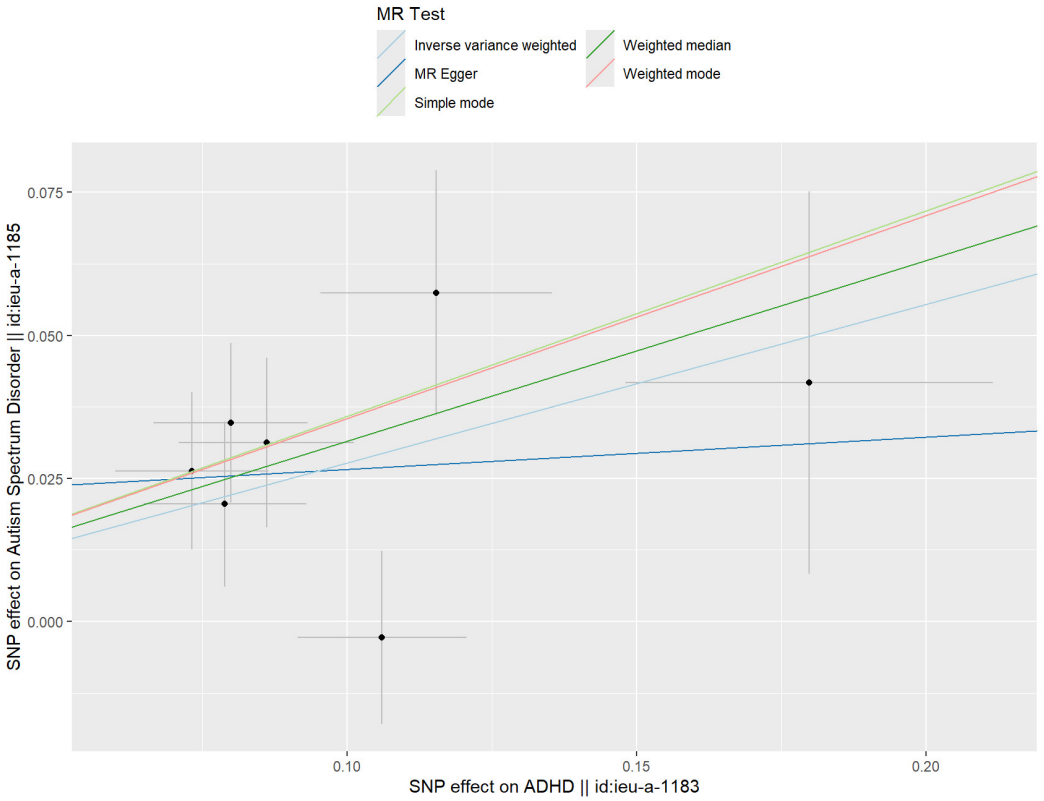

Fig. 3. Scatter plot for ADHD on ASD. The horizontal x-axis indicates the genetic instruments linked to the exposure data, while the vertical y-axis represents the genetic instruments associated with the outcome data. The instrumental variables employed in the MR analysis are indicated by black dots. ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder; SNP, Single nucleotide polymorphism.

Sensitivity Analysis

Among the 12 independent SNPs representing ADHD, there was one palindromic SNP (rs11591402). Setting the outlier screening conditions as NbDistribution = 10,000 and SignifThreshold = 0.05, MR-PRESSO identified four potential outliers (rs1222063, rs281324, rs4916723, rs9677504). As a result, a total of seven SNPs were included in the MR analysis. The Cochran's Q test yielded a *p*-value of 0.068 for the IVW method, which was >0.05, indicating no heterogeneity. The *p*-

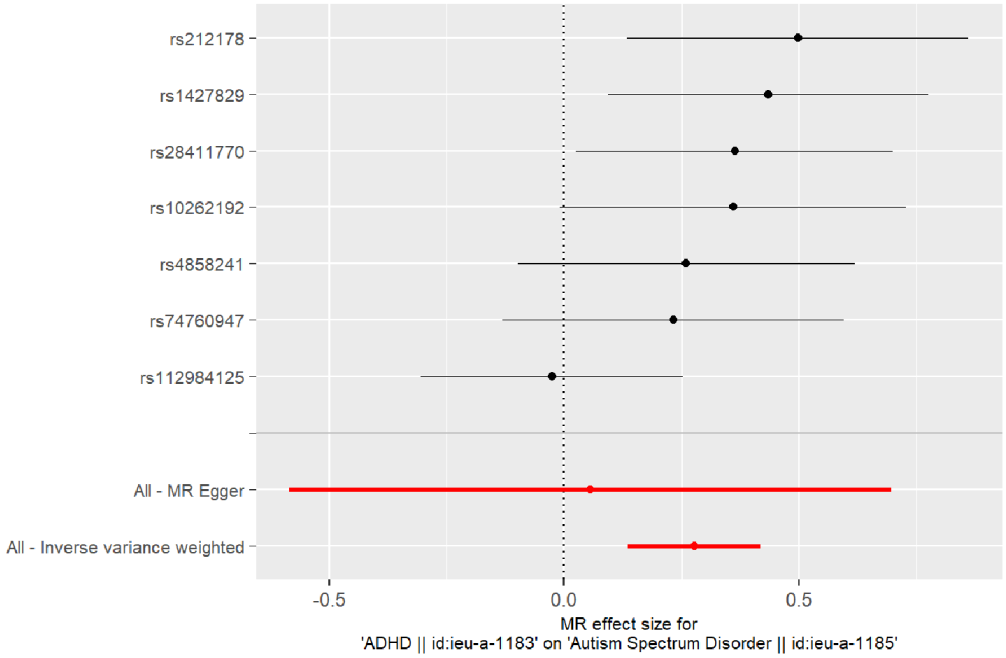

Fig. 4. Forest plot for ADHD on ASD. Each black dot represents a single SNP. ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder.

Table 2. The comparison results of *p*-values before and after Bonferroni correction.

	MR-Egger	Weighted median	Inverse variance weighted	Simple mode	Weighted mode
p-values	0.87	0.0005	0.0001	0.06	0.08
p-values of Bonferroni correction	4.35	0.0025	0.0005	0.28	0.38

value for pleiotropy was 0.94, suggesting no horizontal pleiotropy. The leave-one-out method was used to explore whether individual SNPs had a significant effect on the final results (Fig. 5). Although a deviated value can be observed in the funnel plot (Fig. 6), it was not recognized by MR-PRESSO. When considering the results of other sensitivity analyses, it is reasonable to hypothesize that this SNP has no significant influence on the results. Thus, the results of the MR analysis remain robust.

A Bonferroni correction was applied to the statistical analyses. Following correction, the results of both IVW and WME methods approach statistically significant *p*-values ($p = 0.0005$ and 0.0025, respectively), suggesting a strong positive association. The comparison of *p*-values before and after correction are shown in Table 2.

Discussion

In this study, we used MR to investigate the causal relationship between ADHD and ASD. Based on the genetic data from the IEU GWAS database, genetically tested patients with ADHD have a higher risk for ASD.

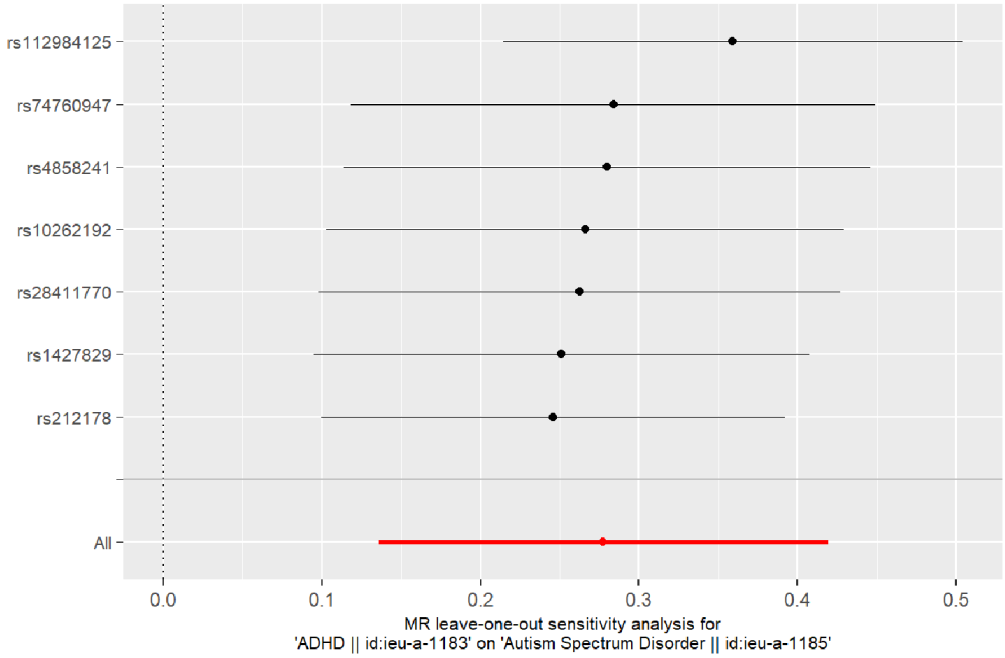

Fig. 5. Leave-one-out sensitivity analysis for ADHD on ASD. The fact that all SNPs, indicated by black dots, are positioned to the right of the '0' cutoff line suggests that there is no significant violation of the overall effect by any individual SNP. ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder; MR, Mendelian randomization; SNP, Single nucleotide polymorphism.

The function of MR differs from conventional studies, which mostly investigate the association of exposure variable with outcome variable and can hardly draw definitive conclusions because they are influenced by reverse, temporal, and confounding factors. By contrast, MR focuses on the genetic level and the selection of SNPs as the IVs to replace the exposure factors, thereby eliminating the effects of temporal and reverse factors on the results. Meanwhile, sensitivity analysis is also used in data processing to eliminate the effects of confounding factors on the results. The use of a publicly available GWAS dataset with a large sample size enables us to establish a causal relationship between ADHD (an exposure variable) and ASD (an outcome variable), and draw a definitive conclusion. In the MR analysis conducted in this study, the *p*-values of the three methods, namely the MR-Egger method, the Simple mode, and the Weighted mode, are all greater than 0.05. As a result, these methods cannot lend support to the conclusion. However, IVW is the main analytical method in MR, and the direction of the β-values of the five methods is the same; thus, the resulting causal relationship has a certain level of stability. At the same time, we performed data processing such as sensitivity analysis to eliminate the biases caused by the effects of confounding factors on ASD, and thus the stability of the results is verified once again.

At present, ASD remains one of the diseases that is difficult to treat. Its incidence rate has increased exponentially, with a greater incidence rate in males than in females, causing a considerable burden on many families (Maenner et al, 2023). The symptoms of ASD are diverse and often accompanied by poor develop-

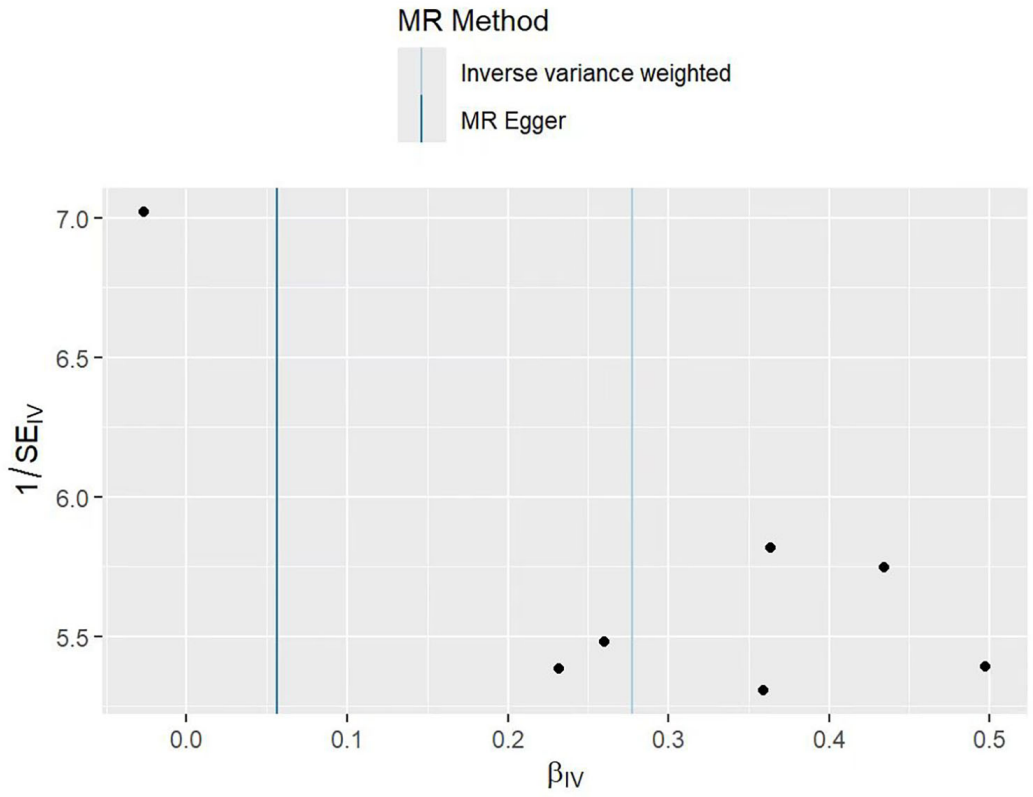

Fig. 6. Funnel plot for ADHD on ASD. Each black dot represents a single SNP. β, Effect estimate; SE, Standard error.

ment, cerebral palsy, ADHD, depression, epilepsy, and fragile X syndrome. Many types of treatment methods for ASD are available, including drug therapy, behavior modification, physical therapy, stem cell therapy, exercise therapy, and traditional Chinese medicine. However, most of these treatment methods are specific to individual phenotypes of ASD, but there is no effective treatment method that is unique to ASD. Benger et al (2018) discovered that ASD has a genetic basis and may be reversible after birth, paving way for the enhanced research focusing on the genetics and raising hope that ASD can be cured one day. There are also case reports that the autism symptoms of fraternal twins were reversed through modifications of personal lifestyle and environment (D'Adamo et al, 2024). In addition, the combination of induced pluripotent stem cells and CRISPR/Cas9 technology has made it possible to construct the cell models of ASD (Sandhu et al, 2023).

ADHD has a close etiological association with ASD. Similar to ASD, the incidence rate of ADHD is also experiencing an increasing trend, with a greater incidence rate in males than in females. ADHD often develops in childhood and is characterized by over-impulsivity, difficulty concentrating, impaired learning abilities, and difficulty fitting into groups. It has been reported that 60% of the adult patients with ADHD suffer from multiple psychiatric disorders concurrently, with affective disorders being a common comorbidity (Salvi et al, 2021). The growing trend of the prevalence of ADHD in adults has attracted global attention because of their over-impulsivity, mental illnesses, difficulty integrating into society, sub-

stance abuse, and antisocial personalities. Given that the unknown pathogenesis of ADHD, there is currently no uniquely tailored, effective treatment method for ADHD; therefore, a common treatment regimen for this disorder includes drugs to increase their attention span and control behaviors.

The findings of this study underscore the importance of controlling the progression of ADHD. While ADHD may ameliorate with age, its co-occurrence with ASD presents a more challenging scenario for treatment. Patients diagnosed with both ASD and ADHD exhibit significantly more severe symptoms of autism compared to those with ASD alone, particularly evident in the domain of social interaction as assessed by the Social Responsiveness Scale and Autism Diagnostic Interview (Kalin, 2024; Lebeña et al, 2023). The study revealed that the improvement in ADHD symptomatology showed positive correlation with improvement in ASD-specific interventions as reflected by change in severity scores (Velarde and Cárdenas, 2022). Other studies concluded that in school-age children with ASD, a higher level of ADHD severity rather than ASD severity is associated with a higher prevalence of comorbid psychiatric symptomatology (Krakowski et al, 2022; Mansour et al, 2017). In clinical practice, the overlap of symptom between ADHD and ASD often poses diagnostic difficulties; therefore, the findings of this study are of profound significance for enhancing diagnostic accuracy. By identifying specific genetic markers or biomarkers, physicians can more precisely distinguish these two disorders, especially in the early stages, thereby providing more targeted intervention measures for patients. Besides, the discoveries of this research will have a crucial impact on public health policies. Incorporating the screening of ADHD and ASD into early childhood development programs can help with earlier identification and support provision for children in need. Additionally, this information can be employed for educating and training medical professionals to improve their understanding and diagnostic capabilities regarding these two diseases. This study identifies ADHD as a risk factor for ASD, highlighting the need for clinicians to meticulously assess whether individuals with ADHD also present symptoms indicative of ASD during diagnosis and treatment. Consideration should be given to potential comorbidity or developmental trends towards comorbidity between ADHD and ASD, enabling early and accurate diagnosis as well as improvement of treatment strategies aimed at managing disease progression.

Regarding treatment, since the specific pathogenesis of ADHD and ASD remains unclear, there are currently no specific therapeutic drugs. Nevertheless, more effective treatment approaches are continuously being updated and developed. Research indicates that pro-inflammatory cytokines and oxidative stress biomarkers may be elevated in both ASD and ADHD (Barron et al, 2021). Hence, vitamin therapy has been recommended to treat and prevent ASD and ADHD to varying extents (Poudineh et al, 2023). Transcranial direct current stimulation (tDCS) can be employed to treat major neurodevelopmental disorders including ADHD and ASD. A clinical randomized controlled trial revealed that in ADHD, stimulating the prefrontal anode tDCS was more efficacious than the right inferior frontal gyrus, whereas in ASD, prefrontal anode tDCS could effectively ameliorate behavioral problems (Salehinejad et al, 2022). In recent years, with the continuous in-depth

research on the microbiota-gut-brain axis, it has been discovered that intestinal microbiome dysregulation may be a trigger for neurodegenerative and neurodevelopmental diseases (Góralczyk-Bińkowska et al, 2022). Accordingly, corresponding treatment methods are proposed: treating mental disorders by using psychobiotics that have a positive impact on neural function, and regulating intestinal microbiome through fecal microbiota transplantation to treat ASD and ADHD (Kwak et al, 2023).

In light of the aforementioned research and the discoveries of this study, we hypothesize that certain treatment drugs and methods currently employed for ADHD may potentially ameliorate the symptoms of ASD and could be tentatively applied in the treatment of ASD. In line with this hypothesis, future studies may consider an in-depth exploration of the potentially common pathogenic mechanism between ADHD and ASD, which may present new therapeutic targets. Targeted drugs can be developed for this specific target. Simultaneously, a series of clinical efficacy trials could be initiated to address the issue where current medications might possess a relatively narrow therapeutic scope. For instance, a single drug may only be capable of managing one particular symptom of a disease. Moreover, scientists can concentrate their research efforts on minimizing the side effects of drugs. This can further enhance the overall performance of patients with only ADHD or ASD as well as those with comorbidities, making it possible to treat ASD symptoms. This idea may significantly enrich the intervention and treatment plans for ASD.

A study of ADHD in relation to ASD, schizophrenia, and four other psychiatric disorders found causal associations between ADHD and ASD, and a positive causal effect between ADHD and schizophrenia (Guo et al, 2024). Although our MR-Egger results were not statistically significant, the findings of this study further support our research outcomes. However, unlike previous studies, we specifically explored the causal relationship between ADHD and ASD, not only revealing its clinical significance but also discussing the potential underlying mechanisms of comorbidity. This suggests that there may be potential drug targets within this comorbidity mechanism, providing a new direction for subsequent research.

The findings of our study should be interpreted in light of certain limitations that could potentially affect the validity of the results. A key consideration is the sample selection bias, which may arise from the recruitment process, resulting in the selection of sample that may not be fully representative of the broader population. Additionally, while we have made every effort to adjust for known confounding variables, the possibility of unmeasured confounders remains, which could influence the observed associations. Furthermore, the geographical limitations of our sample, which are inherently tied to the regions from which participants were drawn, may further restrict the generalizability of our findings to other settings or populations. These limitations underscore the need for future research to address these issues through more inclusive sampling strategies and the incorporation of a wider range of potential confounding factors in the analysis.

Conclusion

Our analysis of the pooled data on ADHD and ASD from the IEU GWAS database demonstrate a significant association between ADHD and ASD in the European population, thereby identifying ADHD as a risk factor for ASD.

Key Points

- This study provides compelling evidence for the causal relationship between ADHD and ASD through Mendelian randomization, which is of significant importance for understanding the comorbidity mechanisms of these two neurodevelopmental disorders.
- This study reveals the association between specific genetic variants and ADHD and ASD, providing clues for understanding the biological connections between the two disorders.
- The findings of this study emphasize the importance of early screening and intervention for children with ADHD to reduce the risk of ASD.
- The results of this study provide a theoretical basis for future exploration of the genetic and environmental interactions between ADHD and ASD.

Abbreviations

ASD, Autism spectrum disorder; ADHD, Attention-deficit hyperactivity disorder; IVs, instrumental variables; SNPs, Single nucleotide polymorphisms; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier test; OR, Odds ratio; IVW, Inverse-variance weighted; CI, Confidence interval; WME, Weighted median estimator; GABA, Gamma-aminobutyric acid; MR, Mendelian randomization; tDCS, Transcranial direct current stimulation.

Availability of Data and Materials

The datasets generated and analysed during the current study are available in the [IEU GWAS] repository [https://gwas.mrcieu.ac.uk/datasets/].

Author Contributions

JJL, QF and YL designed the research study. Under the guidance of JJL, QF and YL, ZJ and JTL performed the study and meanwhile analysed and drafted the manuscript. GL, SZ and ZJ participated in data extraction and analysis results. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

Ahlqvist VH, Sjöqvist H, Dalman C, Karlsson H, Stephansson O, Johansson S, et al. Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability. JAMA. 2024; 331: 1205–1214. https://doi.org/10.1001/jama.2024.3172

Antshel KM, Russo N. Autism Spectrum Disorders and ADHD: Overlapping Phenomenology, Diagnostic Issues, and Treatment Considerations. Current Psychiatry Reports. 2019; 21: 34. https://doi.org/10.1007/s11920-019-1020-5

Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. Molecular Autism. 2017; 8: 21. https://doi.org/10.1186/s13229-017-0137-9

Barron A, McCarthy CM, O'Keeffe GW. Preeclampsia and Neurodevelopmental Outcomes: Potential Pathogenic Roles for Inflammation and Oxidative Stress? Molecular Neurobiology. 2021; 58: 2734–2756. https://doi.org/10.1007/s12035-021-02290-4

Benger M, Kinali M, Mazarakis ND. Autism spectrum disorder: prospects for treatment using gene therapy. Molecular Autism. 2018; 9: 39. https://doi.org/10.1186/s13229-018-0222-8

D'Adamo CR, Nelson JL, Miller SN, Rickert Hong M, Lambert E, Tallman Ruhm H. Reversal of Autism Symptoms among Dizygotic Twins through a Personalized Lifestyle and Environmental Modification Approach: A Case Report and Review of the Literature. Journal of Personalized Medicine. 2024; 14: 641. https://doi.org/10.3390/jpm14060641

Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nature Genetics. 2019; 51: 63–75. https://doi.org/10.1038/s41588-018-0269-7

Doi M, Usui N, Shimada S. Prenatal Environment and Neurodevelopmental Disorders. Frontiers in Endocrinology. 2022; 13: 860110. https://doi.org/10.3389/fendo.2022.860110

Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E. The Microbiota-Gut-Brain Axis in Psychiatric Disorders. International Journal of Molecular Sciences. 2022; 23: 11245. https://doi.org/10.3390/ijms231911245

Granadillo JL, P A Stegmann A, Guo H, Xia K, Angle B, Bontempo K, et al. Pathogenic variants in *TNRC6B* cause a genetic disorder characterised by developmental delay/intellectual disability and a spectrum of neurobehavioural phenotypes including autism and ADHD. Journal of Medical Genetics. 2020; 57: 717–724. https://doi.org/10.1136/jmedgenet-2019-106470

Guo Y, Li J, Hu R, Luo H, Zhang Z, Tan J, et al. Associations between ADHD and risk of six psychiatric disorders: a Mendelian randomization study. BMC Psychiatry. 2024; 24: 99. https://doi.org/10.1186/s12888-024-05548-y

Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nature Reviews. Neurology. 2021; 17: 564–579. https://doi.org/10.1038/s41582-021-00530-8

Hooi SL, Dwiyanto J, Rasiti H, Toh KY, Wong RKM, Lee JWJ. A case report of improvement on ADHD symptoms after fecal microbiota transplantation with gut microbiome profiling pre- and post-procedure. Current Medical Research and Opinion. 2022; 38: 1977–1982. https://doi.org/10.1080/03007995.2022.2129232

Hughes HK, R J Moreno, Ashwood P. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). Brain, Behavior, and Immunity. 2023; 108: 245–254. https://doi.org/10.1016/j.bbi.2022.12.001

Jourdon A, Wu F, Mariani J, Capauto D, Norton S, Tomasini L, et al. Modeling idiopathic autism in forebrain organoids reveals an imbalance of excitatory cortical neuron subtypes during early neurogenesis [published correction appears in Nature Neuroscience. 2023; 26: 2035. https://doi.org/10.1038/s41593-023-01447-9]. Nature Neuroscience. 2023; 26: 1505–1515. https://doi.org/10.1038/s41593-023-01399-0

Kalin NH. Advances in Understanding Schizophrenia, ADHD, and ASD. The American Journal of Psychiatry. 2024; 181: 461–464. https://doi.org/10.1176/appi.ajp.20240325

Kian N, Samieefar N, Rezaei N. Prenatal risk factors and genetic causes of ADHD in children. World Journal of Pediatrics. 2022; 18: 308–319. https://doi.org/10.1007/s12519-022-00524-6

Krakowski AD, Cost KT, Szatmari P, Anagnostou E, Crosbie J, Schachar R, et al. Characterizing the ASD-ADHD phenotype: measurement structure and invariance in a clinical sample. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2022; 63: 1534–1543. https://doi.org/10.1111/jcpp.13609

Kwak MJ, Kim SH, Kim HH, Tanpure R, Kim JI, Jeon BH, et al. Psychobiotics and fecal microbial transplantation for autism and attention-deficit/hyperactivity disorder: microbiome modulation and therapeutic mechanisms. Frontiers in Cellular and Infection Microbiology. 2023; 13: 1238005. https://doi.org/10.3389/fcimb.2023.1238005

Kwon CS, Wirrell EC, Jetté N. Autism Spectrum Disorder and Epilepsy. Neurologic Clinics. 2022; 40: 831–847. https://doi.org/10.1016/j.ncl.2022.03.011

Lebeña A, Faresjö Å, Faresjö T, Ludvigsson J. Clinical implications of ADHD, ASD, and their co-occurrence in early adulthood-the prospective ABIS-study. BMC Psychiatry. 2023; 23: 851. https://doi.org/10.1186/s12888-023-05298-3

Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018; 392: 508–520. https://doi.org/10.1016/S0140-6736(18)31129-2

Lord C, Risi S, Lambrecht L, Cook EH, Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders. 2000; 30: 205–223.

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders. 1994; 24: 659–685. https://doi.org/10.1007/BF02172145

Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. MMWR. Surveillance Summaries. 2023; 72: 1–14. https://doi.org/10.15585/mmwr.ss7202a1

Mansour R, Dovi AT, Lane DM, Loveland KA, Pearson DA. ADHD severity as it relates to comorbid psychiatric symptomatology in children with Autism Spectrum Disorders (ASD). Research in Developmental Disabilities. 2017; 60: 52–64. https://doi.org/10.1016/j.ridd.2016.11.009

Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Molecular Autism. 2017; 8: 13. https://doi.org/10.1186/s13229-017-0121-4

Paulsen B, Velasco S, Kedaigle AJ, Pigoni M, Quadrato G, Deo AJ, et al. Autism genes converge on asynchronous development of shared neuron classes. Nature. 2022; 602: 268–273. https://doi.org/10.1038/s41586-021-04358-6

Poudineh M, Parvin S, Omidali M, Nikzad F, Mohammadyari F, Sadeghi Poor Ranjbar F, et al. The Effects of Vitamin Therapy on ASD and ADHD: A Narrative Review. CNS & Neurological Disorders Drug Targets. 2023; 22: 711–735. https://doi.org/10.2174/1871527321666220517205813

Rodolaki K, Pergialiotis V, Iakovidou N, Boutsikou T, Iliodromiti Z, Kanaka-Gantenbein C. The impact of maternal diabetes on the future health and neurodevelopment of the offspring: a review of the evidence. Frontiers in Endocrinology. 2023; 14: 1125628. https://doi.org/10.3389/fendo.2023.1125628

Salehinejad MA, Ghanavati E, Glinski B, Hallajian AH, Azarkolah A. A systematic review of randomized controlled trials on efficacy and safety of transcranial direct current stimulation in major neurodevelopmental disorders: ADHD, autism, and dyslexia. Brain and Behavior. 2022; 12: e2724. https://doi.org/10.1002/brb3.2724

Salvi V, Ribuoli E, Servasi M, Orsolini L, Volpe U. ADHD and Bipolar Disorder in Adulthood: Clinical and Treatment Implications. Medicina. 2021; 57: 466. https://doi.org/10.3390/medicina57050466

Salmerón-Medina M, Tàpia-Córcoles A, Palou-Artola E, Nicolau-Palou R, Calvo-Escalona R. Análisis del impacto de la COVID-19 en menores de edad con trastorno del espectro autista [Analysis of the impact of COVID-19 on youngsters with autistic spectrum disorder]. Revista de Neurologia. 2022; 74: 181–188. (In Spanish) https://doi.org/10.33588/rn.7406.2021291.

Sandhu A, Kumar A, Rawat K, Gautam V, Sharma A, Saha L. Modernising autism spectrum disorder model engineering and treatment *via* CRISPR-Cas9: A gene reprogramming approach. World Journal of Clinical Cases. 2023; 11: 3114–3127. https://doi.org/10.12998/wjcc.v11.i14.3114

Skogheim TS, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, et al. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environment International. 2021; 152: 106468. https://doi.org/10.1016/j.envint.2021.106468

Song IG. Neurodevelopmental outcomes of preterm infants. Clinical and Experimental Pediatrics. 2023; 66: 281–287. https://doi.org/10.3345/cep.2022.00822

Taniya MA, Chung HJ, Al Mamun A, Alam S, Aziz MA, Emon NU, et al. Role of Gut Microbiome in Autism Spectrum Disorder and Its Therapeutic Regulation. Frontiers in Cellular and Infection Microbiology. 2022; 12: 915701. https://doi.org/10.3389/fcimb.2022.915701

Usui N, Kobayashi H, Shimada S. Neuroinflammation and Oxidative Stress in the Pathogenesis of Autism Spectrum Disorder. International Journal of Molecular Sciences. 2023; 24: 5487. https://doi.org/10.3390/ijms24065487

Velarde M, Cárdenas A. Autism spectrum disorder and attention-deficit/hyperactivity disorder: challenge in diagnosis and treatment. Medicina. 2022; 82: 67–70.

Wang L, Wang B, Wu C, Wang J, Sun M. Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. International Journal of Molecular Sciences. 2023; 24: 1819. https://doi.org/10.3390/ijms24031819

Wang Z, Ding R, Wang J. The Association between Vitamin D Status and Autism Spectrum Disorder (ASD): A Systematic Review and Meta-Analysis. Nutrients. 2020; 13: 86. https://doi.org/10.3390/nu13010086

Wong ICK. Relative age and persistence of ADHD diagnosis in young children. The Lancet. Psychiatry. 2023; 10: 910–911. https://doi.org/10.1016/S2215-0366(23)00334-6

Zhen Lim TX, Pickering TA, Lee RH, Hauptman I, Wilson ML. Hypertensive disorders of pregnancy and occurrence of ADHD, ASD, and epilepsy in the child: A meta-analysis. Pregnancy Hypertension. 2023; 33: 22–29. https://doi.org/10.1016/j.preghy.2023.06.002