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ADHD and anxiety: causality sequences through a biopsychosocial model

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ADHD and anxiety: causality sequences through a biopsychosocial model

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Editorial: ADHD and anxiety: causality sequences through a biopsychosocial model

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KEYWORDS

ADHD, anxiety, comorbidity, biopsychosocial model, Mendelian randomization

Editorial on the Research Topic
ADHD and anxiety: causality sequences through a biopsychosocial model

Background and aims

ADHD and anxiety frequently co-occur, yet the directionality and mechanisms of their relationship remain debated. The biopsychosocial model posits that genetic predispositions, neurobiological processes, cognitive traits, and environmental contexts jointly shape psychopathology. Our Topic asked whether ADHD symptomatology drives anxiety (or vice versa) or if shared heritable risks underlie both? We encouraged work using longitudinal data, causal inference (e.g., Mendelian randomization), neuropsychological testing, preclinical models, and epidemiology to dissect these sequences.

Cognitive and neuropsychological mechanisms

Working memory and inhibitory control deficits

Kofler et al. experimentally compared competing models of working memory and inhibitory control in children with ADHD, finding that deficits in both "hot" and "cool" executive functions contribute to attentional lapses and anxiety symptoms (*Working memory and inhibitory control deficits in children with ADHD*).

Anxiety's impact on working memory

Marsh et al. assessed clinically evaluated children both with and without ADHD, showing that comorbid anxiety selectively impairs visuospatial working memory more than verbal spans and suggesting that anxiety amplifies ADHD's cognitive burden (*Associations between Anxiety and Working Memory Components in Clinically Evaluated Children With and Without ADHD*).

Developmental coordination & motor delay

Lee et al. linked developmental coordination disorder symptoms to distinct neuropsychological profiles in ADHD versus non-ADHD children, indicating that motor delays may mediate anxiety via frustrated self-efficacy (*The association between symptoms of developmental coordination disorder and neuropsychological characteristics in children with and without ADHD*).

Preschool motor development

Cui et al. reported that early motor development delays forecast later ADHD symptom severity and anxiety traits, underscoring early neurodevelopment as a shared vulnerability window (*Association between reported ADHD symptom and motor development delay in preschool children*).

Biological and preclinical pathways

Fatty acids and ADHD risks

In a Mendelian randomization framework, Zhou et al. identified plasma fatty acid profiles causally linked to ADHD risk, implicating lipid-metabolism pathways that may also influence anxiety via neuroinflammation (*Plasma fatty acids and attention deficit hyperactivity disorder: a Mendelian randomization investigation*).

Genetic & socioeconomic interplay

Deng et al. combined genetic instruments (GWAS data) with socioeconomic indicators to show that both inherited variants and environmental deprivation jointly influence risk for ADHD and anxiety, highlighting gene–environment correlation rather than pure causality (*Exploring the genetic and socioeconomic interplay between ADHD and anxiety disorders using Mendelian randomization*).

Gene-level oncology links

Lian et al. unexpectedly uncovered gene-level connections between ADHD, anxiety disorders, and head-and-neck cancer, suggesting that pleiotropic genetic loci may underlie neurodevelopmental and somatic risks (*Gene-level connections between anxiety disorders, ADHD, and head and neck cancer*).

Environmental enrichment in animal models

Wang et al. demonstrated that enriching the environments of neonatal rats reversed ethanol-induced attention deficits and anxiety behaviors, providing a translational model of how early interventions may reset ADHD–anxiety trajectories (*Environmental enrichment reverses prenatal ethanol exposure-induced attention-deficits in rats*).

Conceptual and epidemiological perspectives

Conceptual analysis of stress and anxiety

Bob and Privara reviewed neurodevelopmental disorganization processes that create vulnerability to both ADHD and anxiety, arguing for hierarchical brain-organization models to guide future treatment strategies (*ADHD, stress, and anxiety*).

Nationwide comorbidities in Japan

Okada et al. used population-based registries to document the high prevalence of anxiety and other psychiatric comorbidities among individuals diagnosed with ADHD, underscoring that shared healthcare pathways may facilitate integrated care (*Psychiatric comorbidities of attention deficit/hyperactivity disorder in Japan: a nationwide population-based study*).

Synthesis and future directions

Together, these studies support a multifactorial causality model in which shared genetic risks, early neurodevelopmental disruptions, executive-function deficits, and environmental contexts converge to produce overlapping ADHD and anxiety phenotypes. Mendelian randomization work (Deng et al.; Zhou et al.) bolsters the role of causal lipid and socioeconomic pathways, while preclinical enrichment models (Wang et al.) chart intervention possibilities. Cognitive investigations (Kofler et al.; Marsh et al.) clarify how anxiety amplifies core ADHD deficits, and epidemiology (Okada et al.) highlights public-health implications.

Future research should integrate longitudinal cohorts with multi-omics and digital phenotyping to map individual trajectories from infancy through adulthood. Intervention trials combining cognitive training, nutritional supplementation, and environmental enrichment merit testing. Finally, neuroimaging studies probing hierarchical brain network organization (as suggested by Bob and Privara) could illuminate shared circuit-level mechanisms.

Conclusion

This Research Topic advances our understanding of ADHD–anxiety comorbidity by integrating genetic, neurobiological, cognitive, and environmental perspectives. By unraveling complex causality sequences, these contributions pave the way for precision interventions that address both disorders simultaneously, ultimately improving outcomes for individuals across their lifespan.

Author contributions

HC: Conceptualization, Data curation, Resources, Supervision, Writing – original draft, Writing – review & editing. ST: Investigation, Supervision, Writing – original draft, Writing – review & editing. SL: Investigation, Supervision, Writing – original draft, Writing – review & editing.

Conflict of interest

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Plasma fatty acids and attention deficit hyperactivity disorder: a Mendelian randomization investigation

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Background: Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood, and pathogenesis is not fully understood. Observational studies suggest an association between fatty acids abnormalities and ADHD, but there are contradictions and differences between these findings. To address this uncertainty, we employed a two-sample bidirectional Mendelian Randomization (MR) analysis to investigate the causal relationship between fatty acids and ADHD.

Methods: We conducted a two-sample Mendelian Randomization (MR) study, selecting single nucleotide polymorphisms (SNPs) highly correlated with fatty acid levels from the CHARGE Consortium as our instruments. The outcome data were sourced from the Psychiatric Genomics Consortium (PGC) dataset on ADHD, comprising 225,534 individuals, with 162,384 cases and 65,693 controls. Inverse variance weighting, MR-Egger, and weighted median methods were employed to estimate the causal relationship between fatty acids and ADHD. Cochran's Q-test was used to quantify heterogeneity of instrumental variables. Sensitivity analyses included MR-Egger intercept tests, leave-one-out analyses, and funnel plots.

Results: The MR analysis revealed no significant associations between genetically predicted levels of various saturated, monounsaturated, and polyunsaturated fatty acids (including omega-3 and omega-6) and ADHD risk in the CHARGE and PGC cohorts. Notably, an initial association with Dihomo-gamma-linolenic acid (DGLA) (OR = 1.009, p = 0.032 by IVW) did not persist after correction for multiple testing (adjusted p-value = 0.286). Sensitivity analysis supported our findings, indicating robustness. Moreover, there was a lack of evidence supporting a causal link from ADHD to fatty acids.

Conclusion: While our study on the basis of genetic data does not provide evidence to support the causal role of fatty acids in ADHD, it does not preclude their potential involvement in reducing the risk of ADHD. Further research is needed to explore this possibility.

KEYWORDS

fatty acids, n-3 PUFAs, ADHD, causality, Mendelian randomization

1 Introduction

Attention deficit hyperactivity disorder (ADHD) is a life span disorder, and recognized as the most common neurodevelopmental disorder of childhood (1). Only a small proportion (15%) of individuals with ADHD achieve complete remission during their early adulthood (2, 3). It is marked by age-inappropriate levels of inattention, hyperactivity, and impulsivity, and it can lead to long term social, academic, and mental health issues (4, 5). According to a systematic review and meta-analysis study, the global incidence of ADHD is 7.6% in children aged 3 to 12 years and 5.6% in teenagers aged 12 to 18 (6). The fifth edition (DSM-5) of the Diagnostic and Statistical Manual of Mental Disorders released by the American Psychological Association provided a definition of ADHD as a consistent pattern of inattention and/or hyperactivity- impulsivity that hinders both development and functioning (7, 8). It is often comorbid with various psychological/mental disorders, such as oppositional defiant disorder (ODD), conduct disorder (CD), anxiety/depression disorder, learning disabilities (LD), and tic disorders (TD) among others (9–11).

Fatty acids are the major metabolic products of lipid metabolism (12). They are divided into three categories based on the number of carbon-carbon double bonds: saturated fatty acids, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs). Trans fatty acids (TFAs) are a general term of unsaturated fatty acids containing 1 or more trans nonconjugated double bond structure. There are two sources of TFAs: natural source and industrial source. Natural source means that trans fatty acids are present in meat or dairy products of ruminants, as some trans fatty acids are produced during the fermentation process (is a process of biological hydrogenation) in the rumen of ruminants. Industrial source means that trans fatty acids are present in margarine, cocoa butter substitutes, hydrogenated cream, and fried foods, as these trans fatty acids are produced through pathways such as partial hydrogenation of vegetable oils and high-temperature frying (13).

It is universally known that fatty acids composition and metabolism can be altered during diseases, leading to beneficial (14, 15) or adverse effects (16, 17). It has earlier been considered that altered fatty acids composition may be related to ADHD (18, 19). Observational studies found that PUFAs may be pertinent to the development of mental disorders, such as ADHD (20), autism spectrum disorder (ASD) (21), anxiety disorders (15) and Alzheimer's disease (22). There is also research pointing a possible link between trans fatty acids and ADHD, where children with ADHD have higher levels of trans fatty acids than those without ADHD (23). Some meta-analyses indicate that children and adults with ADHD have elevated ratios of blood omega-6 to omega-3, indicating a disruption in fatty acid metabolism (14).However, the causal relationship between fatty acid abnormalities and the onset of ADHD remains unclear because of the common methodological problems in observation studies, such as residual confounding, reverse causality and misclassification (24, 25). For example, although there are a few observational studies suggesting the presence of fatty acid imbalances in children with ADHD (12, 19, 20, 23), yet conflicting observations regarding fatty acid imbalances in ADHD have been found in different studies. The contradictory result may be caused by residual confounding or reverse causality (26).

Mendelian randomization (MR) is a method that uses genetic variation as instrumental variables (IVs) to examine causal effects (24). Genetic variants are not easily influenced by confounding factors because it randomly assembled at the time of conception (25, 27), and the onset and progression of the disease do not alter the genetic variants. Therefore, MR minimizes biases from residual confounding and reverse causality in observational studies, thereby strengthening the causal inference of exposure-outcome associations (24, 28).

Several Mendelian randomization (MR) studies have investigated the complex relationships between fatty acids and other mental disorders. Some MR studies have revealed that long-chain omega-3 and omega-6 fatty acid levels are associated with a lower risk of schizophrenia (29, 30), while short-chain fatty acids are linked to an increased risk (30). One study has found genetically predicted increases in omega-3 levels were associated with a higher risk of epilepsy (31). Additionally, research on depression identified protective effects of adrenic acid and eicosapentaenoic acid (EPA), while oleic acid (OA) and alpha-linolenic acid (ALA) may be potential risk factors (32). Interestingly, a metabolome-wide MR study identifies dysregulated arachidonic acid synthesis as a potential causal risk factor for bipolar disorder (33). These findings underscore the multifaceted role of various fatty acids in mental disorder.

Given the complex associations and comorbidities among mental disorders (34), along with the shared common risk factors and genetic bases (35), further investigation into the association between fatty acids and ADHD is warranted. Understanding this relationship could provide valuable insights into the prevention and management of ADHD. MR can provide stronger evidence for the causal inference between fatty acids and ADHD. In this study, we applied a two-sample bidirectional MR design to further verify whether fatty acids abnormalities are associated with an increased risk of ADHD.

2 Materials and methods

2.1 Study design

In this study, we performed a two-sample Mendelian randomization analyses using summary statistics from a genome-wide association study (GWAS) to investigate whether fatty acids would have a causal effect on ADHD. Genetic variants were used as instrument variables (IVs) to evaluate the causal effect of the exposure (fatty acids) on the outcome (ADHD). The validity of MR design hinges on three important assumptions that serve as the criteria for screening IVs (24, 28). Assumption 1: IVs are strongly associated with the exposure factors (fatty acids). Assumption 2: There is no correlation between IVs and any potential confounding factors. In short, IVs should be dependent of confounding factors. Assumption 3: IVs can affect outcomes only through exposure factors, not themselves or confounding factors. The study design of our experiment is shown in Figure 1.

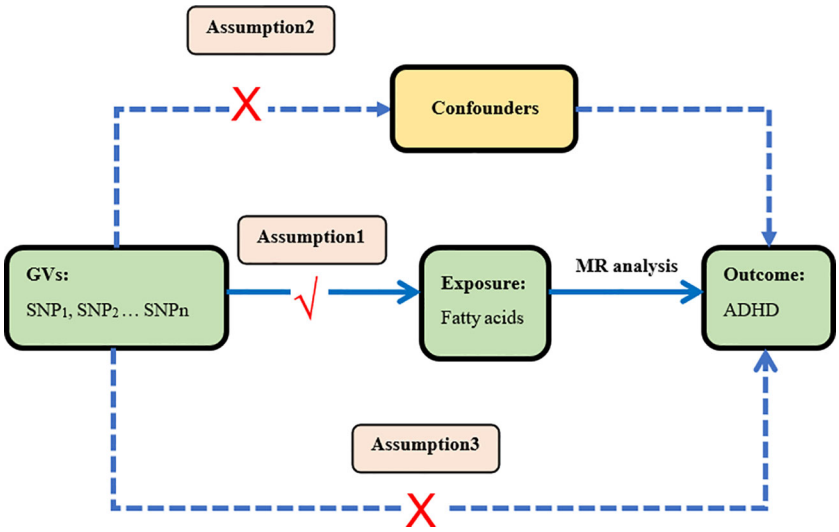

FIGURE 1
Study design This is the causal directed acyclic graph of MR design. The MR design assumptions are that the genetic variants are associated with fatty acids, but not with confounders, and the genetic variants are associated with the risk of ADHD only through fatty acids.

2.2 Data source

2.2.1 GWAS data of fatty acids (exposure)

We selected single nucleotide polymorphisms (SNPs) from fatty acid-related datasets to serve as IVs. The GWAS data on fatty acids were derived from three large-scale meta-analyses involving individuals of European ancestry, conducted by the Cohort for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium [n = 8916 individuals for saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs), n = 8631 individuals for n-6 polyunsaturated fatty acids (PUFAs), and n=8866 individuals for n-3 PUFAs] (29–31). These data included two SFAs, palmitic acid (16:0) and stearic acid (18:0); two MUFAs, palmitoleic acid (16:1n7) and oleic acid (18:1n9) (36); four omega-3 PUFAs, alpha-linolenic acid (ALA) (18:3n3), eicosapentaenoic acid (EPA)(20:5n3), docosapentaenoic acid (DPA)(22:5n3), and docosahexaenoic acid (DHA)(22:6n3) (37); and three omega-6 PUFAs, adrenic acid (AdrA)(22:4n6), gamma-linolenic acid (GLA)(18:3n6), and dihomo-gamma-linolenic acid (DGLA) (20:3n6) (38).

2.2.2 GWAS data of ADHD (outcome)

Data sources for attention-deficit/hyperactivity disorder (ADHD) were obtained from a genome-wide association study (GWAS) meta-analysis of 38,691 individuals with ADHD and 186,843 controls, published by the Psychiatric Genomics Consortium (PGC) (39). These data were combined from the extended Danish Integrative Psychiatric Research (iPSYCH) cohort (25,895 cases; 37,148 controls), the Icelandic deCODE cohort (8,281 cases; 137,993 controls) and 10 European cohorts aggregated by the PGC (4,515 cases; 11,702 controls). The iPSYCH cases were diagnosed with ADHD based on the ICD10 diagnosis codes (F90.0, F90.1, F90.8) and were identified in the Danish Psychiatric Central Research Register and the National Patient Register. The deCODE cases were clinically diagnosed with ADHD according to the ICD10 criteria (ICD10-F90, F90.1, F98.8) or were prescribed medication specific for/to ADHD symptoms. The iPSYCH and deCODE controls were individuals without ADHD. The PGC cases were derived from10 PGC cohorts with European ancestry as a part of a previous GWAS meta-analysis of ADHD. All participants who donated samples provide informed consent. The study identified 27 genome-wide significant loci. The data sources and sample information used in our study are detailed in Table 1.

2.3 Selection of instrumental variables

Figure 2 illustrates the research workflow. We initially selected instrumental variables (IV) from the 11 exposures, requiring single-nucleotide polymorphisms (SNPs) with genome-wide significant associations with exposure $p < 5\times10^{-8}$. However, for all 9 exposures except n-6 PUFA DGLA and n-6 PUFA GLA, only 1-4 SNPs meet this criterion. To ensure a sufficient number of IVs for sensitivity analyses and potentially identify more causal association, the threshold for these 9 exposures was loosened to a threshold of 5×10^{-5}.[18].

Secondly, we eliminated linkage disequilibrium among the screened SNPs by applying thresholds of r2 < 0.001 and kb > 10,000, resulting in independent IVs free from linkage disequilibrium. Subsequently, we utilized the online database PhenoScannerV2 (http://www.phenoscanner.medschl.cam.ac.uk/) to identify potentially related phenotypes. SNPs associated with ADHD outcomes and confounding factors were then filtered out using criteria of r2 ≥ 0.8, none proxies and p-value < 0.001. In the context of the relationship between fatty acids and ADHD, factors

TABLE 1 Information on genetic instruments and outcome source.

Category	Trait	Participant	Population	Consortium
Exposures	SFA	8,916	European	CHARGE
	MUFA	8,916	European	CHARGE
	Omega-3 PUFA	8,866	European	CHARGE
	Omega-6 PUFA	8,631	European	CHARGE
Outcome	ADHD	225,534 (38691 cases and 186,843 controls)	European	PGC

such as genetics, brain structure and function, premature birth and low birth weight, exposure to tobacco smoke and alcohol during pregnancy, and lead exposure are potential and significant confounding factors. All outlier and palindromic SNPs were removed.

Subsequently, we extracted the effect estimates of the selected instrumental variables (IVs) from the "ADHD outcome' dataset and excluded SNPs with palindrome structures. To adhere to the Mendelian first hypothesis, we employed R2 as a genetic tool to elucidate the proportion of trait variance. The R2-value, representing the proportion of phenotypic variations explained by each SNP, was calculated using the formula (40, 41):

$$R^2 = \sum [2 \times (1 - MAF) \times MAF \times \beta_2 \div (SE^2 \times N)]$$

where SE and β represent the standard error and β coefficient for effect size, MAF is the minor allele frequency for each SNP, and N is the sample size. Next, we calculated an F-statistic to assess the overall strength of the selected SNPs in explaining phenotypic variations using the formula (42–44):

$$F = [(N - K - 1)/K] \times [R^2/(1 - R^2)]$$

where N is the sample size, k is the total number of SNPs selected for MR analysis, and R2 is the total proportion of phenotypic variations explained by all the SNPs. An F-statistic > 10 indicates that a SNP is a strong genetic instrument that can elucidate phenotypic variations and effectively reduce potential bias (42). Strong genetic instruments were chosen as the IVs of exposure phenotype for MR analysis. Additionally, we assessed the statistical power to estimate the genetically causal effects of fatty acids on ADHD risk using a web-based application, the mRnd power calculator (https://shiny.cnsgenomics.com/mRnd/) (45).

2.4 Statistical analysis

All our statistical analyses were conducted using the "Two Sample MR (version 0.5.8)" "data. Table (version 1.14.8)" and "MR-PRESSO (Mendelian Randomization Pleiotropy RESidual

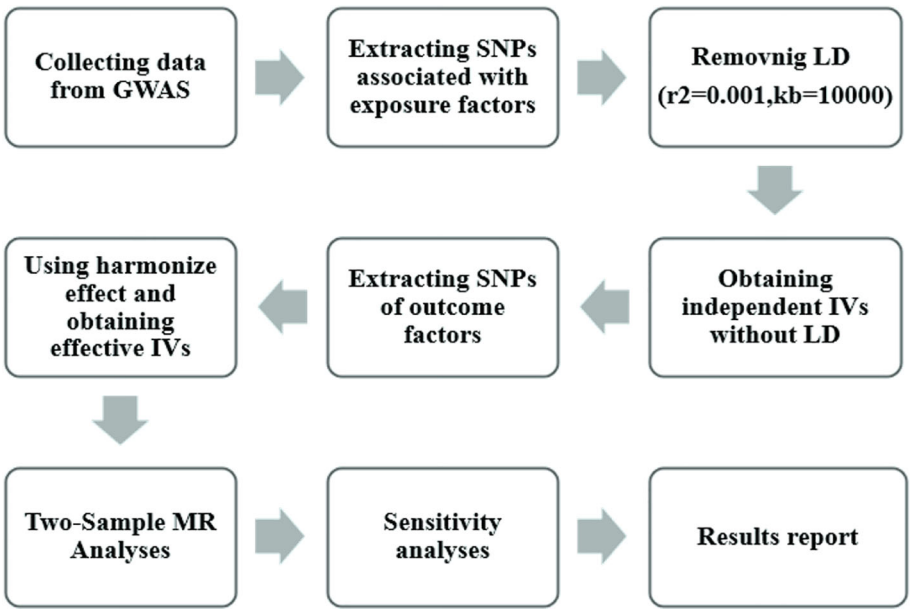

FIGURE 2
Mendelian randomization study flowchart. The gray boxes denote research steps, while the gray arrows signify the general direction. GWAS, genome-wide association study; IV, instrumental variable; LD, linkage disequilibria.

Sum and Outlier)" "LDlinkR" packages in R (2023 The R Foundation for Statistical Computing) (version 4.3.1). Reserved IVs were used to perform two-sample MR analyses.

Five MR methods, including inverse variance weighted (IVW), MR Egger, weighted median, simple mode, and weighted mode, were employed to analyze the causal influence of fatty acids on ADHD outcomes. Sensitivity analyses were conducted using established approaches such as leave-one-out analysis, PRESSO test, pleiotropy test, and heterogeneity test. The IVW method served as the primary analytical tool due to its demonstrated greater statistical power (46). This method assumes the validity and lack of horizontal pleiotropy for all instrumental variables, leading to more stable estimates. Consequently, IVW results were considered the main findings, while MR Egger, weighted median, simple mode, and weighted mode served as supplementary analyses.

Pleiotropy includes horizontal pleiotropy and vertical pleiotropy. Vertical pleiotropy implies that a genetic variant affects only a specific phenotype or feature without influencing others. On the other hand, horizontal pleiotropy suggests that a genetic variant affects multiple different phenotypes or features simultaneously. If horizontal pleiotropy exists, it implies that the genetic variant can influence other phenotypes besides the exposure, which are unrelated to the outcome. This would lead to a violation of the "no horizontal pleiotropy" assumption for the instrumental variable in MR analysis. This assumption essentially requires that the genetic variant only influences the outcome variable through its effect on the exposure. If a genetic variant with horizontal pleiotropy is used as an instrumental variable (IV), it can lead to biased estimates of the causal relationship between the exposure and outcome (47). Despite excluding known confounding SNPs, unknown confounding factors may still exist, leading to genetic polymorphism and biased effect size estimates. To satisfy the second and third hypotheses of MR, we employed MR-Egger for testing horizontal pleiotropy. The regression intercept reflects the magnitude of pleiotropy, with an intercept closer to 0 indicating a lower likelihood of pleiotropy. The P-value from the pleiotropy test signifies directional pleiotropy, and if $P > 0.05$, it indicates nonsignificant pleiotropy, suggesting that exposure is unlikely to affect the outcome through confounding factors or its own effects (48).

Heterogeneity indicates significant differences in the effects of different IVs on the outcome, affecting the stability of results. We utilized IVW and MR-Egger regression to test heterogeneity, evaluating it through the Cochran Q test's Cochran Q value. $P > 0.05$ suggests the absence of heterogeneity (49, 50).

MR-PRESSO was employed to detect outliers and assess differences in estimated values before and after outlier removal, reducing the impact of outliers and enhancing study reliability. Additionally, it evaluates horizontal pleiotropy ($P > 0.05$ is considered indicative of no pleiotropy) (51).

Furthermore, leave-one-out test was applied for sensitivity analysis to demonstrate that the causal effect of fatty acids on ADHD outcomes is not influenced by individual SNP. Effect sizes in MR analysis were presented as odds ratios (OR) with 95% confidence intervals (CI).

3 Results

3.1 Causal effects of fatty acids on ADHD

After IVs selection, we conducted a two-sample Mendelian randomization study using the valid IVs and obtained results (Palmitic acid = 4, R2 = 0.650%, F = 14.421; Stearic acid = 4, R2 = 1.120%, F = 25.561; Palmitoleic acid = 5, R2 = 0.924%, F = 16.498; Oleic acid = 3, R2 = 0.975%, F = 29.145; Alpha-linolenic acid = 2, R2 = 1.745%, F = 78.540; Eicosapentaenoic acid = 1, R2 = 1.299%, F = 116.671; Docosapentaenoic acid = 5, R2 = 5.223%, F = 95.310; Adrenic acid = 5, R2 = 3.977%, F = 70.783; Dihomo-gamma-linolenic acid = 12, R2 = 8.277%, F = 60.866; Gamma-linolenic acid = 48, R2 = 16.831%, F = 30.435); (Supplementary Tables 1–10). We only obtained 1 usable IV for DHA after filtering on F-statistic. Therefore, we were unable to conduct MR analysis on n-3 DHA and ADHD.

As plotted in Figure 3, the results of the IVW analysis revealed results for two types of SFA (16:0 (OR = 1.054, 95% CI 0.941 - 1.180, $p = 0.365$), 18:0 (OR = 1.071, 95% CI 0.973 - 1.180, $p = 0.161$)), and two types of MUFA (161:n7 (OR = 1.234, 95% CI 0.819 - 1.861, $p = 0.315$), 18:1n9 (OR = 1.031, 95% CI 0.959 - 1.108, $p = 0.406$)), two types of n-3 PUFA (ALA (OR =1.888, 95% CI 0.253 - 15.192, $p = 0.550$), DPA (OR =1.075, 95% CI 0.859 - 1.347, $p = 0.526$)) and two types of n-6 PUFA (AdrA(OR =0.999, 95% CI 0.693 - 1.440, $p = 0.996$), GLA (OR =0.987, 95% CI 0.956 - 1.019, $p = 0.430$)), showing no causal relationship with ADHD. Genetically predicted EPA was also showed no causal association between EPA and ADHD (OR = 0.988, 95% CI 0.777 - 1.265, $p = 0.922$ by Wald ratio). MR analyses indicated a causal relationship between DGLA (OR =1.009, 95% CI 1.001 - 1.018, $p = 0.032$). Since we had multiple exposures, we performed FDR correction on this result to prevent the probability of false positives (using the Benjamini-Hochberg method). The adjusted P-value was 0.286, which not reached significance after adjustment. This suggests that DGLA is unlikely to be a risk factor for ADHD. Consistent conclusions were also provided by MR-Egger, MW, and four other methods Figure 3), indicating no association between genetically predicted fatty acid increase and increased risk of ADHD. MR-Egger intercept and MR-PRESSO did not reveal horizontal pleiotropy ($P > 0.05$) among all analyses, and no outliers were identified through MR-PRESSO. Except for palmitic acid (16:0) ($p = 0.023$), Cochran's Q-test yielded P-values greater than 0.05 for the remaining fatty acids, suggesting no significant heterogeneity was observed. Despite the detection of heterogeneity in palmitic acid (16:0), utilizing the random-effects IVW method allowed for balancing the combined heterogeneity, making it acceptable (Table 2). Due to the limited number of available IVs for ALA and EPA, the tests for horizontal pleiotropy and heterogeneity could not be completed. To assess the robustness of our findings, we conducted a leave-one-out sensitivity analysis. In this analysis, we removed each SNP one at a time and re-estimated the causal effects. We observed no substantial changes in the overall effect estimates (Supplementary Figures 1–3). This suggests that our MR results are robust and reliable.

Figures 4–6 shows scatter plots of three types of n-3PUFAs, three types of n-6PUFAs, two types of MUFAs, and two types of

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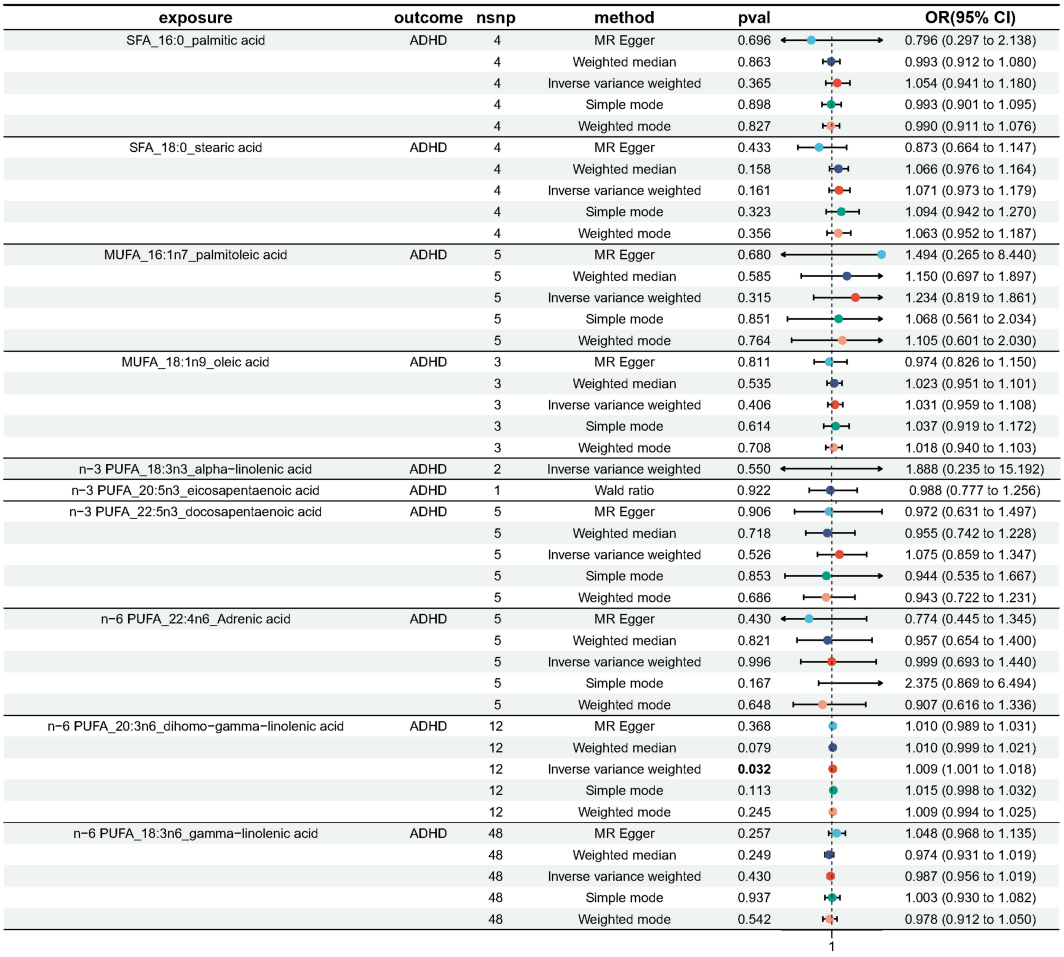

FIGURE 3
Odds ratio plot for genetic associations between 10 fatty acids and ADHD.

TABLE 2 Pleiotropy and heterogeneity test of fatty acids IVs in ADHD GWAS.

Fatty acids	nSNP	Heterogeneity test				Pleiotropy test		
		IVW		MR-Egger		MR-Egger intercept	*p*	MR-PRESSO Global test *p*
		Cochran's Q	*p*	Cochran's Q	*p*			
SFA 16:0	4	9.546	0.023	8.251	0.016	0.042	0.632	0.087
SFA 18:0	5	6.111	0.106	2.807	0.246	0.029	0.265	0.228
MUFA 16:1n7	5	1.826	0.768	1.777	0.620	-0.004	0.837	0.772
MUFA 18:1n9	3	0.786	0.672	0.242	0.623	0.009	0.593	–
n-3 ALA	2	3.318	0.069	–	–	–	–	–
n-3 EPA	1	–	–	–	–	–	–	–
n-3 DPA	5	4.444	0.349	4.024	0.259	0.004	0.615	0.458
n-6 AdrA	5	2.871	0.579	1.414	0.702	0.007	0.314	0.397
n-6 DGLA	12	15.40	0.165	15.397	0.118	-0.0005	0.961	0.173
n-6 GLA	48	50.784	0.327	48.137	0.386	-0.008	0.119	0.328

SFAs with ADHD under different methods. Each point in the scatter plot represents an IV, and the line on each point represents a 95% confidence interval. The x-axis represents the SNP's impact on the exposure factor (fatty acids), the y-axis represents the SNP's impact on the outcome ADHD, and the colored lines indicate the MR fitting results. Forest plots and funnel plots of the individual SNP effects of fatty acids on ADHD are presented in Supplementary Figures 4–9.

3.2 Causal effects of ADHD on fatty acids

We performed MR analysis with ADHD as exposure to explore the possible reverse causality on fatty acids. As shown in Figure 7, genetically predicted ADHD was not associated with any fatty acid traits (Palmitic acid: OR = 1.059, 95% CI 0.826 - 1.358, p = 0.365; Stearic acid: OR = 1.022, 95%CI 0.823 - 1.269, p = 0.845; Palmitoleic acid: OR = 1.004, 95% CI 0.975 - 1.034, p = 0.805; Oleic acid: OR = 1.028, 95% CI 0.866 - 1.221, p = 0.749; ALA: OR = 1.000, 95% CI 0.989 - 1.011, p = 0.974; EPA: OR = 0.974, 95% CI 0.931 - 1.020, p = 0.266; DPA: OR = 0.987, 95% CI 0.961 - 1.014, p = 0.330; DHA: OR = 0.916, 95% CI 0.781 - 1.073, p = 0.275; AdrA: OR = 1.015, 95% CI 0.991 - 1.039, p = 0.216; DGLA: OR = 1.003, 95% CI 0.995 - 1.011, p = 0.503; GLA: OR = 1.054, 95% CI 0.941 - 1.180, p = 0.365). Neither heterogeneity nor pleiotropy was detected in the reverse directional MR analysis (Table 3). The scatter plots, forest plots, funnel plots and leave-one-out of the genetic variance are presented in Supplementary Figures 10–21.

4 Discussion

ADHD, one of the most prevalent neurodevelopmental disorders in children and adolescents, is typically diagnosed during childhood and persists into adulthood. The symptoms of ADHD can disrupt individuals' learning, daily life, family, and employment, placing a significant burden on families. The causes of ADHD are multifaceted, involving factors such as genetics,

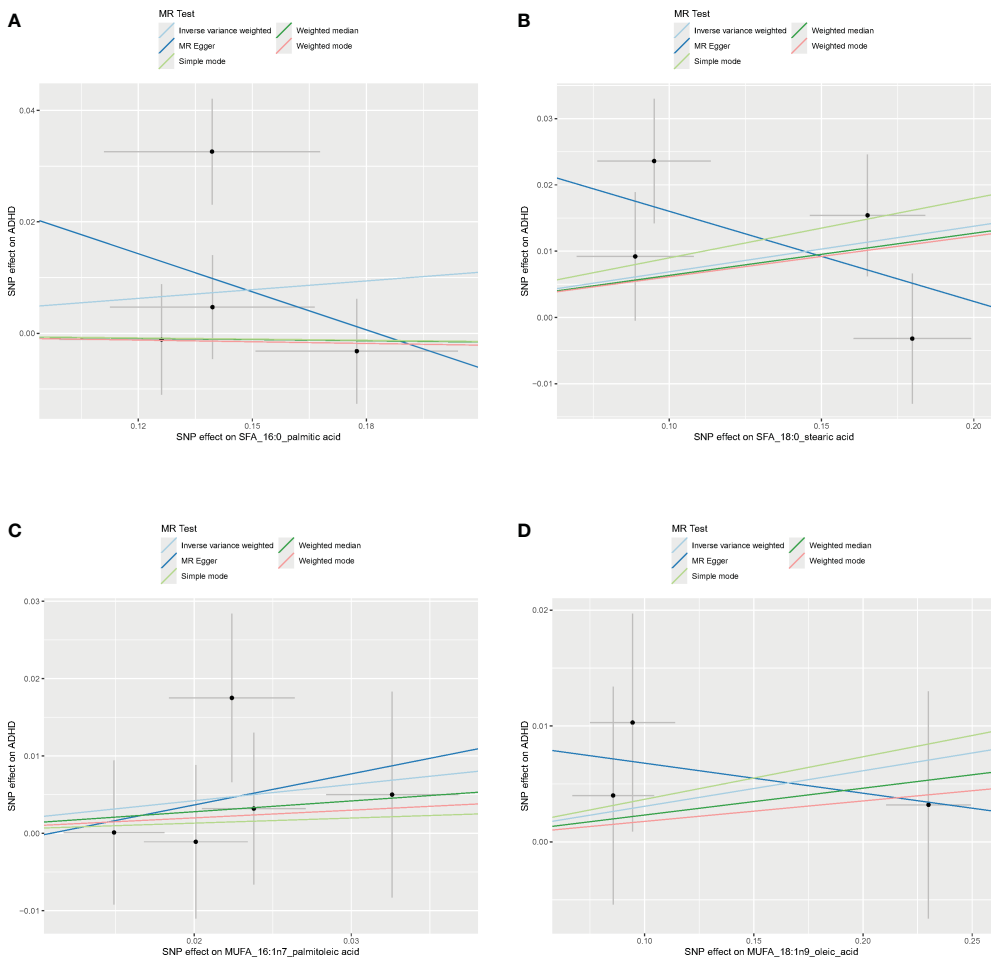

FIGURE 4
Scatter plots of SFA and MUFA. **(A)** Scatter plots of 16:0. **(B)** Scatter plots of 18:0. **(C)** Scatter plots of 16:1n7. **(D)** Scatter plots of 18:1n9. Scatter plots of the five MR results from the two SFAs and two MUFAs related to ADHD. Each point in the scatter plot represents an IV. The line on each point reflects the 95% CI, and the horizontal coordinate is the effect of SNPs on 16:0, 16:1n7, 18:0, 18:1n9. The vertical coordinate is the effect of SNPs on ADHD. SNP effects were plotted into lines for the inverse-variance weighted test (light blue line), MR-Egger regression (dark blue line), simple mode (light green line), weighted median (dark green line), and weighted mode (pink line).

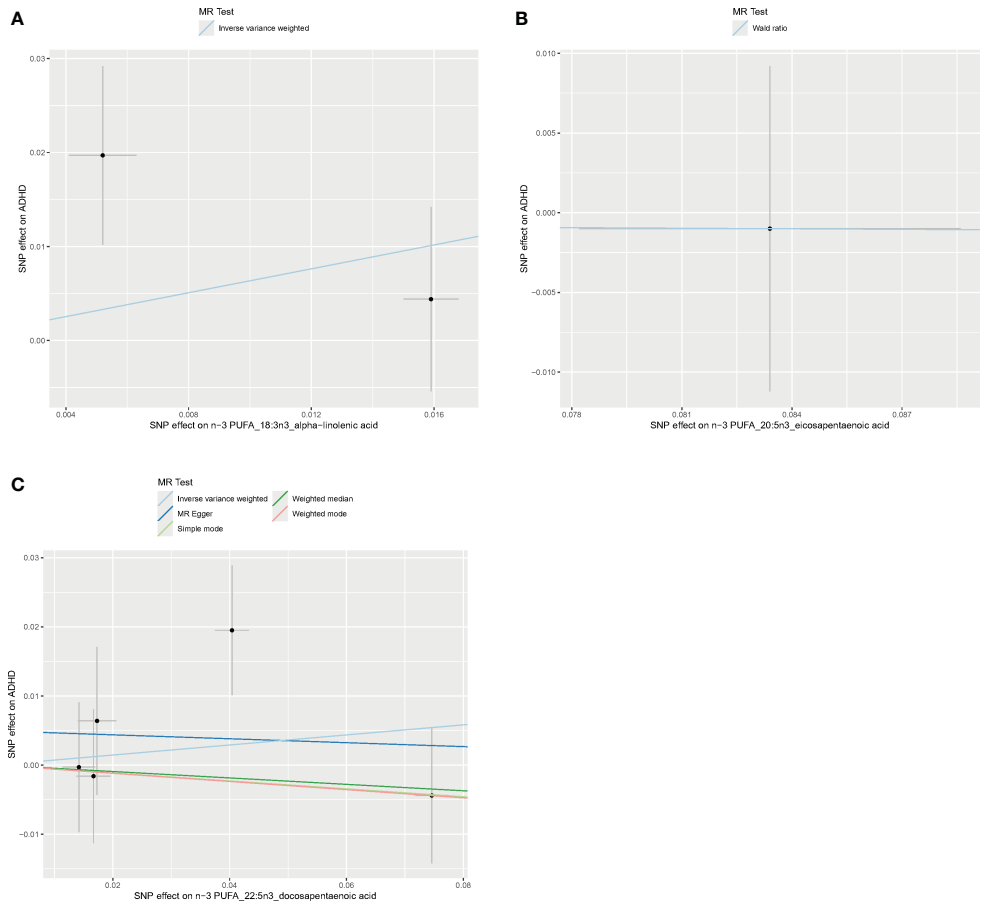

FIGURE 5
Scatter plots of n-3 PUFA. **(A)** Scatter plots of ALA. **(B)** Scatter plots of EPA. **(C)** Scatter plots of DPA. Each point in the scatter plot represents an IV. The line on each point reflects the 95% CI, and the horizontal coordinate is the effect of SNPs on ALA, DPA, EPA. The vertical coordinate is the effect of SNPs on ADHD. SNP effects were plotted into lines for the inverse-variance weighted test (light blue line), MR-Egger regression (dark blue line), simple mode (light green line), weighted median (dark green line), and weighted mode (pink line).

environment, preterm birth, preeclampsia, hypoxia events, and maternal prenatal smoking exposure (52, 53). Extensive evidence from numerous cohort studies and meta-analyses published in recent decades supports the evaluation of pharmacological, non-pharmacological, and combined treatment options for managing ADHD (54–56). Multiple studies have shown that supplementing PUFA, especially n-3 PUFA, has a positive impact on improving ADHD symptoms and cognitive function (57–59). Due to the side effects of commonly used drugs for treating ADHD, many families are seeking alternative therapies for ADHD, such as supplementing with fatty acids.

We utilized MR to strengthen the inferences that can be drawn about the effect of SFA, MUFA, n-3 PUFA and n-6 PUFA on ADHD risk. Our study did not reveal a significant association between ADHD risk and levels of SFA (16:0 PA and 18:0 SA), MUFA (161: n7 PA and 181: n9 OA), n-3 PUFA (ALA, DPA, EPA) and n-6 PUFA (AdrA, DGLA, GLA). Specifically, we did not find any evidence that the 10 fatty acids examined in our study were associated with a reduced risk of ADHD. This finding is inconsistent with some previous observational studies, which reported protective effects of certain fatty acids against ADHD. However, other studies have also found limited efficacy PUFA in the treatment of ADHD, aligning with our results (60–64). A recent meta-analysis further supports this notion, indicating no improvement in core ADHD symptoms with n-3 PUFA supplementation (65). Nevertheless, it is undeniable that some studies have shown potential benefits of fatty acid supplementation, such as improved sleep (66). Additionally, MR studies have suggested protective effects of certain fatty acids against diseases such as schizophrenia and depression (29, 30, 32). Intriguingly, two recent MR studies examining the relationship between LA, DHA, and ADHD reached opposing conclusions (67, 68), highlighting the need for further research in this area.

One study has indicated a positive correlation between essential fatty acid deficiency and ADHD symptoms (69). Children with ADHD show more severe essential fatty acid deficiency, and the n-3 PUFA levels in ADHD patients are significantly lower compared to those in healthy control children (70). Our reverse Mendelian randomization study, designed to explore the potential impact of ADHD on fatty acids, found no genetic indication that ADHD leads to abnormal fatty acid levels.

The mechanisms underlying the therapeutic effects of fatty acids on ADHD remain unclear, although several potential pathways have been explored. Studies suggest that imbalances in omega-3 and omega-6 fatty acid levels in the blood of ADHD patients might

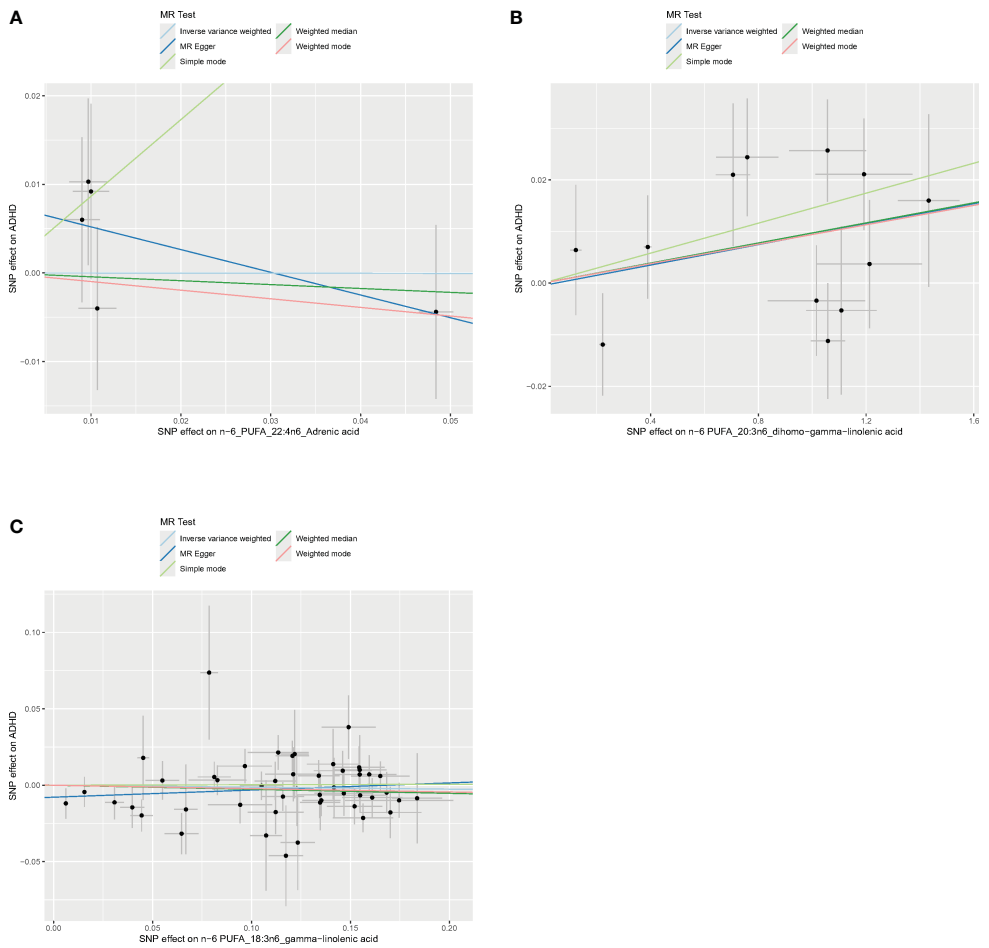

FIGURE 6
Scatter plots of n-6 PUFA. **(A)** Scatter plots of AdrA. **(B)** Scatter plots of DGLA. **(C)** Scatter plots of GLA. Scatter plots of the five MR results from the three n-6 PUFAs related to ADHD. Each point in the scatter plot represents an IV. The line on each point reflects the 95% CI, and the horizontal coordinate is the effect of SNPs on AdrA, DGLA, GLA. The vertical coordinate is the effect of SNPs on ADHD. SNP effects were plotted into lines for the inverse-variance weighted test (light blue line), MR-Egger regression (dark blue line), simple mode (light green line), weighted median (dark green line), and weighted mode (pink line).

contribute to the disorder, possibly due to disrupted fatty acid metabolism or increased inflammation (71, 72). Fatty acids also play a critical role in early brain development, influencing neuronal growth, communication between brain cells (synaptic function), and neurotransmitter signaling. Disruptions in fatty acid metabolism may hinder proper brain development and lead to some ADHD symptoms (73). Some studies propose that essential fatty acids can regulate brain cell signaling through monoamine modulation, signal transduction activation, and modulation of lipid rafts on cell membranes (74). Additionally, DPA and EPA have been shown to enhance anti-inflammatory effects by inhibiting free radical production and oxidative stress (75). Animal experiments suggest that EPA and DHA can restore a normal Firmicutes/Bacteroidetes ratio and improve stress-related inflammation by increasing the abundance of bacteria producing butyrate salts and reducing the levels of pro-inflammatory bacterial genera (76, 77). Moreover, DHA deficiency is associated with disturbances in the transmission of serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, and dopamine, which may be related to cognitive impairments in ADHD (78). These findings, although suggestive of potential mechanisms, do not align with our study's conclusion that there is no causal relationship between fatty acids and ADHD. However, this does not negate the possibility that other PUFA subtypes or a broader assessment of fatty acid metabolism may be relevant to ADHD. These findings highlight the need for further research to comprehensively understand the potential role of PUFA subtypes and broader fatty acid metabolism in ADHD risk.

In the present research, we employed an MR design to minimize residual confounding and reverse causation, improving causal inference regarding the correlation between fatty acids and ADHD. Utilizing ADHD data from the newly released PGC consortium, providing a large sample size for more robust evidence than observational studies. All analyses were confined within populations of European ancestry and genome-association tests adjusted for population stratification bias. Moreover, our dataset was obtained from the CHARGE consortium and PGC consortium, ensuring no overlap in samples. The consistency of effect sizes across different methods, the strength of evidence, and our secondary analyses indicate that our findings are consistent with an effect of fatty acids on ADHD, although the estimate of ALA

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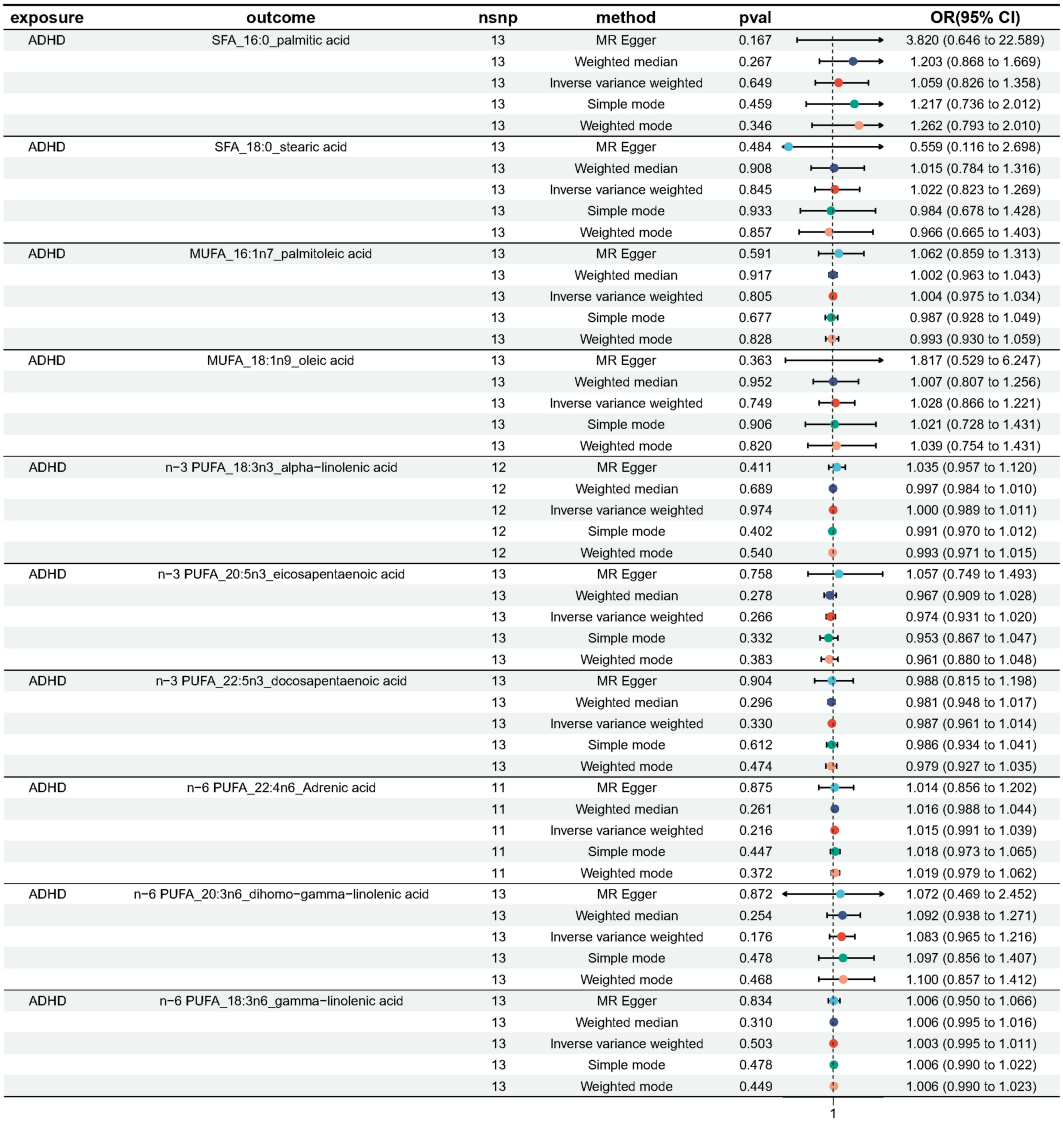

FIGURE 7
Odds ratio plot for genetic associations between ADHD and 10 fatty acids.

and EPA are likely to be underpowered, given the small number of instruments used in these two exposures. Our MR-Egger model and MR-PRESSO analyses revealed no outliers, indicating no horizontal pleiotropy, thereby minimizing the potential bias in causal inference. Additionally, our research provides valuable insights for the health management of ADHD patients. While our study does not definitively establish a causal relationship between fatty acids and ADHD, it is crucial to remain vigilant about the risk factors associated with fatty acid deficiency in individuals with ADHD.

Our study also has inevitable limitations. First, the limitation to individuals of European descent, restricting the generalizability of our study to non-European populations. Second, we did not include fatty acid data from other databases, considering that the quality control standards for genome-wide association analysis vary among different databases, and this difference may lead to heterogeneity, which also resulted in a limited number of available instrumental variables for our partial exposure (ALA, EPA) that could not be used for heterogeneity and pleiotropy analysis, or even unavailable (DHA). Third, ADHD has a male predominance, and our data were not stratified by gender, making it impossible to assess the effect of fatty acids on ADHD risk in different genders, potentially introducing bias. Due to the lack of publicly available dataset, our study could not conduct a stratified analysis on the progression and severity of ADHD, as well as different clinical subtypes. Finally, we must pay attention to the diversity of ADHD population and fatty acid types, and in the future, comprehensive research on ADHD subgroups and multiple fatty acids should be considered.

5 Conclusion

We found no genetic evidence supporting the causal relationship between n-3 PUFAs, n-6 PUFAs, SFA, and MUFAs

TABLE 3 Pleiotropy and heterogeneity test of ADHD IVs in fatty acids GWAS.

Fatty acids	nSNP	Heterogeneity test				Pleiotropy test		
		IVW		MR-Egger		MR-Egger intercept	*p*	MR-PRESSO Global test *p*
		Cochran's Q	*p*	Cochran's Q	*p*			
SFA 16:0	13	5.932	0.919	3.891	0.973	-0.082	0.181	0.917
SFA 18:0	13	18.916	0.091	17.977	0.821	0.039	0.465	0.113
MUFA 16:1n7	13	8.862	0.715	8.588	0.660	-0.004	0.611	0.719
MUFA 18:1n9	13	8.353	0.757	7.520	0.756	-0.037	0.381	0.758
n-3 ALA	12	17.886	0.084	16.625	0.083	-0.002	0.404	0.082
n-3 DHA	13	18.367	0.105	18.135	0.078	0.014	0.715	0.119
n-3 EPA	13	12.014	0.445	11.779	0.380	-0.005	0.649	0.496
n-3 DPA	13	6.941	0.861	6.941	0.804	-7.688e-05	0.990	0.880
n-6 AdrA	11	14.261	0.161	14.260	0.113	4.00099e-05	0.994	0.178
n-6 DGLA	13	5.551	0.937	5.550	0.902	0.0007	0.981	0.934
n-6 GLA	13	7.245	0.841	7.230	0.780	-0.0002	0.119	0.907

in the risk of ADHD. From a public health perspective, our study challenges the notion that supplementing PUFAs can reduce the risk of ADHD. Given the inconsistent evidence from trial data, further MR studies targeting different populations and larger-scale epidemiological research are still needed to validate this conclusion.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

All data are publicly available and are approved by the institutional review committees in their respective studies. Therefore, no further sanction was required. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. QZhang: Investigation, Visualization, Writing – original draft. ZY: Validation, Visualization, Writing – review & editing. YY: Formal analysis, Investigation, Writing – original draft. QZhao: Project administration, Supervision, Writing – review & editing. JW: Funding acquisition, Project administration, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1368942/full#supplementary-material

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Working memory and inhibitory control deficits in children with ADHD: an experimental evaluation of competing model predictions

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Introduction: Children with ADHD demonstrate difficulties on many different neuropsychological tests. However, it remains unclear whether this pattern reflects a large number of distinct deficits or a small number of deficit(s) that broadly impact test performance. The current study is among the first experiments to systematically manipulate demands on both working memory and inhibition, with implications for competing conceptual models of ADHD pathogenesis.

Method: A clinically evaluated, carefully phenotyped sample of 110 children with ADHD, anxiety disorders, or co-occurring ADHD+anxiety (M_{age}=10.35, 44 girls; 69% White Not Hispanic/Latino) completed a counterbalanced, double dissociation experiment, with two tasks each per inhibition (low vs. high) x working memory (low vs. high) condition.

Results: Bayesian and frequentist models converged in indicating that both manipulations successfully increased demands on their target executive function (BF_{10}>5.33x10^8, p<.001). Importantly, occupying children's limited capacity working memory system produced slower response times and reduced accuracy on inhibition tasks (BF_{10}>317.42, p<.001, d=0.67-1.53). It also appeared to differentially reduce inhibition (and non-inhibition) accuracy for children with ADHD relative to children with anxiety (BF_{10}=2.03, p=.02, d=0.50). In contrast, there was strong evidence *against* models that view working memory deficits as secondary outcomes of underlying inhibition deficits in ADHD (BF_{01}=18.52, p=.85).

Discussion: This pattern indicates that working memory broadly affects children's ability to inhibit prepotent tendencies and maintain fast/accurate performance, and may explain the errors that children with ADHD make on inhibition tests. These findings are broadly consistent with models describing working memory as a causal mechanism that gives rise to secondary impairments. In contrast, these findings provide evidence *against* models that view disinhibition as a cause of working memory difficulties or view working memory as a non-causal correlate or epiphenomenon in ADHD.

KEYWORDS

ADHD, working memory, inhibition, experimental psychopathology, anxiety

Introduction

Impaired performance on executive function tests is well established in children, adolescents, and adults with attention-deficit/hyperactivity disorder (ADHD; e.g., 1, 2). Thus, it is not surprising that most contemporary neurocognitive/behavioral models of ADHD make predictions regarding the role of executive dysfunction in the etiology, pathophysiology, and/or recovery from the disorder (3, 4). As the two primary executive functions in school-aged youths (5), working memory and/or inhibitory control have garnered particular attention. They have been proposed to reflect core (causal) underlying neurocognitive deficits in ADHD (6–9), non-causal correlates of ADHD that may nonetheless aid in developmental recovery from the disorder (10), secondary outcomes of other core deficits (11, 12), and/or epiphenomenal difficulties that neither cause ADHD nor affect symptom expression/persistence (13). Among theoretical models that conceptualize one or both executive functions as core influences on ADHD symptom expression/diagnostic status, disagreement remains regarding the extent to which (a) underlying working memory deficits are responsible for poor performance on inhibitory control tests (e.g., 14), (b) underlying inhibitory control deficits are responsible for poor performance on working memory tests (e.g., 6), and/or (c) deficits in working memory and inhibitory control reflect correlated but relatively independent impairments (e.g., 15). Using a double dissociation design, the current study is among the first to experimentally manipulate both working memory and inhibitory control demands while concurrently measuring the effects of each executive function manipulation on performance on tests intended to measure the other executive function. In other words, the current study experimentally tests whether occupying children's limited capacity working memory system by adding complex span-style recall demands disrupts inhibitory control performance. Concurrently, it also experimentally tests whether depleting inhibitory resources via a Stroop interference paradigm disrupts working memory performance in a carefully phenotyped clinical sample of children with ADHD, anxiety disorders, and co-occurring ADHD + anxiety disorders.

Working memory and inhibitory control in ADHD

Executive functions are correlated but distinguishable neurocognitive processes that facilitate goal directed behavior and problem solving (16, 17). There are a plethora of executive function models spanning cognitive, behavioral, neurological, and sociocultural domains. Among these models, factor analytic and theoretical work provides significant support for models that include two primary executive functions in middle childhood: working memory and inhibitory control (for review, see 5). Set shifting, or cognitive flexibility, reflects the third core executive function, but generally does not emerge as a unique executive function until late adolescence or early adulthood (18, 19). *Working memory* refers to processes involved in the updating, dual-processing, and serial/temporal reordering of information held in short-term memory (20–23). *Inhibitory control* refers to processes that facilitate one's ability to stop an ongoing response in the context of goal-directed behavior (24, 25).

Impairments on tests intended to measure working memory and inhibitory control are well established in pediatric ADHD, with meta-analytic effect sizes ranging from Cohen's d=0.69-0.74 for working memory (and potentially as high as d=2.01-2.15 based on construct-valid working memory tests; 2, Kofler et al., in press[1]) to d=-0.03 to 0.63 for inhibitory control (24, 26–28). Cohen's d is a measure of the magnitude of between-group differences, and is interpreted as: small (d=0.20), medium (d=0.50), or large (d=0.80). Similarly, heterogeneity estimates suggest that 62-85% of children with ADHD exhibit working memory deficits and 21-46% have impairments in inhibitory control (for review, see 29). Relevant for the present experiment, very few studies have controlled for one executive function while estimating the extent to which children with ADHD have impairments in the other executive function – an important limitation given their moderate intercorrelations (r=.43; 30) and disagreement among influential conceptual models regarding the primacy and relevance of these neurocognitive functions for explaining the ADHD phenotype (Table 1).

A partial exception to this methodological critique comes from a study finding that covarying working memory eliminated ADHD/neurotypical between-group differences in inhibition, whereas covarying inhibition produced only a small reduction in ADHD/neurotypical working memory differences (45). Similarly, a recent randomized control trial (RCT) found that targeted training of inhibitory control did not produce improvements in working memory for children with ADHD, whereas targeted training of working memory produced superior improvements in inhibitory control relative to the active, credible neurocognitive control training – albeit only on one of two inhibition tests (55). A similar pattern has also been found in training studies of healthy children as well as adults with borderline personality traits (but not healthy adults) – in each case, working memory updating training, working memory maintenance (short-term memory) training, and dual n-back training produced superior improvements on one of two inhibition tests relative to passive controls (56–58; cf. 59, 60).

These findings are generally consistent with *dual-mechanism* accounts of inhibitory control from the cognitive literature (61), which emphasize the impact of working memory capacity for resolving response competition (e.g., between the conflicting color and word dimensions in the Stroop task), maintaining task goals that are not sufficiently reinforced by the environment (62–64), and/or controlling attention to prevent intrusions from irrelevant distractors (65). Applied to ADHD, Rapport and colleagues (7, 14) have argued that inhibitory control difficulties are more parsimoniously viewed as an outcome of working memory difficulties rather than a cause, at least in part because "inhibition is a reaction to external stimuli that must first gain access to and be

1 Kofler MJ, Soto EF, Singh LJ, Harmon SL, Jaisle E, Smith JN, et al. Executive function deficits in attention-deficit/hyperactivity disorder and autism spectrum disorder. *Nat Rev Psychol*. (in press).

TABLE 1 Etiological models of attention-deficit/hyperactivity disorder (ADHD): Predictions regarding working memory and/or inhibitory control.

Model	Model description of ADHD	Model predictions for the current experiment	Representative publications
Basal Ganglia	A model of reinforcement learning which posits that the basal ganglia are responsible for a dynamic gating mechanism that selectively updates the contents of working memory in the prefrontal cortex; environmental reinforcement of updating then "critiques" the gating of the basal ganglia for improved future performance via dopaminergic signals. The model posits that reduced striatal dopamine is responsible for working memory and motivational deficits that are observed in ADHD.	Working memory and response inhibition are viewed as distinct and independent of one another. Observed deficits in working memory are posited as secondary to reduced striatal dopamine, whereas deficits in response inhibition are believed to be secondary to cortical noradrenergic dysfunction. In computational models, sequelae resulting from the dysfunction of dopamine and noradrenaline were independent of one another. If difficulties on working memory and inhibition tests are due to different neurotransmitter deficiencies, it stands to reason that increasing demands on one executive function would not be expected to impact performance on tasks intended to measure the other executive function.	Frank et al. (31, 32); Frank & O'Reilly (33)
Behavioral Inhibition	A core deficit model wherein deficits in behavioral inhibition (stopping pre-potent/ongoing responses and interference control) result in deficits in working memory and three other areas that collectively result in ADHD behavioral symptoms.	Increasing inhibition demands are expected to differentially affect children with ADHD, reflecting their core deficit in this ability. Working memory difficulties are viewed as an outcome of underlying inhibition deficits; therefore, the model would predict that increasing inhibition demands would differentially impact working memory performance for children with ADHD. In contrast, increasing working memory demands should not affect inhibition performance because working memory difficulties are 'downstream' of the core inhibition deficits.	Barkley (6, 34)
Cognitive Neuroenergetic	Decreased ATP production and inadequate lactate supply from deficient astrocyte functioning causes the behavioral features of inefficient and inconsistent performance in individuals with ADHD.	Predictions consistent with Functional Working Memory Model, but views compromised working memory as a secondary outcome of energetic insufficiency that becomes apparent with increases in processing and effort demands; this energetic insufficiency may directly affect other processes without mediation by working memory. Also predicts that ADHD is not characterized by a specific deficit in inhibitory control, but instead that performance is impacted across the board (including on inhibition tests) for children with ADHD due to dysregulated attention/energetic processes. Increasing demands on inhibition processes would not be expected to affect working memory performance because reduced performance on inhibition tests is viewed as attributable to underlying energetic insufficiency/attentional lapses rather than reflective of inhibition difficulties. Predictions regarding working memory are less clear: The model interprets increases in working memory load as a proxy for increases in effort and computational demands, which reveal the impact of inadequate energetic resources, while also positing that working memory difficulties are an outcome rather than causal factor in ADHD. Thus, the model would seem to predict that the current study's working memory manipulation would either produce downstream difficulties on inhibition tests *or* that this manipulation would not further impact inhibition test performance beyond the existing impact of insufficient energetic/effort resources.	Sergeant (35); Killeen et al. (36); Killeen (37)
Default Mode Network	A multiple pathway model that hypothesizes that disruptions in cortico-striato-thalamo-cortical neuroanatomical circuitry–consisting of 'hot' and 'cool' regions–contribute to functional behavioral and cognitive differences in ADHD. Predictable oscillations in default mode (resting state) neural networks interfere with task-oriented neural processing, producing periodic lapses of attention.	Neither working memory nor inhibition deficits are viewed as causal factors in ADHD. Instead, the model predicts that default mode interference competes with task-related processing, causing attentional lapses that lead to increased variability and thus reduced performance on all types of tests, including working memory and inhibitory control tests. Does not imply a relation between working memory and inhibition. If difficulties on both types of tests are secondary to underlying default mode network intrusions, it stands to reason that increasing demands on one executive function would not be expected to impact performance on tasks intended to measure the other executive function.	Sonuga-Barke & Castellanos (38)

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TABLE 1 Continued

Model	Model description of ADHD	Model predictions for the current experiment	Representative publications
Dopamine Transfer Deficit	A neurobiological model that predicts that the anticipatory firing of dopamine neurons, which normally occurs in anticipation of rewards, is reduced or absent in ADHD. This leads to more rapid extinction of unreinforced behaviors (as opposed to slower extinction in the dynamic developmental model) and diminished partial reinforcement effect, which then contributes to impaired learning and motivation that would explain some of the core ADHD symptoms.	The model does not make specific predictions regarding working memory or inhibition. However, the authors posit that processing global contingencies (i.e., longer-term history of reinforcement) may involve working memory as it is a "higher integrative function". Does not imply a relation between working memory and inhibition. Given that the model does not account for, or only peripherally discusses, inhibition and working memory, the model provides no expectations that increasing demands on one would affect performance on tests of the other.	Tripp & Wickens (39)
DSM-5 Clinical Model	Attention problems and hyperactivity/impulsivity reflect the disorder's core deficits. Neurocognitive deficits may be present in a variety of areas, including in working memory and response inhibition, but are not described as core causal factors and it is specifically noted that tests of these abilities are not sufficiently sensitive or specific to serve as diagnostic indices.	Given that working memory and inhibitory control deficits are seen as peripheral rather than causal features, the model provides no expectations that increasing demands on one would affect performance on tests of the other.	DSM-5-TR APA (40)
Dynamic Developmental	A core deficit model that hypothesizes that reduced dopaminergic functioning causes narrower reinforcement gradients and altered extinction processes in normal behavior-consequence relationships. These deficient dual processes contribute to core ADHD symptoms and behavioral variability, which vary based on context, task, and function.	Failure to inhibit responses (disinhibition) reflects the behavioral manifestation of a pattern of inconsistent behavior-response associations affected by deficient reinforcement/extinction mechanisms which, in turn, disrupt the accumulation of simple behavioral response units into more complex and functional response chains. Model does not discuss working memory specifically, but rather posits that attentional deficits/variability also lead to poor executive functioning (behavioral planning) broadly. Given that the model does not account for working memory, and that inhibitory control deficits are seen as peripheral rather than causal features, the model provides no expectations that increasing demands on one would affect performance on tests of the other.	Sagvolden et al. (12)
Extended Temporal Difference	A neurocomputational behavioral model derived from dopamine-driven temporal-difference learning (i.e., reinforcement learning) to explain impulsive behavior in ADHD. This model proposes that performance on a delayed response task depends on four contextual factors that influence preference for immediate rewards, including brittleness (predictability; the extent to which behavior is based on learned responses), action bias (preference for action over inaction), learning rate (rate of behavior change), and the discount factor (a predicable reward delivered in the future is less valuable than the same reward delivered immediately).	This model predicts that variation in simple learning and behavioral parameters predict increased difficulty with inhibition, which may reflect deficient signaling of reward-prediction error and hypo- and hyperfunctioning of the dopamine signal to rewards. On complex cognitive tasks, poor performance on long trials may be attributable to working memory deficits, whereas poor performance on short trials may be attributable to inhibitory control deficits. Given that working memory and inhibitory control deficits are seen as linked with different types of difficulties, the model provides no expectations that increasing demands on one would affect performance on tests of the other.	Williams & Taylor (41); Williams & Dayan (42); Durston et al. (43)
Functional Working Memory	A core deficit model that views ADHD symptoms as phenotypic/behavioral expressions of the interaction between neurobiological vulnerability & environmental demands that overwhelm impaired working memory. Associated features of ADHD, including inhibition difficulties, arise through direct effects of impaired working memory, or indirect effects of impaired working memory through its impact on core behavioral symptoms.	Increasing working memory demands are expected to differentially affect children with ADHD, reflecting their core deficit in this ability. Difficulties on inhibition tests are viewed as an outcome of underlying working memory deficits; therefore, the model would predict that increasing working memory demands would differentially impact inhibition task performance for children with ADHD. In contrast, increasing inhibition demands should not affect working memory performance because inhibition difficulties are 'downstream' of the core working memory deficits.	Rapport et al. (14, 44) Alderson et al. (45); Kofler et al. (29)

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TABLE 1 Continued

Model	Model description of ADHD	Model predictions for the current experiment	Representative publications
Moderate Brain Arousal	A neurocomputational model that views ADHD-related attention and cognitive difficulties, including working memory and inhibition deficits, as a function of low levels of baseline dopamine. Within this theory, environmental noise (e.g., white noise) can compensate for a hypofunctional dopamine system via increasing internal neural noise, which in turn improves cognitive functioning. Cognitive performance and dopamine transmission is further posited to follow an inverted U-shaped curve, such that too low or high levels attenuate performance.	Given that too low or too high brain arousal states are hypothesized to reduce cognitive performance, increasing working memory and inhibition demands to an optimal moderate brain arousal state will result in the best cognitive performance. In other words, too low and high working memory and inhibition conditions are likely to result in worse cognitive performance. Increasing working memory load is posited to *improve* performance in individuals with ADHD as they go from a low to moderate brain arousal state, whereas excessive working memory load is posited to *impair* performance due to a high brain arousal state. Predictions for the current experiment are unclear because we included only two working memory levels and did not directly measure brain arousal state.	Sikstrom & Soderlund (46); Grace (47, 48); Seeman & Madras (49)
Optimal Stimulation	Hyperactive children are chronically under-aroused due to inadequate neurotransmission and/or a shift in the level of stimulation these children find to be optimal. A feedback model based on the assumption that response output functions homeostatically to regulate the level of stimulus input.	The model does not discuss working memory/inhibition or executive functions specifically, but makes prediction regarding complex tasks more generally. During early stages of task acquisition, the tasks' novelty is thought to provide sufficient stimulation. When the task is learned, task stimuli are repetitive, and/or sustained attention is required, the stimulation provided by the task is insufficient and children with ADHD may need to augment their arousal levels by increasing their activity level or altering their attentional response. Whether this activity-generated stimulation interferes with successful task performance will depend on the attentional requirements of the task, the difficulty of the task, and the level of performance. For the current experiment, if we assume that the tasks are not novel (i.e., due to multiple practice rounds), it seems reasonable to assume that the model would predict performance difficulties across all four tasks that are secondary to interfering effects of increased physical movement and visual attention to task-irrelevant stimuli (e.g., looking around, increased verbalizations). It may be further hypothesized that the 'word' task would produce the least interfering behaviors (because it requires the least complex executive processing) and the stroop span condition would produce the most interfering behaviors because it might be viewed as the most 'difficult' (i.e., because it requires both working memory and inhibitory processes). However, because task 'difficulty' is a nebulous concept, the model does not provide testable predictions regarding the impact of working memory on inhibition performance or vice versa.	Zentall & Zentall (50)
Subcortical Deficit	A developmental model that hypothesizes that ADHD is caused by subcortical neural dysfunction that manifests early in ontogeny, remains relatively static throughout life, and is not associated with the remission of symptomatology. ADHD behavioral symptoms reflect unconsciously (i.e., non-prefrontally) mediated deficits in arousal and activation similar to those described by the Cognitive Energetic Model. Executive dysfunction does not cause ADHD symptoms, but developmental growth in executive functions facilitates recovery. Executive functions are viewed as compensatory – they are not causally related to the disorder.	Given that working memory and inhibitory control deficits are seen as non-causal, compensatory features, the model provides no expectations that increasing demands on one would affect performance on tests of the other.	Halperin & Schulz (10); Halperin et al. (51)
Tripartite Pathway	A multiple pathway/equifinality model in which ADHD symptoms are caused by deficits in one or more dissociable cognitive (behavioral inhibition, temporal processing) and/or motivational (delay aversion) processes. Heterogeneity model; ADHD symptoms attributable to inhibition, delay, and/or temporal processing deficits, each affecting some ADHD patients	Working memory is not viewed as a core, causal deficit, whereas inhibitory control reflects the core deficit for a subset of patients. Working memory is discussed as a correlate of all three causal components but the model does not directly discuss the direction of the relation between inhibitory control and working memory (although inhibition is highlighted as a causal factor and working memory is not). Overall, model predictions for the current experiment are generally consistent with the behavioral inhibition model, with the caveat that inhibitory control is a causal factor for only a subset of children with ADHD.	Sonuga-Barke et al. (8); Lambek et al. (52)

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TABLE 1 Continued

Model	Model description of ADHD	Model predictions for the current experiment	Representative publications
Updated Executive Function Model	An update to the Behavioral Inhibition model in which working memory is elevated from a mediator variable to a primary causal factor alongside inhibitory control.	Increasing working memory or inhibition demands are both expected to differentially affect children with ADHD, reflecting their core deficits in these abilities. Working memory and inhibitory control are viewed as correlated core deficits. Therefore, increasing demands on one core process would not be expected to impact performance on tasks intended to measure the other core process.	Barkley (53); Panah et al. (15)
Variability Trait	Childhood ADHD behaviors attributed to excessive variability, both in rate and magnitude of change, in arousal level and reactivity; excessively inconsistent arousal and reactivity result in problems in sustained attention, performance, and social behavior. Excessive variability in autonomic, electrocortical and behavioral response underlies impairments in attention, performance, and social behavior.	Reduced performance on working memory and inhibition tests (as well as all kinds of tests) reflect inconsistent performance; a 'third variable' model in which increasing working memory or inhibition demands would not be expected to affect performance on tests of the other ability because both are outcomes of excessive trait inconsistency.	Hicks et al. (54)

BI, behavioral inhibition; CE, central executive; WM, working memory.

evaluated within working memory" (45, p. 498). Together, these studies appear to provide preliminary support for conceptualizing difficulties on inhibition tests among children with ADHD as, at least in part, artifacts of their underlying working memory difficulties (7).

In contrast, others have argued that inhibitory control deficits in ADHD lead to secondary deficiencies in working memory because inhibition 'sets the occasion' for working memory to function by providing the necessary delay for it to occur (e.g., 6). In this view, inhibition is conceptualized as a limited resource that will be depleted when external demands exceed that resource (30, 66–68; cf. 69–71). When inhibitory resources are depleted, task-irrelevant information is able to gain access to the working memory system. In turn, this produces interference effects that impair maintenance of task goals and rehearsal of to-be-recalled test items (45, 72). Thus, we would expect children with ADHD to have fewer inhibitory resources available to maintain task goals and protect stimuli in working memory, particularly when those inhibitory resources are depleted by imposing interference demands (73). This view is broadly consistent with *depletion* accounts of inhibitory control from the social psychology literature, which describe inhibitory control as a limited, consumable resource that, when depleted (e.g., through engagement with inhibition tasks as in the current experiment) will not be available to support additional executive processing (67, 68).

In partial support for this view, a recent RCT with healthy adults found that adding inhibition demands to an *n*-back training protocol resulted in superior improvements in working memory updating and short-term memory recall relative to a passive control group. However, interpreting these effects as attributable to inhibition training is challenging because the training groups did not show improved inhibition performance relative to the passive control group (60). Similarly, Alderson and colleagues (30) conducted, to our knowledge, the only relevant ADHD experimental/dual-task manipulation study to date. They found that increasing inhibition demands disrupted *n*-back memory performance for children with and without ADHD, whereas increasing *n*-back memory load failed to affect inhibition processes (30). These findings may suggest that inhibition is upstream from working memory in children with and without ADHD, because adding inhibitory demands created a bottleneck that disrupted the cognitive resources available for working memory processing. Interestingly, however, adding inhibition demands appears to have had a larger effect on the neurotypical group than the ADHD group (i.e., between-group differences were significant for the 1-back task but not the 1-back + stop-signal dual task due to differentially reduced performance in the neurotypical control group), calling into question the extent to which inhibition is a causal factor in ADHD-specific working memory difficulties. Further, despite the elegant experimental design, Alderson et al. (30) pointed out that their high working memory condition (2-back) was simply too difficult for all children (i.e., performance at/below chance levels). This may suggest that the working memory manipulation may have been less successful than intended and limit conclusions regarding working memory's impact on inhibitory control functioning.

In addition to mixed evidence supporting each executive function as an upstream driver of ADHD-related difficulties with the other executive function, there is also evidence suggesting that they may reflect independent impairments in ADHD. For individuals with ADHD specifically, Panah et al. (15) directly tested the Barkley inhibition/updated executive function models. They found that the structural equation model with working memory and inhibition as correlated predictors provided a better fit to the data relative to the model in which working memory was modeled as an outcome of inhibition (15), suggesting that these may be relatively independent impairments in ADHD. Similarly, Kofler et al. (9) reported that only 17% of children with ADHD have impairments in both inhibition and working memory (vs. 46% who have working memory but not inhibition deficits, and only 11% who have inhibition deficits but not working memory deficits). Karalunas et al. (74) also found that only 13% of children with ADHD have stable impairments in both inhibition and working memory (vs. 44% who have stable working memory but not inhibition deficits, and only 5% who have stable inhibition deficits but not working memory deficits).[2] The similarity in these estimates is striking, especially given that the former was based on cross-sectional factor-analytic estimates using multiple tests per construct and the latter was based on a single test per construct with latent class growth analysis from a 3-year longitudinal study. Together, these findings suggest that only a small minority of children with ADHD have impairments in both working memory and inhibitory control, and thus appear to support models conceptualizing them as relatively independent impairments in ADHD. Finally, it is also possible that working memory and inhibitory control exert bidirectional effects on each other and/or that depleting resources on either process would impair performance on tests of the other process (75). However, to our knowledge, no current ADHD conceptual models make this prediction.

Working memory and inhibitory control in anxiety

As noted above, children with anxiety disorders served as the clinical comparison group (compared with children with ADHD and ADHD+anxiety) in the current study. This was a pragmatic decision because recruitment of a typically developing control group was not feasible due to funding constraints. Thus, a commentary on the relation between anxiety and executive functioning is warranted. Interestingly, whereas several theoretical models conceptualize executive function deficit(s) as underlying *causes* of ADHD (e.g., 29), they tend to be viewed as *outcomes* of anxiety disorders or involved in the maintenance of anxiety symptoms (76–78). However, studies of executive functioning in children with anxiety disorders have been surprisingly mixed. Regarding inhibitory control, meta-analytic evidence indicates that anxiety disorders are not associated with impairments (*ns*; 79) or are associated with small magnitude impairments (d=-0.31; 80) that are significant based on analysis of response times (d=-0.27) but not accuracy data (*ns*; 81). Regarding working memory, recent meta-analyses diverge in documenting a small magnitude impairment in children with anxiety disorders (d=-0.24; 82), no significant impairment (*ns*; 80), or no significant impairment based on response time data (*ns*) but a small, significant *strength* based on accuracy data (d=0.38; 81) that was also found in a recent empirical study controlling for ADHD status (d=0.19; 83). However, when examined, effect sizes tended to be similar across anxiety disorder categories, anxiety severity, and/or state versus trait anxiety (80–82), at least for the diagnoses included in the current study (please see *Method* section below).

Applied to the current study's outcome data, these meta-analytic estimates suggest that our use of an anxiety disorder group as the clinical comparison group may produce a slight overestimate of ADHD-related working memory deficits (based on accuracy data). It may also either not affect (accuracy data) or produce a small underestimate (response times/RTs) of ADHD-related inhibition deficits. In contrast, co-occurring anxiety disorders do not appear to affect estimates of working memory deficits in children with ADHD but may exert a small protective effect by reducing the magnitude of inhibition deficits in co-occurring ADHD+anxiety relative to ADHD-only groups by d=0.14-0.41 across meta-analyses (79, 83, 84). Thus, estimates of ADHD-related impairments should be interpreted with the clinical nature of the comparison group in mind.

Current study

Taken together, children with ADHD demonstrate difficulties on tasks intended to measure inhibitory control and working memory. However, it remains unclear whether this pattern reflects multiple, distinct impairments or may be more parsimoniously accounted for by a single deficit that broadly affects performance (85, 86). The current study uses a double dissociation design to test competing model predictions regarding the directionality of these impairments in ADHD. Support for working memory-focused models would include significant reductions in inhibitory control performance when working memory demands are experimentally induced (14, 45). In contrast, support for behavioral inhibition-focused models (e.g., 6, 8) would include significant reductions in working memory recall as inhibitory control demands were experimentally increased. Alternatively, support for correlated core deficit, non-causal, recovery, and epiphenomenal models of executive functions in ADHD would include significant evidence *against* changes in one executive function when demands on the other executive function were experimentally increased. Finally, as noted above to our knowledge no ADHD conceptual models predict bidirectional causality (i.e., that increasing working memory demands would disrupt inhibitory control performance *and* increasing inhibitory control demands would disrupt working memory performance).

2 These percentages were not reported directly in Karalunas et al. (74), but were computed using the reported class overlap percentage, the reported number of children with ADHD in each class, and the total ADHD sample size.

Method

Transparency and openness

We report how we determined our sample size, all data exclusions (if any), all manipulations, and all measures in the study. Data were analyzed using JASP v.0.17.2.1 (87). All measure inclusion/exclusion decisions and analytic plans were made *a priori*, prior to accessing the data; however the study was not publicly pre-registered. Data/code and results output are available on our Open Science Framework website: https://osf.io/gts6x/. Descriptions in the *Participants*, *Group Assignment*, *Procedure*, *Overview*, *IQ/SES*, and *Bayesian* sections below are reproduced/adapted from our standard research/clinic recruitment and testing protocols licensed under CC BY 4.0.

Participants

The sample comprised 110 children (44 girls) ages 8 to 13 years (M=10.35, SD=1.30) from the southeastern United States recruited by or referred to the Children's Learning Clinic (CLC) through community resources (e.g., pediatricians, schools, self-referral) between July 2018 – March 2020 and October 2021 – August 2022 for participation in a larger study examining links between children's neurocognitive, attentional, and behavioral functioning. The gap reflects the COVID-19 shutdown followed by our COVID-19 health and safety protocol that temporarily reduced our research battery. The CLC is a research-practitioner training clinic that conducts developmental and clinical child research and provides no-cost diagnostic, psychoeducational, and treatment services. Its client base consists of children with suspected behavioral, learning, or emotional difficulties. Sample ethnicity was mixed and included 76 White Not Hispanic (69.1%), 16 Black or African American (14.5%), 6 Hispanic or Latino (5.5%), and 12 multiracial (10.9%) children.

As noted above, funding constraints prevented us from recruiting a typically developing sample (those without suspected psychological disorders) for the current experiment. Our recruitment strategy thus emphasized participation of children in need of clinical evaluation who were, and were not, suspected of having ADHD. Recruitment of a non-ADHD clinical sample allows for more robust control for the presence of these co-occurring diagnoses in the ADHD group (i.e., it allows us to draw stronger conclusions about processes implicated in ADHD specifically as opposed to processes that may appear to be impaired in ADHD due to the confounding influence of co-occurring conditions; 88). Additionally, given the large number of studies examining working memory and/or inhibitory control in ADHD versus neurotypical samples, our inclusion of a clinical comparison group can be considered a strength because it extends prior work by testing the extent to which ADHD-related impairments in executive functioning are evidenced above and beyond difficulties attributable to another common form of child psychopathology. Parents/children gave informed consent/assent; Florida State University Institutional Review Board approval was obtained/maintained.

Group assignment

All families completed a comprehensive psychoeducational evaluation that included detailed, semi-structured parent clinical interviewing (K-SADS; 89), parent and teacher rating scales (e.g., ADHD-RS-5, BASC-3; 90, 91), and norm-referenced child internalizing disorder screeners. Additional measures were administered based on clinical judgment and presenting problems to facilitate differential diagnosis and accurately capture clinical comorbidities (e.g., semi-structured child clinical interviews, additional testing). Parents received a psychoeducational report; children picked a toy (≤$5) from our prize box.

Three clinical groups of children participated in the current experiment: children with ADHD (without anxiety), children with ADHD + co-occurring anxiety (ADHD+ANX), and children with anxiety (without ADHD). Fifty-nine children (21 girls) met all of the following criteria and were diagnosed with ADHD (without anxiety) based on the comprehensive psychoeducational evaluation: (1) DSM-5 diagnosis of ADHD combined (n = 38), inattentive (n = 20), or hyperactive/impulsive (n = 1) presentations by the CLC's directing clinical psychologist and multidisciplinary team based on K-SADS and differential diagnosis considering all available clinical information indicating onset, course, duration, and severity of ADHD symptoms consistent with the ADHD neurodevelopmental syndrome; (2) borderline/clinical elevations on at least one parent and one teacher ADHD subscale (i.e., > 90th percentile); and (3) current impairment based on parent report. Children with any current ADHD presentation specifiers were eligible given the instability of ADHD presentations (92–94).

The ADHD+ANX group was comprised of an additional 28 children (11 girls) who met criteria for ADHD based on the criteria above (18 combined, 9 inattentive, 1 hyperactive/impulsive presentation), and also met criteria for one or more anxiety disorders (11 generalized, 10 social, 2 separation, 6 other specified, 5 specific phobia [dark]).[3] Finally, the ANX (without ADHD) group was comprised of 23 children (12 girls) who completed the same comprehensive psychoeducational assessment and did not meet criteria for ADHD, but met criteria and were diagnosed with one or more anxiety disorders (9 generalized, 7 social, 1 separation, 8 other specified, 1 specific phobia).

Several children in each group also met criteria for common clinical/learning disorders beyond ADHD and/or anxiety based on the comprehensive psychoeducational evaluation, including oppositional defiant disorder (6.4%)[4], autism spectrum disorders (13.6%), depressive disorders (6.4%), and specific learning disorders (20.0%). To improve generalizability given that comorbidity is the norm rather than the exception for children with ADHD (95), these children were retained in the sample. As described below, the distribution of these additional syndromes was generally evenly distributed among the three clinical groups. Psychostimulants ($N_{prescribed}$= 18) were withheld ≥24 hours prior to neurocognitive testing.

None of the children presented with gross neurological, sensory, or motor impairments that would preclude valid test administration, history of seizure disorder, intellectual disability,

psychosis, or non-stimulant medication that could not be withheld for testing.

Procedure

This experiment was embedded within a larger battery of counterbalanced executive and non-executive research tasks. Study procedures were identical to those reported in the Kofler et al. (85) experiment, with new tasks and a non-overlapping sample. Testing occurred during a larger battery of two, 3-hour sessions. Tasks were counterbalanced within/across sessions to minimize order/fatigue effects. Children whose counterbalancing resulted in them completing one or more of the low memory tasks after previous exposure to one or more of the high memory task variant(s) described below were explicitly told not to remember the colors. Children received brief breaks after each task and preset longer breaks every 2-3 tasks to minimize fatigue. Performance was monitored by an examiner stationed just outside the testing room to provide a structured setting while minimizing performance improvements associated with examiner demand characteristics (96).

Experiment overview

We created a dual dissociation experiment using four computerized tasks to experimentally address the directionality of inhibitory control and working memory deficits in ADHD (Table 2). Two of the four tasks were working memory complex span tasks, adapted for children based on principles underlying the classic reading span and counting span tasks (97), one with low inhibition demands (*word span* task = low inhibition, high working memory) and one with high inhibition demands (*stroop span* task = high inhibition, high working memory). The remaining two tasks omitted the memory demands but were otherwise identical to the complex span tasks: one with low inhibition demands (*word* task = low inhibition, low working memory) and one with high inhibition demands (*stroop* task = high inhibition, low working memory).

Task overview

One hundred and fifty (150) color/word stimuli were presented for each task. In all conditions, children were instructed to always respond to the font color (the color that the word is printed in) and to ignore the meaning of the word. None of the children presented with parent-reported color blindness, and as described below practice trials were completed to ensure children could correctly identify/name the font colors and fluently read the color words. Children responded by clicking colored response boxes on the screen (Figure 1). All tasks were self-paced with a pre-programmed break halfway through. Our *a priori* plan called for removal of anticipatory responses (trial RTs < 150 ms); however, no cases were identified. Internal consistency reliability was excellent for the current sample for all 4 tasks (α=.92-.95).

Practice trials

On-screen performance feedback (correct, incorrect) was provided for every practice response/trial. All task variants began with two practice phases (6 trials each; 80% correct required): In the first practice phase (color naming), children were shown colored rectangles, one at a time, and instructed to verbally name the color. For the second practice phase (color word reading), children were shown color words in black font and asked to read the word and click the response box that matched the word's meaning (e.g., see the word "red" and click the red colored response box).

For the low inhibition tasks (i.e., non-stroop variants: *word*, *word span*), the third practice phase presented neutral, non-color words (e.g., the word "the" printed in red font) and children were required to respond based on the printed font color while ignoring the word meaning (6 trials; 80% correct required). For the high inhibition tasks (i.e., stroop variants: *stroop*, *stroop span*), the third practice phase presented color words printed in incongruent colors (e.g., the word "red" printed in blue font) and children were required to respond based on the printed color while ignoring the word meaning (6 incongruent trials; 80% correct required).

For the high working memory variants *(word span*, *stroop span*), a final practice phase introduced the memory component. This practice phase mirrored the stroop (for *stroop span*) or non-stroop (for *word span*) third practice phase described above, except this time children were instructed to remember the colors in the order presented. For these high working memory conditions, practice trials at memory set 4 were terminated after two 100% correct recall trials.

High inhibition, low working memory

For the stroop color-word identification task (i.e., *stroop* task), children were presented with color words (red, orange, yellow, green, blue, purple) printed in font colors that either matched or did not match the meaning of the color word, one at a time, on the computer monitor. The task's inhibition demands occur because of the overlearned, automatic tendency to read words, combined with task instructions to ignore the word's meaning and instead respond based on the word's font color. The task's well-documented interference effects occur when the color word is printed in a color different than the word's meaning (e.g., the word 'red' printed in blue font), requiring inhibitory control processes to stop the automatic word reading while prioritizing the less automatic color recognition (98).

The stroop task was considered ideal for inducing inhibition processes in the current experiment (99) because it is thought to place demands on both the response inhibition and interference control subcomponents of the inhibitory control construct (100).

3 As noted below, the pattern and interpretation of results was unchanged in sensitivity analyses excluding children whose only anxiety diagnosis was a specific phobia.

4 As recommended in the K-SADS, oppositional-defiant disorder (ODD) was diagnosed only with evidence of multi-informant/multi-setting symptoms.

TABLE 2 Fully-crossed experimental design overview.

		Working Memory Demands	
		Low	High
Inhibitory Control Demands	Low	**Word-Color ('Word') Task** Children identify the font color of each neutral (non-color) word	**Word-Color Span ('Word Span') Task** Identical to the Word-Color Task, with the addition of a recall phase after every 6 stimuli.
	High	**Stroop Color-Word ('Stroop') Task** Children identify the font color of each color word. On 20% of trials, the font color and the printed word do not match, creating interference effects.	**Stroop Color-Word Span ('Stroop Span') Task** Identical to the Stroop Task, with the addition of a recall phase after every 6 stimuli.

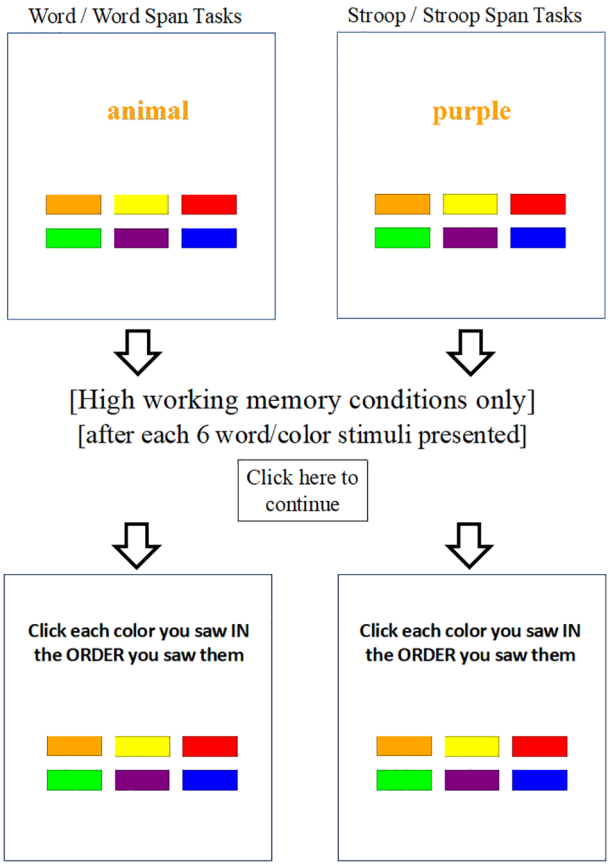

FIGURE 1
Fully-crossed experimental manipulation of working memory and inhibition demands. Each of the 4 counterbalanced tasks presented 150 stimuli, randomly without replacement. High inhibition (i.e., stroop) conditions presented color words and featured an 80:20 ratio of congruent (printed word matches the font color) and incongruent (printed word does not match the font color) trials to maximize prepotency/inhibition demands on the critical incongruent trials. Low inhibition (i.e., word/non-stroop) conditions were identical to the high inhibition versions except they presented neutral, non-color words. Each of the two low/high working memory task pairs were identical except for the omission or addition of concurrent working memory demands. Words/icons outside the boxes were not shown on screen, but are included here to illustrate differences across the four otherwise identical experimental tasks. Note: 'animal' and 'purple' in this example are both printed in orange font color (correct response = clicking orange response box for both). Response boxes from left to right are (top row) orange, yellow, red, (bottom row) green, purple, blue.

The 'experimental stroop' was preferred over the classic version included in standardized neuropsychological test batteries. This decision was made because the latter have been criticized for presenting blocks of all incongruent trials, which reduces prepotency and thus evokes lower demands on the inhibitory control process of primary interest (99, 101). Thus, as recommended by Snyder et al. (99) and following Kane and Engle (61; Experiment 4), our 'experimental stroop' task featured an 80:20 ratio of trials that did not vs. did require participants to inhibit their automatic/prepotent response to reading the color word (24, 99). Thus, on 120 of the 150 trials (80%), the printed word and the word's font color matched (*congruent trials*; e.g., the word 'red' printed in red font). On the critical 30 *incongruent trials* (20%), the printed word and its font did not match (e.g., the word 'red' printed in blue font).

Following Kane and Engle (61), for analytic purposes, 30 of the congruent trials were labeled as 'critical' congruent trials, and the remainder were labeled as 'filler' trials. This labeling occurred in the software backend for scoring purposes; there was no observable distinction between filler and critical congruent trials for participants. All 30 incongruent trials were 'critical' trials. The dependent variables for the stroop task were median response times to correct trials (RT; milliseconds) and accuracy (% correct), separately for the incongruent and critical congruent trials. Median RT was used *in lieu* of mean for all tasks given the well documented variability in reaction times in children with ADHD that are attributable to positive skew (102).

Low inhibition, low working memory

The word-color identification task (i.e., *word* task) was identical to the stroop task except that neutral, non-color words were presented. As with the stroop task, children were instructed to respond based on the font color of the word. The same colored response boxes were used on all tasks (Figure 1); thus, there were no response options related to the meaning of these non-color words (i.e., no interference effects are expected because reading the words does not activate any of the available response options). The neutral words were selected to match the letter length of the stroop condition's color words (the/red, animal/orange, letter/yellow, house/green, word/blue, number/purple). Following Kane and Engle (61), thirty of the stimuli were randomly labeled as 'critical congruent' and an additional 30 were randomly labeled as 'critical incongruent' in the software backend to match the stroop task for scoring and analysis purposes. The dependent variables for the word task were median response times to correct trials (RT; milliseconds) and accuracy (% correct), separately for the 'critical incongruent' and 'critical congruent' trials.

High inhibition, high working memory

For the current experiment, we created a task that combined the experimental stroop task with classic complex span (dual-processing working memory) task design as described above (29, 97, 103). The stroop complex span task (i.e., *stroop span*) was identical to the stroop task except that a recall phase was inserted after every 6 color-word stimuli (25 total recall trials). During the recall phase, children were tasked with remembering and clicking the response boxes corresponding to the font colors that were presented, in the order that they were presented for that trial. Dependent variables are the same as those described for the stroop task, as well as recall accuracy (% of stimuli recalled correctly). Accuracy data based on recall of colors that were presented as congruent and incongruent stimuli were recorded separately to allow more nuanced examination of the extent to which color-word inhibition processes interfere with the encoding of to-be-recalled stimuli.

Low inhibition, high working memory

The word-color identification complex span task (i.e., *word span*) was identical to the stroop span task, except that it used the neutral, non-color words from the word task. Dependent variables are identical to the stroop span task, with 'critical congruent' and 'incongruent' stimuli defined randomly in the software backend as described above for the word task.

Primary outcomes: working memory

The proportion of stimuli correct per trial (% recalled correctly) during the recall phases of the word span and stroop span tasks was used to assess working memory capacity as recommended (29, 97). Performance was assessed for each child separately for each of the two complex span tasks (word span, stroop span). By design, there was no recall phase during the low working memory conditions. Following Kofler et al. (29), scores from these conditions reflect initial encoding accuracy. In other words, the low working memory conditions control for encoding, because the high working memory conditions involve both encoding and working memory maintenance/recall (29, 97). As argued previously (29), we prefer the term "low" rather than "no" working memory because at least some working memory demands are likely involved in all tasks (e.g., maintaining rule sets, attentional control to task demands). As noted above, scores were computed separately for 'congruent' and 'incongruent' stimuli as defined above, which were both included in the statistical models as a within-subjects factor (Trial Type). Higher scores reflect better working memory.

Primary outcomes: inhibitory control

Response times (median RTs to correct trials; milliseconds) and accuracy (% correct) during the primary color identification component of each task were used to assess the components of task performance that are compared to assess individual differences in inhibitory control. Thus, separate scores were recorded for incongruent trials and critical congruent trials as described above, and both were included in each statistical model as a within-subject factor (Trial Type). Smaller reductions in speed and/or accuracy during incongruent relative to congruent trials during the high inhibition tasks (reflected in the within-subject effect Inhibition Low/High x Trial Type Congruent/Incongruent interaction described below) reflect better inhibitory control.

Intellectual functioning (IQ) and socioeconomic status (SES)

IQ was assessed using the 4-subtest Short Form of the *Wechsler Intelligence Scale for Children, Fifth Edition* (WISC-V) (104). SES was estimated using the Hollingshead scoring based on caregiver(s)' education and occupation (105).

Bayesian analyses

Both Bayes Factors (BF) and *p*-values are reported as recommended (106). Bayes Factors are included because they estimate the magnitude of support for both the alternative hypothesis and the null hypotheses, and are thus able to provide support for the null hypothesis rather than just failing to reject it (107). BF_{10} indicates how much more likely the alternative hypothesis (H_1) is relative to the null hypothesis (H_0). BF_{01} is the inverse of BF_{10} (i.e., $BF_{01}=1/BF_{10}$), and is reported when the evidence favors the null hypothesis. As recommended, we used the 'test, then estimate' method, such that we first tested whether an effect likely exists (via *p*-value/Bayes Factor) and then estimated the magnitude (effect size) for significant effects; when the evidence favors the null hypothesis, the most parsimonious effect size estimate is 0.0 (108).

Data analysis overview

The current study used a fully-crossed 2x2 experimental design (within-subjects effects: Inhibition demands Low/High x Working Memory demands Low/High), with 3 groups (between-subjects effect: Group = ADHD, ADHD+ANX, ANX), and 2 outcomes per task (within-subjects effect: Trial Type = Incongruent, Congruent). We thus examined the study's primary hypotheses via mixed-model ANOVAs, using both classical (frequentist) and Bayesian statistics. Following manipulation checks to ensure that each experimental manipulation successfully engaged its target executive function as intended, Tier 1 probed for effects of experimentally increasing inhibition demands on working memory performance (DV: percent correctly encoded or encoded +recalled). Tier 2 tested for effects of increasing working memory demands on inhibitory control performance, with one model for speed (DV: RT to correct trials) and one model for accuracy (DV: % correct). Exploratory analyses were conducted in Tier 3 to probe for alternative explanations for the obtained pattern of results.

Results

Power analysis

To our knowledge, power analysis for Bayesian repeated-measures ANOVA is not yet available. Power analysis with G*Power (v3.1; 109) based on traditional NHST, with alpha=.05, power=.80, 3 groups, and 8 measurements (the 4 tasks described above, with 2 variables from each task in each model) indicates that our N=110 can reliably detect within-group and interaction effects of d=0.20, and between-group effects of d=0.46 or larger. Thus, the study is sufficiently powered to address its primary aims.

Preliminary analyses

Outliers ≥3 *SD* were winsorized relative to the within-group distribution (ADHD=1.6%, ADHD+ANX=2.0%, ANX=0.40% of data points). All parent and teacher ADHD symptom ratings were higher for the ADHD and ADHD+Anx groups relative to the (non-ADHD) ANX group as expected, with one exception (p=.06; Table 3). As shown in Table 3, the groups were equivalent or did not differ based on sex, SES, ethnicity, or co-occurring conditions including ASD, SLD reading, and SLD math. In contrast, all of the ODD cases were in the ADHD-only group, and the ANX group was slightly older than both the ADHD and ADHD+ANX groups, who were equivalent. As described below, sensitivity analyses indicated that the results were robust to control for age. This is the first reporting of data from any of these tasks for any children in the current sample, and none of the children in the current sample were included in any of our prior experimental studies.

Manipulation check

Evidence supporting the success of the separate working memory and inhibitory control experimental manipulations would be (1) for the inhibitory control manipulation, evidence of significant decreases in response times and/or accuracy during incongruent relative to congruent trials only for the high inhibition tasks (indicating that the high inhibition conditions elicited significantly higher stroop interference effects than the low inhibition conditions), and (2) for the working memory manipulation, significantly lower correct recall rates during high working memory (encoding + recall) conditions relative to correct encoding rates during the low working memory (encoding-only) conditions (indicating that the high working memory conditions successfully required working memory processes). As detailed below, both experimental manipulations were successful (i.e., the data were >500 million times more likely under the hypothesis that the manipulations were successful than under the null hypothesis that they were unsuccessful).

Specifically, there was decisive evidence that our manipulation to increase inhibitory control demands successfully evoked high inhibition demands as evidenced by significant Inhibition Demands (Low, High) x Trial Type (Incongruent, Congruent) interactions for both response times ($BF_{10}=5.33 \times 10^8$, $p<.001$) and accuracy ($BF_{10}=76.50$, $p=.002$). *Post-hocs* confirmed the success of the manipulation because this effect was specific to the high inhibition conditions, with the difference between incongruent and congruent trials significant for both RT and accuracy during the high inhibition (RT: $d=-0.60$, $BF_{10}=1.72 \times 10^6$, $p<.001$; accuracy: $d=0.38$, $BF_{10}=2.77 \times 10^3$, $p<.001$) but not low inhibition (RT: $BF_{01}=1.23$, $p=.07$; accuracy: $BF_{01}=3.07$, $p=.18$) conditions. In

TABLE 3 Sample and demographic variables.

Variable	ADHD (*n*=59)		ADHD+ANX (*n*=28)		ANX (*n*=23)		*p*	BF_{10}	BF_{01}	*Post-hocs*
	M	*SD*	*M*	*SD*	*M*	*SD*				
Sex (Girls/Boys)	21/38		11/17		12/11		.39, *ns*		5.17	–
Ethnicity (B/H/M/W)	10/4/6/39		2/1/5/20		4/1/1/17		.65, *ns*		277.30	–
Age	10.26	1.30	9.97	1.24	11.05	1.14	.008	4.56		ADHD = ADHD+ANX < ANX
SES	48.08	8.37	49.27	8.37	47.59	9.24	.77, *ns*		8.68	–
Maternal education level (P/HS/A/B/G)	2/7/12/15/23		1/2/4/12/9		0/1/3/8/11		.79, *ns*		6.69×10^3	–
WISC-V SFIQ (Std. Score)	100.20	14.80	104.50	13.43	102.40	11.48	.40, *ns*		5.01	–
Anxiety Diagnoses (N/Y)										
Generalized AD	59/0		17/11		14/9		<.001	6.65×10^5		ANX = ADHD+ANX > ADHD
Social AD	59/0		18/10		16/7		<.001	3.18×10^4		ANX = ADHD+ANX > ADHD
Separation AD	59/0		26/2		22/1		.14, *ns*		15.16	ANX = ADHD+ANX = ADHD
Other Specified AD	59/0		22/6		15/8		<.001	2.64×10^3		ANX = ADHD+ANX > ADHD
Specific Phobia	59/0		23/5		22/1		.003	2.52		ANX = ADHD+ANX > ADHD
ADHD Symptoms (T-scores)										
BASC-3 Attention Pxs										
Parent	68.75	7.10	69.43	7.82	64.73	8.48	.06, *ns*		1.22	–
Teacher	68.92	6.38	63.04	10.37	58.85	7.95	<.001	4.96×10^3		ADHD > ADHD+ANX = ANX
BASC-3 Hyperactivity/Imp										
Parent	67.14	13.93	70.14	8.78	61.27	14.47	.05		1.11	ADHD = ADHD+ANX > ANX
Teacher	65.97	16.01	60.50	14.75	51.20	9.53	<.001	39.54		ADHD > ANX = ADHD+ANX
Working Memory Recall Performance (% Stimuli Correct)										
Word Span										
Congruent Trials	.53	.22	.53	.23	.77	.10	<.001	1.13×10^3		ANX > ADHD = ADHD+ANX
Incongruent Trials	.52	.22	.51	.23	.75	.14	<.001	298.96		ANX > ADHD = ADHD+ANX
Stroop Span										
Congruent Trials	.53	.20	.59	.21	.72	.16	<.001	39.24		ANX > ADHD = ADHD+ANX

(Continued)

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TABLE 3 Continued

Variable	ADHD (*n*=59)		ADHD+ANX (*n*=28)		ANX (*n*=23)		*p*	BF_{10}	BF_{01}	*Post-hocs*
	M	*SD*	*M*	*SD*	*M*	*SD*				
Working Memory Recall Performance (% Stimuli Correct)										
Incongruent Trials	.52	.22	.57	.23	.72	.17	<.001	33.91		ANX > ADHD = ADHD+ANX
Response Times (Color Naming) (RTs; milliseconds)										
Word										
Congruent Trials	1362.16	391.11	1429.61	463.01	1098.10	179.32	<.001	6.22		ANX < ADHD = ADHD+ANX
Incongruent Trials	1405.89	409.56	1524.37	509.63	1140.58	213.63	<.001	8.20		ANX < ADHD = ADHD+ANX
Stroop										
Congruent Trials	1349.75	406.18	1348.07	344.07	1242.16	294.92	.36, *ns*		5.92	–
Incongruent Trials	1665.84	554.05	1719.64	572.97	1484.03	397.13	.15, *ns*		3.73	–
Word Span										
Congruent Trials	1537.17	474.08	1729.43	521.62	1555.31	540.58	.26, *ns*		3.28	–
Incongruent Trials	1648.50	622.85	1704.68	467.19	1660.70	721.63	.89, *ns*		9.98	–
Stroop Span										
Congruent Trials	1628.65	611.84	1735.00	498.64	1532.50	562.27	.40, *ns*		5.83	–
Incongruent Trials	1928.15	666.43	2053.63	634.94	1814.63	501.77	.33, *ns*		5.26	–
Accuracy (Color Naming) (% Stimuli Correct)										
Word										
Congruent Trials	0.99	0.03	0.99	0.02	0.998	0.01	.06, *ns*		5.04	–
Incongruent Trials	0.98	0.04	0.99	0.02	0.997	0.01	.02		2.13	ANX > ADHD; ADHD = ADHD +ANX; ANX = ADHD+ANX
Stroop										
Congruent Trials	0.996	0.02	0.98	0.10	0.998	0.01	.34, *ns*		3.11	–
Incongruent Trials	0.97	0.04	0.96	0.10	0.97	0.03	.67, *ns*		6.34	–
Word Span										
Congruent Trials	0.98	0.04	0.97	0.08	0.999	0.01	.002		1.41	ANX > ADHD; ADHD = ADHD +ANX; ANX = ADHD+ANX

(Continued)

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TABLE 3 Continued

Variable	ADHD (*n*=59)		ADHD+ANX (*n*=28)		ANX (*n*=23)		*p*	BF_{10}	BF_{01}	*Post-hocs*
	M	*SD*	*M*	*SD*	*M*	*SD*				
Accuracy (Color Naming) (% Stimuli Correct)										
Incongruent Trials	0.97	0.07	0.96	0.09	0.995	0.01	.003		2.43	ANX > ADHD; ADHD = ADHD +ANX; ANX = ADHD+ANX
Stroop Span										
Congruent Trials	0.98	0.03	0.96	0.09	0.996	0.01	<.001	1.31		ANX > ADHD; ADHD = ADHD +ANX; ANX = ADHD+ANX
Incongruent Trials	0.95	0.07	0.95	0.06	0.98	0.03	.045		3.40	ANX > ADHD; ADHD = ADHD +ANX; ANX = ADHD+ANX

BF_{10}, Bayes Factor for the alternative hypothesis over the null hypothesis. BF_{01}, Bayes Factor for the null hypothesis over the alternative hypothesis ($BF_{01}=1/BF_{10}$). P-values are not corrected for family-wise error, and are included to allow interested readers to compare Bayesian and frequentist results. AD, Anxiety Disorder; BASC, Behavior Assessment System for Children. Ethnicity; B, Black or African American; H, Hispanic or Latino; M, Multiracial; White, White Not Hispanic; WISC-V, Wechsler Intelligence Scale for Children, Fifth Edition.
Maternal education: P = partial high school, HS = high school diploma, A = associate's degree, B = bachelor's degree, G = graduate degree.
ns = not significant.

other words, interleaving incongruent and congruent trials within the stroop tasks successfully increased inhibitory control demands relative to the non-stroop tasks as intended.

Similarly, the evidence decisively supported an effect of working memory load on performance (Working Memory Low/High: $BF_{10} = 3.85x10^{14}$, p<.001), such that the high working memory conditions (encoding+recall) evoked higher working memory demands than the low working memory (encoding-only) conditions as intended. Given the success of these manipulations, we next examine whether each manipulation evoked performance decrements on tests/metrics intended to measure the other executive function, and whether these hypothesized effects differentially affected children with ADHD.

Tier 1: effects of inhibitory control demands on working memory performance (working memory performance as DV)

The 2 (within-subjects factor Inhibition Demands: low/high) x 2 (within-subjects factor Working Memory Demands: low/high) x 2 (within-subjects factor Trial Type: incongruent/congruent) x 3 (between-subjects factor Group: ADHD, ADHD+ANX, ANX) mixed-model ANOVA with working memory performance as the DV provided significant evidence for main effects of group ($BF_{10}=2.79 \times 10^3$, p<.001; described below) and trial type ($BF_{10}=3.65$, p=.008, d=0.09; slightly better recall for congruent stimuli). Please see the *Manipulation Check* section above for the main effect of the working memory factor on working memory performance (Figure 2, bottom row). There was strong evidence for the group x working memory interaction ($BF_{10}=2.30 \times 10^3$, p<.001, *d*=1.00) with *post-hoc* tests indicating that all 3 groups showed lower encoding+recall during the high working memory conditions vs. their encoding during the low working memory conditions (*d*=1.69-3.09). The interaction was due to larger decreases in recall accuracy (% correct) for the ADHD and ADHD+ANX groups, relative to the ANX-only group. Specifically, the 3 groups did not differ statistically during the low working memory conditions (BF_{01}=1.48-3.85, p>.99). In contrast, the ADHD (BF_{10}=59.86, p<.001, d=1.45) and ADHD-ANX (BF_{10}=100.15, p<.001, d=1.23) groups showed similar large magnitude impairments relative to the ANX group under high working memory conditions (ADHD/ADHD+ANX: BF_{01}=2.76, p=.93; Figure 2, bottom row).

Importantly, there was strong evidence *against* the hypothesis that increasing inhibition demands would impact working memory performance (main effect of inhibition demands: BF_{01}= 8.52, p=.85; inhibition x trial type interaction: BF_{01}=6.25, p=.55) (Figure 2, top row). There was also evidence against the group x inhibition demands (BF_{01}=2.51, p=.39), inhibition demands x working memory demands (BF_{01}=10.75, p=.34), group x inhibition demands x trial type (BF_{01}=10.42, p=.81), and the 4-way interaction (BF_{01}=5.62, p=.66), indicating that experimentally increasing inhibition demands failed to impact working memory performance in clinically evaluated children with ADHD and/or anxiety. Taken together, these findings indicate

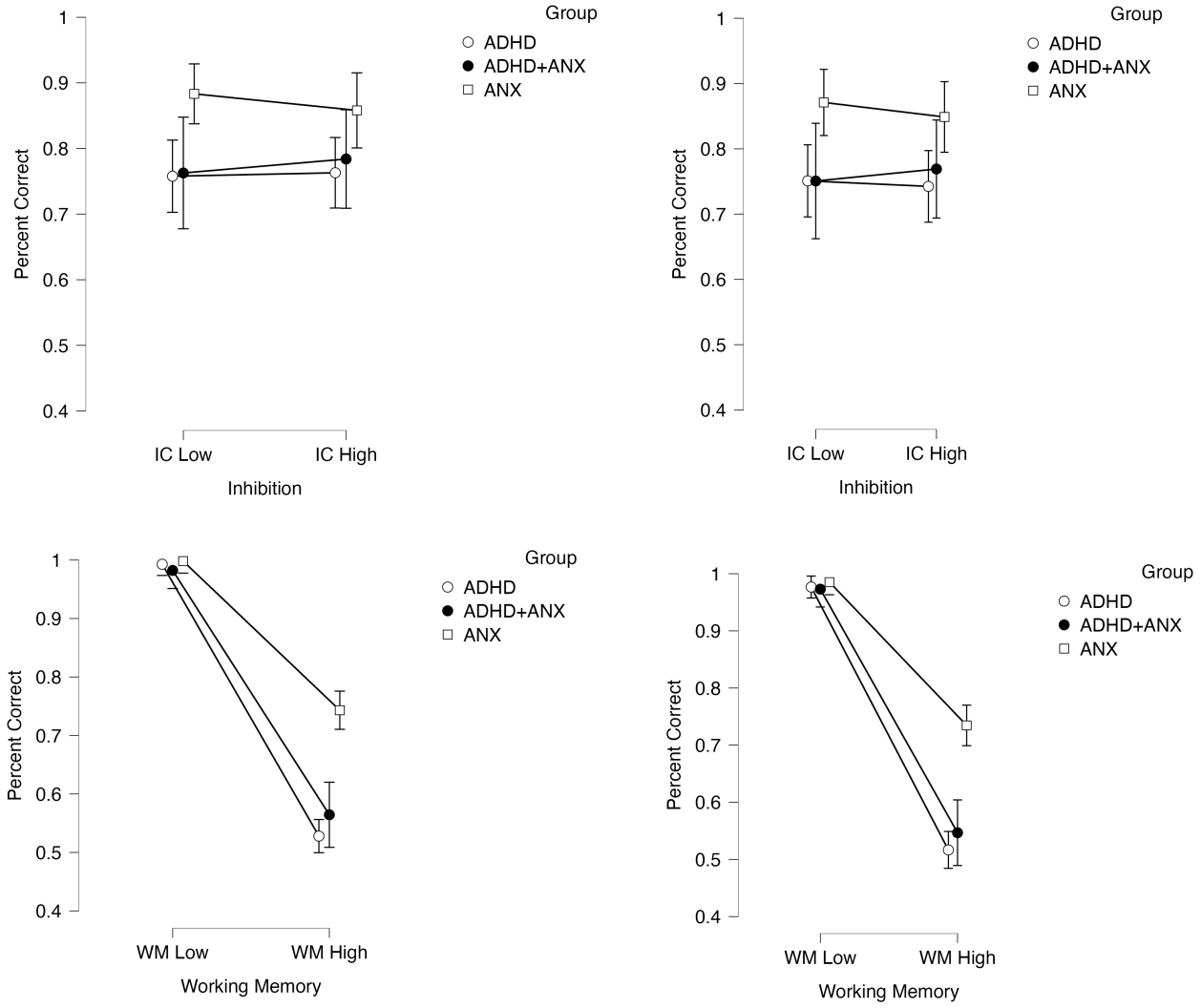

FIGURE 2
Effects of the inhibition and working memory manipulations on working memory performance (DV: percent correct) as a function of experimentally increasing inhibition demands (top row) and increasing working memory demands (bottom row). Effects are shown separately for congruent trials (left) and incongruent trials (right column). Error bars reflect 95% confidence intervals.

that ADHD is associated with large magnitude impairments on working memory tests, while providing significant evidence *against* the hypothesis that these impairments are secondary to underlying inhibitory control deficits that affect working memory performance. In other words, inhibitory control processes do not appear to affect the performance of children with ADHD (with or without anxiety) on tests of working memory.

Tier 2: effects of working memory demands on inhibitory control performance (response times and accuracy as DVs)

Response time model. Results of the 2 (within-subjects factor Inhibition Demands: low/high) x 2 (within-subjects factor Working Memory Demands: low/high) x 2 (within-subjects factor Trial Type: incongruent/congruent) x 3 (between-subjects factor Group: ADHD, ADHD+ANX, ANX) mixed-model ANOVA indicated decisive support for an effect of increasing working memory demands on slowing response times during the primary color identification tasks (main effect of working memory demands: BF_{10}=3.71 x 10^9, p<.001, d=1.53). Please see the *Manipulation Check* section above for the main effect of the inhibition manipulation on interference-related slowing (Figure 3, top row). In contrast, there was no evidence for, and in most cases significant evidence *against*, group x working memory demands (BF_{01}=3.14, p=.24), working memory demands x inhibition demands (BF_{01}=5.24, p=.98), group x working memory demands x trial type (BF_{01}=3.64, p=.10), and the 4-way interaction (BF_{01}=2.34, p=.62). These findings indicate that experimentally increasing working memory demands affects the inhibition and non-inhibition components of these tasks equivalently for clinically-evaluated children (Figure 3, bottom row). Notably, there was also no evidence for, and in most cases significant evidence *against*, effects of group

(BF_{01}=1.29, p=.17), group x inhibition demands (BF_{01}=10.75, p=.82) and group x inhibition demands x trial type (BF_{01}=5.38, p=.41), indicating that children with ADHD (with or without anxiety) did not demonstrate impaired inhibition (based on response speeds) relative to the ANX group.

Accuracy model. Results of the 2 (within-subjects factor Inhibition Demands: low/high) x 2 (within-subjects factor Working Memory Demands: low/high) x 2 (within-subjects factor Trial Type: incongruent/congruent) x 3 (between-subjects factor Group: ADHD, ADHD+ANX, ANX) mixed-model ANOVA indicated decisive support for an effect of increasing working memory demands on reducing accuracy during the primary color identification tasks (main effect of working memory demands: BF_{10}=317.42, p<.001, d=0.67). The main effect of the inhibition manipulation on interference-related accuracy reductions is described in the *Manipulation Check* section above (Figure 4, top row). There was significant evidence *against* the working memory demands x inhibition demands (BF_{01}=9.35x10^5, p=.74), group x working memory demands x trial type (BF_{01}=10.75, p=.53), and the 4-way interaction (BF_{01}=100.00, p=.64), indicating that experimentally increasing working memory demands equally affected children's accuracy on both the inhibition and non-inhibition components of these tasks.

In contrast, there was a significant main effect of group (BF_{10}=3.79, p=.05, d=0.47; ADHD = ADHD+ANX < ANX), and the group x working memory demands interaction was supported based on *p*-value but not Bayes Factor (BF_{01}=1.46, p=.04, d=0.41).[5] *Post-hocs* for these effects indicated that both ADHD groups showed reduced accuracy across tasks relative to the ANX group. Specifically, the interaction was attributable to the ADHD group (BF_{10}=734.4, p=.007, d=0.31) and potentially the ADHD+ANX group (BF_{10}=1.88, p=.03, d=0.38) demonstrating significant reductions in color naming accuracy when working memory demands were increased, whereas this manipulation failed to affect accuracy for the ANX-only group (BF_{01}=8.40, p>.99; Figure 4, bottom row).

Finally, there was significant evidence *against* effects of group x inhibition (BF_{01} = 9.90, p=.53) and group x inhibition x trial type

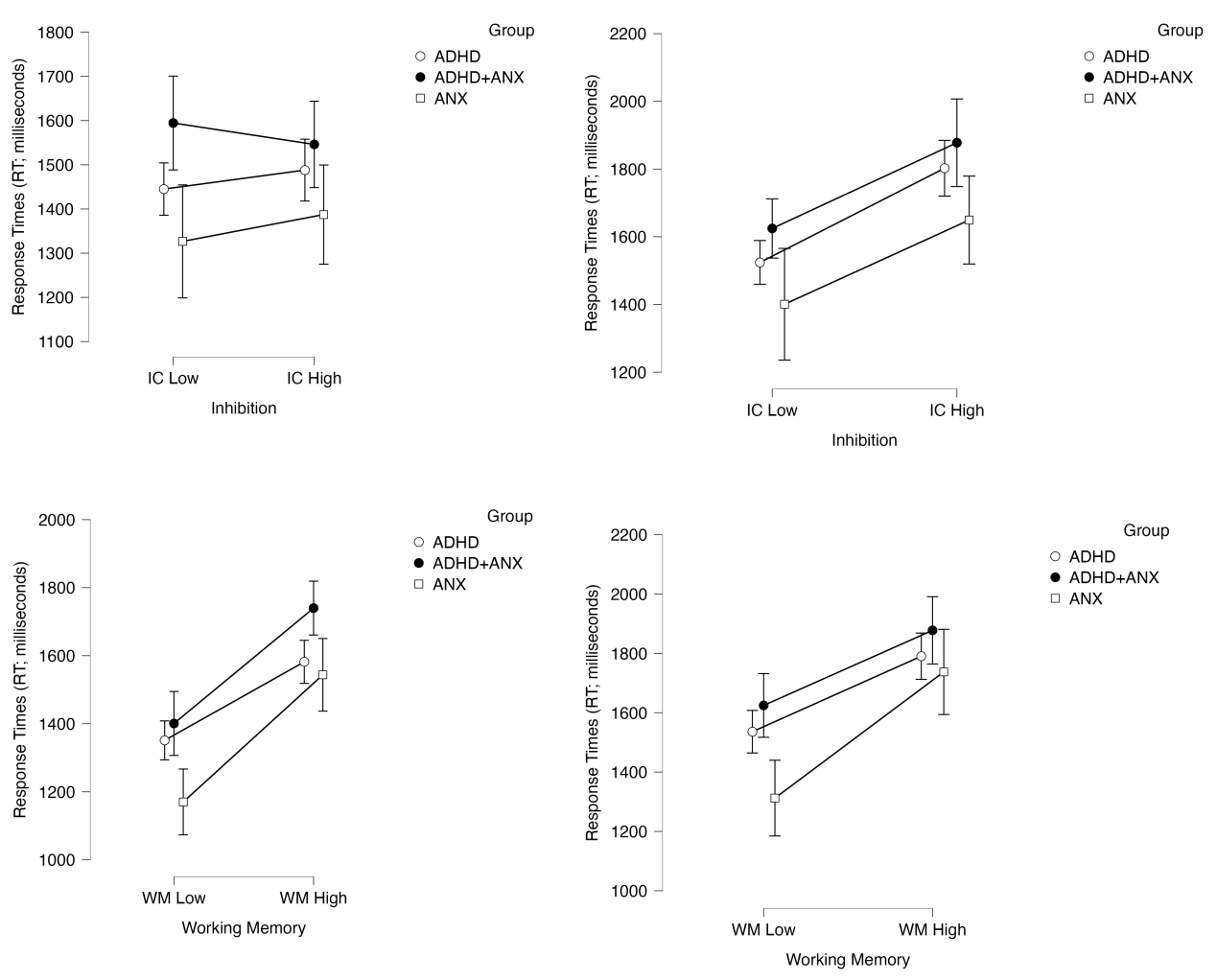

FIGURE 3
Effects of the inhibition and working memory manipulations on response times to correct color naming responses (DV: milliseconds) as a function of experimentally increasing inhibition demands (top row) and increasing working memory demands (bottom row). Effects are shown separately for congruent trials (left) and incongruent trials (right column). Error bars reflect 95% confidence intervals.

(BF_{01}=7.30, p=.53). Combined with the group/group x working memory *post-hoc*s reported above, these findings indicated that the significant main effect of group was attributable to similarly reduced accuracy across the inhibition and non-inhibition components of these tasks, combined with potentially disproportionate reductions across the inhibition and non-inhibition task components as working memory demands increased for children with ADHD (with and without anxiety) relative to children with ANX.

Overall, results of the primary analyses (a) confirmed that our manipulations of working memory and inhibition were successful; and (b) demonstrated that experimentally occupying clinically evaluated children's limited capacity working memory system produces slower response times and reduced accuracy on inhibition tasks – and does so equivalently across the inhibition and non-inhibition components of these tasks. For children with ADHD specifically, these results also (c) provided evidence *against* conceptual models that view working memory deficits as secondary outcomes of underlying inhibition deficits in ADHD; (d) indicated that children with ADHD with and without co-occurring anxiety exhibited similar, large magnitude working memory deficits (d=1.23-1.45); (e) showed that children with ADHD exhibit reduced accuracy on inhibition tasks (d=0.47), but that this impairment was not attributable to the tasks' inhibition demands (i.e., the difficulties were equivalent across the low and high inhibition conditions); and (f) provided evidence that increasing working memory demands may differentially reduces accuracy (but not response times) on inhibition tests for children with ADHD, and also exerts this influence on the non-inhibition components of these tasks. Taken together, working memory appears to reflect an underlying mechanism that broadly affects children's ability to inhibit prepotent tendencies and maintain fast and accurate performance more generally. Working memory may also explain, in large part, the impairments that children with ADHD exhibit on accuracy-based estimates of inhibitory control. Conversely, ADHD-related inhibition deficits, when present, do not appear to be responsible for ADHD-related difficulties on working memory complex span tests. More generally, depleting inhibitory resources via a stroop paradigm did not interfere with children's working memory performance.

5 We conducted exploratory analyses to test the hypothesis that the inconsistent frequentist/Bayes results for this model were due to excessive variability in the ADHD+ANX group relative to the ADHD and ANX groups (see 95%CIs in Figure 4). This hypothesis was confirmed: With the ADHD+ANX removed, the frequentist and Bayesian group x working memory interaction results for accuracy was more consistent (BF_{10}=2.03, p=.02, d=0.50). Still, the strength of the evidence was less strong relative to the other significant results (i.e., the data were only twice as likely under the alternative hypothesis that an effect exists than under the null hypothesis of no effect). Thus, we discuss these findings using more tentative language (e.g., 'potentially', 'appears to'). Significance/interpretation of all other main/interaction effects were consistent with the main text. For completeness, we also checked the RT and working memory recall models; the significance/interpretation of all main/interaction effects remained unchanged with the ADHD+ANX group removed.

Tier 3: sensitivity analyses

Finally, we conducted a series of sensitivity analyses to probe the robustness of our findings and impact of our *a priori* decisions to (a) exclude age as a covariate to conserve power; (b) include children with co-occurring ASD in the sample; (c) retain children diagnosed with reading disabilities in the sample; and (d) categorize children whose only anxiety diagnosis was specific phobia as ANX/ADHD +ANX. Reporting is truncated for readability. First, we repeated the primary Tiers 1 and 2 models, this time covarying child age given the unexpected finding that the ANX group was slightly older than both ADHD groups. Age did not produce a significant main effect or interact with any main or interaction terms in the models with working memory performance (p>.08, BF_{01}>1.47) or inhibition accuracy (p>.29, BF_{01}>3.58). In contrast, in the inhibition RT (speed) model, age demonstrated a significant main effect (p<.001, $BF_{10}=1.42x10^3$; older children demonstrated faster response times) but age did not interact with any main or interaction terms in the models to affect response times (p>.08, BF_{01}>1.43).

Next, we repeated the primary analyses a second time, this time excluding children with ASD (*n*=15). Results of all models were unchanged with these children excluded, with one minor exception: The main effect of group in the inhibition accuracy model became non-significant at p=.06 (BF_{10}=1.08) despite a near identical effect size compared to the primary analyses (d=0.50 with ASD excluded vs. 0.48 in the primary model), suggesting this was likely an artifact of lower power rather than specific to our decision to retain children diagnosed with ASD in our study. We then tested the extent to which the results were impacted by our retention of children with reading disabilities in the sample given that reading the color words is necessary to evoke their interference effects. As noted above, all children were able to fluently read the color words based on practice trials, and the manipulation check provided decisive evidence that the high inhibition tasks elicited the expected interference effects. Thus, it was unsurprising that the pattern and interpretation of results was unchanged when children with reading disabilities (n=17) were excluded. Finally, we probed our decision to categorize children with specific phobias (all 6 = phobias of the dark) with the other anxiety disorders, given that the novel, evaluative setting with unfamiliar adults likely did not evoke anxiety symptoms that might interfere with test performance for these children like it presumably would for children with anxiety disorders characterized by performance evaluation (social, generalized) and/or separation worries (81). The pattern and interpretation of results was unchanged with these children excluded.

Discussion

The current study was among the first to use a dual-dissociation experimental design to systematically manipulate demands on both working memory and inhibitory control in a relatively large, clinically evaluated, and carefully phenotyped sample of children with ADHD and/or anxiety, with implications for conceptual

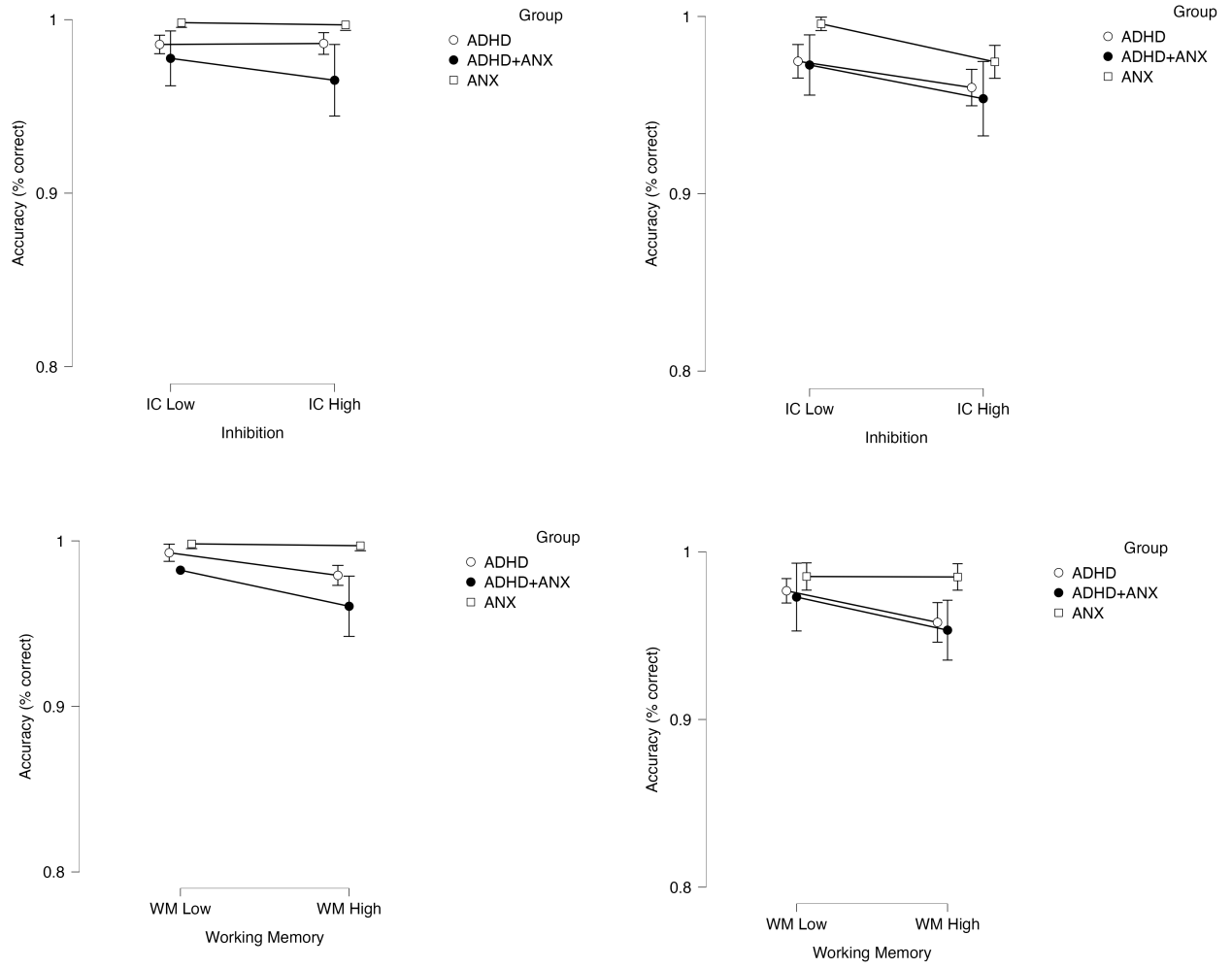

FIGURE 4
Effects of the inhibition and working memory manipulations on color naming accuracy (DV: percent correct) as a function of experimentally increasing inhibition demands (top row) and increasing working memory demands (bottom row). Effects are shown separately for congruent trials (left) and incongruent trials (right column). Error bars reflect 95% confidence intervals.

models of the primacy and relevance of core executive functions in ADHD. Confidence in the findings is supported by study strengths including (a) decisive evidence that both experimental manipulations were successful, (b) comparison of the ADHD group to a clinical comparison group of children with anxiety disorders as well as a group of children with both ADHD and anxiety, (c) relatively large sample size (for clinical child research), (d) adoption of the experimental stroop paradigm that provides improved construct validity relative to classic neuropsychological versions (99), and (e) the experimental design that allows stronger conclusions regarding causality.

Overall, we found strong evidence that depleting inhibitory resources (via a stroop interference paradigm) does *not* impact children's performance on working memory tests – a null finding that was equivalent for all three clinical groups. In contrast, we found decisive evidence that occupying children's limited capacity working memory system (by adding complex span-style recall demands) affects both speed and accuracy on inhibition tests, and appears to differentially affect the ability of children with ADHD (with and without anxiety) to maintain high levels of accuracy on inhibition tasks. Interestingly, working memory broadly impacted children's performance, in that it impacted both the inhibition and non-inhibition components of the inhibition tests equally. Expanded discussion of these findings and implications for theoretical models of ADHD are discussed below.

(Null) effects of inhibitory control processes on working memory performance

As noted above, experimentally increasing inhibition demands failed to affect children's performance on working memory tests, with Bayesian statistics providing strong/decisive support for the null hypothesis that inhibition (a) is *not* a causal factor affecting performance on working memory tests for clinically-evaluated children and (b) cannot explain the working memory difficulties exhibited by children with ADHD. Thus, these findings directly

contradict conceptual models predicting that inhibition deficits underlie working memory difficulties in children with ADHD. Instead, this pattern of results is consistent with recent clinical trial data indicating that targeted training of inhibitory control does not produce downstream improvements in working memory for children with ADHD (29). It is consistent also with evidence that experimentally increasing inhibition demands does not disrupt computationally modeled cognitive information processing or encoding/motor processes, but rather equivalently causes children with and without ADHD to adopt more cautious response styles (63).

In contrast, at first glance these findings appear to contradict the only other (to our knowledge) experiment to manipulate both working memory and inhibitory control in ADHD, which found that depleting inhibition resources using a stop-signal paradigm produced significant reductions in *n*-back accuracy for children with and without ADHD (30). At the same time, *n*-back tasks have been criticized as measures of working memory because they correlate poorly with complex span tests of working memory (meta-analytic r=.20; 110), likely because *n*-back tasks require only passive recognition. In contrast, complex span tasks require active recall processes (111), recruit different cortical regions (112), and produce performance differences under otherwise identical conditions (14, 113).

Notably, the current study evoked inhibition demands via a stroop paradigm that is thought to evoke both response inhibition and interference control subcomponents of the inhibitory control construct, whereas Alderson et al. (30) used a stop-signal paradigm that is typically considered an index of response inhibition. Thus, it may be that only specific subcomponents of inhibitory control influence working memory processing. This conclusion appears unlikely, however, based on experimental evidence indicating that both task types share a common inhibitory control mechanism (98, 114) and factor analytic evidence indicating that both tasks load together (e.g., 5, 17). Instead, the discrepancy between the current study and Alderson et al. (30) might be best understood through the lens of the Fosco et al. (63) experiment described above. In this view, adopting a more cautious response strategy when inhibition demands are increased reduces the likelihood that children will be able to recognize and respond quickly enough when a letter repeats itself (i.e., respond correctly on an *n*-back task), whereas inhibition's lack of impact on cognitive information processing would be less likely to affect the more cognitively demanding task of retaining information in working memory in the face of interference (29).

Effects of working memory processes on inhibitory control performance

There was decisive evidence that working memory is important for fast and accurate responding on inhibition tasks. These findings appear to support conceptual models predicting that working memory deficits underlie difficulties on inhibition tasks for children with ADHD. However, a more nuanced interpretation appears warranted based on careful inspection of the results. First, increased working memory demands appear to disproportionately affect accuracy for children with ADHD, with equivalent effects on the inhibition and non-inhibition components of the tasks, indicating that failure to account for working memory is likely to result in overestimates of inhibition deficits in ADHD by approximately d=0.41-0.50 when using accuracy-based scores. In contrast, working memory also impacts response speeds on inhibition tests, but appears to have similar impact across the three clinical groups. Perhaps more importantly, the robust impact of working memory occurred across both low and high inhibition conditions and across congruent and incongruent trials – regardless of whether accuracy or response times were used to estimate performance. This pattern indicates that working memory broadly affects children's performance on inhibitory and non-inhibitory components of these types of tasks. This pattern of results was consistent with prior experimental evidence demonstrating that occupying children's limited capacity working memory system disrupts computationally modeled processing speed for children with and without ADHD (85). It is also broadly consistent with a recent RCT indicating that training working memory may produce general improvements on both inhibition and choice-response tasks for children with ADHD (29, 115). In contrast, increasing memory demands using an *n*-back paradigm failed to affect inhibition performance in Alderson et al. (30) – through the lack of effect in that study was likely because the high memory condition was too difficult for both groups as noted above.

Implications for ADHD neurocognitive research

Taken together, these findings have several implications for neurocognitive research in ADHD. First, the dual dissociation finding that working memory affected inhibition task performance but not vice versa argues against the simple view that doing two tasks at once is always more difficult than doing one task. It is also inconsistent with models suggesting a non-specific effect in which engaging any executive function process produces generalized reductions in subsequent performance on executive functioning more broadly (75). Instead, the current and prior findings (e.g., 29) indicate that, for clinically evaluated children with and without ADHD at least, it matters what those tasks/processes are, and how they are combined. Second, the finding that working memory is a directional, if not causal, mechanism underlying performance on both the inhibition-specific and non-inhibition aspects of inhibition tests urges caution when interpreting the results of inhibition tests for children with ADHD, and clinically evaluated children more generally. In particular, the current results suggest that neuropsychological and research tests of inhibitory control that rely on a single score (e.g., accuracy, commission errors, response times) are likely to be particularly confounded by the tests' working memory demands. As such, inhibition scores that control for performance on the non-inhibition components of the test are likely to provide more construct valid estimates of inhibitory processing specifically – particularly when used as part of a battery of inhibition tests that

can be combined statistically to produce latent performance estimates (e.g., 99).

Third, the finding that working memory difficulties appear to exaggerate estimates of inhibition deficits in ADHD by *d*=0.41-0.50 (for accuracy) is striking given that it falls squarely within the range of meta-analytic estimates of inhibitory control deficits in ADHD (*d*=-0.03 to 0.63; 24, 26–28). Although these effect sizes are not directly comparable because they reflect performance changes vs. between group differences, this finding is consistent with evidence that only 5-11% of children with ADHD have inhibition deficits without co-occurring working memory deficits (9, 74) and calls into question the extent to which children with ADHD have deficits in inhibitory control versus perform poorly on inhibition tests due to their underlying working memory difficulties (45).

Taken together, the current findings appear most consistent with conceptual models that place working memory as an underlying causal mechanism affecting performance on inhibitory control tasks (e.g., 14), with the caveat that there appears to be a small subset of children with ADHD who have inhibition difficulties that cannot be explained by working memory difficulties as noted above. In this view, environmental demands that challenge working memory (in this case by adding a concurrent memory load) interact with a preexisting neurobiological vulnerability (e.g., underdeveloped cortical structures that support working memory; 44) to produce secondary impairments including goal maintenance failures (61), reduced information processing efficiency (85), and reduced attentional filtering (65). In turn, these secondary impairments result in failure to inhibit when needed as well as more general lapses of attention (e.g., 116) that broadly reduce accuracy. In contrast, working memory appears to affect response speeds more similarly for children with ADHD and/or anxiety, which is broadly consistent with prior experimental and RCT findings (55, 85, 115).

Finally, this pattern of results is consistent with recent calls to reconceptualize inhibition as an outcome rather than a process/mechanism that produces outcomes (117). In this view, inhibition is not something we *use* to suppress a response; instead, the *goal* is to inhibit and we rely on other processes to do so successfully (117), including engaging working memory (this study) to adopt more cautious response strategies (63), maintain task goals (61, 64), and filter out irrelevant information (65).

Limitations

The following caveats should be considered. First, due to funding constraints we were unable to recruit a typically developing control group. Although both ADHD groups differentiated themselves from the anxiety disorders comparison group, and the anxiety group performed similarly to the non-ADHD groups in our prior experiments (with non-overlapping samples; e.g., 63, 85), anxiety may be associated with small impairments, or potentially a small strength, across executive functions and thus the obtained effect sizes may be modest over- or under-estimates of ADHD-related impairments more broadly. Replications that include a typically developing group are warranted. Similarly, the strength of support for the differential impact of working memory on inhibition accuracy for children with ADHD vs. ANX (*d*=0.50) was only twice as likely under the alternative vs. null hypothesis (i.e., BF_{01} = 2.03), requiring more tentative conclusions. Second, we used a complex span-based verbal working memory task and a stroop-interference inhibition task. Replications that systematically manipulate additional working memory processes (e.g., continuous updating, serial/temporal reordering; 63), additional short-term storage subsystems (e.g., spatial storage/rehearsal; 22), as well as additional exemplars/subcomponents of inhibitory control (e.g., action restraint/cancellation; 45) are needed despite their consistency with prior work in the cognitive literature (e.g., 61). Finally, although our experimental manipulations were successful in evoking their target mechanisms, they may have also evoked increases in other processes as well. Experimental studies of those mechanisms/processes are needed to understand the extent to which the reported effects were specifically attributable to working memory/inhibition.

Conclusions and future directions

Overall, the current findings are consistent with evidence from the cognitive literature and prior ADHD experimental work implicating working memory capacity as a core, underlying mechanism that broadly affects performance across a variety of neurocognitive tasks (e.g., 85, 115). The findings also highlight the importance of differentiating between neurocognitive abilities and neurocognitive test performance. A significant proportion (if not the majority) of the variance in any neuropsychological/neurocognitive test is attributable to factors other than the construct(s) of interest (i.e., the '*task impurity problem*'; 99); thus, the use of multiple tests per construct and control for known processes that impact performance on tests of the constructs of interest is warranted (e.g., accounting for working memory when studying inhibitory control as suggested by the current findings). Future work is also needed to identify 'mechanisms of the mechanisms' (e.g., potential factors beyond working memory that affect working memory test performance).

More broadly, the field would benefit from increased application of the experimental psychopathology framework to determine the impact of these executive functions, and other putative causal mechanisms, in producing ADHD behavioral symptoms and functional impairments (e.g., 63, 116, 118). Experimental methodologies hold considerable promise for complementing longitudinal findings and helping to differentiate among competing conceptual models of ADHD. For example, most longitudinal studies have linked improvements in working memory, or executive functioning more generally, with remission of ADHD symptoms (e.g., 74). Interestingly, however, these findings are equally supportive of (1) models that position working memory/executive functioning as underlying causes of ADHD – i.e., when the underlying impairments/causes become less severe, so do the

behavioral outcomes/effects of those impairments, and (2) models that view working memory/executive functioning as non-causal factors that instead help compensate for persisting impairments in other domains. In both cases, the models predict executive/behavioral associations over time. In contrast, experimental studies can provide clear evidence for/against these competing models because only the causal models predict that environmental demands that challenge these children's underdeveloped executive function(s) will produce measurable, in-the-moment increases in ADHD behaviors (e.g., 73, 118). Nonetheless, experimental studies are unable to document potential cumulative effects of neurocognitive difficulties over time, track development across the lifespan, or determine how growth in executive functioning affects ADHD symptom presence/severity. Longitudinal studies are also clearly needed. In contrast, conclusions from ADHD cognitive training studies have been highly limited because most protocols have not shown large enough improvements in the trained/targeted cognitive abilities to realistically expect detectable downstream behavior changes, even if the causal models are correct (for review see 119) – although newer neurocognitive training protocols appear to be showing more robust improvements in their target mechanisms (e.g., working memory; 55, 120) and thus may hold promise for further clarifying the extent to which associations between executive function(s) and ADHD behaviors are causal vs. correlational.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Center for Open Science: https://osf.io/gts6x/.

Ethics statement

The studies involving humans were approved by Florida State University Human Subjects Committee (STUDY00001032). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MK: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – original draft. NG: Conceptualization, Writing – review & editing. EC: Conceptualization, Writing – review & editing. CM: Writing – review & editing. AC: Writing – review & editing. FG: Writing – review & editing. EC: Writing – review & editing. MT: Writing – review & editing. LS: Conceptualization, Data curation, Writing – review & editing.

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Conflict of interest

The principal investigator MK holds a patent for neurocognitive interventions that target central executive working memory and inhibitory control. These interventions were not used in the current study. MK discloses travel reimbursement from the American Professional Society for ADHD and Related Disorders APSARD and consulting payments from Sky Therapeutics and Boys Town National Research Hospital in the past 2 years (no prior disclosures). None of the other investigators have potential conflicts to report.

Publisher's note

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The association between symptoms of developmental coordination disorder and neuropsychological characteristics in children with and without ADHD

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Objective: Attention-deficit/hyperactivity disorder (ADHD) frequently co-occurs with developmental coordination disorder (DCD). This study aimed to evaluate the association between DCD symptoms and neuropsychological characteristics in children with and without ADHD.

Methods: We recruited 298 children aged 5–12 years. Motor performance was assessed using the Developmental Coordination Disorder Questionnaire (DCDQ), while ADHD symptoms were assessed using the ADHD Rating Scale (ARS) and the Advanced Test of Attention (ATA). Cognitive characteristics were measured using the Wechsler Intelligence Scale, and behavioral characteristics were assessed using the Korean Personality Rating Scale for Children.

Results: The children had a mean age of 7.6 ± 1.7 years, with 214 (71.8%) being boys. Among children diagnosed with ADHD (n = 176), 39.2% exceeded the DCDQ cutoff score, compared to 4.1% in the neurotypical group (n = 122). In the correlation analysis, the DCDQ total score was significantly correlated with ARS, omission and commission errors in visual and auditory ATA, and full-scale intellectual quotient. In addition, symptoms of depression, social dysfunction, and psychosis were correlated with the DCDQ total score. In the between-group analysis, children with both ADHD and DCD exhibited more omission errors on the auditory ATA and behavioral problems related to depression, social dysfunction, and psychosis compared to children with ADHD only.

Conclusion: Our study indicates that children with ADHD exhibit more difficulties in motor performance. Children with both ADHD and DCD may present with a greater burden of psychiatric conditions than children with ADHD only, suggesting the need for careful monitoring in clinical practice.

KEYWORDS

attention deficit hyperactivity disorder (ADHD), developmental coordination disorder (DCD), developmental coordination disorder questionnaire (DCDQ), cognitive profile, behavioral characteristics

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity. ADHD is common, with prevalence estimates of 5–7% in children and adolescents (1, 2). ADHD often co-occurs with other psychiatric disorders, with approximately 70–80% of individuals having a comorbid condition (3). These comorbidities are important in that they influence symptom presentation, complicate treatment, and predict long-term outcomes.

Among the common comorbidities of ADHD is developmental coordination disorder (DCD), which is classified as a neurodevelopmental disorder (4). DCD manifests as difficulties in fine and gross motor skills, significantly impacting daily activities and functioning both in school and home settings (5). Tasks such as using scissors, buttoning clothing, catching balls, and climbing stairs are challenging for children with DCD. With prevalence estimates ranging from 2–5%, DCD is a prevalent condition that often co-occurs with ADHD (6, 7).

The co-occurrence rate of ADHD and DCD is high, with approximately half of children diagnosed with ADHD meeting the criteria for DCD (8, 9). While the concept of attention deficits, motor control, and perception was introduced in the 1970s (10), motor difficulties were not regarded as a distinct condition from ADHD symptoms (11). Consequently, the co-occurrence of ADHD and DCD has been relatively understudied, and debates continue regarding their neurobiological similarities and differences (12). Furthermore, existing literature comparing the neuropsychological characteristics of children with ADHD with and without comorbid DCD is limited by small sample sizes, thus warranting further investigation (13).

In this study, our primary objective was to explore the association between DCD symptoms and neuropsychological characteristics in children with and without ADHD. Specifically, we aimed to examine the correlation between motor performance and neuropsychological profiles, and to compare the neuropsychological characteristics between children with ADHD with DCD, children with ADHD without DCD, and neurotypical children. By addressing these objectives, we aimed to contribute to understanding the interplay between ADHD and DCD.

Methods

Study participants

A total of 298 children aged 5–12 years participated in this study, including 176 children diagnosed with ADHD and 122 neurotypical children. The children were enrolled between May 2014 and May 2020. Children with ADHD were recruited at the Children's Hospital of Asan Medical Center, located in Seoul, Republic of Korea. ADHD was diagnosed by board-certified child and adolescent psychiatrists according to the fourth and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-5) and the Kiddie–Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADS-PL). Neurotypical children were recruited through advertisements in the hospital and on internet sites. Neurotypical children were screened for any psychiatric disorder according to the DSM-IV/DSM-5 and K-SADS-PL. Children were excluded from the study if they had a Full-Scale Intellectual Quotient (FSIQ) lower than 70, as confirmed by the Wechsler Intelligence Scale for Children, when they were diagnosed with autism spectrum disorder, schizophrenia, organic mental disorder, or neurologic disorders such as epilepsy. Informed consent was obtained from the parents or guardians of the study participants, and assent was obtained from the study participants, where appropriate. The study was performed in line with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Asan Medical Center (2014-0157).

Clinical assessment

The developmental coordination disorder questionnaire

The DCDQ is a questionnaire that evaluates the motor performance of a child (14). DCDQ is administered by parents or

caregivers and involves a comparison of the child's motor abilities with those of other children in the same age group. The questionnaire assesses three sub-components of motor performance, which are control during movement, fine motor/handwriting, and general coordination. The DCDQ is composed of 15 items, which are rated on a 5-point Likert scale. Children are classified as indication of DCD or probably not DCD, according to their age and total score (indication of DCD: total score ≤46 for age 5:0–7:11 years; total score ≤55 for age 8:0–9:11 years; and total score ≤57 for age 10:0–15:11 years).

ADHD rating scale

The severity of ADHD symptoms was assessed using the ARS, completed by parents or caregivers. The ARS is designed to evaluate ADHD symptoms in school-age children and consists of 18 items divided into two subscales: inattention and hyperactivity/impulsivity. The validity and reliability of the scale have been well established (15).

Korean personality rating scale for children

Behavioral characteristics of children and adolescents were evaluated using the KPRC, which was completed by parents or caregivers (16). The KPRC is an adapted version of the Personality Inventory for Children and comprises 177 items categorized into 10 subscales, namely verbal development delay, physical development delay, anxiety, depression, somatization, delinquency, hyperactivity, family dysfunction, social dysfunction, and psychosis. This scale was previously standardized in a sample of 2,639 children and adolescents in Korea, and its reliability and validity have been established (16).

Wechsler intelligence scale for children–fourth edition and Wechsler preschool and primary scale of intelligence–fourth edition

Intelligence was evaluated using the WISC-IV and WPPSI-IV (17, 18), which were administered by clinical psychologists. The WISC-IV is used in children aged 6:0–16:11 years and includes four primary indices: verbal comprehension, perceptual reasoning, working memory, and processing speed. The WPPSI-IV is used in children aged 2:6–7:7 years and includes five primary indices: verbal comprehension, visual-spatial, fluid reasoning, working memory, and processing speed. The FSIQ is derived from the four or five primary indices. This widely used test exhibits good to excellent internal consistency. For the primary indices analysis, only results from the WISC-IV were used (n = 255).

Advanced test of attention

The neuropsychological profile of attention was examined using the ATA, administered by clinical psychologists (19). ATA is a computerized continuous performance test, and four major variables, including omission errors, commission errors, response time, and response time variability, are collected and transformed into Z-scores. The ATA was standardized in the Korean population, and the psychometric properties of the test have been established (19).

Statistical analysis

The ADHD and neurotypical groups were compared for demographic characteristics and motor performance. Categorical variables were compared using a chi-square test, and continuous variables were compared using a student's t-test. Correlations between DCDQ scores and neuropsychological measures were assessed using the Pearson correlation method. ANOVA was used to compare the three groups, namely the "ADHD with DCD," "ADHD without DCD," and "neurotypical" groups. When a significant difference existed among the three groups, a *post-hoc* Bonferroni test for multiple comparisons was performed to evaluate the differences between the groups. For the estimation of effect sizes, eta squared (η^2) values were calculated. Data analyses were performed using R Statistical Software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The demographic characteristics of the children who participated in this study are summarized in Table 1. **A** total of 298 children participated in the study (age 7.6 ± 1.7 years old, 71.8% boys). The ADHD and neurotypical groups did not show significant differences in age and familial income. However, compared to the neurotypical group, the ADHD group consisted predominantly of boys, and were more often diagnosed with tic disorder. The education level of fathers of children in the ADHD group showed a significant difference compared to the neurotypical group.

We compared the motor performance of the ADHD and neurotypical groups as evaluated by the DCDQ (Table 2). In the ADHD group, 39.2% (n = 176) of the children were classified as indication of DCD, whereas in the neurotypical group, 4.1% (n = 5) were classified as indication of DCD. The DCDQ total score and the three sub-component scores were significantly lower in the ADHD group than in the neurotypical group, indicating more difficulties in motor performance.

The correlation between DCDQ scores and neuropsychological measures was examined (Figure 1). The DCDQ total score was significantly correlated with ADHD symptoms measured by K-SADS-PL and ARS. Specifically, the DCDQ total score showed a negative correlation with both inattentive symptoms (K-SADS-PL, r = -0.342; ARS, r = -0.338) and hyperactivity-impulsivity symptoms (K-SADS-PL, r = -0.291; ARS, r = -0.316). The DCDQ total score showed a higher correlation with inattentive symptoms than with hyperactivity-impulsivity symptoms. In addition, the DCDQ total score showed a significant correlation with omission and commission errors of visual ATA (r = -0.265 and r = -0.130, respectively), and omission errors, commission errors, reaction time, and reaction time standard deviation of auditory ATA (r = -0.228, r = -0.147, r = 0.201, and r = -0.115, respectively). The omission errors of both visual and auditory ATA showed the largest extent of correlation with the DCDQ total score, compared to that with other ATA variables. The DCDQ total score showed a significant correlation with FSIQ (r = 0.275) and perceptual

TABLE 1 Summary sample characteristics.

Variables	ADHD (n = 176)	Neurotypical (n = 122)	*p*
Age, mean (SD), month	7.5 (2.1)	7.6 (1.5)	0.628
Sex, n (%)			
Boys	152 (87.9%)	62 (50.8%)	<0.001
Presentation of ADHD diagnosis, n (%)			
Inattentive	60 (34.1%)	–	
Hyperactive/impulsive	4 (2.3%)	–	
Combined	95 (54.0%)	–	
Unspecified	17 (9.7%)	–	
Comorbid diagnosis, n (%)			
ODD	17 (9.7%)	0 (0%)	0.001
SAD	1 (0.6%)	2 (1.6%)	0.748
Social phobia	3 (1.7%)	1 (0.8%)	0.888
Specific phobia	5 (2.8%)	3 (2.5%)	1.000
GAD	1 (0.6%)	0 (0%)	1.000
Enuresis	4 (2.3%)	0 (0%)	0.244
Tic disorder	24 (13.7%)	5 (4.1%)	0.011
Family income, n (%)			
Low	19 (10.8%)	5 (4.1%)	0.109
Middle	70 (40%)	50 (41.3%)	
High	86 (49.1%)	66 (54.5%)	
Education, father, n (%)			
High school or less	33 (18.9%)	4 (3.3%)	<0.001
Bachelor's degree	117 (66.9%)	106 (87.6%)	
Graduate school	25 (14.3%)	11 (9.1%)	
Education, mother, n (%)			
High school or less	30 (17.1%)	9 (7.4%)	0.050
Bachelor's degree	121 (69.1%)	95 (78.5%)	
Graduate school	24 (13.7%)	17 (14%)	

ADHD, Attention Deficit Hyperactivity Disorder; GAD, Generalized Anxiety Disorder; ODD, Oppositional Defiant Disorder; SAD, Separation Anxiety Disorder; SD, Standard Deviation.

reasoning, working memory, and processing speed indices (r = 0.263, r = 0.226, and r = 0.241, respectively). Behavioral characteristics were examined with KPRC, where all subscales showed a significant correlation with the DCDQ total score. Of the subscales, physical development delay, psychosis, verbal development delay, and depression showed relatively high correlation coefficients (r = -0.508, r = -0.448, r = -0.417, and r = -0.415, respectively).

The correlation between DCDQ sub-components and neuropsychological measures was examined (Figure 1). Among the three sub-components, fine motor/handwriting exhibited the largest extent of correlation with a majority of the measures, except for the subscales of KPRC, including anxiety, depression, family dysfunction, and social dysfunction.

TABLE 2 Comparison of motor skills among ADHD and neurotypical groups.

Variables	ADHD (n = 176)	Neurotypical (n = 122)	*p*
DCDQ cutoff, n (%)	69 (39.2%)	5 (4.1%)	<0.001
DCDQ, mean (SD)			
Total score	52.8 (8.2)	59.4 (11)	<0.001
Control during movement	23.0 (3.6)	25.0 (5)	<0.001
Fine motor/handwriting	14.7 (2.4)	17.8 (3.7)	<0.001
General coordination	15.1 (4.1)	16.6 (4.2)	0.008

DCDQ, Developmental Coordination Disorder Questionnaire.

Next, we assessed whether neuropsychological characteristics differed according to the presence of DCD in the ADHD group (Table 3). To this end, we compared the "ADHD with DCD," "ADHD without DCD," and "neurotypical" groups. Compared to the "ADHD without DCD" group, the "ADHD with DCD" group showed significantly higher omission error scores on auditory ATA and higher verbal development delay, physical development delay, depression, social dysfunction, and psychosis subscale scores on KPRC.

Discussion

In this study, we observed that DCD is nine times more prevalent in children with ADHD when compared to neurotypical children. The ADHD group exhibited lower DCDQ total and subscale scores than that in neurotypical children, indicating more difficulty in overall motor performance. In the correlation analysis, the DCDQ total score exhibited a significant correlation with ADHD symptoms and omission and commission errors in the continuous performance test and FSIQ. In addition, symptoms of depression, social dysfunction, and psychosis were correlated with the DCDQ total score. In between-group comparisons, the "ADHD with DCD" group showed higher levels of omission errors in the auditory continuous performance test than that in the "ADHD without DCD" group. Similarly, when assessing behavioral characteristics, the "ADHD with DCD" group exhibited higher scores on subscales related to verbal and physical development delay, depression, social dysfunction, and psychosis than the "ADHD without DCD" group.

The prevalence of DCD, based on the DCDQ cutoff score, was 39.2% in the ADHD group, compared to 4.1% in the neurotypical group. Previous studies conducted in Europe, Canada, and Australia, reported 30–50% prevalence of DCD among children with ADHD (20–22). These findings are comparable to those of our study conducted in South Korea, suggesting that the prevalence rate is consistent across different regions. Analysis of the DCDQ subscales, which assess control during movement, fine motor/handwriting, and general coordination, revealed significantly

	DCDQ total score (*r*)	*p*	Control during movement (*r*)	*p*	Fine motor/ handwriting (*r*)	*p*	General coordination (*r*)	*p*
K-SADS-PL number of symptoms								
Inattention criteria	-0.342	***	-0.240	***	-0.444	***	-0.199	**
Hyperactivity-impulsivity criteria	-0.291	***	-0.235	***	-0.349	***	-0.157	**
ARS								
Inattention	-0.338	***	-0.224	***	-0.414	***	-0.230	***
Hyperactivity-Impulsivity	-0.316	***	-0.275	***	-0.326	***	-0.197	**
ATA, visual								
Omission Errors	-0.265	***	-0.225	***	-0.290	***	-0.170	**
Commission Errors	-0.130	*	-0.089		-0.179	**	-0.065	
Reaction Time	-0.036		-0.066		-0.035		-0.001	
Reaction Time Standard Deviation	-0.108		-0.062		-0.166	**	-0.058	
ATA, auditory								
Omission Errors	-0.228	***	-0.162	**	-0.268	***	-0.173	**
Commission Errors	-0.147	*	-0.093		-0.213	***	-0.090	
Reaction Time	0.201	**	0.200	**	0.244	***	0.074	
Reaction Time Standard Deviation	-0.115	*	-0.119	*	-0.154	**	-0.030	
Intelligence scale								
FSIQ	0.275	***	0.209	***	0.351	***	0.157	**
Verbal Comprehension Index[a]	0.102		0.020		0.141	*	0.114	
Perceptual Reasoning Index[a]	0.263	***	0.203	**	0.324	***	0.156	*
Working Memory Index[a]	0.226	***	0.157	**	0.306	***	0.115	
Processing Speed Index[a]	0.241	***	0.237	***	0.309	***	0.066	
KPRC								
Verbal Development Delay	-0.417	***	-0.335	***	-0.432	***	-0.290	***
Physical Development Delay	-0.508	***	-0.435	***	-0.477	***	-0.367	***
Anxiety	-0.303	***	-0.248	***	-0.215	***	-0.276	***
Depression	-0.415	***	-0.355	***	-0.342	***	-0.328	***
Somatization	-0.119	*	-0.062		-0.104		-0.115	
Delinquency	-0.275	***	-0.158	**	-0.344	***	-0.202	**
Hyperactivity	-0.348	***	-0.279	***	-0.397	***	-0.204	***
Family Dysfunction	-0.231	***	-0.154	**	-0.204	***	-0.214	***
Social Dysfunction	-0.372	***	-0.349	***	-0.277	***	-0.283	***
Psychosis	-0.448	***	-0.391	***	-0.414	***	-0.318	***

FIGURE 1
Correlation between DCDQ scores and neuropsychological measures. Positive correlations are displayed in red and negative correlations in blue. The color shade corresponds to the correlation coefficients, with darker shades indicating stronger correlations. *p<0.05; **p<0.01, ***p<0.001; ARS, ADHD Rating Scale; ATA, Advanced Test of Attention; DCDQ, Developmental Coordination Disorder Questionnaire; FSIQ, Full Scale Intelligence Quotient; KPRC, Korean Personality Rating Scale for Children; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. [a]Primary indices from the WISC-IV were used (n = 255).

lower scores in the ADHD group than those in the neurotypical group, indicating deficits across various aspects of motor performance. Of these subscales, fine motor/handwriting exhibited the strongest correlation with ADHD symptoms. Given that complex motor activities necessitate higher-order cognitive skills, including executive function (23), fine motor/handwriting may require greater attentional resources and consequently show a stronger correlation with ADHD symptoms compared to other motor subscales.

In our analysis, we observed that among ADHD symptoms, inattention exhibited a stronger correlation with overall motor performance compared to hyperactivity/impulsivity. This observation highlights the significance of the inattentive symptoms in DCD. Children with DCD commonly present impairments in attention (24), working memory (25), and planning (26). However, the underlying mechanism driving the correlation between inattention and motor coordination remains unclear. One proposed explanation involves impaired inhibitory control, which may lead to reduced ability in action planning and motor learning (27). Another plausible model is the cognitive-energetic model, which emphasizes deficits in information processing (11). According to this model, encoding difficulties could contribute to attentional deficits in DCD. Our results indicate that symptoms of inattention, measured by clinicians, parents, and omission errors in the continuous performance test, are closely related to motor performance.

Motor performance exhibited a significant correlation with intelligence, as measured by FSIQ. The relationship between motor skills and cognitive function has long been recognized, tracing back to the sensorimotor stage of Piaget's cognitive development theory (28). The execution of new motor skills facilitates cognitive processes in infants and children, enabling them to explore new aspects of their environment, thereby shaping their perceptions, particularly those related to spatial abilities and executive functions (29, 30). In our study, perceptual reasoning, working memory, and processing speed were correlated with motor performance, while verbal comprehension was not. This result is in concordance with previous studies (31, 32), where verbal comprehension, reflecting crystallized aspects of intelligence, did not exhibit a significant association with motor performance.

TABLE 3 Comparison of neuropsychological measures among the ADHD with DCD, ADHD without DCD, and neurotypical groups.

	ADHD with DCD (n = 69)	ADHD without DCD (n = 107)	Neurotypical (n = 122)	F	η^2	*p*
	Mean (SD)	Mean (SD)	Mean (SD)			
K-SADS-PL number of symptoms						
Inattention criteria	7.5 (1.3)	7.2 (1.4)	0.9 (1.4)	791.1	0.845	<0.001[b,c]
Hyperactivity-impulsivity criteria	5.2 (2.7)	5.8 (2.3)	0.7 (1.2)	209.4	0.591	<0.001[b,c]
ARS						
Inattention	14.6 (5.2)	13.3 (5.5)	3.6 (3.0)	180.5	0.550	<0.001[b,c]
Hyperactivity-impulsivity	11.0 (5.7)	11.0 (5.7)	2.4 (2.4)	122.2	0.453	<0.001[b,c]
ATA, visual						
Omission errors	5.0 (4.9)	3.9 (5.2)	1.0 (2.8)	22.6	0.134	<0.001[b,c]
Commission errors	3.0 (3.3)	4.1 (4.1)	1.3 (2.4)	20.6	0.124	<0.001[b,c]
Reaction time	1.2 (1.7)	0.7 (1.6)	0.9 (1.3)	2.7	0.018	0.069
Reaction time standard deviation	2.4 (2.5)	2.8 (3.2)	0.8 (2.5)	15.3	0.095	<0.001[b,c]
ATA, auditory						
Omission errors	2.0 (2.8)	1.1 (1.9)	0.2 (1.5)	18.1	0.111	<0.001[a,b,c]
Commission errors	2.0 (2.7)	2.2 (2.2)	0.4 (1.8)	22.9	0.136	<0.001[b,c]
Reaction time	-0.8 (1.5)	-1.0 (1.5)	0.0 (0.9)	19.3	0.117	<0.001[b,c]
Reaction time standard deviation	0.1 (1.2)	0.5 (1.1)	-0.4 (0.9)	19.0	0.116	<0.001[b,c]
Intelligence scale						
FSIQ	93.3 (15.0)	95.8 (14.2)	109.5 (13.5)	39.1	0.211	<0.001[b,c]
Verbal comprehension index	101.7 (13.6)	98.9 (11.0)	107.7 (12.3)	12.3	0.089	<0.001[b,c]
Perceptual reasoning index	99.2 (16.7)	99.5 (16.0)	109.1 (15.7)	11.5	0.084	<0.001[b,c]
Working memory index	92.0 (14.3)	93.8 (15.3)	109.1 (13.8)	38.0	0.232	<0.001[b,c]
Processing speed index	84.9 (14.4)	88.8 (13.5)	99.3 (13.7)	25.4	0.168	<0.001[b,c]
KPRC						
Verbal development delay	60.2 (11.7)	52.6 (11.7)	45.3 (9.1)	42.6	0.228	<0.001[a,b,c]
Physical development delay	61.5 (10.0)	51.2 (10.3)	43.7 (10.3)	65.7	0.312	<0.001[a,b,c]
Anxiety	54.6 (10.0)	51 (11.0)	46.2 (11.2)	13.5	0.086	<0.001[b,c]
Depression	58.8 (10.8)	52.4 (10.4)	46.6 (9.8)	31.3	0.178	<0.001[a,b,c]
Somatization	47.5 (9.8)	46.3 (10.2)	42.6 (8.6)	7.1	0.047	0.001[b,c]
Delinquency	59.5 (11.6)	60.2 (12.7)	44.7 (9.5)	64.5	0.309	<0.001[b,c]
Hyperactivity	65.5 (11.5)	63.8 (11.6)	43.4 (9.5)	136.5	0.486	<0.001[b,c]
Family dysfunction	54.3 (13.2)	54.4 (14.0)	45.6 (10.1)	18.0	0.111	<0.001[b,c]
Social dysfunction	54.9 (12.0)	49.8 (10.1)	46.6 (9.7)	13.8	0.087	<0.001[a,b,c]
Psychosis	63.0 (12.2)	55.1 (12.2)	45.5 (9.6)	55.2	0.276	<0.001[a,b,c]

ATA, Advanced Test of Attention; DCD, Developmental Coordination Disorder; FSIQ, Full Scale Intelligence Quotient; KPRC, Korean Personality Rating Scale for Children; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; SD, Standard Deviation.

[a]Significant difference between ADHD with DCD and ADHD without DCD.

[b]Significant difference between ADHD with DCD and neurotypical children.

[c]Significant difference between ADHD without DCD and neurotypical children.

Considering the association between motor performance and verbal development in children aged 3–6 years (33, 34), further studies are warranted to evaluate the role of age as a moderator in the relationship between motor performance and verbal development.

Children in the "ADHD with DCD" group exhibited more symptoms related to depression, social dysfunction, and psychosis than those in the "ADHD without DCD" and "neurotypical" groups. Studies addressing psychiatric problems in children with ADHD with and without DCD are limited and have primarily been conducted in Western countries. Missiuna et al. (35) compared psychological distress in adolescents with ADHD + DCD, ADHD alone, DCD alone, and in neurotypical children. In adolescents with ADHD + DCD, the prevalence of depression was 15 times higher than that in neurotypical children, and 3 to 5 times higher than that in adolescents with DCD or ADHD only. Another study with a smaller sample size reported increased peer victimization and emotional problems in the ADHD + DCD group compared to those in the DCD-only group (36). To the best of our knowledge, no study has compared psychosis-like behavior in children with ADHD with and without DCD. Considering the age group of the children enrolled in our study and the nature of the questions used in the KPRC, a higher score on the psychosis subscale suggests the presence of odd and eccentric behaviors, rather than true psychotic symptoms such as hallucination and delusion. Altogether, these findings underscore the heightened severity of behavioral problems in children with both ADHD and DCD, implying that psychiatric comorbidity needs to be carefully monitored.

This study has certain limitations. First, the children who participated in the study were recruited from a single hospital, limiting the generalizability of the findings to a broader population. Nonetheless, the consistency in diagnosis and measures applied across participants may enhance the reliability of the results. Second, while statistically significant, the correlations observed in the correlation analysis were at best moderate, if not weak (37). This may explain why most of the variables that show a significant correlation with motor performance did not demonstrate significant differences in the three-group comparison analysis between the ADHD groups with and without DCD and the neurotypical group. Third, the definition of DCD for group comparison relied on the DCDQ, which may lead to inaccurate group classification and potentially impact the study outcomes. Finally, considering the six-year enrollment period, the sample size of the study is modest.

In conclusion, we explored motor performance using the DCDQ in 298 children aged 5–12 years. Among children diagnosed with ADHD, 39.2% exceeded the cutoff scores of the DCDQ, contrasting with 4.1% in the neurotypical group. When compared to children with ADHD only, those with ADHD and DCD exhibited more omission errors on the auditory continuous performance test, along with behavioral problems related to depression, social dysfunction, and psychosis. Our study indicates that children with both ADHD and DCD may present with a greater burden of psychiatric conditions that need careful monitoring in clinical practice.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Institutional Review Board of Asan Medical Center (2014-0157). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

TL: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. JL: Data curation, Project administration, Writing – review & editing. SK: Formal analysis, Software, Writing – review & editing. JK: Data curation, Project administration, Writing – review & editing. KP: Data curation, Project administration, Writing – review & editing. Y-SJ: Conceptualization, Supervision, Writing – review & editing. H-WK: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Exploring the genetic and socioeconomic interplay between ADHD and anxiety disorders using Mendelian randomization

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Background: ADHD and anxiety disorders often co-occur, sharing symptoms and dysfunctions, yet the underlying mechanisms remain elusive.

Methods: To explore the shared and distinct genetic variations between ADHD and anxiety disorders, we applied Mendelian randomization (MR) analysis to ADHD, anxiety disorders, and three socioeconomic factors: income, educational attainment (EA), and intelligence. MR analysis utilized genome-wide association study summary datasets (anxiety disorder: 7,016 cases and 14,745 controls; ADHD: 38,691 cases and 275,986 controls; EA: 766,345 participants; intelligence: 146,808 participants; household income: 392,422 participants), with inverse-variance weighting as the primary method.

Results: Our MR analysis revealed no discernible genetic-level causal effect between ADHD and anxiety disorders ($p > 0.77$). Additionally, the independent variables for ADHD (25 SNPs) and anxiety disorders (18 SNPs) did not overlap, highlighting the genetic distinction between the two conditions. Higher income ($p < 0.002$) and EA ($p < 0.005$) were found to serve as protective factors for both ADHD and anxiety disorders. Genetic predisposition to higher income (86 SNPs) and EA (457 SNPs) were identified as a potential common protective factors for both conditions. Lastly, genetic predisposition to higher intelligence was found to potentially guard against ADHD ($p < 0.001$) but not against anxiety disorders ($p > 0.55$).

Conclusion: Our findings indicate that the shared symptoms observed between ADHD and anxiety disorders are more likely influenced by genetic predispositions related to socioeconomic factors rather than by the genetic predispositions specific to the disorders themselves.

KEYWORDS

ADHD, anxiety disorders, Mendelian randomization, income, educational attainment, intelligence

1 Introduction

ADHD, or Attention Deficit Hyperactivity Disorder, is a common neurodevelopmental disorder that affects both children and adults, with a global prevalence of approximately 5% in children and 2.5% in adults (1). ADHD can have profound effects on academic, social, and occupational outcomes, highlighting the importance of early diagnosis and intervention for long-term prognosis and quality of life (2). Personalized treatment strategies combining medication, therapy, and behavioral interventions are essential for managing ADHD symptoms and enhancing quality of life (3, 4). The development of ADHD is influenced by a complex interplay of genetic predisposition, environmental exposures such as prenatal tobacco exposure and child maltreatment, and neurobiological abnormalities (5).

Anxiety disorders are highly prevalent mental health conditions globally, impacting an estimated 264 million individuals, with varying rates among different demographics and a higher incidence in women (6, 7). In the United States, approximately 31% of adults will experience an anxiety disorder at some stage in their lives (8). The burden of anxiety disorders on public health systems and society is substantial, manifested through increased healthcare utilization, reduced quality of life, and the presence of comorbidities (9). Effective treatment strategies, such as cognitive-behavioral therapy and medication, are crucial for enhancing overall well-being (10). Genetic predisposition, environmental stressors, and brain chemistry imbalances contribute to anxiety disorders development, with risk factors including family history, trauma, chronic stress, and certain medical conditions (11). Tailored interventions, like the 'screen-and-treat' approach, and ongoing research efforts are essential for addressing the complexities of anxiety disorders (12–14).

Although ADHD and anxiety disorders distinct each other from their classification, diagnostic properties, and treatment (1), these two diseases often co-occur with each other, worsening symptoms and function. Shared developmental origins may complicate diagnosis and treatment, affecting medication use and cardiometabolic risk, especially in autistic individuals (1, 15, 16). There has been frequent misdiagnosis of anxiety disorders and ADHD before an autism diagnosis, particularly in women. This underscores the complex relationship and diagnostic challenges between these conditions and the need for improved practitioner awareness (17).

Moreover, ADHD increases the risk of anxiety disorders, with symptoms overlapping and exacerbating each other, leading to impaired daily functioning. Coexistence of ADHD and anxiety affects emotional well-being, possibly influenced by genetic variants (3, 18). However, whether causal-relationship exists or not remain uncertain.

We hypothesize that both shared and distinct genetic variations exist between ADHD and anxiety disorders, which determine their shared and unique clinical features. To disentangle these relationships, we conducted a bidirectional Mendelian randomization (MR) analysis between ADHD and anxiety disorders to directly test the effect of genetic liability to one disease on the other. Additionally, we employed MR analysis to examine the impact of common socioeconomic-related factors, including income, educational attainment (EA), and intelligence, on both ADHD and anxiety disorders. Our study aims to enhance the understanding of the interplay and distinctions between ADHD and anxiety disorders.

2 Methods

The workflow was carried out as follows: First, a two-sample MR analysis was performed to investigate the causal relationship between ADHD and anxiety disorders, using independent instrumental variables (IVs) for the study. Next, a functional annotation analysis was undertaken to examine the roles of the selected IVs and corresponding genes in relation to ADHD and anxiety disorders. Additionally, an MR analysis was conducted to assess the impact of three socioeconomic factors-educational attainment (EA), income, and intelligence-on ADHD and anxiety disorders. This was done to understand how these common factors influence both conditions.

2.1 GWAS summary data for MR analysis

The anxiety disorder and ADHD summary GWAS datasets were sourced from the Psychiatric Genomics Consortium (PGC). The anxiety disorder data comprise 7,016 cases and 14,745 controls (19), with samples come from USA, Switzerland, Netherlands, Germany, and Australia. The ADHD dataset comprises 38,691 cases and 275,986 controls, all of European ancestry (20). The datasets on educational attainment (EA) included 766,345 participants (21), with EA measured by the number of years of schooling completed. All association analyses were conducted at the cohort level in samples limited to individuals of European descent. Additionally, GWAS datasets for intelligence (fluid intelligence score) and household income were obtained from Yang Lab (https://yanglab.westlake.edu.cn/) (22), involving 146,808 and 392,422 participants, respectively. All the participants in the datasets were of European origin. Please note that education year, income level, and intelligence level are quantitative traits. Unlike case/control studies, GWAS datasets with quantitative traits were analyzed using linear regression to identify significant SNPs as IVs.

2.2 MR analysis

The primary MR analysis was conducted using the inverse-variance weighted (IVW) method as main method, with additional support from the weighted median (WM) and MR-Egger methods provided by TwoSampleMR (23). Single-nucleotide polymorphisms (SNPs) linked to outcome ($P < 5\times10^{-5}$) were chosen from exposure as potential genetic variants.

To ensure the reliability of instrumental variables (IVs), we meticulously selected SNPs from GWAS datasets based on their genome-wide significance ($p < 5.00E-08$). When genome-wide significance was not met or the number of suitable instruments

was 10 or fewer, we carefully adjusted the threshold for selecting IVs in the MR approach to a p-value of 1.00E-05. This threshold was chosen because a more relaxed threshold would result in IVs with weaker effects, potentially compromising the reliability of MR analysis results (23). These selected SNPs were further refined within a 10 Mb window using a clustering r2 cutoff of 0.001. In each MR analysis, we systematically excluded SNPs absent in the outcome dataset, those with intermediate allele frequencies, and redundant SNPs. This stringent curation process ensured the quality and reliability essential for the MR analysis.

In addition, the intercept from the MR-Egger model was used to assess directional pleiotropy. Heterogeneity was assessed using Cochran's Q test and I^2 statistics, with significance thresholds set at $P < 0.05$ and $I^2 > 0.25$ (24).

2.3 Annotation analysis

To understand the genetic instrumental variables (SNPs) chosen for the MR analysis regarding ADHD and anxiety disorders, we initially mapped these SNPs to genes utilizing the SNP-Gene mapping tools provided by AIC LLC (https://www.gousinfo.com/en/snpmap2gene.html). Then, we performed annotation analysis using the 'Functional Annotation Tool' of DAVID (https://david.ncifcrf.gov) and literature data mining (LDM) tools from AIC LLC (https://www.gousinfo.com/en/advancedsearch.html). These tools were employed to scrutinize the genetic variants and their associated genes. The functional analysis primarily concentrated on examining the individual functions of these genes or genetic variants and their connections to anxiety disorders and ADHD. In DAVID, we utilized three gene ontologies (GOTERM_BP_DIRECT, GOTERM_CC_DIRECT, and GOTERM_MF_DIRECT) and three pathways (REACTOME_PATHWAY, WIKIPATHWAYS, and KEGG_PATHWAY). The pathways or functional groups that these genes are enriched in will help in understanding the function of the corresponding genes. Concurrently, the AIC LDM tools were used to investigate existing scientific literature linking these genetic variants and genes to ADHD and anxiety disorders. Specifically, LDM was conducted for each relationship between the diseases, genes, and SNPs with the purpose of identifying supporting scientific references from a wide range of sources, including scientific literature (PubMed, arXiv, and bioRxiv), scientific databases (GEO, GenBank, Protein Data Bank (PDB), and Ensembl), and documents and reports from research organizations (the World Health Organization (WHO), National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC)) (https://www.gousinfo.com/en/userguide.html).

3 Results

3.1 MR analysis for ADHD and anxiety disorders

We found that genetic liability to anxiety disorder was not associated with the risk of ADHD ($p > 0.83$). Meanwhile, genetic liability to ADHD was not associated with the risk of anxiety disorder ($p > 0.55$). As shown in Table 1, 25IVs were selected for ADHD, and 18 for anxiety disorders. However, none of the three methods (IVW, WM, and MR-Egger) showed statistical significance. These results indicate that while the selected IVs are related to ADHD or anxiety disorders, they do not influence the other condition.

The heterogeneity analysis suggests that the directions of causal effects across the set of applied techniques were largely the same. No directional pleiotropy ($P > 0.05$ and MR-Egger intercept < 0.01) or heterogeneity ($P > 0.05$) was detected. We provided the scatter plot and the forest plot of the bidirectional MR analysis in Figure 1.

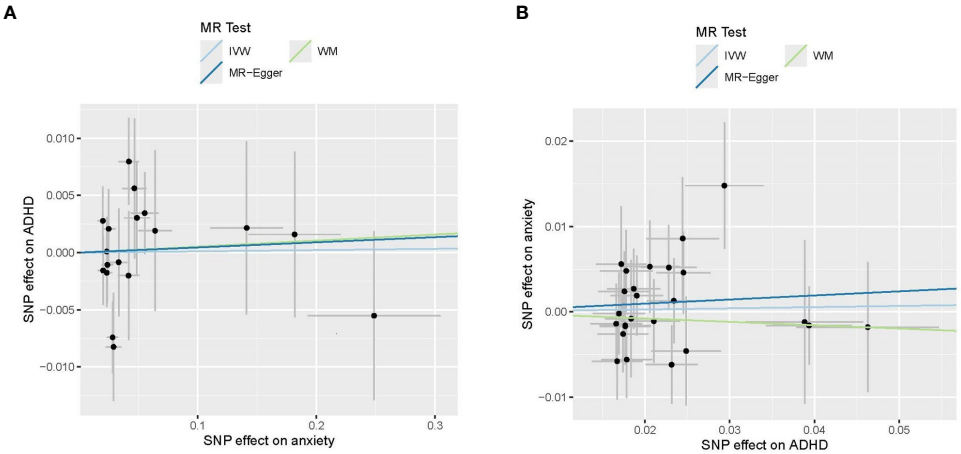
In Figure 1A, the Scatter plot depicts the associations between genetic variants and anxiety disorders (X-axis) and ADHD (Y-axis) used in the MR analysis. Each point represents an individual genetic variant (SNP). The slope of the regression line (solid line) indicates the estimated causal effect of anxiety on ADHD. The R-squared value is about 17%, indicating the proportion of variance in ADHD explained by the genetic variants via anxiety disorders. The intercept of the regression line is about 0, representing the average pleiotropic effect across SNPs.

In Figure 1B, the Scatter plot depicts the associations between genetic variants and ADHD (X-axis) and anxiety disorders (Y-axis) used in the MR analysis, with R-squared value of about 17% and regression line intercept of about 0.

Figures 1C, D are the Forest plot of the effect sizes (odds ratios) for the association between different exposure and outcome. The horizontal lines represent the 95% confidence intervals (CIs) for each study. The size of the square for each study represents the weight of the study in the meta-analysis. P-values indicate the

TABLE 1 Mendelian randomization analysis results for ADHD and AD.

Exposure	Outcome	Method	N_IV	P_IV	b (se)	OR [95%CI]	P
ADHD	Anxiety	IVW	25	5.00E-08	0.014 (0.046)	1.01 [0.93-1.11]	0.77
		WM	25	5.00E-08	-0.039 (0.065)	0.96 [0.85-1.09]	0.55
		MR-Egger	25	5.00E-08	0.048 (0.158)	1.05 [0.77-1.43]	0.77
Anxiety	ADHD	IVW	18	1.00E-05	0.001 (0.018)	1.00 [0.97-1.04]	0.95
		WM	18	1.00E-05	0.005 (0.024)	1.01 [0.96-1.05]	0.83
		MR-Egger	18	1.00E-05	0.005 (0.026)	1.00 [0.95-1.06]	0.87



C

Exposure	Outcome	Method	OR [95%CI]	P
ADHD	Anxiety disorder	IVW	1.01 [0.93−1.11]	0.765
ADHD	Anxiety disorder	WM	0.96 [0.85−1.09]	0.548
ADHD	Anxiety disorder	MR−Egger	1.05 [0.77−1.43]	0.765
Anxiety disorder	ADHD	IVW	1.00 [0.97−1.04]	0.951
Anxiety disorder	ADHD	WM	1.01 [0.96−1.05]	0.830
Anxiety disorder	ADHD	MR−Egger	1.00 [0.95−1.06]	0.867

D

Exposure	Outcome	Method	OR [95%CI]	P
EA	ADHD	IVW	0.72 [0.69−0.74]	1.70E−79
EA	ADHD	WM	0.74 [0.71−0.77]	1.22E−52
EA	ADHD	MR Egger	0.78 [0.68−0.89]	4.02E−4
EA	Anxiety disorder	IVW	0.95 [0.91−0.98]	4.98E−3
EA	Anxiety disorder	WM	0.93 [0.88−0.99]	0.021
EA	Anxiety disorder	MR Egger	0.92 [0.78−1.09]	0.326
Income	ADHD	IVW	0.76 [0.70−0.81]	2.07E−15
Income	ADHD	WM	0.80 [0.74−0.85]	2.01E−10
Income	ADHD	MR Egger	1.01 [0.72−1.43]	0.944
Income	Anxiety disorder	IVW	0.89 [0.83−0.95]	2.41E−4
Income	Anxiety disorder	WM	0.90 [0.82−0.99]	0.028
Income	Anxiety disorder	MR Egger	1.02 [0.74−1.40]	0.901

FIGURE 1
MR analysis results for ADHD and anxiety disorders. **(A)** Causal effects of anxiety disorder on ADHD; **(B)** Causal effects of ADHD on anxiety disorder. **(C)** Forest plot of the causal effects between ADAD and anxiety disorders. **(D)** Forest plot of the causal effects of Educational attendance (EA) and Income on ADAD and anxiety disorders.

statistical significance of the effect sizes. In Figure 1C, the p values are not significant (p-value>0.05), which indicate that the effect observed in the study could be due to random variation or chance. In Figure 1D, the p values are significant for the main MR methods (IVW method; p-value<0.005), which indicate that both Educational Attainment (EA) and Income serve as common influential factors for both ADHD and anxiety disorders.

3.2 Annotation for IVs and corresponding genes

Table 2 lists the IVs and their mapped genes for ADHD and anxiety disorders. For ADHD, 25 SNPs are associated with genes such as ANO10, SORCS3, CDH8, TEX41, FOXP1, COL19A1, and others. Certain SNPs (e.g., rs1162202 and rs115111850) are found

TABLE 2 List of IVs and mapped genes for ADHD and anxiety disorders.

IVs of ADHD		IVs of Anxiety disorders	
SNP Name	Gene Symbol	SNP Name	Gene Symbol
rs115111850	ANO10	rs1067394	CAMKMT
rs11596214	SORCS3	rs116274579	ARPP19
rs1162202	LOC105371305	rs11998109	LOC105377795
rs1162202	CDH8	rs13340324	LINC02263
rs1438898	TEX41	rs17823065	SOCS5
rs17718444	FOXP1	rs4724582	TNS3
rs2025286	COL19A1	rs56242606	VWDE
rs2582895	LINC02758	rs6068466	TSHZ2
rs4916723	MIR9-2HG	rs62156215	LMAN2L
rs4925811	ARHGAP39	rs62516012	CASC21
rs549845	PTPRF	rs62516012	CASC8
rs6537401	LSM6	rs72850179	NCKAP5
rs73145587	LOC105375341	rs79310980	LMCD1-AS1
rs7506904	DCC	rs9949003	ATP9B
rs76284431	LOC105370656	rs11190870	/
rs9969232	FOXP2	rs112311059	/
rs10875612	/	rs113789029	/
rs11255890	/	rs759707	/
rs17576773	/	rs7910612	/
rs2886697	/	/	/
rs6082363	/	/	/
rs704061	/	/	/
rs7613360	/	/	/
rs76857496	/	/	/
rs77960	/	/	/
rs7844069	/	/	/

to be associated with multiple genes. For instance, rs1162202 is linked to genes LOC105371305 and CDH8. For anxiety disorders, 18 SNPs are linked to genes including CAMKMT, ARPP19, SOCS5, TNS3, VWDE, TSHZ2, and others. Some SNPs like rs62516012 are mapped to multiple genes, such as CASC21 and CASC8. Additionally, a few SNPs are not associated with any gene. Importantly, the SNPs for ADHD and anxiety disorders presented zero overlap, indicating distinct genetic markers for each condition. This table highlights the genetic distinctions between ADHD and anxiety disorders through their respective IVs and gene mappings.

To understand the role of the IVs and mapped genes in ADHD and AD, we first used DAVID to annotate the function of the mapped genes at an individual level, identifying the pathways and cellular processes these genes are involved in. Then, we used LDM tools from AIC LLC (https://www.gousinfo.com/en/advancedsearch.html) to explore the connections of these SNPs, genes, and cellular processes to ADHD and AD. Based on these results, we constructed two networks centered on the two conditions, as shown in Figures 2, 3, respectively.

Figure 2 presents a detailed network illustrating the intricate connections among ADHD, specific genetic variations (SNPs), mapped genes, and cellular processes. Direct associations with ADHD are highlighted for genes such as FOXP2, SORCS3, FOXP1, DCC, CDH8, and a specific SNP (rs4916723), along with the cellular process of 'Cell adhesion.' Conversely, genes like ANO10, TEX41, and LOC105371305 indirectly implicate ADHD through their genetic variations. Moreover, genes like PTPRF, CDH8, and COL19A1, known to participate in cell adhesion, potentially establish connections to ADHD. This comprehensive network effectively delineates the genetic and cellular landscape related to ADHD but not anxiety disorders and showcases both direct and indirect associations. Please note that only 8 out of the 25 IVs (SNPs) used in MR analysis have been included in the network, suggesting that more research is needed to study the remaining IVs and their connections with ADHD.

To note, each edge depicted in Figures 2, 3 signifies a relationship between the two entities it links. In the case of connections between diseases (ADHD or anxiety disorder), cell processes (such as cell adhesion, metal binding, and metal ion binding), and genes, the edge represents an association supported by existing literature. When it comes to genes and SNPs, it indicates that the SNP has been mapped to that specific gene.

Figure 3 portrays a network illustrating the interconnections between anxiety disorders and its associated IVs (SNPs), mapped genes, and biological processes. Notably, entities such as CAMKMT, NCKAP5, CASC8, and rs56242606 exhibit positive associations with anxiety disorders. Conversely, anxiety disorders demonstrate negative relationships with the biological processes of Metal binding and metal ion binding. This comprehensive network offers insights into the genetic and cellular landscape specific to anxiety disorders, distinguishing it from ADHD, and showcasing both direct and indirect associations. It's important to highlight that only 8 out of the 18 IVs (SNPs) utilized in MR analysis are represented in the network, underscoring the need for further research to explore the remaining IVs and their connections with anxiety disorders.

3.3 Influence of socioeconomic related factors on AD and ADHD

To explore the mechanism of the common influential factors on AD and ADHD, we also conducted a one-way MR analysis to study the effect of three important factors, namely educational attainment (EA), intelligence and income, on both ADHD and AD. The MR analysis has been done in a previous study (25) and we were able to replicate the process in this study. We present the details of the results in Table 3 and expand the discussion based on it.

In MR-Egger analysis, the Egger intercept values range from -0.005 to 0.004 (see Supplementary Table 1). None of the p-values

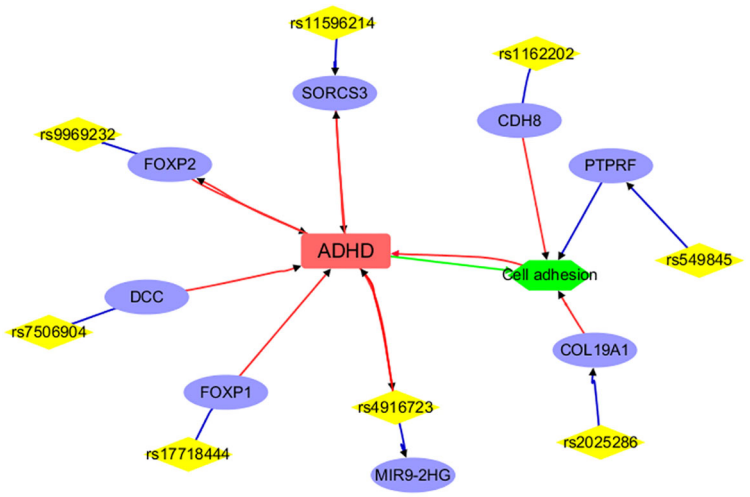


FIGURE 2
Annotation results for the IVs selected and mapped genes from ADHD. Edges in red and green represent positive and negative relationships, respectively. Edges in blue represent no polarity.

for pleiotropy are below the typical significance threshold of 0.05, indicating there is no evidence of directional pleiotropy in the dataset.

For ADHD, EA, Income, and Intelligence show a consistent protective causal effect across IVW and WM methods (OR ∈ [0.72, 0.95]; $p < 0.028$). Although MR Egger indicates non-significant pleiotropy (p-values > 0.09), significant heterogeneity is observed in several analyses where Q_p <0.001 and I^2 >0.5, indicating that the IVs from Income, Intelligence, and EA may not all be valid in estimating the same underlying causal effect on ADHD.

For anxiety disorders, EA and Income show a consistent protective causal effect across IVW and WM methods (OR ∈ [0.89, 0.95]; $p < 0.033$), while Intelligence shows no significant effect (OR ∈ [0.86, 0.99]; $p > 0.555$). MR Egger results indicate no significant pleiotropy (p-values > 0.091). Additionally, heterogeneity is generally low across analyses, as indicated by Q_p >0.4 and I^2<0.01, suggesting that the IVs from Income, Intelligence, and EA are likely valid in estimating the causal effect on anxiety disorders.

The MR analysis results indicate that both Educational Attainment (EA) and Income serve as common influential factors for both ADHD and anxiety disorders, as shown in Figure 1D. Notably, while a large number of instruments from both Income (>86 IVs) and EA (>458 IVs) may not all accurately estimate the

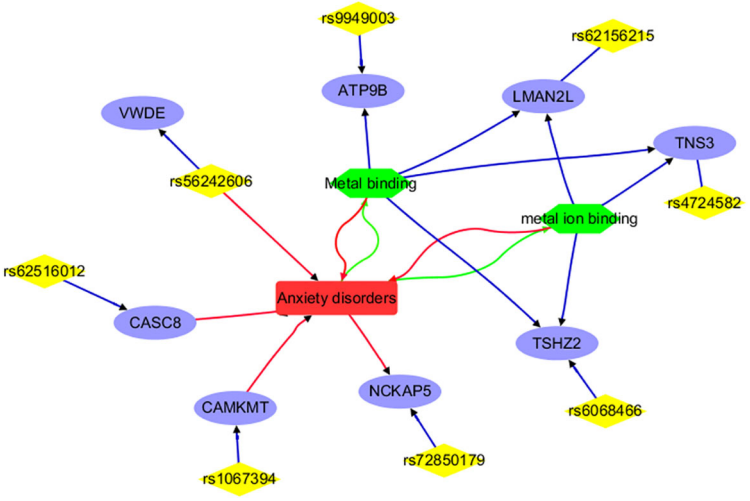


FIGURE 3
Annotation results for the IVs selected and mapped genes from Anxiety disorders. Edges in red and green represent positive and negative relationships, respectively. Edges in blue represent no polarity.

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TABLE 3 Causal effects of EA, Income, and Intelligence on ADHD and AD.

Exposure	Outcome	Method	N_IV	P_IV	b (se)	OR [95%CI]	P
EA	ADHD	IVW	457	5E-8	-0.333 (0.018)	0.72 [0.69-0.74]	<0.001
		WM	457	5E-8	-0.300 (0.020)	0.74 [0.71-0.77]	<0.001
		MR Egger	457	5E-8	-0.249 (0.070)	0.78 [0.68-0.89]	<0.001
EA	AD	IVW	458	5E-8	-0.056 (0.020)	0.95 [0.91-0.98]	0.005
		WM	458	5E-8	-0.070 (0.030)	0.93 [0.88-0.99]	0.021
		MR Egger	458	5E-8	-0.084 (0.085)	0.92 [0.78-1.09]	0.326
Income	ADHD	IVW	86	5E-8	-0.280 (0.035)	0.76 [0.70-0.81]	<0.001
		WM	86	5E-8	-0.229 (0.036)	0.80 [0.74-0.85]	<0.001
		MR Egger	86	5E-8	0.012 (0.175)	1.01 [0.72-1.43]	0.944
Income	AD	IVW	87	5E-8	-0.121 (0.033)	0.89 [0.83-0.95]	<0.001
		WM	87	5E-8	-0.103 (0.047)	0.90 [0.82-0.99]	0.028
		MR Egger	87	5E-8	0.020 (0.162)	1.02 [0.74-1.40]	0.901
Intelligence	ADHD	IVW	78	5E-8	-0.158 (0.028)	0.85 [0.81-0.90]	<0.001
		WM	78	5E-8	-0.113 (0.026)	0.89 [0.85-0.94]	<0.001
		MR Egger	78	5E-8	-0.060 (0.124)	0.94 [0.74-1.20]	0.632
Intelligence	AD	IVW	76	5E-8	-0.005 (0.026)	0.99 [0.95-1.05]	0.833
		WM	76	5E-8	-0.021 (0.036)	0.98 [0.91-1.05]	0.555
		MR-Egger	76	5E-8	-0.153 (0.148)	0.86 [0.64-1.15]	0.306

same underlying causal effect on ADHD, all IVs appear valid in estimating the underlying causal effect on anxiety disorders. Consequently, we can infer that genetic predispositions to EA and Income may largely serve as common protective factors for both anxiety disorders and ADHD.

In contrast, while Intelligence demonstrates a potential to reduce the risk of ADHD, as indicated by its significant protective effects across various analytical methods, its impact on anxiety disorders appears less clear. The data suggests that Intelligence may not consistently serve as a protective factor for anxiety disorders, as evidenced by non-significant findings across multiple analyses. Thus, genetic predisposition to Intelligence may not uniformly confer protection against both anxiety disorders and ADHD.

4 Discussion

While ADHD and anxiety disorders are distinct in their diagnostic criteria and treatment approaches (1), they frequently co-occur, exacerbating symptoms and often leading to misdiagnosis (17). Understanding the shared and unique causal factors and underlying mechanisms of both conditions is crucial for improving diagnosis and treatment outcomes. This study examined the genetic-level causal effects between ADHD and anxiety disorders, as well as their associations with educational attainment (EA), income, and intelligence. The findings revealed both distinct and shared genetic variables influencing both ADHD and anxiety disorders.

Our study found no causal association between anxiety disorder and ADHD at the genetic level, aligning with a recent MR study that also utilized European-origin datasets with a relatively smaller sample size (26). Despite selecting instrumental variables for both conditions, none of the methods used (IVW, WM, and MR-Egger) showed statistical significance. These results suggest that while the selected genetic variables may be related to either ADHD or anxiety, they do not impact the risk of the other condition.

Functional annotation analysis showed that a large part of the IVs and corresponding genes selected for ADHD were already implicated in the disorder (Figure 2). Specifically, variations in the FOXP2 gene (27, 28) impact language and cognitive functions, potentially contributing to ADHD traits. The SORCS3 gene (20), FOXP1 gene (29), and the rs4916723 polymorphism (29) are associated with increased ADHD risk, with SORCS3 potentially involved in neurodevelopmental pathways. Additionally, cell adhesion, which is vital for neuronal development, synaptic connectivity, and brain circuitry, may impact ADHD pathophysiology via disruptions in cell adhesion molecules and genetic abnormalities in ganglioside metabolism (30). Cell adhesion-related genes like COL19A1, PTPRF, and CDH8 (31, 32) were implicated in neuronal development and synaptic function and may contribute to ADHD susceptibility through disruptions in cell adhesion molecules and synaptic connectivity. Moreover, it is noted that 17 out of the 25 ADHD IVs (SNPs) used in the MR analysis did not yield results from functional annotation analysis. This indicates the need for further research to investigate the remaining IVs and their connections with ADHD.

For anxiety disorders, 8 out of the 18 IVs (SNPs) or their corresponding genes are highlighted by the functional annotation analysis (Figure 3). These include CAMKMT, NCKAP5, CASC8, rs56242606, ATP9B, LMAN2L, TNS3, and TSHZ2. Specifically, CAMKMT influences anxiety disorders through CAMKII methylation, which impacts neuronal function and synaptic plasticity, showing significant genetic associations in European populations (19, 33). NCKAP5 may contribute to the pathophysiology of anxiety disorders by affecting synaptic plasticity and neuronal development (34). CASC8's role in anxiety disorders is linked to its influence on neural development and function, with the haplotypic block rs4733767 indicating genetic susceptibility (35). The rs56242606 variant (on the VWDE gene) is associated with an increased risk of anxiety disorders, potentially impacting gene regulation related to anxiety and brain traits such as smaller amygdala volume (36).

The relationship between anxiety disorders and metal ion binding is notable; anxiety can disrupt metal homeostasis, leading to oxidative stress, while dysregulated metal binding can exacerbate anxiety through neuronal dysfunction (37, 38). Metal binding affects anxiety disorders by influencing neurotransmitter function and oxidative stress. Interventions such as berberine, bisdemethoxycurcumin (BDMC), and maternal zinc supplementation show promise in alleviating anxiety by modulating metal binding (39–41). Genes related to metal binding or metal ion binding (e.g., ATP9B, LMAN2L, TNS3, and TSHZ2) may play a role in the development of anxiety disorders. These findings suggest the need for further investigation into the remaining 10 IVs to understand their connection with anxiety disorders.

Notably, none of the selected IVs or their mapped genes overlap between ADHD and anxiety disorders. The distinct IVs identified for ADHD and anxiety disorders may illustrate the differences between these two conditions, potentially explaining their distinct diagnostic and treatment approaches.

Our MR analysis unveils Educational Attainment (EA) as a shared influential factor impacting both ADHD and anxiety disorders. Notably, a multitude of instruments from EA (>458 IVs) and Income (>86 IVs) highlight their complex interplay in shaping the risk landscape for these conditions. While the accuracy of estimating the causal effect on ADHD varies across these instruments, all IVs demonstrate validity in estimating the underlying causal effect on anxiety disorders. This suggests a nuanced relationship wherein genetic predisposition to EA and Income may partially converge as common protective factors for both anxiety disorders and ADHD. These findings underscore the intricate role of EA in the etiology of both conditions, prompting further investigation into the mechanisms underlying this association.

While some studies suggested potential relationships between ADHD and Intelligence, the results are non-consistent (42, 43). Our MR analysis results indicate that genetic liability to higher intelligence may protect again ADHD, but not Anxiety disorder.

EA emerges as a pivotal factor influencing both ADHD and anxiety disorders. In the context of ADHD, lower EA is associated with negative academic outcomes, including reduced graduation rates and academic achievement, possibly due to challenges in focus and organization (44). Conversely, for anxiety disorders, higher EA serves as a protective factor, correlated with lower rates of anxiety disorders and offering effective coping mechanisms. In contrast, lower EA correlates with elevated anxiety levels, potentially impeding academic performance (7, 45). Moreover, the interplay between genetic factors, income, and educational attainment further modulates the relationship between ADHD and EA (46, 47). These findings highlight the intricate relationship between EA and both ADHD and anxiety disorders, emphasizing the need for targeted interventions to address academic challenges and mental health concerns in educational settings.

Income serves as another common influential factor for both ADHD and anxiety disorders. In the context of ADHD, lower income levels are associated with a higher prevalence of ADHD diagnosis, potentially influenced by socioeconomic disparities and limited access to healthcare and education (48–50). Additionally, higher family income has been correlated with reduced ADHD symptoms in early childhood, possibly mediated through factors such as asthma and physical fitness. For anxiety disorders, reduced income levels can exacerbate the condition by decreasing productivity and increasing the risk of job loss, ultimately contributing to financial instability (51). Notably, income disparities are particularly evident among vulnerable populations such as migrants and perinatal groups affected by anxiety disorders (52).

The MR analysis of EA and income on ADHD and anxiety disorder not only provides genetic support for the previously observed effects of socioeconomic factors on these disorders but also uncovers potentially shared genetic factors and their influential paths. These findings may offer insights into understanding the shared characteristics and co-occurrence of ADHD and anxiety disorder.

It should be noted that the results of MR analysis vary across different methods. This is expected, as the IVW method generally has the highest statistical power among the three methods, often resulting in significant outcomes. In contrast, the WM and MR-Egger methods have less power, making it more difficult to achieve statistical significance with the same set of IVs and effect sizes (23). Although some datasets showed significant heterogeneity, indicating variability in the causal effects among IVs, no significant direct pleiotropy was detected. This suggests that the IV influences the outcome solely through its effect on the exposure, supporting the validity of our MR analysis.

A key strength of this study is our use of MR analysis to evaluate the causal relationship between ADHD and anxiety disorder at genetic level, as well as potential influencing factors such as educational attainment, income, and intelligence. This approach takes advantage of the random allocation of genetic variants during inheritance, which naturally protects these variables from confounding factors like environmental influences and lifestyle choices. Consequently, MR analysis can provide more robust genetic evidence and strengthen the persuasiveness of causal inferences.

However, this study has several limitations that should be addressed in future research. First, the participants in the datasets used for MR analysis are all of European origin. It is essential to examine data from other racial groups to corroborate the findings of

this study. Additionally, the results only reflect the connection and distinction between ADHD and anxiety disorder at the genetic level. Since these two disorders are complex in their pathology, their interplay at different levels (e.g., cellular processes, organ/tissue interactions) should also be studied.

5 Conclusion

Our findings suggest that the shared symptoms between ADHD and anxiety disorders are more likely influenced by genetic predispositions related to socioeconomic factors, rather than by genetic predispositions specific to the disorders themselves.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

The data utilized in this study are publicly available. The original studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

XD: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. HR: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. SW: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. HJ: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. CG: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1439474/full#supplementary-material

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Psychiatric comorbidities of attention deficit/hyperactivity disorder in Japan: a nationwide population-based study

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Introduction: This study aimed to estimate prevalence and incidence of attention deficit/hyperactivity disorder (ADHD) and comorbid relationships between ADHD and other psychiatric disorders in Japan.

Methods: Using the real-world JMDC Claims Database, we conducted a cross-sectional study (analysis years 2017–2021) and retrospective cohort study (observation 2 years before/after the initial ADHD diagnosis; data collection 2005–2021; enrollment 2017–2019). Patients were male or female, aged 0–57 years. Cross-sectional study patients had an ADHD or other psychiatric disorder diagnosis (with or without medication) and were continuously registered in each analysis year; retrospective study patients had an ADHD diagnosis and ≥2 years' observation before and after diagnosis. Endpoints were annual prevalence and incidence of ADHD in Japan, prevalence and risk ratio of each psychiatric comorbidity in patients with ADHD, prevalence and risk ratios of ADHD in patients with each psychiatric comorbidity, and prevalence of psychiatric disorders before/after the initial ADHD diagnosis.

Results: ADHD prevalence in children/adolescents and adults increased each year from 2017 to 2021. Prevalence in boys was 3.5–4.1 times higher than in girls. Prevalence in adults was lower than in children/adolescents, with a small sex difference. ADHD was highly comorbid with various psychiatric disorders. In 2019, the most common comorbidity in children/adolescents with ADHD was autism spectrum disorder (ASD; 54.4%); in adults, it was mood disorders (60.9%). ADHD prevalence in patients with various psychiatric disorders was higher than in the control population. ADHD prevalence was highest in patients with oppositional defiance disorder among both children/adolescents and adults (77.2% and 69.2%, respectively). In the retrospective cohort study (N = 14,940), the most common psychiatric disorders diagnosed prior to ADHD diagnosis were ASD in children/adolescents (33.9% of patients), and mood disorders and sleep disorders in adults (36.9% and 23.8% of patients, respectively).

Discussion: ADHD was comorbid with various psychiatric disorders in Japan. In children and adolescents with ADHD, ASD was often diagnosed prior to ADHD. Psychiatric disorders, especially mood disorders and sleep disorders, were frequently diagnosed prior to the initial ADHD diagnosis in adults. The likelihood of comorbid ADHD should be considered when diagnosing adult patients with psychiatric disorders.

KEYWORDS

ADHD, autism spectrum disorder, claim database, complications, depression, incidence, prevalence, risk ratio

1 Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impaired levels of inattention and hyperactivity/impulsivity that negatively impacts social, academic, and occupational functioning (1–3). ADHD is often first diagnosed in childhood, and some patients have remission or partial remission as they grow; however, others continue to have symptoms at levels that meet diagnostic criteria into adulthood (1–3). In such cases, symptoms can change over time; generally, inattention persists and hyperactive-impulsive symptoms wane (4). While twin studies demonstrated that ADHD is highly heritable with heritability estimates in the range of 70–80% (5, 6), in most cases ADHD is considered to be caused by the accumulation of various genetic as well as environmental risk factors. Consistent with the multifactorial etiology of ADHD, patients with ADHD exhibit considerable variation in profiles of symptoms, type and severity of impairments, and complicating factors (2, 3).

The worldwide prevalence of ADHD in childhood and adolescence has been estimated by meta-analysis to be 7.2% (7) and is higher in boys than in girls (8). Meta-analyses have estimated the prevalence of ADHD in adulthood, based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, to be 2.5–2.8% (9, 10). Additionally, the prevalence of ADHD has been shown to vary according to geographic location (11) and national income level (9). However, the prevalence of ADHD in Japan has not been fully investigated, and evidence for nationwide estimates is limited to date. Epidemiological surveys conducted at the municipal level, which provided a more accurate estimate of the prevalence of ADHD, have reported that the ADHD prevalence in children in Japan is 5.8% (12). Nationwide studies using hospital administrative (13) and claims-based databases (14) showed a gradual increase in diagnosis of ADHD in children and adolescents in Japan from 2012 to 2018 and from 2005 to 2015, respectively. In an epidemiological study in Hamamatsu city in central Japan, the prevalence of ADHD in adults was estimated to be 1.65% (15). There have been no nationwide studies on the prevalence of ADHD in adults in Japan.

People with ADHD often have various psychiatric comorbidities. Previous studies have shown that ADHD often coexists with various psychiatric disorders in childhood, including mood disorders, anxiety disorders, conduct disorders, oppositional defiant disorder (ODD), learning disorders, Tourette syndrome, borderline personality disorder, and autism spectrum disorder (ASD) (16, 17). Twelve-month comorbidities in adults with ADHD were examined using the results of the United States National Comorbidity Survey Replication (18) and the World Health Organization survey (9); these analyses concluded that adults and adolescents with ADHD had a high risk of psychiatric disorders such as anxiety disorders, mood disorders, ODD, and substance use disorders. The coexistence of psychiatric comorbidities imposes an additional burden on patients with ADHD. ADHD itself is associated with an increased risk of suicide attempts (19), and when combined with comorbidities, this risk escalates further. In addition, ADHD is associated with an increased risk of all-cause and premature mortality (20), and psychiatric comorbidities contribute to this increased risk. The prevalence of psychiatric disorders including ADHD has been shown to vary by geographic location, national income level, and cultural differences (21). Comorbidities of ADHD may also differ depending on the temperament and culture of the people. Therefore, it is important to determine the prevalence and comorbidities of ADHD in individual countries or cultures. However, psychiatric comorbidities associated with ADHD have not been widely investigated in Japan. Therefore, we conducted a nationwide claims-based study to identify the prevalence and incidence of ADHD and associated psychiatric comorbidities in Japan using a cross-sectional study design. In addition, using a longitudinal study design, we examined whether ADHD or other psychiatric disorders are diagnosed first.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; OTC, over-the-counter; Q, quartile; SDD, specific developmental disorder(s).

2 Materials and methods

2.1 Study design

This was a cross-sectional study and a retrospective cohort study for longitudinal analysis using real-world data from the JMDC Claims Database (JMDC Inc., Tokyo, Japan). This nationwide claims-based database includes health insurance claims data, medical examinations data, and ledger information received from Japanese health insurance associations contracted by JMDC since 2005; however, these are not national insurance data as patients in the database are employed people living in Japan and their dependents (22). Health insurance associations included in the database are associated with companies; self-employed workers and public servants and their families in Japan, who are members of other insurance associations, are not included in the database. As of November 2023, the cumulative database population size was approximately 17 million people (22). This study accessed data collected from 2005 to 2021.

A cross-sectional study was conducted on a yearly basis to investigate the prevalence and incidence of ADHD, the prevalence and risk ratios of psychiatric comorbidities in patients with ADHD, and the prevalence and risk ratio of ADHD in patients with specific psychiatric comorbidities. In the cross-sectional study, the total data collection period was from January 2017 to December 2021.

A retrospective cohort study, to enable longitudinal analysis, with an observation period of 2 years before and after the initial diagnosis of ADHD was used to investigate the order of diagnosis of psychiatric disorders in patients with ADHD. In the retrospective cohort study, the total data collection period was from January 2005 to December 2021. The enrollment period was from January 2017 to December 2019.

This study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice published by the International Society for Pharmacoepidemiology and local laws and regulations. This study was an observational study using anonymized information that had already been created by the JMDC; therefore, it was judged unnecessary to conduct ethical review, and informed consent was not required. The study was not registered.

2.2 Study population

The overall study population was male or female people living in Japan, aged 0–57 years, and who were registered in the JMDC database. The age cutoff was set to provide 10-year age categories for the adult population (18–27, 28–37, 38–47, and 48–57 years) and because there are very few people aged ≥60 years in the database. Study populations for both the cross-sectional and retrospective cohort analyses included people with a diagnosis of ADHD or other psychiatric disorders in the JMDC database, as described in detail below. In both analyses, patients with ADHD were defined in two ways. The first definition was by diagnosis: these patients had a diagnostic code for ADHD per the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classification codes F90.x (hyperactivity disorder) and F98.8 (other specified behavioral and emotional disturbances that usually develop in children and adolescents) recorded in the database. Diagnostic codes for ADHD were selected in alignment with previous studies (17, 23–26). The second definition was by diagnosis and medication: these patients had a diagnostic code for ADHD and prescription code(s) for ADHD medication(s) approved in Japan recorded in the database (see Supplementary Methods for the Anatomical Therapeutic Chemical drug codes).

ADHD guidelines recommend that treatment of the more serious disorder should be prioritized in ADHD patients with psychiatric comorbidities (27, 28). ADHD is considered to predominate in patients prescribed ADHD medications. However, in cases where patients have concurrent psychiatric comorbidities, treatment of these other conditions may be prioritized, which can result in ADHD medications not being prescribed to patients with ADHD. Thus, patients with ADHD were defined in two ways to confirm whether a similar trend was seen in patients with predominant ADHD and those with predominant other psychiatric disorders.

2.2.1 Cross-sectional study populations

In the cross-sectional study, five analysis populations were defined: overall, Population 1A, Population 1B, Population 2, and Population 3. The overall population consisted of patients who were continuously registered in the database for 12 months of the analysis year; analysis years were 2017–2021, and each analytical year was defined as January to December. For each analysis year, Population 1A included patients with a diagnosis of ADHD in that year; a patient could be enrolled for multiple years. The age of each patient was defined as their age as of April in each enrollment year. Patients must have had ADHD diagnosed at least once in the year of analysis; the index date was the month of initial diagnosis of ADHD in the year of analysis. Population 1B included patients with a diagnosis of ADHD and prescription of ADHD medication in each year. Patients must have had ADHD diagnosed and prescription of ADHD medication at least once in the year of analysis; the index date was the month of the first prescription of ADHD medication in the year of analysis. Population 2 included patients with a diagnosis of each psychiatric disorder in each year; a patient could be enrolled for multiple years and a patient could have more than one psychiatric disorder. Patients must have had a diagnosis of each psychiatric disorder at least once in the year of analysis; the index date was the month of initial diagnosis of each psychiatric disorder in the year of analysis (see Supplementary Methods for ICD-10 codes for psychiatric disorders). Population 3 included patients with no diagnosis of ADHD at baseline or during the entire period of registration. A baseline period was established for Population 3, defined as the preceding 2 years from the year of analysis; for example, if the year of analysis was 2021, 2019–2020 was the baseline period. If patients had been registered for ≥2 years, it was confirmed that they had no diagnosis of ADHD during the entire registered period.

Control populations were also defined. The Population 1A control (non-ADHD) population was defined as people continuously present in the database for 12 months in the year of analysis with no ADHD diagnosis in the year of analysis. The Population 1B control (non-ADHD) population was defined as people continuously present in the database for 12 months in the year of analysis without prescription of any ADHD medications in the year of analysis. The Population 2 control (no psychiatric disorders) populations were defined as people continuously present in the database for 12 months in the year of analysis and never diagnosed with each psychiatric disorder in the year of analysis.

2.2.2 Retrospective cohort study populations

Cohort 1 consisted of patients with a diagnosis of ADHD. To meet the inclusion criteria for this cohort, patients were required to have ≥1 diagnosis of ADHD within the enrollment period and an established baseline period of the past 2 years including the index month. The index date was defined as the month of initial diagnosis of ADHD during the enrollment period. Patients must not have had a diagnosis of ADHD during the baseline period; if patients had been registered for ≥2 years, it was confirmed that they had no diagnosis of ADHD during the entire registered period. For children aged <2 years, the inclusion condition was that they could be followed up from birth, and the baseline period was defined as the period from birth to index.

Cohort 2 consisted of patients with a diagnosis of ADHD and prescribed ADHD medications, that is, patients from Cohort 1 who were prescribed ADHD medications at least once during the enrollment period in addition to their ADHD diagnosis. Included patients had an established baseline period of the past 2 years including the index month and must not have had a prescription of ADHD medication during the baseline period. If patients had been registered for ≥2 years, it was confirmed that they had no diagnosis of ADHD during the entire registered period. For Cohort 2 the index date was the month of the first prescription of ADHD medication during the enrollment period.

For both cohorts, a follow-up period was established, defined as 2 years from the month following the index month.

2.3 Variables/outcome measures

Patient demographic data included age (0–5 years, 6–11 years, 12–17 years, 18–27 years, 28–37 years, 38–47 years, 48–57 years), children and adolescents (0–17 years) or adults (18–57 years), and sex (male, female). Psychiatric disorders included substance use disorders; schizophrenia and schizotypal disorder; other psychotic disorders; mood disorders (including bipolar affective disorder, depressive episode, and recurrent depressive disorder); anxiety disorders; obsessive-compulsive disorder (OCD); reaction to severe stress, and adjustment disorders; dissociative disorders; somatoform disorders; eating disorders; intellectual disability (referred to as 'mental retardation' in the ICD-10); tic disorders; sleep disorders; ODD; conduct disorders (excluding ODD); specific developmental disorders (SDDs) of scholastic skills; SDD of motor function; ASD; and epilepsy.

This was a non-interventional study, and treatment was prescribed in accordance with current clinical practice at the discretion of the treating physician. ADHD medications data included prescriptions of ADHD medications approved in Japan; namely, osmotic-release oral system methylphenidate hydrochloride, lisdexamfetamine mesilate, atomoxetine hydrochloride, and guanfacine hydrochloride extended-release.

2.4 Endpoints

The cross-sectional study had several endpoints. The first endpoint was the annual prevalence and incidence of ADHD in Japan, in the overall population and Population 3, respectively. Absence of an ADHD diagnosis during the entire registered period was defined as a condition for new onset. Patients who had an established baseline period of the past ≥2 years were included in this study. The extended estimation for the Japanese population was calculated from the JMDC data after adjusting the number of patients in the JMDC database for age (in increments of 1 year) and sex (male, female) distribution in Japan using government statistics data (Supplementary Methods). The second endpoint was the prevalence and risk ratio of each psychiatric comorbidity in patients with ADHD (Population 1A and 1B) in each year. The control groups for risk ratio calculation were the Population 1A and 1B controls (non-ADHD populations), respectively, and the prevalence was calculated in the same manner as the ADHD population. The age and sex of the non-ADHD population were matched to those of the ADHD population to calculate the risk ratio (sample size ratio of 5:1). The risk ratio was calculated as "prevalence in the ADHD population/prevalence in the non-ADHD population." The third endpoint was the prevalence and risk ratio of ADHD in patients with each psychiatric disorder (Population 2) in each year. The control group for risk ratio calculation constituted the Population 2 controls (no psychiatric disorders populations), and the prevalence was calculated in the same manner as the psychiatric disorder population. The age and sex of the no psychiatric disorders populations were matched to those of the psychiatric disorder population to calculate the risk ratio (sample size ratio of 2:1).

The endpoints for the retrospective cohort study were the prevalence of the first diagnosis of psychiatric disorders during the baseline (before initial ADHD diagnosis) and follow-up (after initial ADHD diagnosis) periods; the number of psychiatric disorders diagnosed during the baseline and follow-up periods (if the psychiatric disorder was diagnosed in both the baseline and follow-up periods, it was not counted in the follow-up period); and the time (months) from the index to the first diagnosis of each psychiatric disorder during the baseline and follow-up periods.

2.5 Statistical analysis

This cross-sectional study and cohort study used an existing database and are a descriptive epidemiological study without

hypothesis verification; therefore, no sample size calculation was performed, and all patients who met the inclusion criteria were included. Categorical variables are summarized as number and proportion of patients.

In the cross-sectional study, the annual prevalence of ADHD in the JMDC database from 2017 to 2021 was calculated from the overall population; annual incidence of ADHD from 2017 to 2021 was calculated from Population 3. Estimates of ADHD prevalence and incidence in the overall Japanese population are shown for each year from 2017 to 2021. Annual prevalence and incidence of ADHD were calculated for the following subgroups: male children and adolescents (0–17 years), female children and adolescents (0–17 years), male adults (18–57 years), and female adults (18–57 years). For each of Populations 1A and 1B, and Population 1A and 1B controls (non-ADHD populations), the prevalence of each psychiatric comorbidity and risk ratio relative to the age- and sex-matched Population 1A and 1B controls (with 95% CI) were calculated by year from 2017 to 2021. For Population 2, the prevalence of ADHD and risk ratio relative to the age- and sex-matched Population 2 control (non-psychiatric comorbidity population) and 95% CI were calculated by year from 2017 to 2021. Although prevalence and risk ratios for Populations 1A, 1B, and 2 were calculated for each year from the JMDC database, only the data from 2019 are shown in this article; 2019 was selected as it precedes any potential mental health impact of the COVID-19 pandemic. Prevalence of psychiatric comorbidities among ADHD patients and prevalence of ADHD among psychiatric patients were calculated for the subgroups of children and adolescents (0–17 years) and adults (18–57 years).

In the longitudinal study, for Cohorts 1 and 2, the number and proportion of patients diagnosed with each psychiatric disorder during the baseline period or follow-up period were calculated (shown as percentage values only). The number of comorbid psychiatric disorders in the baseline period or follow-up period was calculated, together with summary statistics (mean, SD, minimum, Quartile 1 (Q1), median, Quartile 3 (Q3), and maximum). Summary statistics were also calculated for the number of months from the diagnosis of each psychiatric disorder to the index date (initial diagnosis of ADHD) during the baseline period and for the number of months from the index date to the initial diagnosis of each psychiatric disorder during the follow-up period.

No imputation was performed for missing values. The software programs used for statistical analysis were Amazon Redshift Version 1.0.47357 (Amazon Web Services, Seattle, WA, USA), SAS Version 9.4 (TS1M6) (SAS Institute Inc., Cary, NC, USA), and Python Version 3.11 (https://www.python.org/).

3 Results

3.1 Cross-sectional study patient disposition

The full analysis population increased from 4,682,474 to 7,779,860 people from 2017 to 2021 (Figure 1). The number of patients with diagnosis codes of ADHD (Population 1A) increased from 17,396 to 45,983. The number of patients with a diagnosis of ADHD and prescription of ADHD drugs (Population 1B) increased from 10,464 to 28,187. The number of patients with a diagnosis of each psychiatric disorder (Population 2) also increased each year in most cases.

3.2 Cross-sectional study outcomes

3.2.1 Annual prevalence and incidence of ADHD in Japan from 2017 to 2021

In children and adolescents, the estimated prevalence of ADHD in Japan increased from 2017 to 2021 in both boys and girls (Figure 2A). The prevalence of ADHD in boys was 3.5–4.1 times higher than that in girls. The prevalence of ADHD in adults also increased from 2017 to 2021, although it was lower than in children and adolescents, with only a small sex difference (Figure 2B). In 2021, the mean prevalence of ADHD in children and adolescents (both sexes combined) was estimated to be approximately 1.5%.

The estimated incidence of ADHD in children and adolescents in Japan increased from 2017 to 2021 in both boys and girls, except for a temporary decline in 2020 (Figure 2C). The incidence of ADHD in boys was 2.6–3.4 times higher than that in girls. ADHD incidence in adults was lower than in children, with a small difference between males and females (Figure 2D). While the incidence of ADHD among male adults did not show any clear changes, the incidence of ADHD among female adults slightly but steadily increased (except in 2020). Similar trends were observed for the estimated annual prevalence and annual incidence of ADHD in Japan when estimated from Population 1B data (Supplementary Figure 1).

3.2.2 Twelve-month psychiatric comorbidities of ADHD

In 2019, children and adolescents with ADHD in the JMDC database had a higher prevalence of all psychiatric disorders tested than the control (non-ADHD) population (Table 1). The most common comorbidity in children and adolescents with ADHD was ASD (54.4%). Other common comorbidities (prevalence ≥5%) in children and adolescents with ADHD were sleep disorders (13.7%); schizophrenia and schizotypal disorder (13.1%); mood disorders (9.1%; including depressive episode 6.3%); intellectual disability (8.7%); somatoform disorders (8.7%); reaction to severe stress, and adjustment disorders (7.7%); anxiety disorders (6.9%); epilepsy (6.1%); and SDDs of scholastic skills (5.0%). Children and adolescents with ADHD had risk ratios >1 for all psychiatric disorders tested except recurrent depressive disorder (risk ratio could not be calculated). Risk ratios were high (≥25) for ODD (111.4), conduct disorders excluding ODD (56.1), schizophrenia and schizotypal disorder (44.5), SDDs of scholastic skills (41.3), other psychotic disorders (38.6), bipolar affective disorder (36.4), and ASD (26.4). The lowest risk ratio observed was for substance use disorders (2.9). When ADHD was defined by prescriptions for ADHD medications in addition to diagnostic codes, risk ratios for many psychiatric disorders tended to decrease slightly (Supplementary Table 1). The reduction in risk ratio was more

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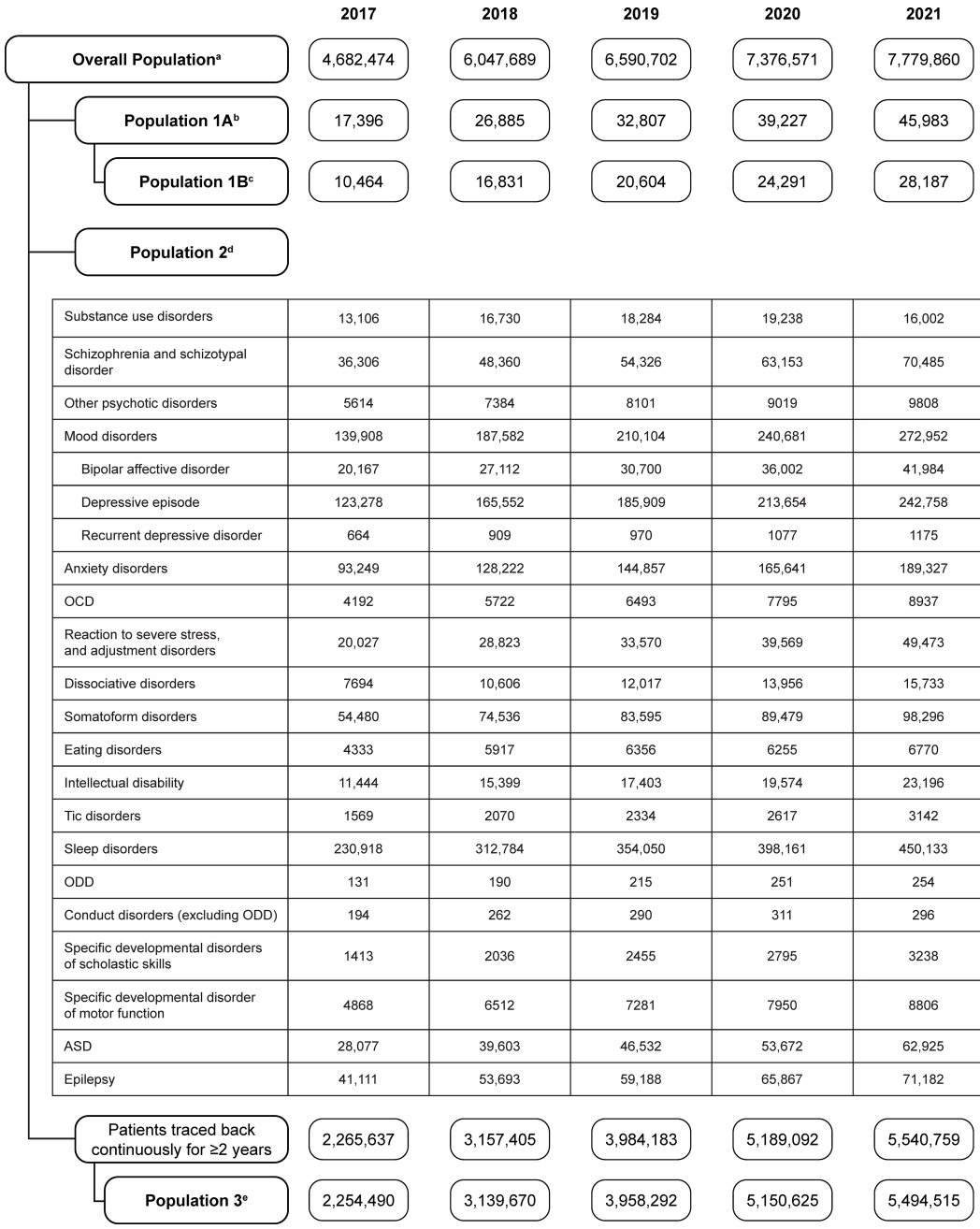

Substance use disorders	13,106	16,730	18,284	19,238	16,002
Schizophrenia and schizotypal disorder	36,306	48,360	54,326	63,153	70,485
Other psychotic disorders	5614	7384	8101	9019	9808
Mood disorders	139,908	187,582	210,104	240,681	272,952
Bipolar affective disorder	20,167	27,112	30,700	36,002	41,984
Depressive episode	123,278	165,552	185,909	213,654	242,758
Recurrent depressive disorder	664	909	970	1077	1175
Anxiety disorders	93,249	128,222	144,857	165,641	189,327
OCD	4192	5722	6493	7795	8937
Reaction to severe stress, and adjustment disorders	20,027	28,823	33,570	39,569	49,473
Dissociative disorders	7694	10,606	12,017	13,956	15,733
Somatoform disorders	54,480	74,536	83,595	89,479	98,296
Eating disorders	4333	5917	6356	6255	6770
Intellectual disability	11,444	15,399	17,403	19,574	23,196
Tic disorders	1569	2070	2334	2617	3142
Sleep disorders	230,918	312,784	354,050	398,161	450,133
ODD	131	190	215	251	254
Conduct disorders (excluding ODD)	194	262	290	311	296
Specific developmental disorders of scholastic skills	1413	2036	2455	2795	3238
Specific developmental disorder of motor function	4868	6512	7281	7950	8806
ASD	28,077	39,603	46,532	53,672	62,925
Epilepsy	41,111	53,693	59,188	65,867	71,182

FIGURE 1
Patient flow diagram for the cross-sectional study, showing the number of patients in each population from 2017 to 2021. [a]The overall population was the population who were continuously observed for 12 months in the year of the analysis. [b]Population 1A was the population with a diagnosis of ADHD in each year. [c]Population 1B was the population with a diagnosis of ADHD and prescription of ADHD medication in each year. [d]Population 2 was the population with a diagnosis of a psychiatric comorbidity in each year. [e]Population 3 was the population with no diagnosis of ADHD at baseline or during the entire period of registration. ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder.

pronounced for externalizing disorders, SDDs of scholastic skills, and other psychotic disorders.

In 2019, adult patients with ADHD also had a higher prevalence of all psychiatric disorders tested than the control population (Table 1). The most common comorbidity in adult patients with ADHD was mood disorders (60.9%; including depressive episode [51.8%] and bipolar affective disorder [18.7%]). Other common comorbidities (prevalence ≥5%) in adults with ADHD were sleep disorders (48.4%); schizophrenia and schizotypal disorder (23.1%); anxiety disorders (22.6%); ASD (22.0%); epilepsy (11.5%); reaction to severe stress, and adjustment disorder (11.4%); and somatoform disorders (7.5%). Adult patients with ADHD had risk ratios >1 for all psychiatric disorders tested except ODD (risk ratio could not be calculated). In particular, the risk ratios were high (≥25) for patients with tic disorders (100.0), SDDs of scholastic skills (93.3), ASD (60.4), conduct disorders excluding ODD (50.0), other psychotic disorders (37.8), bipolar

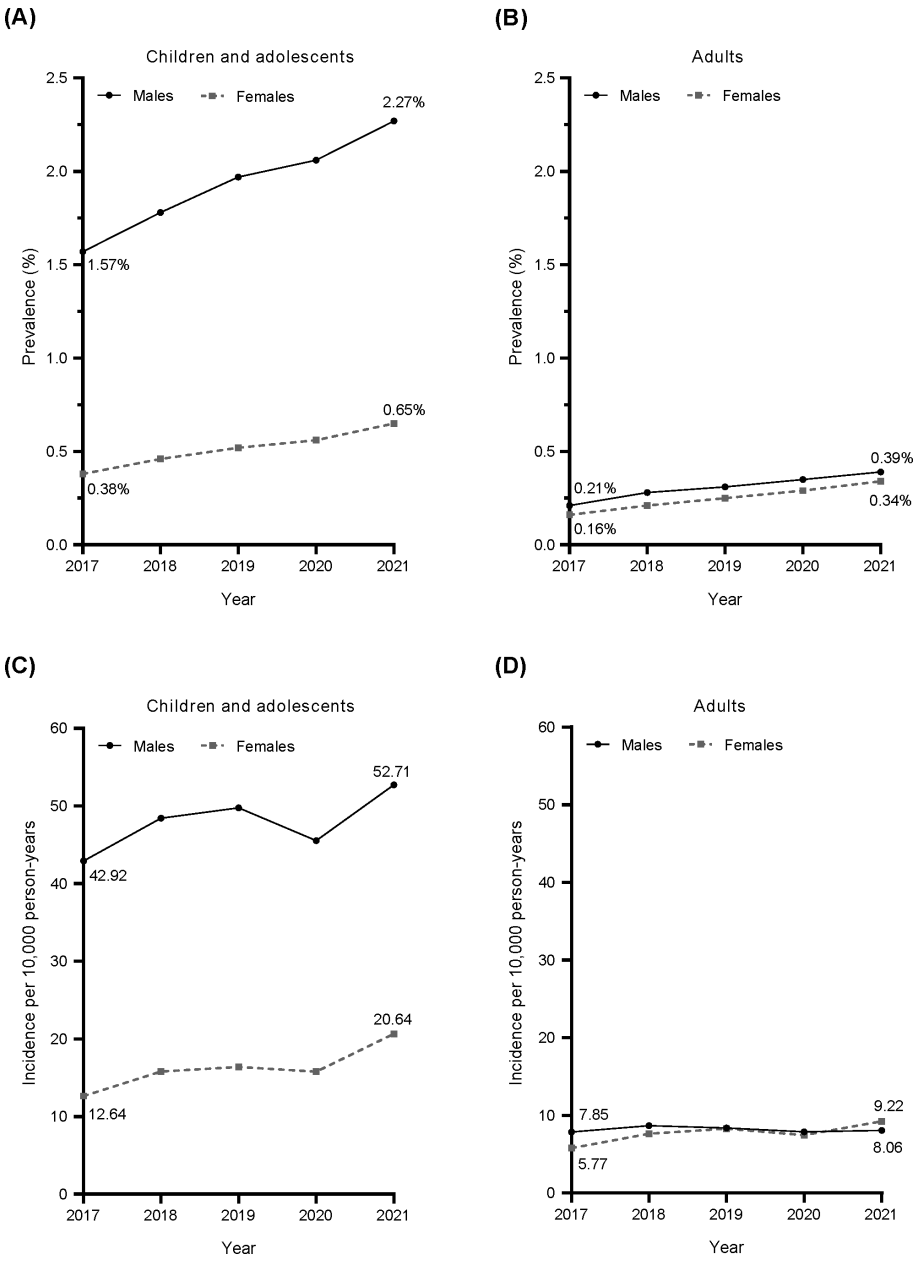

FIGURE 2
Annual prevalence **(A, B)** and incidence **(C, D)** of ADHD defined by diagnostic code (ICD-10 code) from 2017 to 2021. Circles and solid line: males; squares and dotted line: females. ADHD, attention deficit/hyperactivity disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision.

affective disorder (36.9), schizophrenia and schizotypal disorder (26.6), recurrent depressive disorder (25.6), and dissociative disorders (25.3). The lowest risk ratio observed was for substance use disorders (4.6). When ADHD was defined by prescriptions for ADHD medications in addition to diagnostic codes, risk ratios for many psychiatric disorders tended to decrease slightly (Supplementary Table 1). The reduction in risk ratio was more pronounced for conduct disorders, recurrent depressive disorder, eating disorders, tic disorders, and other neurodevelopmental disorders such as ASD, SDDs of scholastic skills, SDD of motor function, and intellectual disability.

There was no obvious change in the prevalence patterns of most of the 12-month psychiatric comorbidities of ADHD in children/adolescents and adults observed from 2017 to 2021 (only 2019 data shown). However, the prevalence of ASD among children/adolescents with ADHD tended to increase over time (51.2% in 2017 to 56.1% in 2021), while the risk ratios tended to decrease (27.3 in 2017 to 24.2 in 2021). The prevalence of mood disorders among adults with ADHD did not change over time (62.1% in 2017 to 61.2% in 2021), while the risk ratios tended to decrease (21.1 in 2017 to 16.5 in 2021).

TABLE 1 Twelve-month psychiatric comorbidities of ADHD[a] in 2019.

Psychiatric disorder Disorder subclassification	Children and adolescents			Adults		
	With ADHD (Population 1A) N = 20,220	Without ADHD (Population 1A control)[b] N = 101,100	Risk ratio (95% CI)	With ADHD (Population 1A) N = 12,416	Without ADHD (Population 1A control)[b] N = 62,080	Risk ratio (95% CI)
Substance use disorders	7 (<0.1)	12 (<0.1)	2.9 (1.1–7.4)	208 (1.7)	228 (0.4)	4.6 (3.8–5.5)
Schizophrenia and schizotypal disorder	2642 (13.1)	297 (0.3)	44.5 (39.5–50.1)	2872 (23.1)	540 (0.9)	26.6 (24.3–29.1)
Other psychotic disorders	255 (1.3)	33 (<0.1)	38.6 (26.9–55.5)	582 (4.7)	77 (0.1)	37.8 (29.8–47.9)
Mood disorders	1843 (9.1)	416 (0.4)	22.2 (19.9–24.6)	7559 (60.9)	2078 (3.3)	18.2 (17.4–19.0)
Bipolar affective disorder	481 (2.4)	66 (0.1)	36.4 (28.2–47.1)	2320 (18.7)	314 (0.5)	36.9 (32.9–41.5)
Depressive episode	1272 (6.3)	313 (0.3)	20.3 (18.0–23.0)	6436 (51.8)	1815 (2.9)	17.7 (16.9–18.6)
Recurrent depressive disorder	1 (<0.1)	0 (0.0)	–	41 (0.3)	8 (<0.1)	25.6 (12.0–54.6)
Anxiety disorders	1392 (6.9)	558 (0.6)	12.5 (11.3–13.7)	2803 (22.6)	1274 (2.1)	11.0 (10.3–11.7)
OCD	184 (0.9)	58 (0.1)	15.9 (11.8–21.3)	277 (2.2)	75 (0.1)	18.5 (14.3–23.8)
Reaction to severe stress, and adjustment disorders	1559 (7.7)	455 (0.4)	17.1 (15.4–19.0)	1419 (11.4)	375 (0.6)	18.9 (16.9–21.2)
Dissociative disorders	108 (0.5)	41 (<0.1)	13.2 (9.2–18.69)	496 (4.0)	98 (0.2)	25.3 (20.4–31.4)
Somatoform disorders	1761 (8.7)	1024 (1.0)	8.6 (8.0–9.3)	927 (7.5)	657 (1.1)	7.1 (6.4–7.8)
Eating disorders	81 (0.4)	100 (0.1)	4.1 (3.0–5.4)	114 (0.9)	73 (0.1)	7.8 (5.8–10.5)
Intellectual disability	1760 (8.7)	770 (0.8)	11.4 (10.5–12.4)	403 (3.2)	151 (0.2)	13.3 (11.1–16.1)
Tic disorders	342 (1.7)	159 (0.2)	10.8 (8.9–13.0)	40 (0.3)	2 (<0.1)	100.0 (24.2–413.7)
Sleep disorders	2777 (13.7)	904 (0.9)	15.4 (14.3–16.5)	6012 (48.4)	2666 (4.3)	11.3 (10.8–11.8)
ODD	156 (0.8)	7 (<0.1)	111.4 (52.3–237.6)	9 (0.1)	0 (0.0)	–
Conduct disorders (excluding ODD)	101 (0.5)	9 (<0.1)	56.1 (28.4–110.9)	20 (0.2)	2 (<0.1)	50.0 (11.7–213.9)
SDDs of scholastic skills	1017 (5.0)	123 (0.1)	41.3 (34.3–49.8)	112 (0.9)	6 (<0.1)	93.3 (41.1–212.1)
SDD of motor function	479 (2.4)	315 (0.3)	7.6 (6.6–8.8)	22 (0.2)	12 (<0.1)	9.2 (4.5–18.5)
ASD	11,003 (54.4)	2082 (2.1)	26.4 (25.3–27.6)	2728 (22.0)	226 (0.4)	60.4 (52.8–69.0)
Epilepsy	1243 (6.1)	873 (0.9)	7.1 (6.5–7.8)	1425 (11.5)	516 (0.8)	13.8 (12.5–15.2)

All data are n (prevalence %) unless otherwise stated. [a]ADHD was defined by ICD-10 diagnostic codes (F90 and F98.8). [b]Non-ADHD population, age- and sex-matched to Population 1A (sample size ratio of 5:1). ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SDD, specific developmental disorder.

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3.2.3 ADHD as a 12-month comorbidity of various psychiatric disorders

In 2019, the prevalence of ADHD as a comorbidity in child and adolescent patients with psychiatric disorders in the JMDC database (Population 2) was generally higher than in each Population 2 control group (Table 2). ADHD prevalence was highest (≥20%) among patients with ODD (77.2%); conduct disorders excluding ODD (49.3%); SDDs of scholastic skills (48.6%); schizophrenia and schizotypal disorder (41.3%); bipolar affective disorder (35.7%); other psychotic disorders (34.2%); ASD (30.8%); mood disorders (22.5%); and reaction to severe stress, and adjustment disorders (21.5%). The risk ratio for having ADHD was >1 for all psychiatric diseases in children and adolescents, except for those with recurrent depressive disorder (risk ratio could not be calculated). Risk ratios for ADHD were highest (≥25.0) among patients with ODD (44.6), ASD (35.4), conduct disorders excluding ODD (33.7), bipolar affective disorder (30.1), schizophrenia and schizotypal disorder (29.7), and SDDs of scholastic skills (27.1).

In 2019, the prevalence of ADHD was also higher in adult patients with various psychiatric disorders than in each Population 2 control group (Table 2). The highest prevalence (≥20%) of adult ADHD was found in patients with ODD (69.2%), SDDs of scholastic skills (32.0%), ASD (25.6%), and conduct disorders excluding ODD (24.1%). The risk ratio for having ADHD was >1 for all psychiatric diseases in adults, except for those with ODD, conduct disorders excluding ODD, and SDD of motor function (risk ratios could not be calculated). Psychiatric disorders with a high risk of comorbid ADHD (risk ratio ≥25.0) in adults included SDDs of scholastic skills (224.0), tic disorders (80.0), ASD (70.9), mood disorders (47.2), bipolar affective disorder (44.2), recurrent depressive disorder (41.0), depressive episode (35.6), schizophrenia and schizotypal disorder (31.6), and other psychotic disorders (30.6).

When the presence of ADHD was defined by prescriptions for ADHD medications in addition to diagnostic codes, the risk ratio for ADHD was slightly increased for children and adolescents with many psychiatric disorders (Supplementary Table 2). The risk ratio for ADHD remained unchanged for adults with most psychiatric disorders, slightly increased for adults with bipolar affective disorder and recurrent depressive disorder, and decreased for adults with eating disorders, intellectual disability, tic disorders, SDDs of scholastic skills, and ASD.

There was no obvious change in the trend of 12-month ADHD prevalence among psychiatric comorbidities observed from 2017 to 2021 in both children/adolescents and adults (only 2019 data shown).

3.3 Longitudinal study outcomes

3.3.1 Retrospective cohort study patient disposition

There were 10,080,294 people registered in the JMDC database between January 2017 and December 2019 (Figure 3). There were 58,087 patients with an ADHD diagnosis, and 37,364 patients with an ADHD diagnosis and prescribed ADHD medications. Among patients diagnosed with ADHD, the number of patients included in Cohort 1 was 14,940. Among patients diagnosed with ADHD and receiving ADHD medication, the number of patients included in Cohort 2 was 9550. The proportion of patients in each age subcategory was generally similar between the cohorts, with the exception of patients aged 0–5 years, who comprised 1.4% of Cohort 2 versus 14.9% of Cohort 1.

3.3.2 Psychiatric disorders diagnosed before and after initial ADHD diagnosis

In children and adolescents with ADHD, the psychiatric disorder most commonly diagnosed prior to diagnosis of ADHD was ASD (33.9%) (Figure 4A). Other psychiatric disorders diagnosed prior to the initial diagnosis of ADHD in ≥5% of patients were sleep disorders (7.1%); reaction to severe stress, and adjustment disorders (6.4%); anxiety disorders (5.8%); somatoform disorders (5.5%); intellectual disability (5.3%); and mood disorders (5.2%). The median number of psychiatric disorders diagnosed before the initial ADHD diagnosis in child and adolescent ADHD patients was 1 (Q1–Q3: 1–2). The median number of psychiatric disorders diagnosed after the initial ADHD diagnosis was also 1 (Q1–Q3: 1–2). ASD was substantially more likely to be diagnosed before ADHD (33.9% of patients diagnosed within 2 years before ADHD diagnosis) than after (9.7% of patients diagnosed within 2 years after ADHD diagnosis) (Figure 4A). Other psychiatric disorders more likely to be first diagnosed before than after the initial ADHD diagnosis included mood disorders (including depressive episodes); anxiety disorders; reaction to severe stress, and adjustment disorders; somatoform disorders; intellectual disability; SDDs of scholastic skills; and SDD of motor function.

In adults with ADHD, the most prevalent psychiatric disorder prior to the initial diagnosis of ADHD was mood disorders (36.9%; including depressive episode [33.0%] and bipolar affective disorder [9.2%]) (Figure 4B). Other psychiatric disorders diagnosed prior to the initial diagnosis of ADHD in ≥5% of patients were sleep disorders (23.8%); anxiety disorders (17.9%); ASD (14.1%); reaction to severe stress, and adjustment disorders (11.5%); schizophrenia and schizotypal disorder (9.2%); and somatoform disorders (6.0%). In adult patients with ADHD, the median number of psychiatric disorders diagnosed before the initial ADHD diagnosis was 2 (Q1–Q3: 1–3); the median number of psychiatric disorders diagnosed after the initial ADHD diagnosis was also 2 (Q1–Q3: 1–4). In adults, the psychiatric disorders that were more commonly diagnosed before than after the initial diagnosis of ADHD included substance use disorders; schizophrenia and schizotypal disorder; other psychotic disorders; mood disorders (including bipolar affective disorder, depressive episode, and recurrent depressive disorder); anxiety disorders; OCD; reaction to severe stress, and adjustment disorders; dissociative disorders; somatoform disorders; intellectual disability; sleep disorders; ASD; and epilepsy (Figure 4B).

Common psychiatric disorders diagnosed before and after the initial diagnosis of ADHD were similar when ADHD was defined by prescribing ADHD medications in addition to the ADHD

TABLE 2 ADHD[a] as a 12-month comorbidity of various psychiatric disorders in 2019.

Psychiatric disorder Disorder subclassification	Children and adolescents					Adults				
	With each psychiatric disorder (Population 2)		Without each psychiatric disorder (Population 2 control)[b]		Risk ratio (95% CI)	With each psychiatric disorder (Population 2)		Without each psychiatric disorder (Population 2 control)[b]		Risk ratio (95% CI)
	Population N	ADHD prevalence, n (%)	Population N	ADHD prevalence, n (%)		Population N	ADHD prevalence, n (%)	Population N	ADHD prevalence, n (%)	
Substance use disorders	271	7 (2.6)	542	2 (0.4)	7.0 (1.5–33.5)	15,510	208 (1.3)	31,020	82 (0.3)	5.1 (3.9–6.5)
Schizophrenia and schizotypal disorder	6395	2642 (41.3)	12,790	178 (1.4)	29.7 (25.6–34.4)	42,911	2872 (6.7)	85,822	182 (0.2)	31.6 27.2–36.6)
Other psychotic disorders	745	255 (34.2)	1490	22 (1.5)	23.2 (15.1–35.5)	6504	582 (8.9)	13,008	38 (0.3)	30.6 (22.1–42.5)
Mood disorders	8173	1843 (22.5)	16,346	169 (1.0)	21.8 (18.7–25.5)	178,468	7559 (4.2)	356,936	320 (0.1)	47.2 (42.2–52.8)
Bipolar affective disorder	1348	481 (35.7)	2696	32 (1.2)	30.1 (21.1–42.7)	26,636	2320 (8.7)	53,272	105 (0.2)	44.2 (36.4–53.7)
Depressive episode	6421	1272 (19.8)	12,842	119 (0.9)	21.4 (17.8–25.7)	158,694	6436 (4.1)	317,388	362 (0.1)	35.6 (32.0–39.5)
Recurrent depressive disorder	6	1 (16.7)	12	0 (0.0)	–	843	41 (4.9)	1686	2 (0.1)	41.0 (9.9–169.1)
Anxiety disorders	9399	1392 (14.8)	18,798	217 (1.2)	12.8 (11.1–14.8)	113,233	2803 (2.5)	226,466	410 (0.2)	13.7 (12.3–15.2)
OCD	944	184 (19.5)	1888	23 (1.2)	16.0 (10.4–24.5)	5198	277 (5.3)	10,396	28 (0.3)	19.8 (13.4–29.1)
Reaction to severe stress, and adjustment disorder	7268	1559 (21.5)	14,536	205 (1.4)	15.2 (13.2–17.5)	25,096	1419 (5.7)	50,192	140 (0.3)	20.3 (17.1–24.1)
Dissociative disorders	1064	108 (10.2)	2128	20 (0.9)	10.8 (6.7–17.3)	9475	496 (5.2)	18,950	46 (0.2)	21.6 (16.0–29.1)
Somatoform disorders	15,545	1761 (11.3)	31,090	414 (1.3)	8.5 (7.7–9.5)	56,366	927 (1.6)	112,732	231 (0.2)	8.0 (7.0–9.3)
Eating disorders	2006	81 (4.0)	4012	36 (0.9)	4.5 (3.1–6.6)	3860	114 (3.0)	7720	26 (0.3)	8.8 (5.7–13.4)
Intellectual disability	11,458	1760 (15.4)	22,916	300 (1.3)	11.7 (10.4–13.2)	5880	403 (6.9)	11,760	56 (0.5)	14.4 (10.9–19.0)

(Continued)

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TABLE 2 Continued

Psychiatric disorder Disorder subclassification	Children and adolescents					Adults				
	With each psychiatric disorder (Population 2)		Without each psychiatric disorder (Population 2 control)[b]		Risk ratio (95% CI)	With each psychiatric disorder (Population 2)		Without each psychiatric disorder (Population 2 control)[b]		Risk ratio (95% CI)
	Population N	ADHD prevalence, n (%)	Population N	ADHD prevalence, n (%)		Population N	ADHD prevalence, n (%)	Population N	ADHD prevalence, n (%)	
Tic disorders	2028	342 (16.9)	4056	69 (1.7)	9.9 (7.7–12.8)	286	40 (14.0)	572	1 (0.2)	80.0 (11.1–579.0)
Sleep disorders	16,802	2777 (16.5)	33,604	375 (1.1)	14.8 (13.3–16.5)	257,711	6012 (2.3)	515,422	513 (0.1)	23.4 (21.4–25.6)
ODD	202	156 (77.2)	404	7 (1.7)	44.6 (21.3–93.2)	13	9 (69.2)	26	0 (0.0)	–
Conduct disorders (excluding ODD)	205	101 (49.3)	410	6 (1.5)	33.7 (15.0–75.4)	83	20 (24.1)	166	0 (0.0)	–
SDDs of scholastic skills	2093	1017 (48.6)	4186	75 (1.8)	27.1 (21.6–34.1)	350	112 (32.0)	700	1 (0.1)	224.0 (31.4–1597.5)
SDD of motor function	6955	479 (6.9)	13,910	122 (0.9)	7.9 (6.5–9.6)	325	22 (6.8)	650	0 (0.0)	–
ASD	35,756	11,003 (30.8)	71,512	621 (0.9)	35.4 (32.7–38.4)	10,670	2728 (25.6)	21,340	77 (0.4)	70.9 (56.6–88.8)
Epilepsy	13,543	1243 (9.2)	27,086	341 (1.3)	7.3 (6.5–8.2)	38,769	1425 (3.7)	77,538	194 (0.3)	14.7 (12.7–17.1)

All data are n (prevalence %) unless otherwise stated. [a]ADHD was defined by ICD-10 diagnostic codes (F90 and F98.8). [b]Age- and sex-matched to Population 2 (sample size ratio of 2:1). ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SDD, specific developmental disorder.

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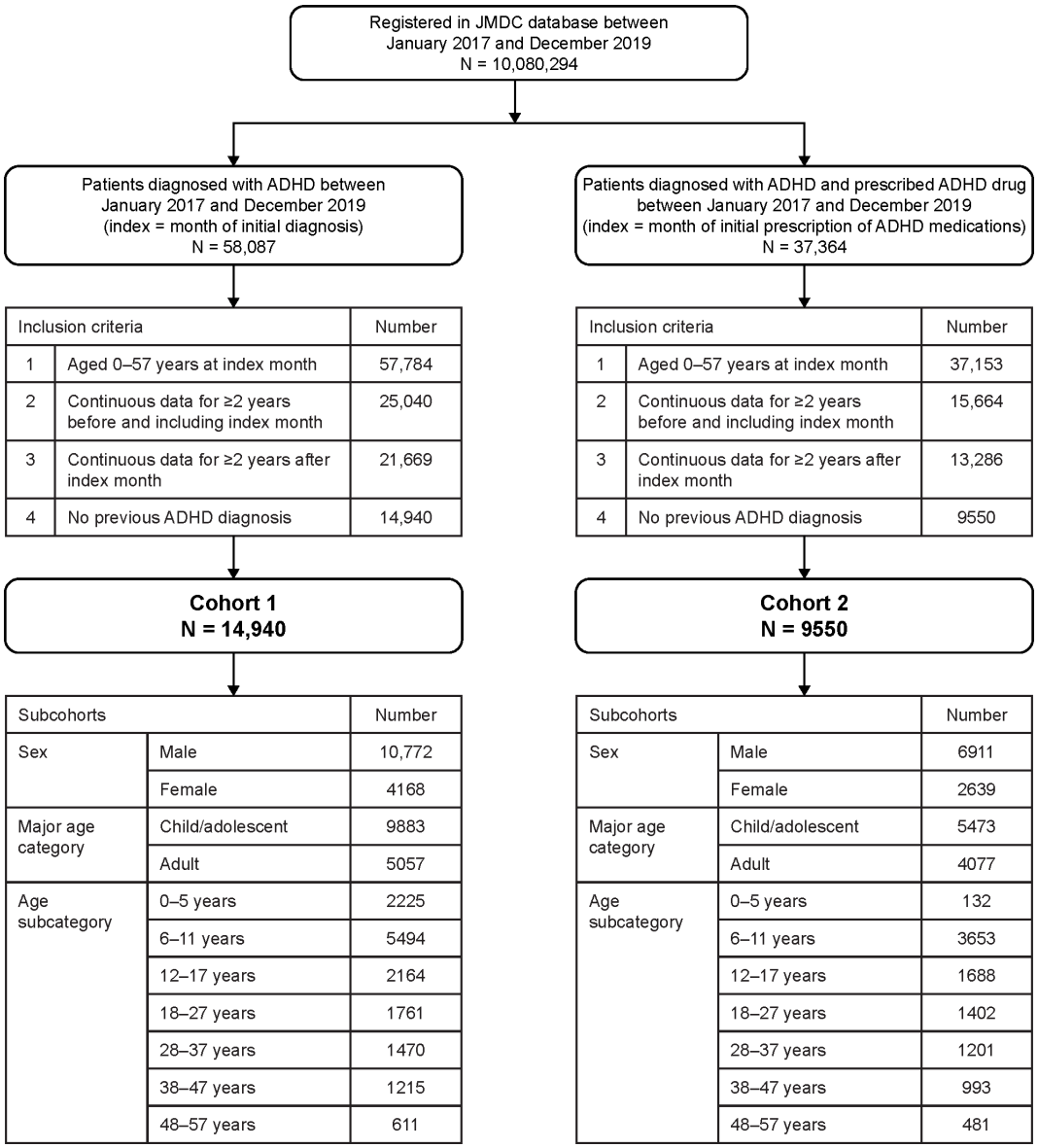

Inclusion criteria		Number
1	Aged 0–57 years at index month	57,784
2	Continuous data for ≥2 years before and including index month	25,040
3	Continuous data for ≥2 years after index month	21,669
4	No previous ADHD diagnosis	14,940

Subcohorts		Number
Sex	Male	10,772
	Female	4168
Major age category	Child/adolescent	9883
	Adult	5057
Age subcategory	0–5 years	2225
	6–11 years	5494
	12–17 years	2164
	18–27 years	1761
	28–37 years	1470
	38–47 years	1215
	48–57 years	611

Inclusion criteria		Number
1	Aged 0–57 years at index month	37,153
2	Continuous data for ≥2 years before and including index month	15,664
3	Continuous data for ≥2 years after index month	13,286
4	No previous ADHD diagnosis	9550

Subcohorts		Number
Sex	Male	6911
	Female	2639
Major age category	Child/adolescent	5473
	Adult	4077
Age subcategory	0–5 years	132
	6–11 years	3653
	12–17 years	1688
	18–27 years	1402
	28–37 years	1201
	38–47 years	993
	48–57 years	481

FIGURE 3
Patient flow diagram for the retrospective cohort study (longitudinal study). ADHD, attention deficit/hyperactivity disorder.

diagnosis for both children/adolescents and adults (Supplementary Figure 2).

The intervals between diagnoses of ADHD and diagnoses of other psychiatric disorders are shown in Supplementary Figure 3 for both children and adolescents (Supplementary Figures 3A, B) and adults (Supplementary Figures 3C, D). When other psychiatric disorders were diagnosed before ADHD, a median interval ≤2 months was observed between a diagnosis of other psychotic disorders; mood disorders; depressive episode; anxiety disorders; reaction to severe stress, and adjustment disorders; intellectual disability; tic disorders; SDDs of scholastic skills; and ASD, and a diagnosis of ADHD in both children and adolescents (Supplementary Figure 3A) and in adults (Supplementary Figure 3C). The median time from a diagnosis of substance use disorders, schizophrenia and schizotypal disorder, OCD, dissociative disorders, somatoform disorders, eating disorders, sleep disorders, SDD of motor function, and epilepsy to a diagnosis of ADHD was 3–7 months in children and adolescents and 3–8 months in adults. In some cases, the diagnosis of ADHD took up to 2 years after the diagnosis of other psychiatric disorders. When ADHD was diagnosed before other psychiatric disorders, the median interval before other psychiatric disorders were diagnosed in children and adolescents was 4–16 months (Supplementary Figure 3B). In adults, median intervals between ADHD diagnosis and diagnosis of other psychiatric disorders were 6–15 months (Supplementary Figure 3D). When ADHD was defined by prescribing ADHD medications in addition to the ADHD diagnosis, there was an overall slight increase in the intervals between diagnoses for both children/adolescents and adults (Supplementary Figure 4).

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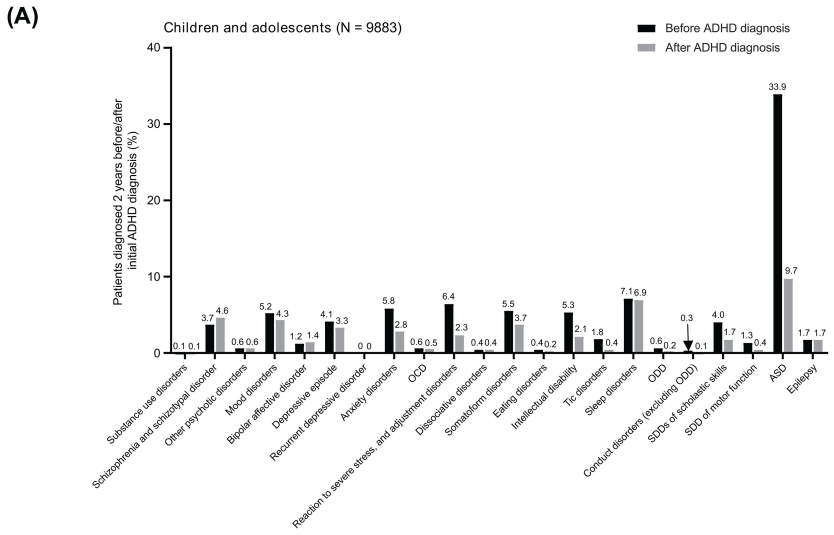
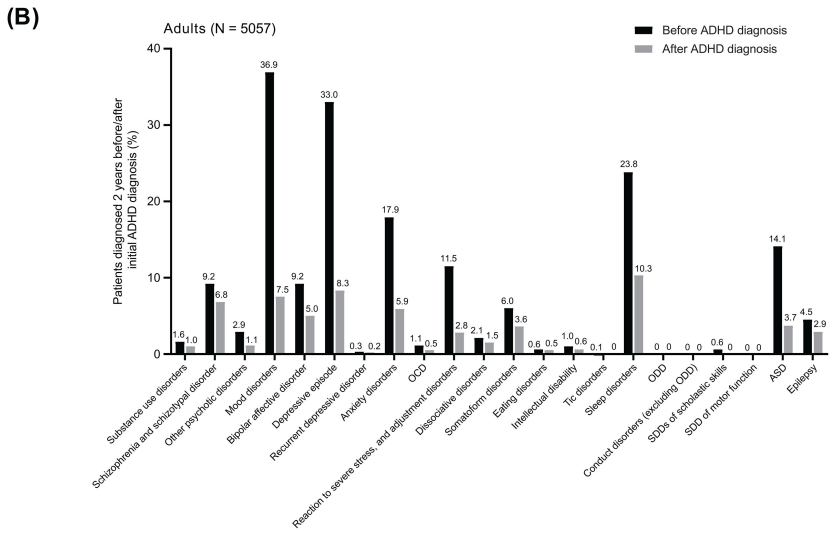


	Number of psychiatric disorders	
	First diagnosed before initial ADHD diagnosis	First diagnosed after initial ADHD diagnosis
Mean (SD)	1.5 (1.3)	1.7 (1.5)
Median	1.0	1.0
Min, max	0, 10	0, 11
Q1–Q3	1–2	1–2



	Number of psychiatric disorders	
	First diagnosed before initial ADHD diagnosis	First diagnosed after initial ADHD diagnosis
Mean (SD)	2.5 (1.8)	2.5 (1.8)
Median	2.0	2.0
Min, max	0, 12	0, 11
Q1–Q3	1–3	1–4

FIGURE 4
Percentage of child and adolescent patients **(A)** and adult patients **(B)** with ADHD who were first diagnosed with a psychiatric disorder 2 years before (black columns) or after (grey columns) the initial diagnosis of ADHD. Tables show summary statistics for the number of psychiatric disorders diagnosed before and after the initial ADHD diagnosis. ADHD was defined by ICD-10 diagnostic codes (F90 and F98.8). ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; max, maximum; min, minimum; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; SDD, specific developmental disorder; Q, Quartile.

4 Discussion

This nationwide population-based real-world study demonstrated that there is a high risk of ADHD being comorbid with psychiatric disorders in children and adolescents and in adults in Japan. This study also demonstrated that ASD was commonly diagnosed prior to the initial diagnosis of ADHD in children and adolescents, and various psychiatric disorders were diagnosed prior to the initial diagnosis of ADHD in adults. The primary clinical implication of this study is that it is important to carefully assess the likelihood of comorbid ADHD when diagnosing patients with psychiatric disorders.

In this claims-based database study, the prevalence of ADHD among children and adolescents in 2017 (1.6% in males and 0.4% in females) was higher than reported in previous Japanese database studies (13, 14); prevalence then increased from 2017 to 2021. It is likely that improved awareness of ADHD has led to increased diagnosis, and thus more recent studies may have higher estimates than older studies, and prevalence is likely to increase over time. The maximum prevalence estimated for children and adolescents in this study was 2.3% in male children and 0.6% in female children in 2021. Both estimates were lower than those obtained from an epidemiological survey conducted in municipal areas of Japan in 2009–2011 (5.8%) (12), US counties in 2016–2018 (12.9%) (29), and provinces of Canada in 1996–2016 (2.6–8.6%) (30). The nationwide estimate of ADHD prevalence in adults in this study was 0.3–0.4%, similar to a database-based estimate of prevalence in male adults in the UK (0.3%) (31), but lower than an epidemiological survey estimate of prevalence in the Japanese city of Hamamatsu (1.65%) (15). These differences in prevalence estimates are most likely primarily a result of differences in study design (claims-based database studies vs epidemiological surveys). Previous epidemiological surveys likely show a more accurate estimate of the prevalence of ADHD in the general population as they are based on screening, identification, and assessment of people with ADHD traits who fit the diagnostic criteria, albeit within a limited geographic area. The current claims-based study only included people diagnosed by a physician at a medical institution, so it is unsurprising that the estimated prevalence rate is lower than in previous epidemiological surveys in Japan. The lower prevalence in the current study suggests that there may be a population of people with ADHD who have not been diagnosed and therefore were not detected in our database study. In our database study, the mean prevalence of ADHD in children and adolescents (both sexes combined) was estimated to be about 1.5%, which is approximately one-quarter of 5.8%, the ADHD prevalence estimated from a previous epidemiological survey (12).

In this study, from 2017 to 2021, the incidence of ADHD in children and adolescents increased from 42.92 to 52.71 per 10,000 person-years in males and from 12.64 to 20.64 per 10,000 person-years in females. These results are generally consistent, during the overlapping time periods, with a previous Japanese national database study between 2010 and 2019 (24). However, the previous study by Sasayama et al. showed that the incidence of ADHD in Japan slowed from 2018 to 2019, after a robust increase in the preceding years (24), while our results showed an increase in the incidence of ADHD for both male and female children and adolescents from 2017 to 2021 (except for a transient decrease in 2020). In adult females in the present study, there was a small increase in incidence from 5.77 to 9.22 per 10,000 person-years from 2017 to 2021. However, in adult males in the present study, the annual incidence was ~8 per 10,000 person-years, with no major change in incidence from 2017 to 2021. Nonetheless, there was a noticeable decrease in incidence for both males and females in 2020, which could be attributed to a reluctance to seek hospital visits amid the spread of the COVID-19 pandemic (32). The annual incidences of ADHD in Japanese children/adolescents and adults in our study were higher than those reported from a UK database study in 2000–2018 (31). National differences in the incidence of ADHD are most likely influenced by differences in both culture and healthcare systems.

In this study, patients with ADHD had a high risk of psychiatric comorbidities, and patients with other psychiatric disorders had a high risk of comorbid ADHD. This was the case for both children/adolescents and adults, and a very similar pattern was seen in each year from 2017 to 2021 (only 2019 data shown). In 2019, which was selected because it preceded any potential mental health impact of the COVID-19 pandemic, the 12-month psychiatric comorbidities of ADHD in children with the highest risk ratios were externalizing disorders (ODD, conduct disorders), SDDs of scholastic skills, schizophrenia and schizotypal disorder, other psychotic disorders, bipolar affective disorder, and ASD. When comorbidity of ADHD was examined in children and adolescents with various psychiatric disorders, the risk ratio for ADHD was highest in patients with externalizing disorders, ASD, bipolar affective disorder, schizophrenia and schizotypal disorder, and SDDs of scholastic skills. These results are generally consistent with previous reports of common psychiatric comorbidities of ADHD in childhood, particularly the comorbidity of ADHD with ASD (16, 17, 33).

In adults with ADHD, the prevalence of neurodevelopmental disorders and externalizing disorders was lower than that in children, and the prevalence of internalizing disorders (for example, schizophrenia and schizotypal disorder, mood disorders, and anxiety disorders) was higher than that in children and adolescents. In particular, the prevalence of both mood disorders, including bipolar affective disorder and depressive episodes, and sleep disorders was higher than that in children and adolescents. Risk ratios for neurodevelopmental disorders such as ASD and tic disorders were higher in adults with ADHD than in child and adolescent patients, probably because the prevalence in the adult control population was lower than in the control population for children and adolescents. Similarly, risk ratios for mood disorders and psychotic disorders were lower in adults with ADHD than in children and adolescents, probably because the prevalence in the adult control population was higher than in the child and adolescent control population. In adults with psychiatric disorders, the prevalence of comorbid ADHD was lower than that in children and adolescents for almost all psychiatric disorders. For adults with ASD, prevalence of comorbid ADHD was only slightly lower than in children and adolescents (25.6% vs 30.8%, respectively). However, the risk ratio of ADHD for adults with ASD was higher than that for children and adolescents, probably because of the lower prevalence of comorbid ADHD in the adult control population than in the child and adolescent control population.

The prevalence of psychiatric disorders observed as 12-month comorbidities of ADHD in adults in Japan were broadly consistent with previous reports of 12-month comorbidities of ADHD in adults in other countries (9, 18). However, the prevalence of mood disorders was higher and the prevalence of substance use disorders was lower in Japanese adults with ADHD than reported in other countries (9, 18). In the present study, in many Japanese adults with ADHD, mood disorders were diagnosed before ADHD, suggesting that mood disorder symptoms may prompt patients to

visit a hospital and subsequently be diagnosed with ADHD. In addition, public awareness of depression is relatively high in Japan as the mental health of employees is regularly screened under the Government's Stress Check Program (34), and there is easily accessible public health education about depression. These features of Japanese society and health care may partly explain why the prevalence of mood disorders, especially depressive episodes, was higher in our database study than in overseas epidemiological studies. By contrast, the prevalence of substance use disorders is known to be generally lower in Japan than in Western countries (35). In addition, substance use disorders in Japan associated with the abuse or overdose of over-the-counter (OTC) drugs are increasing, and this form of substance use disorders may not be as readily captured in claims databases (36). In addition, it appears that abuse of OTC drugs in Japan is more strongly associated with mood disorders and neurotic, stress-related, and somatoform disorders than with behavioral and emotional disorders, including ADHD (36).

In the present study, we also examined the order of diagnosis of ADHD and other psychiatric conditions. In Japanese children, the most common psychiatric diagnosis prior to a diagnosis of ADHD was ASD. Symptoms of ASD are often noted before symptoms of ADHD, and incidence of ASD tends to peak at an earlier age (23). ASD is often diagnosed by 3 years of age, whereas ADHD in children may be more frequently identified and diagnosed in school-aged children, often when children are facing challenges in school. Adults with ADHD in the present study had a larger range of psychiatric diseases diagnosed in the 2 years prior to ADHD diagnosis than did children. The psychiatric disorders diagnosed in ≥10% of patients before the diagnosis of ADHD in adults included mood disorders, including depressive episodes; anxiety disorders; reaction to severe stress, and adjustment disorders; sleep disorders; and ASD. This is somewhat consistent with a previous study from Spain, in which mood disorders and anxiety disorders were commonly diagnosed before ADHD; however, substance use disorders were the most commonly diagnosed disorder prior to ADHD in the Spanish population (37). If the diagnosis of another psychiatric disorder precedes the diagnosis of ADHD, ADHD symptoms or problems in daily life may not have improved despite treatment of the other psychiatric disorder, leading to the subsequent diagnosis of ADHD. It is therefore important to carefully assess the likelihood of comorbid ADHD when diagnosing adult patients with psychiatric disorders.

In the present study, ADHD was defined in two ways: by diagnostic codes only, and by diagnostic codes and prescription of ADHD medications. This approach was taken to confirm whether similar outcomes were seen in patients with predominant ADHD and those with predominant other psychiatric disorders, who may not be prescribed ADHD medications. Overall, we observed similar patterns in prevalence and risk ratios regardless of which ADHD definition was used. Both in children and adolescents and in adults, risk ratios for many diseases tended to decrease slightly when ADHD medication was added to the definition of ADHD. In children and adolescents, the reduction in risk ratio was more pronounced for externalizing disorders, SDDs of scholastic skills, and other psychotic disorders. In adults, the reduction in risk ratio was more pronounced for conduct disorders, recurrent depressive disorder, eating disorders, tic disorders, and other neurodevelopmental disorders. This may suggest that patients with ADHD who are prescribed ADHD medication may be at a lower risk of psychiatric comorbidities, or prescription of ADHD medications may have been withheld in patients with specific psychiatric disorders. When ADHD drug prescriptions were included in the definition of ADHD, the risk ratio for ADHD was slightly increased for children and adolescents with many psychiatric disorders. The risk ratio for ADHD remained unchanged or slightly increased for adults with many psychiatric disorders, while the risk ratio for ADHD among adults with some psychiatric disorders, including intellectual disability and tic disorders, decreased. This may indicate that children and adolescents with each psychiatric disorder were at higher risk of being prescribed ADHD medications than the control population, and that the effect was generally relatively smaller in adult patients, because of the higher proportion of adults who were prescribed ADHD medications. It may also be the case that the proportion of ADHD medications prescribed was lower in adults with some psychiatric disorders, such as intellectual disability and tic disorders.

A strength of this study was its design, which included not only a cross-sectional study with 5 analysis years, but also a retrospective cohort study for longitudinal analysis with an observation period of 2 years before and after the initial diagnosis of ADHD. The study had a large population, which included over 45,000 patients with ADHD and over 28,000 patients prescribed ADHD medications in the final study year. The use of the JMDC database enabled tracking of all diagnoses and treatments across various medical hospitals and clinics. In addition, ADHD was defined using two distinct criteria of ICD-10 codes only and ICD-10 code plus prescription of ADHD medications, and the study identified both similarities and differences in results between these definitions. Furthermore, the outcome measures included a large variety of psychiatric comorbidities. This is the first study to use big data to calculate risk ratios for a number of psychiatric disorders in patients with ADHD, to calculate risk ratios for ADHD in patients with psychiatric disorders, and to evaluate the diagnostic sequence of ADHD and psychiatric disorders.

This study also had several limitations. The JMDC database is not generalized and representative in Japan and only includes data from health insurance associations contracted by JMDC. Additionally, the database only includes patients who present to a hospital and therefore may be biased toward patients with more moderate-to-severe symptoms; people with milder symptoms of ADHD may not have been captured in the database. On the other hand, if patients who have belonged to the same health insurance association for a long time are included, there may have been an increased bias toward inclusion of patients with relatively mild symptoms because of the characteristics of the disease. If a patient changed or lost their job and therefore experienced a change in health insurance association, it may not be possible to track their medical history in the JMDC database. The accuracy of data captured for each individual in the database depends on the quality of information entered into the medical records by healthcare professionals. This limitation is common to research

using electronic medical records. It is also unclear whether the disease name, once recorded in the medical record, was updated appropriately. It is hoped that the findings obtained in this study will be clarified in prospective studies. Furthermore, it is essential to recognize that the population within the JMDC database, consisting of employed patients and their dependents but not including self-employed people or public servants, may not be directly comparable to other subgroups of the Japanese population. In addition, it has been reported that ADHD in adults is associated with high unemployment in Western countries. In at least one Japanese study, the employment rate of adults with ADHD was numerically lower than that of non-ADHD adults (38). Thus, adults with ADHD may be underrepresented in the JMDC database. Finally, we note that the retrospective cohort study was restricted to 2 years before and after the initial ADHD diagnosis. Increasing the duration of baseline/follow-up periods results in a smaller sample size, so the 2-year baseline and follow-up periods were set to ensure an adequate sample size for the retrospective cohort study.

In conclusion, this population-based study provides a first nationwide assessment of risks of a wide range of psychiatric disorders in patients with ADHD in Japan. ADHD and other psychiatric disorders are comorbid in both children/adolescents and adults in Japan. In particular, ASD in children/adolescents and mood and sleep disorders in adults were commonly diagnosed prior to the initial diagnosis of ADHD.

Data availability statement

The data analyzed in this study were obtained from JMDC Inc. (https://www.jmdc.co.jp/en/) and used under license; therefore, restrictions apply, and the data are not publicly available. Requests to access these datasets should be directed to JMDC, https://www.jmdc.co.jp/en/inquiry/.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

TO: Methodology, Visualization, Writing – review & editing. TS: Methodology, Visualization, Writing – review & editing, Writing – original draft. MO-S: Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. NN: Conceptualization, Funding acquisition, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

TO reports payments or honoraria for lectures from Shionogi & Co., Ltd. and Takeda Pharmaceutical Company Limited. TS, MO-S, and NN are employees of and minor shareholders in Takeda Pharmaceutical Company Limited.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1359872/full#supplementary-material

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Association between reported ADHD symptom and motor development delay in preschool children

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Objective: To explore whether the motor developmental level is associated with the attention deficit/hyperactivity disorder (ADHD) symptoms severity reported by parents in preschool children.
Methods: Preschool children aged 4–6 years old with the chief complaint of reported inattention or hyperactivity by kindergarten teachers or parents were recruited in this study. All participants were consulted by at least one experienced developmental behavior pediatrician, according to DSM-V diagnostic criteria of ADHD. Their neuromotor developments were assessed by the Children's Neuropsychological and Behavior Scale and recorded as developmental quotient (DQ) score in gross motor, fine motor, and other domains. Regarding the evaluation of ADHD symptoms, parents of the 4-year-old group completed the Conners' Parent Symptom Questionnaire, while parents of the 5-year-old group completed The Vanderbilt ADHD Diagnostic Parent Rating Scale.
Results: A total of 137 preschool children aged 4–4.9 years (4-year-old group) and 252 were aged 5.0–5.9 years (5-year-old group) were included in the study. Children exhibiting ADHD symptoms were at a much higher risk of fine motor delays compared to gross motor delays, particularly among the younger age group. Correlation analysis and hierarchical regression showed that in the 4-year-old ADHD group, better gross motor development was associated with increased severity of parent-reported ADHD symptoms. In the 5-year-old ADHD group, poorer fine motor development was linked to higher ADHD symptom severity. For children who do not meet ADHD diagnostic criteria, no significant correlations were found between gross or fine motor developmental quotients (DQ) and the severity of ADHD symptoms.
Conclusions: Preschool children exhibiting ADHD symptoms are at a notable high risk of fine motor delays. Motor development in preschool children who meet ADHD diagnostic criteria is related to the severity of their symptoms. It is important to monitor both fine and gross motor development in preschool children with ADHD.

KEYWORDS

preschool children, attention-deficit/hyperactivity disorder (ADHD), fine motor, gross motor, developmental quotient

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsiveness (1). ADHD symptoms often emerge in preschool children, with prevalence estimated about 5.5% (95% CI, 3.3–7.7) for preschoolers (2). Understanding the early characteristics of children with ADHD symptoms is of great significance for early identification and intervention.

Studies have noted motor skill delays in preschoolers with ADHD (3–5). However, the relationship between motor skills and ADHD symptoms remains unclear. Motor skills encompass gross and fine motor abilities, both significantly linked to executive function (6). Good gross motor skills were a risk factor for ADHD symptoms in infancy (7), and specific gross motor behaviors at early ages correlate with later ADHD severity (8, 9). Impaired fine motor skills were consistently observed in school-age children with ADHD (10, 11). However, little study research on the relationship between motor development in preschool children and ADHD symptoms.

Preschool years witness rapid sensorimotor brain area development (12), paralleling cognitive and motor skill maturation. Children with ADHD often exhibited atypical sensorimotor and cognitive brain network development (13). Increased ADHD severity was associated with altered white matter organization which support motor skills and cognitive abilities (14). It was also reported a strong correlation between motor skills and cognitive abilities (e.g., executive function) in typically developing preschool children (15, 16). Motor development is integral to academic, social, and communication skills, and delays or imbalances in motor development are common in neurological disorders like ADHD. The exact mechanisms undelaying ADHD remained unclear, but hypotheses suggested immature or dysfunctional brain connectivity involving motor areas and high order cognitive related brain areas.

Previous research noted motor delays in children with ADHD and their association with future symptom severity and brain development (14, 17). But the relationships between gross/fine motor development and ADHD symptoms in preschoolers remain unexplored. This study aimed to address this gap in children aged 4–6 years. Given the high activity levels of preschoolers, not all active children meet ADHD diagnostic criteria. This study included ADHD and ADHD symptom-like groups aged 4.0–5.9 years to examine the motor-symptom relationship. Hypothesis 1 proposed a delayed fine and gross motor development in preschool ADHD children. Hypothesis 2 proposed that symptom severity was associated with respective motor development levels. Exploring the motor-symptom association aids in understanding ADHD brain development mechanisms and differentiating symptom severity.

Materials and methods

Participants

All participants were recruited from the developmental behavior clinic in the same hospital between March 2021 and January 2024. The children met the following inclusion criteria were included: right-handed; aged from 4.0 to 5.9 years, with the chief complaint of inattention or hyperactivity reported by kindergarten teachers or parents. Participants were excluded for developmental quotient (DQ) below 70 on the Children Neuropsychological and Behavior Scale, language disorder, visual or hearing impairment, psychoactive medication use, and other neurological or psychiatric disorders except ADHD.

There were 137 children aged 4.0–4.9 years and 252 children aged 5.0–5.9 years, referred to as the 4-year-old group and the 5-year-old group, respectively. For each age group, children were categorized into either the ADHD group or the ADHD symptom-like group by one or two clinicians based on the DSM-5 criteria. During the diagnostic process, clinicians relied on at least two sources of information, such as interviews and observations conducted by the clinician, parent questionnaires, behavioral observations performed by trained professionals, and videos of the child's daily activities provided by parents. Children were classified into the ADHD group if the clinician's interviews and observations met DSM-5 criteria, and the parent questionnaire scores were above the threshold. If the clinician's interviews or behavioral observations did not meet DSM-5 criteria, the child was categorized into the ADHD symptom-like group. Thus, based on both age and diagnosis, there were a total of four categories of children. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Research Ethics Committee of the authors' institution.

Clinical and neuropsychological assessments

All patients were interviewed by one or two experienced developmental behavior pediatricians. Overall developmental levels were assessed by the Children Neuropsychological and Behavior Scale. Regarding the evaluation of ADHD symptoms, parents of the 4-year-old group completed the Conners' Parent Symptom Questionnaire, while parents of the 5-year-old group completed the Vanderbilt ADHD Diagnostic Parent Rating Scale.

The Children Neuropsychological and Behavior Scale (CNBS) is a diagnostic assessment tool which is widely used in Chinese hospitals to assess the DQ of children aged 0–6 years (18, 19). It includes five separate subscales: gross motor, fine motor, adaptive behavior, language, and personal-social. DQ is calculated by the following formula: $DQ = (\text{mental age}/\text{chronological age}) \times 100$. Children were tested one-on-one by a trained nurse, which takes about 20 min. Full DQ refers to the average value of the five

subscales. For each subscale, a DQ less than 70 indicates a developmental delay, a DQ between 70 and 79 is slightly below the threshold for developmental delay, and a DQ of 80 or above is considered to be within the normal range (18).

The Conners' Parent Symptom Questionnaire (PSQ) is a 48-item parent-report assessment for children aged 3–17 years (20). The PSQ contains 6 subscales: conduct problem, learning problem, psychosomatic problem, impulsivity-hyperactivity, anxiety, and hyperactivity index. Symptom items are rated using a 4-point Likert scale (*never* to *very often*). Fan and colleagues developed the Chinese urban norms, which has been widely used in Chinese hospitals (21).

The Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) is a 55-item parent-report assessment for children aged 5–12 years (22). It contains six dimensions of symptoms: inattention (9 items), hyperactivity (9 items), oppositional defiant disorder (8 items), conduct disorder (14 items), anxiety/depression (7 items) and functional impairment (8 items). Symptom items are also rated using a 4-point Likert scale (*never* to *very often*). The VADPRS score is calculated for each subscale as sum score of parent ratings (23).

Statistical analyses

To address the main research problem, the following analyses were conducted:

(a) Descriptive statistics were utilized to compute the mean and standard deviation of all measures.
(b) To explore the motor developmental delays among children with primary ADHD symptoms. A DQ below 70 was used as the criterion for developmental delay, while a DQ of 70 or above indicated mild or no delay (24). The rates of delayed gross motor DQ and fine motor DQ were calculated across the four categories of children.
(c) To explore the relationship between ADHD symptoms and motor development, independent sample *t*-tests were employed to compare differences in various indicators between ADHD group and ADHD symptom-like group for each age group. Pearson's correlation coefficients were calculated among all measures to explore potential correlations between different domains of DQ and ADHD symptoms. Hierarchical regression was used to examine the relationship between symptom severity and motor DQ for each group, with age, gender, adaptive behavior DQ, language DQ, and personal-social DQ as control variables.

For the 4-year-old group, symptom severity was determined by the sum of scores on the impulsive-hyperactive dimension and the hyperactivity index dimension in the PSQ. For the 5-year-old group, the severity of attention-deficit/hyperactivity symptoms was assessed by the sum of scores on the attention-deficit symptoms dimension and the hyperactive-impulsive symptoms dimension in the VADPRS.

Results

Demographic characteristics of all the groups were shown in Table 1, including age, gender, birth weight, gestational age and birth delivery mode. The study involved 137 participants in the 4-year-old group, with 45 in ADHD group 1 (mean age 4.53 ± 0.26, 31 boys) and 92 in symptom-like group 1 (mean age 4.54 ± 0.28, 81 boys). After excluding missing values, there were 4 participants (10.81%) in ADHD Group 1 and 6 participants (8.96%) in Symptom-Like Group 1 with a gestational age of less than 37 weeks. In the 5-year-old group, there were 252 participants, with 120 in ADHD group 2 (mean age 5.47 ± 0.29, 94 boys) and 132 in symptom-like group 2 (mean age 5.50 ± 0.28, 90 boys). After excluding missing values, there were 7 participants (7.87%) in ADHD Group 2 and 5 participants (5.56%) in Symptom-Like Group 2 with a gestational age of less than 37 weeks.

Table 2 presents scores on various indicators of the CNBS and PSQ for the 4-year-old group. Both the ADHD gourp1 and symptom-like group 1 demonstrated normal gross motor

TABLE 1 Demographic characteristics of different groups.

Category	Item	4-year-old group (*N* = 137)		5-year-old group (*N* = 253)	
		ADHD group 1 (*N* = 45)	Symptom-like group 1 (*N* = 92)	ADHD group 2 (*N* = 120)	Symptom-like group 2 (*N* = 132)
Child's age (in years)		4.53 ± 0.26	4.54 ± 0.28	5.47 ± 0.29	5.50 ± 0.28
Child's gender (*N*)	Female	14	9	26	42
	Male	31	81	94	90
Birth weight (*N*)	Less than 2.5 kg	1	3	4	5
	2.5 kg–4.0 kg	34	60	78	79
	More than 4.0 kg	2	4	3	4
	Missing data	8	25	35	44
Gestational age (*N*)	Less than 37 weeks (preterm)	4	6	7	5
	37–42 weeks (full term)	33	61	82	85
	Missing value	8	25	31	42
Birth delivery mode (*N*)	Vaginal delivery	17	25	48	44
	Cesarean delivery	8	27	21	23
	Missing data	20	40	51	65

TABLE 2 The score of the 4-year-old group on CNBS and PSQ.

Scales	No.	Index	ADHD group 1		Symptom-like group 1			
			N = 45		*N* = 92			
			Mean	SD	Mean	SD	*T*	*p*
CNBS	1	Full DQ	90.93	8.49	91.25	7.50	−0.22	0.825
	2	Gross motor DQ	90.47	10.38	88.53	9.84	1.07	0.289
	3	Fine motor DQ	81.34	13.02	79.80	14.85	0.59	0.554
	4	Adaptive behavior DQ	92.92	10.78	93.52	9.53	−0.33	0.739
	5	Language DQ	95.53	14.31	96.82	11.40	−0.57	0.568
	6	Personal-social DQ	93.98	11.89	97.59	9.97	−1.87	0.064
PSQ	8	Conduct problem	1.29	0.45	0.71	0.34	8.32	<0.001
	9	Learning problem	1.86	0.51	1.18	0.50	7.36	<0.001
	10	Psychosomatic problem	0.22	0.28	0.18	0.29	0.88	0.382
	11	Impulsivity-hyperactivity	2.07	0.44	1.05	0.48	11.86	<0.001
	12	Anxiety	0.57	0.43	0.42	0.33	2.33	0.021
	13	Hyperactivity index	1.82	0.39	0.99	0.38	11.79	<0.001
	14	Symptom severity[a]	3.89	0.75	2.05	0.81	12.78	<0.001

CNBS, The Children Neuropsychological and Behavior Scale; PSQ, The Conners' Parent Symptom Questionnaire; DQ, developmental quotient.
[a]Symptom severity = Impulsivity-hyperactivity + Hyperactivity index.

TABLE 3 Number of children with a motor developmental delay according to the subscale DQ of the CNBS (*N*, %).

Group	Gross motor		Fine motor	
	Delay (DQ < 70)	Mild to normal (DQ ≥ 70)	Delay (DQ < 70)	Mild to normal (DQ ≥ 70)
ADHD group 1	1 (2.2%)	44 (97.8%)	9 (20.0%)	36 (80.0%)
Symptom-like group 1	0 (0%)	92 (100%)	28 (30.4%)	64 (69.6%)
ADHD group 2	8 (6.7%)	112 (93.3%)	10 (8.3%)	110 (91.7%)
Symptom-like group 2	10 (7.6%)	122 (92.4%)	18 (13.6%)	114 (86.4%)

CNBS, The Children Neuropsychological and Behavior Scale; DQ, developmental quotient.

development, with gross motor delay rates of 2.2% and 0%, respectively (see Table 3). However, both groups exhibited significant delays in fine motor development. The average fine motor DQ were 81.34 and 79.80, respectively, with fine motor delay rates of 20.0% and 30.4%, respectively (see Table 3). Table 4 presents scores on various indicators of the CNBS and VADPRS for the 5-year-old group. Although *t*-tests did not reveal significant differences between the two groups on CNBS scores, the symptom-like group 2 had higher rates of gross motor delay (7.6%) and fine motor delay (13.6%) compared to ADHD group 2 (6.7% and 8.3%, respectively). Similar to the 4-year-old group, *t*-tests showed that ADHD group 2 exhibited more severe oppositional defiant disorder, conduct disorder, and anxiety/depression symptoms (see Table 2).

TABLE 4 The score of the 5-year-old group on CNBS and VADPRS.

Scales	No.	Index	ADHD group 2		Symptom-like group 2			
			N = 120		*N* = 132			
			Mean	SD	Mean	SD	*T*	*p*
CNBS	1	Full DQ	90.57	8.37	90.06	8.20	0.48	0.629
	2	Gross motor DQ	90.83	14.41	89.91	13.61	0.52	0.602
	3	Fine motor DQ	84.62	10.35	82.97	11.39	1.20	0.233
	4	Adaptive behavior DQ	89.07	12.18	89.70	10.53	−0.44	0.662
	5	Language DQ	95.81	11.38	95.47	9.10	0.26	0.793
	6	Personal-social DQ	92.46	9.14	92.31	8.96	0.14	0.892
VADPRS	15	Inattentive	16.33	3.65	10.73	3.21	12.96	<0.001
	16	Hyperactive	17.82	3.80	10.36	3.65	15.91	<0.001
	17	Oppositional defiant	10.22	4.61	7.16	3.50	5.97	<0.001
	18	Conduct disorder	3.01	2.50	1.52	1.62	5.66	<0.001
	19	Anxiety/depression	4.67	3.18	3.39	2.73	3.42	0.001
	20	Symptom severity[a]	34.15	5.42	21.09	5.95	18.16	<0.001

CNBS, The Children Neuropsychological and Behavior Scale; VADPRS, The Vanderbilt ADHD Diagnostic Parent Rating Scale; DQ, developmental quotient.
[a]Symptom severity = Inattentive + Hyperactive.

Pearson correlation analysis indicated a weak correlation between gross motor DQ and hyperactivity index ($r = 0.35$, $p = 0.020$), as well as symptom severity ($r = 0.32$, $p = 0.030$) in ADHD group 1. However, fine motor DQ showed no correlation with hyperactivity index, impulsivity, or overall symptom severity in 4-year-old group (see Figure 1). Pearson correlation analysis also revealed a weak correlation between fine motor DQ and hyperactive-impulsive symptoms ($r = -0.25$, $p = 0.006$), as well as symptom severity ($r = -0.22$, $p = 0.016$) in ADHD group 2. However, gross motor DQ showed no correlation with hyperactive-impulsive symptoms, attention deficit symptoms, or overall symptom severity in 5-year-old group (see Figure 1).

Due to the four comparisons made within each age group during the hierarchical regression analysis, the alpha value was adjusted to $0.05/4 \approx 0.017$, corrected with Bonferroni correction. The hierarchical regression results indicated that, after including control variables (age, gender, adaptive behavior DQ, language DQ, and personal-social DQ), gross motor DQ in ADHD group 1 remained positively correlated with symptom severity ($\beta = 0.46$, $p < 0.05$, Bonferroni corrected; see Table 5). In ADHD group 2, fine motor DQ exhibited a negative correlation with symptom severity ($\beta = -0.35$, $p < 0.05$, Bonferroni corrected; see Table 6). The relationships between motor DQ and symptom severity were not significant in all other cases ($p > 0.05$, Bonferroni corrected).

Discussion

The present study explored the relationship between motor development and ADHD symptom severity in preschool children aged 4.0–5.9 years. Consistent with Hypothesis 1, we found that preschool children identified by parents or teachers as exhibiting ADHD-related symptoms, regardless of whether they met the full diagnostic criteria, often showed delays in fine motor development. Contrary to Hypothesis 1, significant gross motor delays were only observed in the 5-year-old group.

Our findings regarding the rate of motor development delays in preschool children with ADHD are consistent with previous research. For instance, a nationwide epidemiological study in Egypt reported that among children aged 3–6, 2.2% experienced

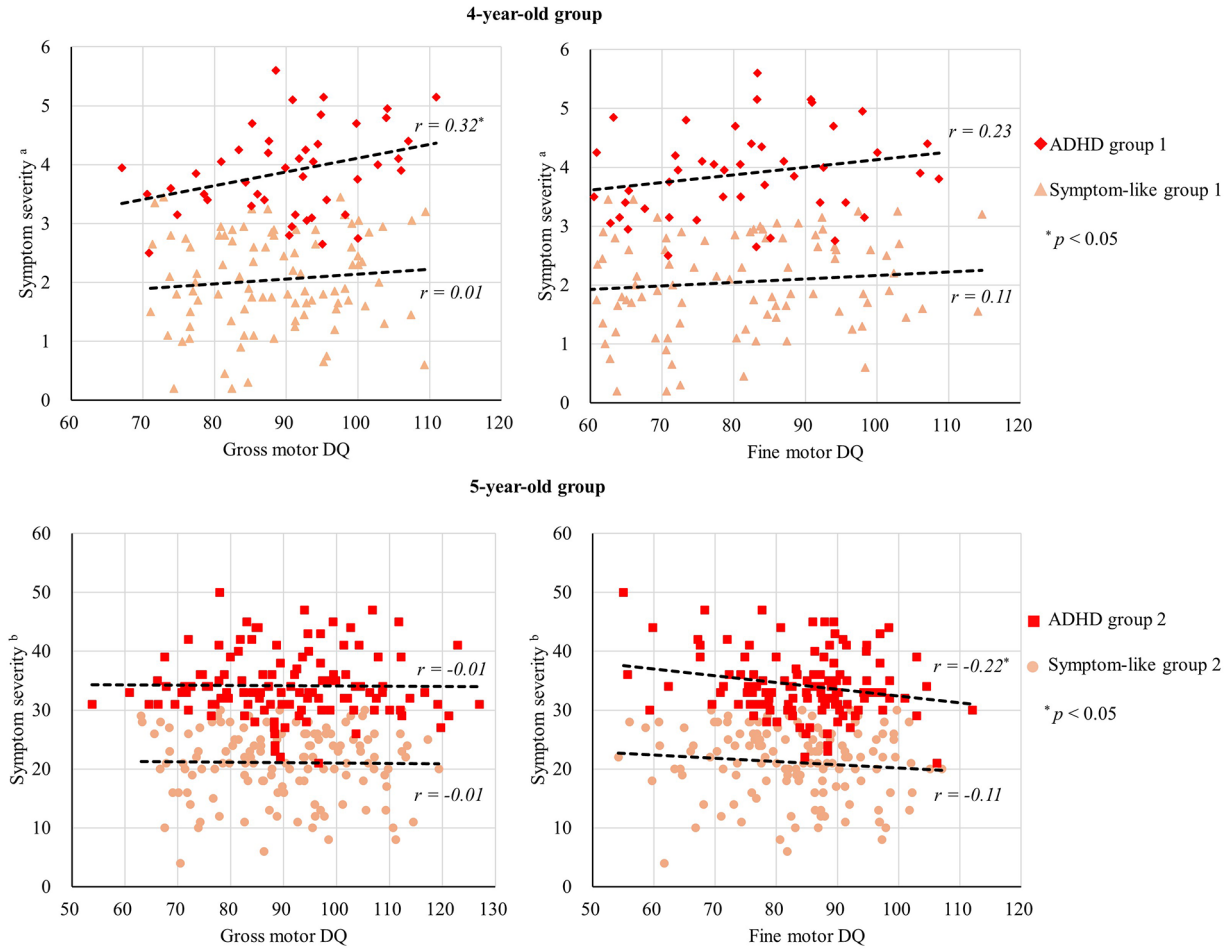

FIGURE 1
Scatter plots of gross motor DQ, fine motor DQ and symptom severity. [a]Symptom severity = Impulsivity-hyperactivity + Hyperactivity index. [b]Symptom severity = Inattentive + Hyperactive. The dashed line represents the regression line depicting the relationship between the *x*-axis and *y*-axis variables for each group.

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TABLE 5 Hierarchical regression models to predict symptom severity from gross motor DQ and fine motor DQ in 4-year-old group.

Group	Explanatory variables	Step 1	Step 2a	Step 2b
		β	β	β
ADHD group 1	Age	−0.10	−0.01	−0.05
	Gender	−0.51*	−0.50*	−0.56*
	Adaptive behavior DQ	−0.11	−0.34	−0.24
	Language DQ	0.11	0.22	0.07
	Personal-social DQ	0.04	0.06	0.06
	Gross motor DQ		0.46*	
	Fine motor DQ			0.34
		$R^2 = 0.31$	$R^2 = 0.48$*	$R^2 = 0.40$*
			$\Delta R^2 = 0.17$*	$\Delta R^2 = 0.09$
Group	Explanatory variables	Step 1	Step 2a	Step 2b
		β	β	β
Symptom-like group 1	Age	0.19	0.20	0.17
	Gender	−0.38*	−0.42*	−0.39*
	Adaptive behavior DQ	−0.07	−0.05	−0.08
	Language DQ	0.16	0.14	0.13
	Personal-social DQ	0.09	0.03	0.09
	Gross motor DQ		0.19	
	Fine motor DQ			0.08
		$R^2 = 0.21$*	$R^2 = 0.24$*	$R^2 = 0.21$*
			$\Delta R^2 = 0.03$	$\Delta R^2 = 0.01$

The alpha value is set to $0.05/4 \approx 0.017$.

*$p < 0.05$, corrected with Bonferroni correction. The response variable is symptom severity (Impulsivity-hyperactivity + Hyperactivity index).

TABLE 6 Hierarchical regression models to predict symptom severity from gross motor DQ and fine motor DQ in 5-year-old group.

Group	Explanatory variables	Step 1	Step 2a	Step 2b
		β	β	β
ADHD Group 2	Age	−0.03	−0.02	−0.04
	Gender	0.20	0.22	0.25*
	Adaptive behavior DQ	0.08	0.10	0.13
	Language DQ	−0.09	−0.09	−0.05
	Personal-social DQ	0.08	0.10	0.15
	Gross motor DQ		−0.11	
	Fine motor DQ			−0.35*
		$R^2 = 0.05$	$R^2 = 0.06$	$R^2 = 0.15$*
			$\Delta R^2 = 0.01$	$\Delta R^2 = 0.10$*
Group	Explanatory variables	Step 1	Step 2a	Step 2b
		β	β	β
Symptom-like Group 2	Age	−0.12	−0.12	−0.10
	Gender	−0.09	−0.09	−0.07
	Adaptive behavior DQ	−0.06	−0.05	−0.04
	Language DQ	−0.14	−0.14	−0.11
	Personal-social DQ	0.21	0.22	0.22
	Gross motor DQ		−0.04	
	Fine motor DQ			−0.11
		$R^2 = 0.05$	$R^2 = 0.05$	$R^2 = 0.06$
			$\Delta R^2 = 0.00$	$\Delta R^2 = 0.01$

The alpha value is set to $0.05/4 \approx 0.017$.

*$p < 0.05$, corrected with Bonferroni correction. The response variable is symptom severity (Inattentive + Hyperactive).

gross motor delays, and 2.8% experienced fine motor delays (25). However, in children with ADHD symptoms or at risk for ADHD, there is a noticeable difference in the prevalence of gross and fine motor delays. A Spanish epidemiological study reported that 22.6% of children aged 3–7 years who were likely to have ADHD had fine motor difficulties (26). In contrast, only 3.6% of children who were unlikely to have ADHD experienced similar issues (26). However, there was no significant difference in the prevalence of gross motor difficulties between the two groups, with both around 3.6% (26). This study similarly found that children exhibiting ADHD symptoms had a much higher risk of fine motor delays compared to gross motor delays, particularly among the younger children.

Consistent with Hypothesis 2, our study found a relationship between motor development and symptom severity in preschool children with ADHD. Specifically, only in the 4-year-old group, there was a positive correlation between better gross motor DQ and higher ADHD symptom severity. Conversely, only in the 5-year-old group, the ADHD group exhibited a negative correlation between poorer fine motor DQ and higher severity of parent-reported hyperactive-impulsive symptoms. No significant correlations were observed between gross motor DQ, fine motor DQ, and parent-reported ADHD symptoms in the ADHD symptom-like group.

Although ADHD symptoms are considered continuous, our study's results tend to support the interpretation that ADHD may involve specific brain developmental structures (27–30). The observed associations between motor development and symptoms in both age groups may stem from specific changes in brain structure or function during the developmental process in children with ADHD. For instance, neuroimaging studies have indicated impaired inhibitory mechanisms in the sensorimotor brain network and structural and functional alterations in the corpus callosum among children with ADHD (31, 32). The bilateral corticospinal tract (CST), which transmits motor signals from the primary motor cortex down the spinal cord to the trunk and limb muscles, may also serve as a crucial brain structure linking motor skills and ADHD symptom severity. Previous study on children aged 9–11 has found that increased ADHD symptom severity is associated with reduced white matter organization in fronto-pontine fibers projecting to and from the supplementary motor area (14). Furthermore, increased fiber density in the CST during adolescence and early adulthood has been linked to a greater reduction in hyperactivity and impulsivity symptoms over the preceding 3–4 years (17).

Furthermore, the inconsistency in the motor-symptom associations between fine and gross motor skills across different age groups may arise from differences in the developmental rates of these two types of movements, leading to atypical development of motor-related brain networks. The negative correlation between fine motor skills and symptom severity, consistent with previous findings in school-aged children, suggests that fine motor impairments correlate with ADHD symptoms (33). However, the positive correlation between gross motor skills and symptom severity indicates that this atypical motor development cannot solely be attributed to fine motor impairment. Unlike in school-aged children (34), the results of this study suggest that, for younger children, higher levels of gross motor development may not provide a protective effect against ADHD symptoms.

The present study may inform future interventions targeting motor skills in preschool children exhibiting ADHD symptoms. For younger children, it is important to ensure they have sufficient opportunities for gross motor development while simultaneously encouraging participation in fine motor activities, such as using chopsticks or buttoning clothing. For older preschoolers, a comprehensive approach should be taken to monitor both gross and fine motor development. Activities such as ball games, climbing, stringing beads, and playing with playdough can be beneficial for the development of either gross or fine motor skills. Previous research on school-aged children has also suggested that motor interventions can reduce ADHD symptoms and enhance cognitive and academic outcomes (3, 10, 35, 36). When designing interventions to address the motor abilities of children with ADHD, it is vital to consider their developmental stage and the specific processes affecting the corresponding motor-related brain networks.

Limitations and strengths

Interpretation of the results should be tempered by the limitations of this study. The sample was drawn from a clinic population of Chinese preschool children with reported attention problems, lacking healthy controls. The existing data derived from the clinic-based sample may introduce bias and may not accurately represent the broader preschool population. Furthermore, the utilization of different ADHD parent questionnaires for the two preschool groups complicates the comparison of ADHD symptom severity between them and may impact result interpretation.

Despite these limitations, the study possesses several strengths. It filled a gap in previous research concerning the relationship between fine motor development and ADHD in preschool children. By considering the continuum of ADHD symptoms and investigating both children meeting diagnostic criteria and those with symptomatic presentations, the study results are more generalizable. By distinguishing between fine and gross motor development, this study offers insights for future motor intervention strategies targeting preschool children with ADHD.

As a retrospective cross-sectional study, the present study offers preliminary insights into the relationship between ADHD symptoms and motor DQ in children across two age groups. However, we acknowledge that further longitudinal studies would be valuable in exploring the developmental trajectories of motor skills in children with ADHD symptoms. Additionally, exploring the brain structures and functions of motor-related brain regions will also enhance our understanding of this research field.

Conclusion

The results of present study indicate that preschool children with ADHD symptoms exhibit high rates of motor

developmental delays, particularly in fine motor development, regardless of whether they meet diagnostic criteria. However, whether in the 4-year-old group or the 5-year-old group, correlations between ADHD symptom severity and motor development were found only within the ADHD group. Therefore, the study indicates a need for increased focus from both parents and healthcare professionals on the motor development status of children meeting diagnostic criteria for ADHD.

Data availability statement

The datasets presented in this article are not readily available because these medical data involve the privacy of the child. Requests to access the datasets should be directed to Aimin Liang, liang-aimin@163.com.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZC: Data curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. SL: Investigation, Methodology, Writing – original draft, Writing – review & editing. AL: Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. HH: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. XN: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ADHD, stress, and anxiety

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Recent findings on stress and anxiety in attention deficit hyperactivity disorder (ADHD) suggest that specific processes related to brain developmental disorganization could create a vulnerable background that increases sensitivity to stress stimuli from the psychosocial environment. These basic neurodevelopmental processes are closely related to the developmental mechanisms of primitive functions and their integration or disintegration. In this context, the psychopathological processes that manifest in ADHD are linked to the mechanisms of disturbed inhibitory functions that may cause incongruent neural interactions ("neural interference") between the more primitive functions and the higher levels of attentional and cognitive neural processes. These disturbed developmental processes may also determine increased sensitivity to stressful experiences that, in ADHD cases, could lead to the manifestations of various psychopathological symptoms such as disturbed attentional and motor functions, anxiety, and depression, among other cognitive and affective disturbances. These findings, based on previous research, suggest novel framework and hypothesis on how this neurodevelopment-based increased sensitivity to stress stimuli could manifest in the etiopathogenesis of ADHD in its relationship with cognitive, affective, and motor deficits.

KEYWORDS

ADHD, anxiety, depression, stress, developmental disintegration, primitive reflexes, neural interference

Introduction

Recent findings related to research on the retained primitive reflexes in patients with attention deficit hyperactivity disorder (ADHD) indicate that the basic processes in ADHD etiopathogenesis may be related to dysfunctions in hierarchical organization during central nervous system (CNS) development when the different brain developmental stages are interconnected on various hierarchical and functional levels (1, 2). Uncovering these processes in more detail is extremely important for future treatment strategies and for the understanding of the complex etiopathogenesis of the disease. Current findings suggest that, in cases of dysfunctional neural development, these hierarchical and functional levels may manifest incongruent interactions (the so-called neural interference) between the early and the later developed brain functions during ontogenesis (1, 3). This neural interference may manifest in the case when the emergence of a new function that should have inserted the older one is not related to the diminishing or sufficient inhibition of this older function, which could lead to "neural disintegration" caused by incongruent neural processes. In this

context, recent findings focused on the etiopathogenesis of ADHD suggest that these processes related to brain developmental disorganization could create a vulnerable background that increases sensitivity to stress stimuli from the psychosocial environment (2, 4). This increased sensitivity to stress stimuli that might occur in the etiopathogenesis of ADHD could then be related to various forms of cognitive, affective, and motor deficits that often manifest in individuals with ADHD (1, 3, 4). In this biopsychosocial context, this conceptual analysis focused on recent findings on the retained primitive reflexes in ADHD (2, 3) and provides novel perspectives into understanding the multiple etiopathogenetic factors of this condition. The main focus and objectives of the analysis are the interactions of the neurobiological developmental mechanisms with stress influences in the etiopathogenesis of ADHD, with main implications for developmental disorganization in its relationship with cognitive and affective disintegration and the related psychopathological symptoms that could manifest in ADHD. The currently available models and theories on the pathogenesis of ADHD are mainly focused on the neurobiological developmental mechanisms of this condition, but do not explain how these neural processes during development might interact with stress influences from the psychosocial environment. With this aim to link the neurobiological findings on the pathogenesis of ADHD, we briefly summarize the diagnostic definitions of ADHD to show how basic conceptualizations of "organic" minimal brain dysfunctions change during the time for a more complex understanding of this condition. From this historical perspective, this requirement for a more detailed understanding was mainly influenced by findings that the psychosocial environment and mainly stress stimuli strongly interact with the developmental abnormalities specifically related to the etiopathogenesis of ADHD.

Definitions and epidemiology of ADHD

ADHD represents a historically heterogeneous concept that started with the introduction of "minimal brain dysfunction" by Still in 1902 (5), who provided detailed descriptions of the hyperactivity and hyperkinetic symptoms. Much later, in the 1970s, attentional dysfunctions were described by Douglas (6). The historical term "minimal brain dysfunction" was replaced in 1968 by the conceptualization and definition of hyperactivity, but even then was still understood mainly as a result of some biological origin more than of environmental causes (7–9). This concept was later incorporated into the official diagnostic nomenclature described in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) (7, 10) as a disorder characterized by overactivity, restlessness, distractibility, and short attention span, particularly in young children, that usually diminishes in adolescence (7–9, 11).

The diagnostic definitions of ADHD in the last decades have reflected an increased knowledge of this condition and its developmental etiopathogenesis. Its recent definitions included in basic diagnostic classification systems, such as the International Classification of Diseases, 10th revision (ICD-10), DSM-IV, and DSM-V, describe the behavioral characteristics of ADHD as related to deficits in "executive functions" that negatively influence the control and regulation of cognitive processes and "self-control" (12). In the case of ADHD as a typical developmental disorder, these neurocognitive characteristics often manifest in the different ontogenetic stages from early childhood to adulthood, which are mainly related to specific deficits in attentional and executive functions (13, 14).

Most typical symptoms according to DSM-IV-TR (DSM-IV, text revision) include excessive motor activity, inattention, and impulsiveness that manifest in childhood (11), while according to the DSM-V definition (15), ADHD is characterized by a pattern of behavior that can be divided into two categories: inattention, and hyperactivity and impulsivity. Children must have at least six symptoms from either (or both) the inattention group of criteria and the hyperactivity and impulsivity criteria, while older adolescents and adults (over 17 years old) must show at least five symptoms. According to DSM-V, symptoms of ADHD must be present prior to age 12 years, compared to 7 years as the age of onset in DSM-IV. In addition, DSM-V does not include the exclusion criteria for people with autism spectrum disorder as the symptoms of both disorders may co-occur.

According to epidemiological data, symptoms of ADHD developed later in adolescence are very similar to ADHD in children with typically increased attentional deficits that are more frequent than hyperactivity and impulsivity, and the treatment procedures in adolescence are also very similar (2, 16–18). Reported evidence also shows that adult symptoms of ADHD, due to disturbances of the executive functions, are significantly related to a higher prevalence of antisocial personality and behavioral disorders. These data show that antisocial personality disorder manifests in 12%–28% of adults with ADHD (in healthy controls, it is 2%–8%), while behavioral disorders manifest in 22%–62% of adults with ADHD (only 4%–8% in healthy controls) (2, 14, 17–25). These highly prevalent antisocial personality and behavioral disorders in adults with ADHD are also related to increased manifestations of criminal behavior, mood disorders, anxiety disorders, and addictive behavior in comparison to healthy controls (19, 25–27). In addition, reported data have shown that antisocial behavior in children is often related to the same difficulties in adulthood in approximately 20%–45% of adults with an ADHD diagnosis (2, 7, 14, 18, 20). For example, according to reported data, approximately 10% or more of individuals in prison have a diagnosis of ADHD (28, 29).

Important prediction factors of later difficulties and bad prognosis are also early manifestations of symptoms of ADHD, and reported data have shown that later manifestations of these ADHD symptoms indicate better prognosis (30–33). Other very important negative factors for future prognosis represent the early occurrence of oppositional defiant disorder, mood disorder and anxiety, and a lower level of intelligence (2, 17, 19, 25, 34, 35). Major negative factors also represent the occurrence of psychopathology

in parents, ADHD in other family members, the social and economic status of the family, and frequent conflicting situations and psychosocial stress (2, 24, 25, 34, 36).

Executive functions, psychosocial stress, and ADHD

The major results in recent ADHD research show that the processes of executive control are typically affected in ADHD and mainly include dysfunctions in inhibitory control (2, 37–39). In addition, recent empirical findings and theoretical conceptualizations indicate that, together with inhibitory dysfunctions, increased emotional excitation may play a role in ADHD deficits. For example, the "cool" cognitive deficits in executive functions are closely linked to attentional dysfunctions; on the other hand, "hot" deficits are related to the dysfunctional ability to process emotional information that produces hyperactivity and impulsivity (2, 39–42). These recent findings indicate that ADHD cannot be explained solely as a consequence of frontal lobe executive dysfunctions. An important role can also be attributed to emotional dysregulation associated with increased excitability in the limbic system, which may cause ADHD disturbances even when frontal executive dysfunctions are not a primary factor in the etiopathology of ADHD (39–42).

Altogether, these findings suggest the so-called dual-pathway concept of the two basic developmental trajectories that could lead to ADHD (43). The first is represented by frontal executive dysfunctions (2, 39, 42–44), while the second is mainly linked to dysfunctions in brain systems related to emotions and motivation (45).

Recent findings suggest that attentional and executive dysfunctions may be related to impulsivity, often observed in ADHD, which can also contribute to social dysfunctions and increased vulnerability to stress-related influence (39). For example, recent findings show that children with ADHD often manifest antisocial behavior, most likely due to deficits in executive functions, impulsivity, and aggressive behavior related to stressful situations (4, 39, 42). Impulsivity is often associated with antisocial behavior, which occurs in 20%–45% of adults with ADHD and contributes to interpersonal problems (14, 18, 20). According to some data, approximately 10% or more of individuals from populations who display various forms of criminal behavior have ADHD (2, 14, 28, 29).

According to epidemiological data, ADHD is related to significantly increased levels of mental stress (4, 39, 46, 47). For a more detailed understanding of how stress could influence individuals with ADHD, it seems extremely important to note that the various functional changes in ADHD and posttraumatic stress disorder (PTSD) are frequently similar, and it is possible to expect that the different processes described in stress-related disorders are extremely important in the etiopathogenesis of ADHD (4, 36, 39, 48, 49).

In this context, recent evidence indicates that experiencing traumatic events or repeated stressors in childhood often may cause severe mental problems that could have delayed effects and lead to various neurobiological changes that influence attentional dysfunctions, disturbed cognitive control, and emotional dysregulation (4, 39, 50–52). The development of ADHD is also linked to deficits of neural mechanisms that might underlie specific changes in attentional functions and decreased cognitive control, often associated with impaired inhibitory functions (2, 39–44).

Brain developmental stages, neural disintegration, and ADHD

According to neurodevelopmental findings, later developed functions during the ontogenesis of the CNS tend to replace the older ones when higher stages of CNS development have been successfully achieved (1, 53, 54). The development of neural functions based on ontogenetically successive complex neuronal levels enables the performance of more adaptive functions; on the other hand, disinhibition or the release of developmentally older functions from inhibitory control manifests in various neurological and psychiatric disorders (1, 2, 54).

As recent findings show, the highest risk of neural disintegration is during the sensitive developmental stages of brain functions that are also particularly vulnerable to various insults, such as brain damage, toxic influences, or psychological stress (4, 55–57). The particularly important postnatal developmental deficits of higher motor and cognitive functions that likely also have various etiological backgrounds are persisting "primitive reflexes" (3, 58–60), such as symmetric tonic neck reflex (STNR) and asymmetric tonic neck reflex (ATNR), among others (59, 61). These primitive (or primary) reflexes (3, 62, 63) present specific forms of innate "behavioral movement patterns" (64) that are replaced by higher motor and cognitive functions (58–60), and when they occur in the later stages of development, they may present a form of "soft neurological signs" (65).

In this context, recent clinical evidence indicates that manifestations of primitive reflexes in later age than is ontogenetically typical are likely linked to frontal lobe dysfunctions and cortical disinhibition and may occur in various neuropsychiatric syndromes such as ADHD, schizophrenia, depressive and anxiety disorders (3, 66), dementia and Parkinsonism (67), and delirium (68), among other neuropsychiatric disorders (59, 60, 69). These data suggest that persistent (or retained) primary reflexes in general represent evolutionary lower levels of neurophysiological processes that may interfere with processing on higher levels and cause neural disintegration, which may be linked to different neuropsychiatric conditions including ADHD, anxiety, mood disorders, and other mental disorders (1, 54).

Stress, ADHD, and anxiety

According to current evidence, ADHD shares a high comorbidity with anxiety disorders. These findings show that symptoms of anxiety may increase the symptoms of ADHD; on the other hand, deficits of executive functions related to ADHD may increase anxiety (25, 70).

Nevertheless, the causal relations where the anxiety would predict ADHD, or the ADHD would predict anxiety, were not found, indicating that both diagnoses could coexist as comorbidities. However, there is no evidence that ADHD could create anxiety as its symptom or that anxiety would implicate ADHD (25, 71). These findings are in agreement with the "dual-pathway" trajectory in the etiopathogenesis of ADHD based on the two interacting systems, where the first is represented by frontal executive dysfunctions and the second is mainly linked to dysfunctions in brain systems related to emotions and motivation (39, 42). This mutual comorbidity and "interplay" between ADHD symptoms and anxiety indicates that inhibitory deficits specifically interact with emotional excitation related to stress stimuli, and the dysfunctional inhibitory systems could cause higher vulnerability with respect to stress stimuli from the social environment (2, 4). On the other hand, in cases of ADHD where the executive dysfunctions are not the main etiopathogenetic factors, increased emotional excitation caused by stress stimuli may also play a role in ADHD deficits and symptoms (2, 4). This interplay between executive dysfunctions and emotional dysregulation due to stressful experiences may then also implicate the observed comorbidities and relationships between the attentional symptoms related to ADHD and the anxiety-related emotional dysregulation in patients with ADHD (2, 4). This interplay between the attentional symptoms of ADHD and the symptoms of anxiety also reflects the dual pathway between the "cool" cognitive deficits mainly related to executive dysfunctions and the "hot" deficits related to the dysfunctional ability to process emotional information that often may produce anxiety, hyperactivity, and impulsivity (39–42). These recent findings on the relationship between ADHD symptoms and anxiety also confirm that ADHD and its symptoms cannot be explained only as a consequence of frontal lobe executive dysfunctions and that important influences on the etiopathogenesis of ADHD are also related to emotional dysregulation that is closely linked to increased excitability in the limbic system (4, 39, 42).

Conclusion

Recent findings suggest that the etiopathogenesis of ADHD could represent a process related to the "incongruent interactions" of the more primitive neural mechanisms, such as the primitive reflexes with higher levels of brain functions, due to an insufficiently developed cognitive and motor integration. This developmental disintegration is also related to the disturbed balance in ADHD (2, 3). In some cases of ADHD, these retained reflexes and incoordination are related to the disturbed balance and attentional dysregulation linked to incongruent interactions (or conflict) between the higher and lower levels of cognitive and motor functions during brain processing (46, 47).

Recent findings also show that a high proportion of individuals with ADHD manifests altered balance and motor abnormalities (72–74). According to brain imaging studies, these balance deficits are likely linked to prefrontal cortex deficits that influence the attention and executive functions (75–77). These dysfunctions could also have a cerebellar origin: individuals with ADHD, in many cases, exhibit atrophy in the cerebellar regions associated with balance and gait control, and these balance and motor dysfunctions are linked to inhibitory deficits due to cerebellar abnormalities (72, 78–80).

In future research, this relationship between the dysregulation of emotional systems and executive dysfunctions could also help in understanding the unresolved relationship between internalizing the symptoms of ADHD, which are mainly related to anxiety and depression, and externalizing the symptoms related to behavioral dysfunctions, which mainly manifest as conduct problems, aggressive behavior, and oppositional defiant disorder (2).

Author contributions

PB: Conceptualization, Writing – original draft, Writing – review & editing. MP: Writing – original draft, Writing – review & editing.

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Conflict of interest

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Gene-level connections between anxiety disorders, ADHD, and head and neck cancer: insights from a computational biology approach

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Background: Anxiety disorders (AD), ADHD, and head and neck cancer (HNC) are complex conditions with potential genetic interconnections that remain to be fully elucidated. The purpose of this study is to investigate gene-level connections among ADHD, AD, and HNC.

Method: A comprehensive literature mining approach identified potential gene-disease relationships from PubMed and bioinformatics databases, analyzing 19,924 genes. An AI-driven computational process constructed a gene-disease relationship table using the Adjusted Binomial Method Algorithm (ABMA) to evaluate association reliability. Overlapping genes were analyzed through protein-protein interaction (PPI) networks, functional annotations, and literature-based pathway analyses to elucidate shared and unique genetic mechanisms linking these diseases.

Results: The analysis identified 141 significant genes associated with AD, 153 with ADHD, and 1,065 with HNC (q-value < 0.05). These genes demonstrated significant overlap (odds ratio ≥ 1.8; p ≤ 2.58E-2) and high interconnectivity (PPI network density ≥ 0.39, clustering coefficient ≥ 0.76, and diameter ≤ 3). Centrality analysis revealed core genes such as IL-6, MYC, NLRP3, and CXCR4 as critical mediators. Functional enrichment analysis identified key pathways, including serotonergic synapse, inflammatory response, and Toll-like receptor signaling, highlighting the involvement of neuronal and immune mechanisms. Functional pathway analysis demonstrated reciprocal genetic influences among AD, ADHD, and HNC, emphasizing shared and distinct gene-level connections that may underlie their co-occurrence and mutual risk factors.

Conclusion: This study reveals a complex and interconnected genetic network among AD, ADHD, and HNC, highlighting shared pathways, unique mechanisms, and critical genes, providing valuable insights into the genetic underpinnings of these conditions and potential avenues for therapeutic exploration.

KEYWORDS

gene-level connections, anxiety disorders, ADHD, head and neck cancer, therapeutic exploration

Introduction

Anxiety disorders (AD) are a group of mental health conditions characterized by excessive fear, worry, and related behavioral disturbances. Epidemiologically, ADs are highly prevalent, affecting approximately 19.1% of adults in the United States in a given year, with a lifetime prevalence of around 29% (1). These disorders can arise from a combination of genetic, environmental, and psychological factors, making understanding their epidemiology crucial for effective prevention and treatment strategies (2).

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity, and impulsivity that can interfere with functioning or development. ADHD affects approximately 6-7% of children worldwide (3), with varying prevalence rates across different regions and populations.

Head and Neck Cancer (HNC) encompasses a diverse group of malignancies that arise in the oral cavity, pharynx, larynx, and other related structures. Epidemiologically, HNC accounts for approximately 4% of all cancers in the United States, with an estimated 54,540 new cases and 10,780 deaths projected for 2023 (4).

To clarify terminology, AD in this study refer to the broad spectrum of anxiety-related conditions as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), including but not limited to generalized anxiety disorder (GAD), panic disorder, separation anxiety disorder, and social anxiety disorder. While these subtypes differ in their specific symptomatology, they share core features of excessive fear, worry, and behavioral disturbances. We use the term AD to encompass this spectrum, acknowledging that this inclusive approach may obscure subtype-specific nuances but allows for a broader exploration of shared genetic mechanisms. Importantly, AD in this context refers specifically to Anxiety Disorders and not Alzheimer's disease, which is another psychiatric condition with distinct pathophysiology and clinical presentation.

Similarly, HNC encompasses a diverse group of malignancies arising in the oral cavity, pharynx, larynx, sinuses, and salivary glands. This includes squamous cell carcinomas, adenocarcinomas, and other histological subtypes. By using the term HNC, we aim to capture the shared genetic and clinical features across these malignancies, recognizing that this broad categorization may overlook subtype-specific differences. In this study, gene-disease associations were analyzed at the level of full clinical diagnoses rather than individual symptoms to ensure consistency across ADHD, AD, and HNC. While ADHD is generally treated as a single diagnostic entity, AD and HNC encompass multiple subtypes with distinct but overlapping genetic underpinnings. While this approach facilitates a comprehensive analysis of shared genetic pathways, it also necessitates caution in interpreting findings, as the heterogeneity within HNC subtypes may influence results.

Associations have been suggested between ADHD and AD, with ADHD often co-occurring with some form of anxiety (5). Genome-wide association studies have demonstrated significant genetic correlations between ADHD and AD (rg = 0.34), with both conditions sharing genetic risks linked to neuroticism (rg = 0.81) and major depressive disorder, suggesting a common polygenic architecture that may explain their frequent comorbidity (6, 7). Mendelian randomization analyses further reveal that socioeconomic factors, such as higher educational attainment and income, serve as protective influences for both ADHD and anxiety disorders, underscoring the role of gene–environment interactions in their co-occurrence (8). Together, these findings highlight the importance of exploring the shared and unique genetic factors underlying these conditions.

Extending this framework to HNC involves investigating shared biological pathways such as neuroinflammation and immune dysregulation. In HNC patients, higher pretreatment anxiety levels are significantly associated with poorer 2-year overall survival, with tumor response mediating this relationship, suggesting that AD may negatively impact cancer outcomes (9). Conversely, HNC patients, particularly those who have undergone radiotherapy, may develop anxiety and depressive disorders (10). Moreover, shared genes have been identified as playing roles in all three disorders, including CYP2D6 (11–13). Emerging hypotheses propose that systemic inflammation—implicated in ADHD and anxiety through genetic variants in pathways like IL6 and TNF-α—may also contribute to oncogenic processes in HNC (14, 15). For instance, chronic inflammation and oxidative stress, common in neuropsychiatric conditions, are established drivers of carcinogenesis. Although direct genetic links between HNC and

psychiatric disorders remain underexplored, the overlap in inflammatory pathways provides a plausible mechanistic bridge. Additionally, while ADHD-associated behaviors (e.g., tobacco use) may elevate HNC risk, genetic predispositions to immune dysregulation could further compound susceptibility (16). By elucidating these shared mechanisms, research may uncover transdiagnostic therapeutic targets and inform preventive strategies across neurodevelopmental, psychiatric, and oncological conditions.

This study aims to address the gap in knowledge by exploring gene-level connections among these conditions using a computational biology approach. We hypothesize that there are significant overlapping genetic pathways and core genes that contribute to the co-occurrence and mutual risk factors of AD, ADHD, and head and neck cancer. The findings of this study could provide valuable insights into the genetic underpinnings of these conditions, potentially informing future research and therapeutic strategies.

Method

Study workflow

This study followed a structured multi-step workflow to explore the genetic relationships among ADHD, AD, and HNC. First, relevant gene-disease associations were retrieved from multiple bioinformatics databases and literature sources, including PubMed and the AIC Bioinformatics Database (ABD). Next, an AI-driven data processing pipeline was applied to filter and refine gene-disease associations, ensuring high-quality data for subsequent analysis. Overlapping and unique gene sets across the three diseases were identified, and statistical enrichment analyses were conducted to assess their biological significance. Finally, functional and pathway analyses were performed to investigate potential mechanisms linking ADHD, AD, and HNC. Details of each step, including data sources, computational approaches, and statistical methods, are provided in the subsequent sections. The workflow of the current study is depicted in Figure 1. To note, as described in the Introduction, AD refers to anxiety disorders as defined by DSM-5, and HNC encompasses multiple malignancies arising in the head and neck region. This study considers ADHD as a single diagnostic entity, while AD and HNC include multiple subtypes with shared genetic features.

Disease gene identification using literature-based mining

To systematically identify gene-disease associations for ADHD, AD, and HNC, we conducted a comprehensive literature mining approach utilizing multiple bioinformatics resources. The analysis encompassed whole-genome genes (19,924 genes) and aimed to extract relevant disease-gene relationships from curated scientific literature.

First, we employed the Entrez API (http://www.ncbi.nlm.nih.gov/Entrez/) to programmatically query PubMed (https://pubmed.ncbi.nlm.nih.gov) for relevant publications. This automated process retrieved references containing associations between the three diseases and specific genes. The extracted information included metadata such as PMID, DOI, publication title, abstract, author details, and publication date, ensuring a structured dataset for downstream analysis.

Additionally, we leveraged the AIC Bioinformatics Toolbox (ABT) to extract disease-gene relationships from the AIC Bioinformatics Database (ABD) (https://www.gousinfo.com/en/

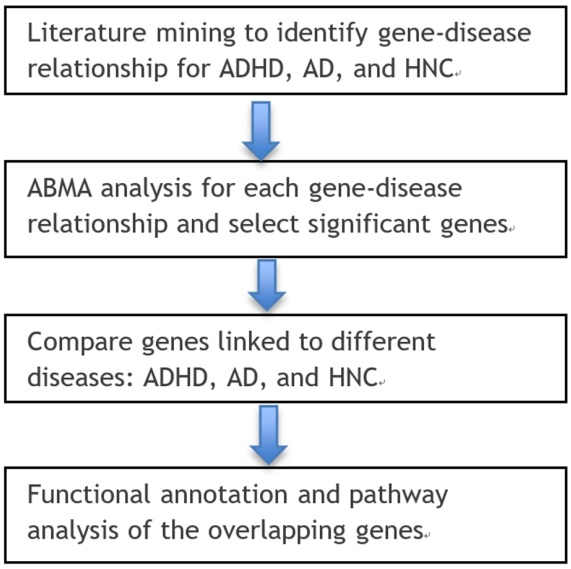

FIGURE 1
Workflow diagram of this study. Generated using https://bioinfogp.cnb.csic.es/tools/venny/.

userguide.html). This database integrates information from various genomic and biomedical data sources, facilitating a more comprehensive collection of gene-disease associations. The data were formatted to ensure uniformity and compatibility with PubMed-extracted references.

The retrieved reference data were compiled and formatted into an Excel worksheet, where each entry was cross-referenced for relevance and quality. Further post-processing steps, including data filtering, duplicate removal, and relevance scoring, were performed to refine the dataset before proceeding with statistical and functional analyses. To ensure consistency, gene-disease associations were analyzed at the level of full diagnoses rather than individual symptoms. While AD comprises multiple subtypes with distinct diagnostic criteria, only studies explicitly linking genetic markers to diagnosed AD subtypes were included in the analysis. Similarly, HNC subtypes were collectively analyzed, focusing on shared genetic components rather than subtype-specific variations.

AI-based relationship table construction

For the references identified, an AI-based quality control process was used to extract relationship details and remove non-qualified references. The relationship between each gene-disease pair was then constructed, with polarity and direction assigned using an AI-driven computational approach. To assess the reliability of these relationships, the Adjusted Binomial Method Algorithm (ABMA) was applied using the scipy.stats package in Python, which offers functions for hypothesis testing. The core idea of ABMA is to refine the estimation of association strength by adjusting for different types of observations—positive, negative, and inconclusive findings. This ensures that the influence of each type of observation is properly accounted for in the final association score. ABMA assumes that the proportions of positive, negative, and inconclusive findings are representative of the underlying relationships between the gene and the disease. The method also adjusts for uncovered samples based on an estimated factor (α), which is assumed to be a reasonable estimate of missing data. While this approach helps refine the association estimation, any inaccuracies in the assumptions (e.g., the coverage of uncovered samples or the distribution of findings) could influence the final results. A False Discovery Rate (FDR) correction was applied to control for false positives, and relationships with a q-value ≤ 0.05 were considered significant.

Adjusted binomial method algorithm

To assess the association between two entities, such as a gene and a disease, we implemented the Adjusted Binomial Method algorithm, which applies an adjusted binomial test to evaluate statistical significance. This method accounts for multiple types of observations—positive, negative, and inconclusive findings—to provide a refined estimation of association strength.

The algorithm was executed using the scipy.stats package in Python (https://docs.scipy.org/doc/scipy/reference/stats.html), which offers statistical functions for hypothesis testing. The key principle behind this method is to determine whether the observed proportion of a dominant outcome (e.g., positive associations between a gene and a disease) significantly deviates from an expected probability threshold (p_0).

Total observations calculation

The total sample size N is calculated using the following formula:

$$N = n_p + n_n + n_0 + n_x$$

where, N represents the total effective sample size, n_p, n_n, and n_0 represent the sample size of positive, negative, or unknown relationship, and n_x represent uncovered samples.

where n_p, n_n, and n_0 represent the number of studies reporting a positive, negative, or unknown association, respectively, while n_x represents the number of uncovered samples. To account for potential publications not identified through the initial search, we use an uncovered sample fraction factor α, which represents the ratio of uncovered to covered samples:

$$n_x = \alpha * (n_p + n_n + n_0)$$

For this study, the fraction factor α is set to 1. This choice is based on the assumption that PubMed and the ABD database together provide comprehensive coverage of bioinformatics and biology studies, capturing around 50% of publications in the field. Therefore, assuming uncovered samples to be at most equal to identified samples is a reasonable estimate.

H0 testing using adjusted binomial test

Null Hypothesis (H0): The true proportion of major results is equal to p0.

Alternative Hypothesis (H1): The true proportion of positive results >p0.

Decision rule: If the calculated p-value is less than or equal to the significance level (<0.05), the null hypothesis is rejected, indicating a statistically significant association (Table 1). In the following description, we use positive association as the dominant finding as example.

The tail probability was calculated using the function below:

$$p - value = P(X \geq n_p) = binom.sf(n_p - 1, N, p0)$$

where $binom.sf$ is the survival function for a binomial distribution with N trials and success probability p0.

To determine the total number N, the success probability $p0$, we consider the following two cases:

1) Case 1: We hypothesize that the uncovered n_x samples have the same distribution as the identified samples. Under this

hypothesis, the adjusted total number of observations is:

$$N = 2 * (n_p + n_n + n_0)$$

with the number of dominant findings is doubled:

$$n_p = 2 * n_p$$

In this case, the observed proportion of dominant associations out of the total adjusted observations is:

$$n_{obser} = \frac{n_p}{N} \in (0.33, 1]$$

Based on this range, we set $p0 = 0.34$, which represents the lower bound at which n_p dominates the observations.

2) Case 2: We hypothesize that the uncovered n_x samples are different from the identified samples. In the extreme scenario, all n_x samples are null associations. Here, the adjusted total number of observations is:

$$N = 2 * (n_p + n_n + n_0)$$

and the number of dominant findings n_p does not change. Therefore, the observed proportion of dominant associations out of the total adjusted observations is:

$$n_{obser} = \frac{n_p}{N} \in (0.17, 1]$$

Therefore, in this case, we set $p0 = 0.17$, which represents the lower bound at which n_p dominates the observations.

Gene comparison across diseases

The gene lists associated with each of the three diseases—ADHD, AD, and HNC—were compared to identify unique and overlapping genes. Fisher's exact test was used to assess the significance of the overlap, and a Venn diagram was employed for visualization. While we compared both all disease-related genes and those that were statistically significant, our subsequent analysis will focus primarily on the genes showing statistical significance.

Functional analysis of overlapping genes

We employed the Functional Annotation Tool of Database for Annotation, Visualization, and Integrated Discovery (DAVID) (https://david.ncifcrf.gov) to systematically analyze the overlapping gene set. The functional annotation covered Gene Ontology (GO) Analysis: Biological Process (BP) (GOTERM_BP_DIRECT), investigating the biological roles of genes (e.g., immune response, neurodevelopment, apoptosis); Cellular Component (CC) (GOTERM_CC_DIRECT), identifying subcellular localization (e.g., nucleus, cytoplasm, synapse); and Molecular Function (MF) (GOTERM_MF_DIRECT), examining gene product functions (e.g., kinase activity, DNA binding). Additionally, Pathway Enrichment Analysis was conducted: BBID Pathway, exploring regulatory interactions; BIOCARTA Pathway, providing manually curated molecular interactions; and KEGG Pathway, identifying involvement in well-defined biological pathways (e.g., cancer, metabolism, neurodevelopment).

Additionally, a protein-protein interaction (PPI) analysis was performed to explore functional connections between these genes, with relationships between proteins established based on prior literature.

Finally, a functional pathway analysis was conducted to construct potential associations among ADHD, AD, and HNC at the gene level. Gene interactions were identified based on known biological pathways and established functional connections in curated databases. The analysis does not infer direct causation but highlights potential regulatory relationships that could mediate interactions between these conditions. While gene expression and functional annotation suggest possible influence, experimental validation is necessary to establish causal mechanisms.

Results

AI-based disease-gene identification results

Out of 19,924 genes, our AI-based computational approach identified 2,301 genes associated with Anxiety (supported by 4,884 references), 1,199 genes associated with ADHD (supported by 3,283 references), and 6,629 genes associated with HNC (supported by 17,477 references) (see Figure 2a). When applying a significance threshold (q-value ≤ 0.05), 141 genes were identified for Anxiety (784 references), 153 for ADHD (1,005 references), and 1,065 for HNC (4,458 references) (see Figure 2b).

The overlap analysis between Anxiety and ADHD indicates a statistically significant association. For the set of significant genes (q-value ≤0.05), 32 overlapping genes were identified, yielding an odds ratio of 36.80 and a p-value of 1.24e-34. When considering all identified genes, 723 genes overlapped, with an odds ratio of 7.15 and a p-value of 1.31E-252. These results indicate a consistent association between AD and ADHD.

In comparison, the overlap between Anxiety and HNC showed 22 significant overlapping genes with an odds ratio of 3.12 and a p-value of 1.36e-05 (Table 1). For all genes, the overlap increased to 1,521 genes, with an odds ratio of 3.91 and a p-value of 1.34e-201. This suggests a statistically significant, although less pronounced, genetic overlap between AD and HNC.

For the ADHD and HNC comparison, 15 overlapping significant genes were identified (odds ratio = 1.80, p-value = 2.58e-02) (Table 1). When all genes were considered, 766 overlapping genes were observed, with an odds ratio of 3.54 and a p-value of 1.64e-97. While these associations are statistically significant, they are relatively weaker compared to the overlaps involving Anxiety and ADHD.

PPI analysis

ADHD and HNC

The PPI analysis for the 15 overlapping genes between ADHD and HNC (including *ACD, ADORA2A, CRP, CYP2D6, DCT, DYRK1A, FER, IGF-1, IL-6, MYC, NF1, NGF, NLRP3, NR4A2*, and *PER3*) produced a network with 15 nodes and 87 edges (see Figure 3a). The network has a density of 0.41, an average path length of 1.67, an average clustering coefficient of 0.79, one connected component, and a diameter of 2. The Total Weight of the network is 304 (based on supporting references). Centrality analysis identified five genes (*IL-6, MYC, NLRP3, IGF-1*, and *CRP*) as network hubs, based on consistently high centrality measures.

Anxiety and HNC

The PPI network for overlapping genes associated with Anxiety and HNC consists of 22 nodes and 201 edges (see Figure 3b). This network exhibits a density of 0.44, an average path length of 1.63, a diameter of 2, and an average clustering coefficient of 0.85, indicating moderate connectivity with a single connected component. The Total Weight is 757. Key genes based on centrality metrics include SIRT1, IL-6, CXCR4, CCL2, FOS, and TLR2, with IL-6 showing the highest betweenness centrality (0.18).

ADHD and anxiety

For the overlapping genes between ADHD and Anxiety, the PPI network comprises 33 nodes and 411 edges (see Figure 3c). The network density is 0.39, the average path length is 1.69, and the average clustering coefficient is 0.76, with one connected component and a network diameter of 3. The total edge weight is 1,190. Centrality analysis highlighted IL-6, IMPACT, COPD, HR, and COMT as prominent nodes. In particular, IL-6 exhibited high in-degree (0.62), out-degree (0.78), and a betweenness centrality of 0.16, while COMT had a notable eigenvector centrality (0.23).

Functional annotation analysis results

Anxiety and ADHD

The functional enrichment analysis for overlapping genes between Anxiety and ADHD (Figure 4a) identified several significant biological terms and pathways. For example, the term "dendrite" (GO:0030425) was enriched (p = 1.46e-06) with a fold enrichment of 12.97, involving genes such as APP, ADORA2A, and CACNA1C. The "Serotonergic synapse" pathway (hsa04726) was also enriched (p = 9.06e-05) with a fold enrichment of 19.22, including genes such as MAOA and HTR1B. Additional terms such as "synapse" (GO:0045202, p = 4.21e-04), "endoplasmic reticulum lumen" (GO:0005788, p = 6.46e-04), "growth cone" (GO:0030426, p = 7.20e-04), and "presynaptic membrane" (GO:0042734, p = 7.35e-04) were significantly enriched, emphasizing the involvement of neuronal structure and signaling.

Anxiety and HNC

For overlapping genes between Anxiety and HNC (Figure 4b), functional enrichment analysis identified terms such as "inflammatory response" (GO:0006954, p = 7.85e-08), involving genes like IL22, IL6, and CXCR4, and the "Toll-like receptor signaling pathway" (hsa04620, p = 1.96e-06) with contributions from IL6 and TLR9. Additional enriched pathways include "Chagas disease" (hsa05142, p = 4.69e-05) and "Cytokine-cytokine receptor interaction" (hsa04060, p = 0.00266). Other immune-related pathways, such as "Th17 cell

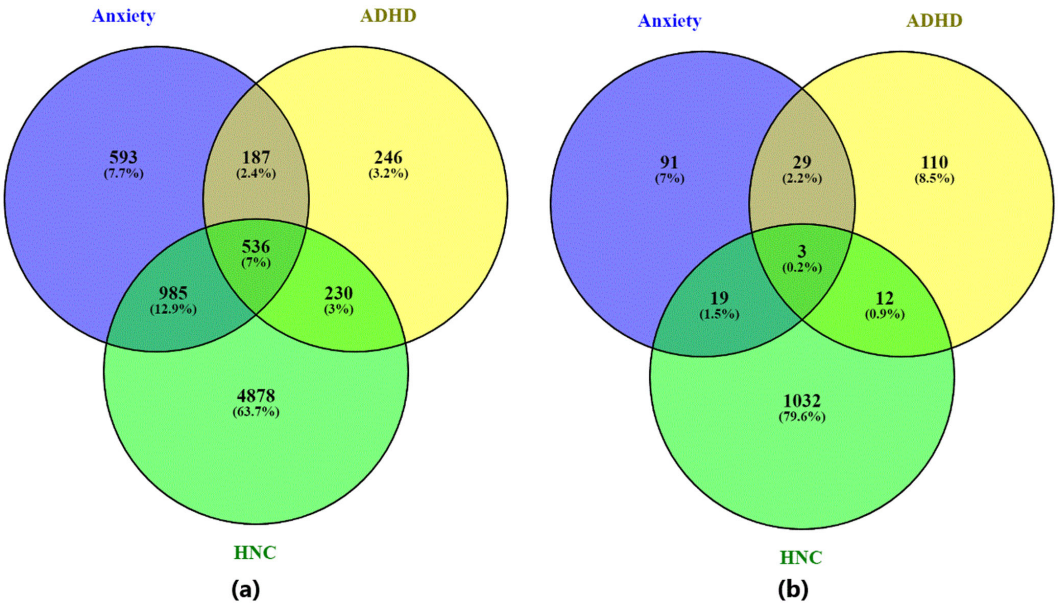

FIGURE 2
Venn diagram illustrating the overlap between genes associated with the three diseases—ADHD, anxiety disorder, and head and neck cancer. **(a)** Venn diagram based on all identified disease-related genes; **(b)** Venn diagram based on statistically significant disease-related genes (q-value ≤ 0.05). Generated using visualize_pathwayInExcel() function within NetworkAnalysis.py.

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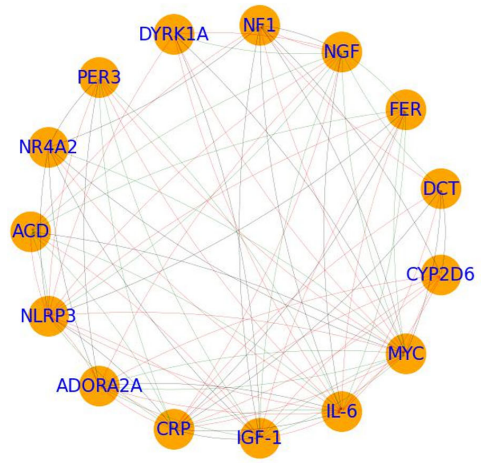
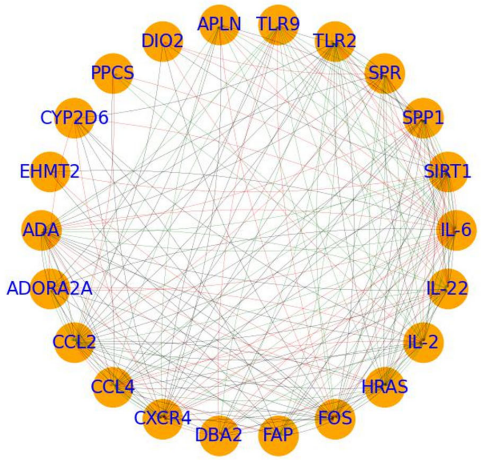
TABLE 1 Venn diagram statistics for overlapping genes among three diseases.

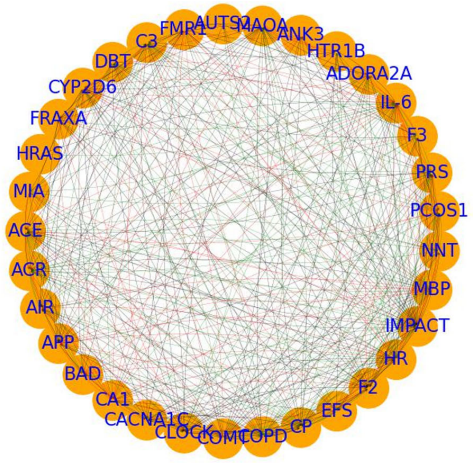
Gene Category	Source Disease	Target Disease	#genes Source	#genes Target	Overlap	Odds ratio	p-value
Significant Genes (q-value ≤0.05)	Anxiety disorders	ADHD	141	153	32	36.80	1.24e-34
	Anxiety disorders	HNC	141	1065	22	3.12	1.36E-05
	ADHD	HNC	153	1065	15	1.8	2.58E-02
All genes	Anxiety disorders	ADHD	2301	1199	723	7.15	1.31E-252
	Anxiety disorders	HNC	2301	6629	1521	3.91	1.34E-201
	ADHD	HNC	1199	6629	766	3.54	1.64e-97



(a) ADHD and HNC



(b) Anxiety disorders and HNC



(C) Anxiety disorders and ADHD

FIGURE 3
PPI analysis showing the interplay between the overlapping genes. **(a)** PPI network of the genes shared by ADHD and HNC; **(b)** PPI network of the genes shared by Anxiety disorder and HNC; **(c)** PPI network of the genes shared by Anxiety disorder and ADHD. Generated using excel file with data from Enrichment analysis (see Functional Annotation.xlsx).

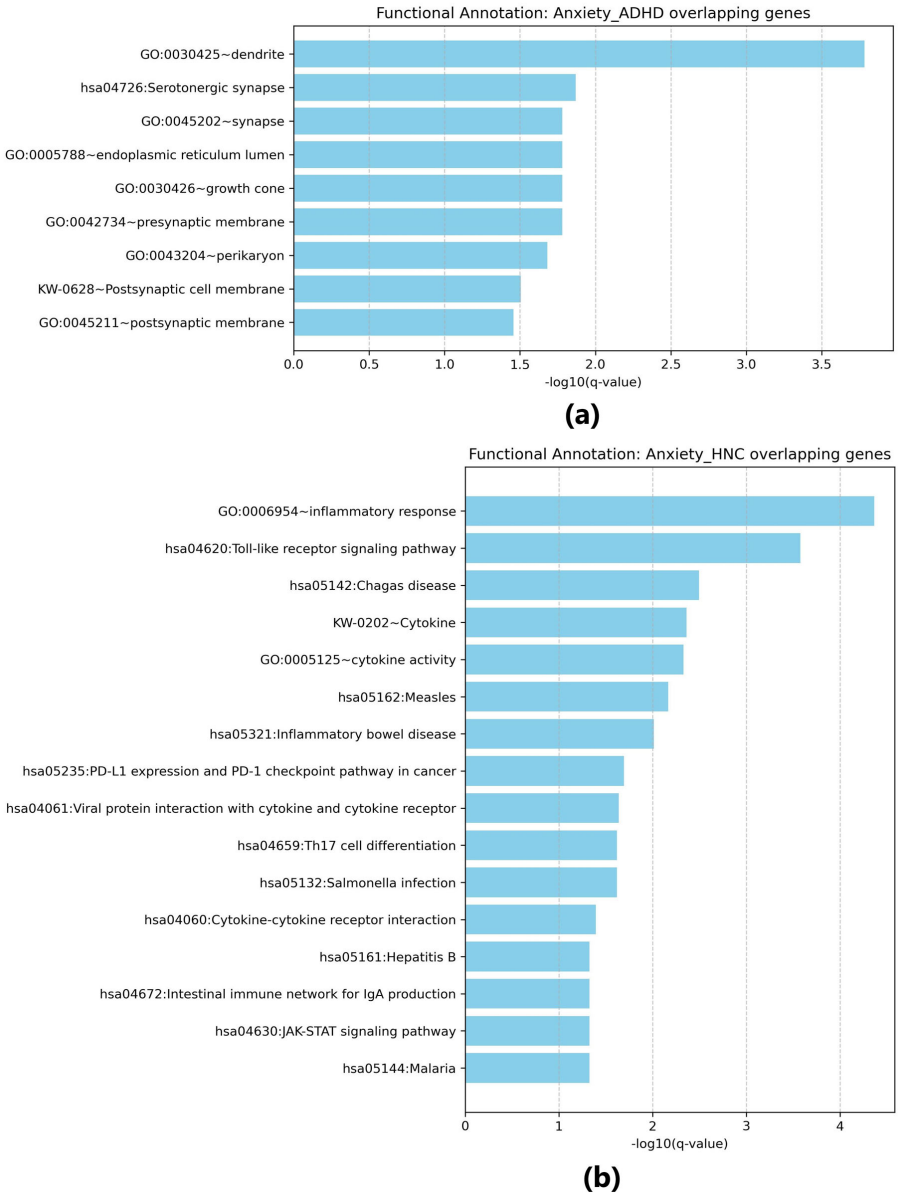


FIGURE 4
Functional enrichment analysis for overlapping genes. **(a)** Results for overlapping genes associated with both Anxiety disorders and ADHD; **(b)** Results for overlapping genes associated with both Anxiety disorders and head and neck cancers. Generated using Cytoscape.

differentiation" (hsa04659, p = 0.00127) and "Cytokine activity" (GO:0005125, p = 3.47e-05), were also noted, with fold enrichment values up to 28.63 (e.g., for "Inflammatory bowel disease", hsa05321). These findings point to a significant association with immune and inflammatory responses in the overlapping genes.

Pathway connecting AD, ADHD, and HNC

The functional pathway analysis (Figure 5) indicates that ADHD, AD, and head and neck cancer (HNC) may influence each other through the regulation of multiple genes.

AD and ADHD: AD may influence ADHD via intermediary genes such as F2, HR, F3, and MBP. Conversely, ADHD may affect AD through genes including CLOCK, ACR, BAD, ADORA2A, ANK3, COPD, and IMPACT.

AD and HNC: AD appear to affect HNC through genes such as CYP2D6, ADA, FOS, and SIRT1, while HNC may influence AD via genes like SPR, CCL4, CXCR4, DIO2, and SPP1.

ADHD and HNC: ADHD may impact HNC through genes such as CYP2D6, PER3, ACD, MYC, and NGF, although the reciprocal influence of HNC on ADHD was not evident.

Overall, these pathway analyses reveal a complex genetic network that may underlie the co-occurrence or shared risk

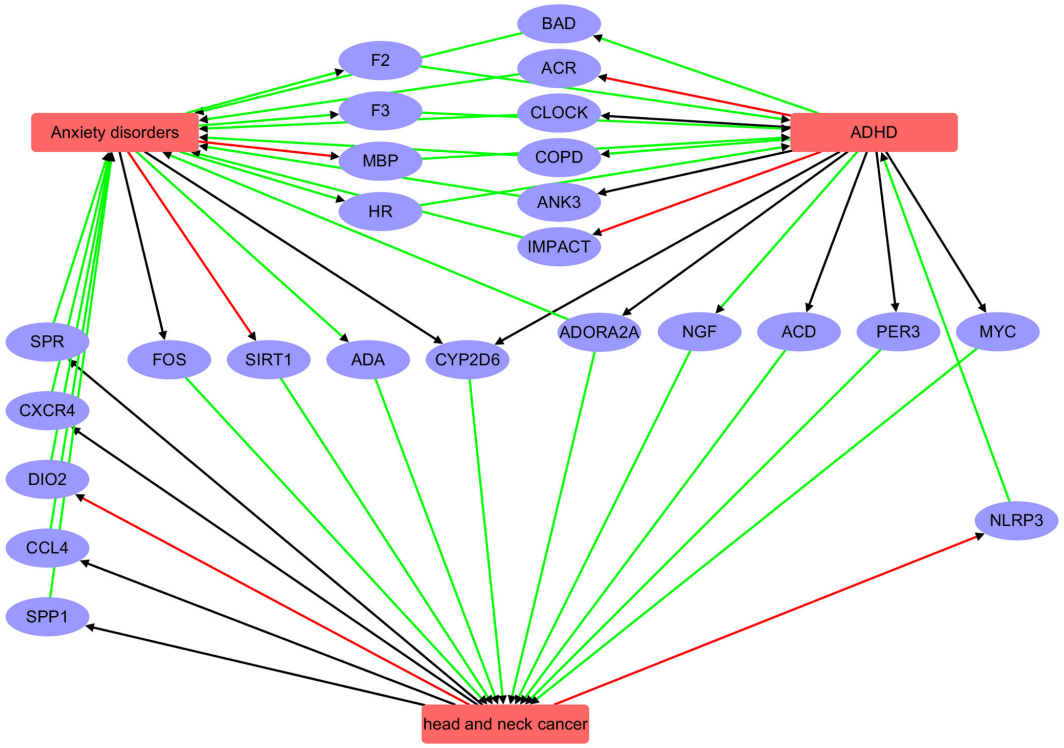


FIGURE 5
Pathway connecting three diseases: Anxiety disorder, ADHD, and head and neck cancer. Red edge indicates a negative association, green positive association, and black unknown association.

factors among these three conditions. While these findings suggest potential regulatory pathways, they do not establish direct causation. Further experimental studies, such as gene expression validation and mechanistic investigations, are needed to confirm these inferred relationships.

Discussion

The study employs an AI-based computational approach to identify genes associated with AD, ADHD, and head and neck cancer (HNC) from a pool of 210,741 genes. It reveals significant gene overlaps among these diseases, suggesting shared genetic factors. The analysis identifies 2,301 genes linked to anxiety, 1,199 to ADHD, and 6,629 to HNC, with statistically significant overlaps and high odds ratios, particularly between anxiety and ADHD. Protein-protein interaction (PPI) networks highlight core genes like IL-6 and SIRT1, indicating robust connectivity and potential shared pathways. Functional enrichment analysis underscores the involvement of synaptic, immune, and inflammatory processes. The study suggests complex genetic networks linking these conditions, with shared genes potentially contributing to co-occurrence or mutual risk factors.

Functional enrichment analysis underscores the involvement of synaptic, immune, and inflammatory processes. For instance, a study identified 181 out of 235 genes associated with ADHD that were enriched in 100 pathways, highlighting multiple associations with ADHD (17). Additionally, a genome-wide association study revealed shared genetic components between tinnitus and psychiatric disorders, such as bipolar disorder, suggesting common pathways (18). These findings suggest complex genetic networks linking these conditions, with shared genes potentially contributing to co-occurrence or mutual risk factors.

The current study identifies a significant overlap of 32 genes between AD and ADHD, with an odds ratio of 510.68, indicating a substantial genetic association. Previous studies have also suggested shared genetic factors, but the magnitude of overlap and specific genes involved may vary, with some research highlighting different sets of candidate genes or weaker associations. Conflicts may arise from variations in sample sizes, methodologies, and the specific populations studied, which can lead to differing conclusions about the extent and nature of the genetic links between these disorders. For instance, a study on Lebanese populations highlighted various factors associated with ADHD, such as maternal stress and familial history, analyzed using Fisher's exact test, but did not focus on genetic overlap with AD (19). Another study found a significant association between ADHD and psychiatric disorders in patients with epilepsy, again using Fisher's exact test, but did not explore genetic links with AD (20). In contrast, studies on AD have shown significant associations with other conditions, such as impulse control disorders in Parkinson's disease, using Fisher's exact test, but did not delve into genetic overlaps with ADHD (21).

The current study identifies 22 overlapping genes between AD and HNC, with a significant odds ratio of 37.14. This statistically significant genetic overlap suggests that, despite the distinct clinical presentations of psychiatric disorders and malignancies, shared biological pathways may underlie their co-occurrence. Prior research has shown that chronic psychological stress—a central feature of AD—can alter neuroendocrine function and modulate immune responses, thereby influencing cancer progression (22, 23). For example, stress-induced dysregulation of cortisol and catecholamine levels can activate inflammatory pathways that promote tumorigenesis. At the same time, other studies have reported distinct genetic mechanisms involved in the pathophysiology of AD and HNC, underscoring the complexity of these associations. These findings highlight the need for further research to elucidate the specific molecular and cellular mechanisms linking AD with HNC.

This finding also aligns with previous research that has linked anxiety not only to other neuropsychiatric conditions (24) and cognitive impairments (25) but also to adverse clinical features in cancer. In the context of HNC, several studies have reported that patients experiencing anxiety are more likely to report chronic pain after radiotherapy (26) and that higher anxiety levels are associated with socioeconomic deprivation, which may further influence treatment adherence and overall outcomes (27). The use of AI-based computational approaches in our study offers a novel perspective on these genetic overlaps, suggesting that the shared genetic factors may partially underlie these clinical associations. However, while our findings point to a statistically significant genetic link, the specific pathways—such as those mediating inflammatory responses or neuroendocrine dysregulation—remain to be fully delineated. Therefore, further investigation is warranted to clarify these mechanisms and to explore their implications for the treatment and management of both AD and HNC.

The identification of 15 overlapping genes between ADHD and HNC, with an odds ratio of 21.69, suggests a previously unexplored genetic link between these conditions. While prior research has examined their individual genetic and environmental factors, potential genetic intersections have received little attention. For example, some studies have primarily focused on associations with factors such as maternal anemia, stress, and familial history in ADHD (19), and genetic predispositions in HNC, such as the protective role of certain VEGF alleles (28). Our findings highlight the need for further investigation into shared biological pathways, which may provide new insights into the underlying mechanisms connecting neurodevelopmental and oncogenic processes.

AD and ADHD share several neurobiological pathways that contribute to their comorbidity, particularly those involving the serotonergic system, synaptic plasticity, and neuronal connectivity. Dysregulation of serotonergic signaling, crucial for mood regulation and cognitive functions, has been implicated in both disorders, with ADHD linked to alterations in circuits involving the Pet-1 transcription factor and Cadherin-13, affecting serotonin neuron migration and synaptic balance (29, 30). Similarly, AD benefit from treatments targeting serotonergic synapses, such as selective serotonin reuptake inhibitors, emphasizing the shared importance of this pathway (31). Beyond serotonin, both conditions exhibit disruptions in synaptic and dendritic processes. ADHD is associated with synaptic dysfunction and altered neurotransmitter release (32), while AD involve changes in synaptic plasticity and dendritic spine morphology, affecting emotional regulation and cognition (33). Additionally, disruptions in protein processing within the endoplasmic reticulum lumen may impair neurotransmitter release, further linking the two disorders through impaired synaptic transmission. These shared pathways suggest that neurodevelopmental and emotional dysregulations in ADHD may predispose individuals to AD, with a common neurobiological substrate underlying their comorbidity. Understanding these mechanisms could guide the development of targeted therapies addressing the overlapping neurobiological features of AD and ADHD.

AD may influence the development and progression of HNC through several biological mechanisms, including immune dysregulation and the promotion of a pro-inflammatory state. Chronic anxiety is associated with altered cytokine profiles—such as elevated levels of interleukin-6 and tumor necrosis factor-α—which can contribute to tumorigenesis (34, 35). In addition, stress-related activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) can modify the expression of cytokine–cytokine receptor interaction pathways in key brain regions like the amygdala, further linking neuroendocrine changes to inflammatory responses (36). These observations suggest that part of the genetic overlap observed between AD and HNC may be explained by shared molecular pathways that mediate neuroendocrine and immune responses under conditions of chronic psychological stress.

In the context of HNC, the inflammatory response is a critical driver of tumor progression by regulating angiogenesis, cell proliferation, and metastasis (37). Stress-induced hormonal alterations can modify the tumor microenvironment by enhancing the production of pro-inflammatory cytokines and growth factors, thereby creating conditions that favor tumor growth and dissemination (38). Together, these findings underscore the complex interplay between psychological stress, inflammation, and cancer biology, and highlight the need for further investigation into the specific molecular mechanisms linking AD to HNC.

Chronic inflammation in HNC can intensify anxiety symptoms by disrupting neural circuits that regulate stress responses, potentially creating a feedback loop that worsens clinical outcomes. For example, inflammatory cytokines may alter neurotransmitter systems involved in mood regulation, thereby increasing anxiety levels in HNC patients. Targeting these inflammatory pathways could offer a novel therapeutic strategy to alleviate anxiety and improve quality of life in this population (9). To note, this interplay may be influenced by behavioral and environmental factors, such as smoking or stress-related immune suppression, which can modulate inflammatory pathways and exacerbate both anxiety and cancer progression (39).

Emerging evidence suggests that transcriptional dysregulation may underlie both oncogenic processes in HNC and aspects of neurodevelopment relevant to ADHD. For instance, the MYC oncogene—frequently amplified in HNC (40)—is well known for

its role in driving cell proliferation and tumor progression. Although the direct contribution of MYC to ADHD pathophysiology remains to be fully elucidated, recent studies indicate that aberrant MYC-related transcriptional programs can impact neurodevelopment and may be linked to behavioral phenotypes observed in ADHD (41). Additionally, research has identified various genes associated with ADHD, such as Cadherin-13 (CDH13), which impacts synaptic function and is implicated in neurodevelopmental processes relevant to ADHD (42). Similarly, studies have shown that the MYC gene is frequently amplified in head and neck squamous cell carcinoma (HNSCC), contributing to tumor progression (43). These findings suggest that shared genetic factors may underlie the co-occurrence of these conditions.

In addition to transcriptional regulators, the enzyme CYP2D6 plays a critical role in the metabolism of many psychostimulant and nonstimulant medications used in ADHD treatment. Polymorphisms in CYP2D6 can lead to considerable variability in drug metabolism, as evidenced by its established impact on the pharmacokinetics of atomoxetine (44). While CYP2D6 genetic variations have been linked to altered susceptibility to HNC (45), it is important to note that there is no direct evidence suggesting a shared mechanism that would cause ADHD itself. The dual relevance of CYP2D6 in ADHD medication efficacy and cancer risk reflects complex interactions between genetic factors and environmental exposures but does not imply a single, common mechanism underlying the development of ADHD.

Advantage

The study employs an AI-based computational approach to identify disease-gene associations, which allows for the analysis of a vast number of genes (19,924) and the identification of significant overlaps among AD, ADHD, and HNC. The use of Fisher's exact test and odds ratios provides robust statistical validation of these overlaps, highlighting shared genetic factors across these conditions. The integration of PPI network analysis further elucidates the connectivity and functional roles of key genes, offering insights into potential shared pathways and molecular mechanisms underlying these diseases.

Limitation

This study examines genetic overlaps between psychiatric disorders and HNC, highlighting the distinct diagnostic criteria and biological mechanisms of these conditions. While data mining offers valuable insights, it is important to acknowledge the potential pitfalls of analyzing large, non-specific datasets. Without rigorous data curation and validation, the risk of misinterpretation increases, which could lead to false associations. As noted in a review on clinical data mining, "the exotic predictions of data mining are difficult to apply directly in local medical institutions" (46).

Additionally, the study's reliance on existing literature for gene-disease associations introduces potential bias, as it depends on the availability and quality of prior research. The focus on statistical significance may overlook biologically relevant genes with smaller effect sizes. Furthermore, the absence of experimental validation of the identified gene associations limits the direct applicability of these findings to clinical settings.

While shared genetic pathways have been identified between psychiatric disorders and HNC, the biological significance of these overlaps remains to be fully elucidated. The complexity of gene expression and regulation in both conditions suggests that these shared pathways may operate differently across tissues and contexts. Gene-environment interactions and behavioral factors could further influence these findings, highlighting the need for a comprehensive understanding of how environmental factors may shape the genetic underpinnings of these conditions.

Therefore, further research is imperative to understand the functional implications of these genetic overlaps and their potential impact on disease pathogenesis and treatment strategies. In conclusion, while the identification of common genetic factors between psychiatric disorders and HNC is a promising avenue for research, it is crucial to approach these findings with a critical perspective. Recognizing the diagnostic differences and the limitations inherent in data mining methodologies will ensure that future studies yield meaningful and clinically relevant insights.

Conclusion

This study uncovers a complex and interconnected genetic network among AD, ADHD, and HNC, highlighting shared pathways, unique mechanisms, and critical genes. These findings provide valuable insights into the genetic underpinnings of these conditions and open potential avenues for therapeutic exploration. Furthermore, understanding these genetic connections could guide future research into targeted interventions and inform clinical practice by identifying new biomarkers and therapeutic targets for these disorders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. HL: Writing – original draft, Writing – review & editing. ZZ: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. JF: Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

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All data to generate Figures 1-4 are generated by analyzing the raw data (see Supplementary Materia rawData) using the Python package developed by the authors (see Supplementary Material Python package).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2025.1552815/full#supplementary-material

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Environmental enrichment reverses prenatal ethanol exposure-induced attention-deficits in rats

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Introduction: There is a high prevalence of fetal alcohol spectrum disorders (FASD) in the US and the world, which is caused by prenatal ethanol exposure (PE). Most individuals with FASD show attention deficit hyperactivity disorder (ADHD) -like symptoms. Using a rat model of FASD, we have successfully demonstrated that moderate and heavy PE leads to persistent attention deficits, including augmented impulsivity and impaired sustained attention. Anxiety is another primary symptom of FASD. Anxiety and ADHD are closely associated in clinical studies. However, the causal relationship between anxiety and ADHD is not clear. In the present study, we used the strategy of environmental enrichment to reduce anxiety after PE in rats and investigated if attention deficits could be ameliorated.

Methods: A 2nd-trimester binge-drinking pattern of heavy PE was used. Environmental enrichment consisted of neonatal handling and postweaning complex housing. Action impulsivity and sustained attention were tested in adult males and females using the 2-choice reaction time task.

Results: The results show environmental enrichment effectively ameliorated action impulsivity and improved sustained attention in male and female PE rats. Action impulsivity was also improved in control rats with environmental enrichment. In addition, environmental enrichment improved the efficiency of obtaining rewards in male and female control but not PE rats. Environmental enrichment altered the pattern of reaction time components, favoring slower movement initiation but faster movement.

Discussion: These observations support that environmental enrichment could be an effective strategy in ameliorating ADHD-like symptoms in FASD. The reduced anxiety could contribute to such an effect.

KEYWORDS

attention deficit-hyperactivity disorder, anxiety, fetal alcohol spectrum disorders, impulsivity, sustained attention

Introduction

As one of the most common developmental disorders, attention-deficit/hyperactivity disorder (ADHD) is associated with a variety of genetic and environmental risk factors. Recent studies elucidate that genetic risk factors, prenatal stress factors and/or postnatal adverse environment all contribute to ADHD (1, 2). Results from preclinical and clinical studies have shown prenatal ethanol exposure (PE) during pregnancy could lead to ADHD-like symptoms (3–8). Prenatal ethanol exposure leads to fetal alcohol spectrum disorders (FASD), which has a high prevalence (2-5%) in the US (9, 10). The incidence of ADHD in individuals diagnosed with fetal alcohol spectrum disorders (FASD) can be as high as 49 – 94% (4, 6, 8). The estimated prevalence of ADHD in the general population is around 5% (11, 12). Therefore, prenatal ethanol exposure could represent a key environmental risk factor for ADHD.

When compared with ADHD cases without FASD, attention deficits in individuals with FASD could differ in severity and/or symptoms (4, 13), have an earlier onset, and have differential responses to stimulant treatment (8, 14). On the other hand, our previous preclinical study demonstrates that chronic psychostimulant treatment used in treating ADHD is effective in normalizing altered dopamine neuron activities, which play a critical role in mediating impulsivity and attention behaviors (15), supporting the efficacy of psychostimulant treatment in attention deficits in FASD.

At the present time, there are few treatment options available using medication for FASD, (14, 16). A variety of cognitive/behavioral deficits could be ameliorated when children with FASD are raised in favorable environments (17), which is consistent with animal studies showing the efficacy of environmental enrichment in alleviating PE-induced behavioral deficits (18–21)and PE-induced neuroinflammation (22). To maximize the effectiveness of environmental enrichment intervention in rats, we have combined neonatal handling and post-weaning complex housing to provide persistent enrichment throughout development (23). This approach has been shown to ameliorate multiple behavioral deficits after PE, including the increased drug addiction risk (20), impaired habituation in sensory processing (21), and augmented anxiety (24). Among all these beneficial effects of environmental enrichment, reduced anxiety could be critical for attention deficits. In clinical studies, attention deficits and anxiety are closely associated (25), but the causal relationship between these two behavioral phenotypes is not clear. Our previous preclinical study demonstrates that increasing trait anxiety exacerbates attention deficits (26), supporting that increased anxiety contributes to attention deficits. Because environmental enrichment can reduce anxiety (20, 27), we anticipate that environmental enrichment could ameliorate ADHD-like symptoms by reducing anxiety. Such a result would further verify that anxiety modulates the severity of attention deficits.

There are two major symptoms of ADHD: inattention and hyperactivity/impulsivity. Subtypes of ADHD could be predominantly inattentive, predominantly hyperactive, or showing combined presentation (DSM-5, 28). The two symptoms could be mimicked in rodent models, typically by tasks including multiple choices and requiring short reaction time (29). In our laboratory, we utilize a 2-choice reaction time (2-CRT) task with variable, challenging hold time requirements, which meets the above criteria. Using this 2-CRT task, we have demonstrated ADHD-like symptoms in rats with heavy and moderate PE (5, 7) as well as rats with increased trait anxiety (26). The training period for the 2-CRT task is relatively brief, which does not confound attention deficit symptoms. As such, we employed the 2-CRT task in the present study to investigate if environmental enrichment affects attention deficits in rats with heavy PE.

Materials and methods

Animal breeding and prenatal ethanol exposure

The breeding procedure has been described in detail previously (30). We bred rats in-house to avoid transportation stress during pregnancy. Male Sprague-Dawley breeders and virgin females (Envigo, Indianapolis, IN, USA) were housed in pairs in wire-bottom breeding cages in a 12 h/12 h light/dark cycle room. Gestational day (GD) 0 was designated when copulatory vaginal plugs were found. Pregnant dams were randomly assigned to the control or PE group and singly housed in standard plastic cages.

A second-trimester binge drinking pattern model of PE is used, which is comparable to heavy alcohol exposure in humans (31, 32). From GD 8 – 20, pregnant dams were treated via intragastric gavage twice (5 – 6 h apart) every weekday during the light phase with 3 g/kg ethanol (15% w/v) or isocaloric vehicle (22.5% w/v sucrose). The total dose of ethanol is 6 g/kg/day. A single dose of 4 g/kg ethanol was given on each weekend day. The blood alcohol level 1 hour after the 2nd gavage was 116.8 ± 10.5 mg/dl (30). We chose the gavage procedure to control ethanol dosing precisely. We have shown that stress caused by our gavage procedure is minimal (33). Controls were pair-fed with PE rats to equalize daily nutrient intake during ethanol administration. To prevent possible thiamine deficiency during ethanol exposure or by the pair-feeding procedure, dams received vitamin B injections (8 mg/kg; i.m.; twice a week) during ethanol administration (34, 35).

On postnatal day 1, each litter was randomly culled to 10 pups with 5 males and 5 females. Cross-fostering was performed on PD 1 to minimize the possible alcohol withdrawal effects on maternal behavior, which might impact the rearing of the pups. Ethanol-exposed pups were transferred to foster dams who received no treatment except daily weighing and gave birth 2 days earlier. Control litters were cross fostered by switching the control dams. This way, all litters were cross-fostered. In humans, fostering could have long-lasting effects on mental health in some individuals (36). Results from preclinical studies suggest that cross-fostering could reduce anxiety and PE effects (37, 38). In our lab, we do not observe any difference in body weight at weaning between fostered and non-

fostered pups in either control or PE groups (unpublished data). On PD 21, litters were weaned, and same-sex rats were housed in pairs in standard cages. One hundred fifty-five rats from 42 litters were used in the 2-CRT test (24 control males in standard condition/8 litters, 24 PE males in standard condition/9 litters, 16 control females in standard condition/6 litters, & 15 PE females in standard condition/6 litters, 20 control males in the enriched condition/7 litters, 20 PE males in enriched condition/8 litters, 18 control females in enriched condition/5 litters, & 18 PE females in enriched condition/5 litters). In 6 control litters and 6 PE litters, both sexes were used. All the animal-related procedures followed the guidelines of the National Institutes of Health regarding laboratory animal care and use and were approved by the Institutional Animal Care and Use Committee of the University at Buffalo.

Rearing conditions

Rats were reared in the standard housing condition or enriched condition. Before weaning, pups reared in the standard condition were not disturbed except for weekly cage changes. All pups reared in the enriched condition underwent neonatal handling consisting of a brief (15 min/day) maternal separation and handling of each pup from postnatal day 2 - 20. The goal was to provide enrichment by enhancing maternal behavior when pups were reunited with the dam (20, 21, 39–41). After weaning (postnatal day 21), rats in the standard housing condition were housed in pairs in standard plastic cages. Rats in the enriched condition were group housed (10 – 20/cage) with the same sex and prenatal treatment in large 4-level wire cages (L × W × H: 92 × 64 × 160 cm; Model: CG-71111; Petco, San Diego, CA, USA). Each cage contained 30 pet toys, ropes, hideouts, etc./cage (Petco), which were moved or changed every weekday to create novelty (see more details in (20). The rearing conditions were maintained until the completion of the study.

Apparatus

Sixteen locally made operant chambers were used, which were described in detail previously (3, 42). In the right wall panel, there were two water dispensers, each inside a snout poke hole on either side of a centrally located snout-poke hole. There was a stimulus light above each of the water dispensers. Snout pokes into the snout poke holes were monitored with infrared sensors. A drop of water (0.03 ml/drop), as a reinforcer was delivered into dispensers by a syringe pump (PHM-100; MED Associates, Fairfax, VT, USA). All chambers were controlled by MED Associates interface and software.

2-CRT task

A modified 2-CRT task was used. Six-week-old rats were water-restricted (water available for 0.5 h/day), so water served as a reinforcer. The rats underwent *18* daily 30 min training sessions and 3 additional 30 min testing sessions during the dark phase. A trial was initiated by the rat inserting its snout into the center hole. The rat was required to hold the snout in the center hole for a predetermined period (hold time) until one of the stimulus lights turned on. The hold time was cumulative for the duration each time the rat put the snout in; no matter how many times the rat pulled out of the center hole. When the hold time was up, either the left or right stimulus light was turned on. The rat would obtain the water reward only when a correct trial was made - enter into the poke hole/water dispenser under the lit stimulus light - in a timely manner. The time elapsed between snout withdrawal from the center hole and entering the water dispenser was defined as total RT, which consisted of initiation time - the time between the stimulus light onset and snout withdrawal from the center hole - and movement time - the time between snout withdrawal from the center hole and entering the water dispenser. An incorrect trial (entering the water dispenser not associated with the lit stimulus light) would terminate the trial immediately, with no water delivery. An extremely slow response (i.e., when RT > maximal trial duration, which was 2 s in the final testing sessions) was considered an omission, leading to no water reward. Choice trials consisted of correct trials, incorrect trials, and omissions.

Forced trials (training trials) were also programmed to avoid spontaneous alteration (43) and facilitate correct responses. After an incorrect trial, a forced trial took place. The trial with the same stimulus light was repeated until the rat chose the right water dispenser. This last correct trial was reinforced but still counted as a forced trial.

Rats were also trained to respond in a timely way. To that end, variable criterion RTs (maximal RT allowed) for reinforcement were used (3). In each choice trial, if the actual RT > the set criterion RT, no reward was given. If 2 correct responses were made in a row under a specific RT, the criterion RT would decrease for the subsequent trial. If 1 incorrect or slow response (without reinforcement) occurred, the criterion RT would increase for the subsequent trial. The training could accommodate both fast- and slow-responders. The decrement/increment schedule (in seconds) was 27.00, 10.00, 5.00, 2.50, 1.00, 0.89, 0.79, 0.71, 0.63, 0.56, 0.50, 0.45, 0.40, 0.35, 0.32, 0.28, 0.25, 0.22, 0.20, 0.18, 0.16, 0.14, 0.13, 0.12, 0.11, & 0.01. At the beginning of a session, the criterion RT was set at 0.71 s. Under the adjustments of criterion RTs, the goal was for rats to obtain 60% to 75% reinforcements for correct trials.

The rats' behavior was trained in stages. In sessions 1-2, water was also available in the center hole contingent upon snout pokes. For sessions 1-8, the stimulus light would turn on only one side for all trials. From session 9, the stimulus light would illuminate on the left or the right side randomly. The hold time also increased gradually and transitioned from a fixed length to a variable length with each session. In the final 3 testing sessions, 20 different hold times were used with the mean hold time = 6 s (in seconds: 0.0798, 0.246, 0.4212, 0.6066, 0.8034, 1.0134, 1.2414, 1.4814, 1.7466, 2.031, 2.3466, 2.697, 3.0918, 3.5436, 4.071, 4.7052, 5.514, 6.5712, 8.22, & 12.5868). In addition, the duration of stimulus light in each trial decreased from 3600 s to 1 s. The maximal RT allowed decreased from 3600 s to 2 s.

Dependent variables

To evaluate overall performance and possible deficits in operant learning, the number of choice trials, forced trials, and reinforced trials were analyzed (Figure 1). Premature responses, including premature initiations and false alarms, were used to assess action impulsivity. Premature initiations occurred when rats repeatedly withdrew the snout from the center hole and reinserted it before the stimulus light turned on. False alarms occurred when rats entered the water dispenser before the stimulus light turned on. Lapses of attention lead to wrong or slow responses, accessed by % incorrect responses over choice trials and % omissions over choice trials. In addition, infrequent long RTs were measured by the skewness of the RT distribution because they lead to the positively skewed distribution of RTs. Infrequent long RTs are also observed in individuals with ADHD (44). In the present study, we used an *adjusted Fisher-Pearson standardized moment* coefficient for skewness, as computed by the following formula (45):

$$skewness = n\frac{\sum (X_i - Mean_i)^3}{(n-1)(n-2)*\sigma^3}$$

where σ was the standard deviation, and n was the number of trials (5, 7).

Data analysis

All the analyses were based on the 3 final testing sessions. Rats were removed from data analysis if the average number of trials/sessions was consistently< 75 for males or< 60 for females. The criterion was lower for females because female rats had lower body weights than males (by 20 – 35%), and thus, they consumed less water.

Two-way or three-way mixed-design or non-mixed design analyses of variances (ANOVA) were used. We applied statistical methods to control for possible litter effects when more than 2 littermates were used in the same sex per group. Litter as a nested factor was used in ANOVA to examine possible litter effects. (21, 41, 46). If a significant litter effect was found, then results from the ANOVA with litter as a nested factor were reported. If the litter effect was not significant, then results from ANOVAs without using litter as a nested factor were reported. Pairwise comparisons were performed using planned comparisons after ANOVA. Statistica 7 (Tibco Software Inc., Palo Alto, CA, USA) software was used for data processing and analysis. The significance level was set at 0.05. Data are presented as Mean ± SEM in the text and figures unless specified otherwise.

Results

Birth outcome after PE

Twenty control (11 standard and 9 enriched) and 22 PE (13 standard and 9 enriched) dams were used in this study. Prenatal ethanol exposure did not lead to a reduction in litter size or number of male pups (Table 1). However, PE led to fewer female pups/litter

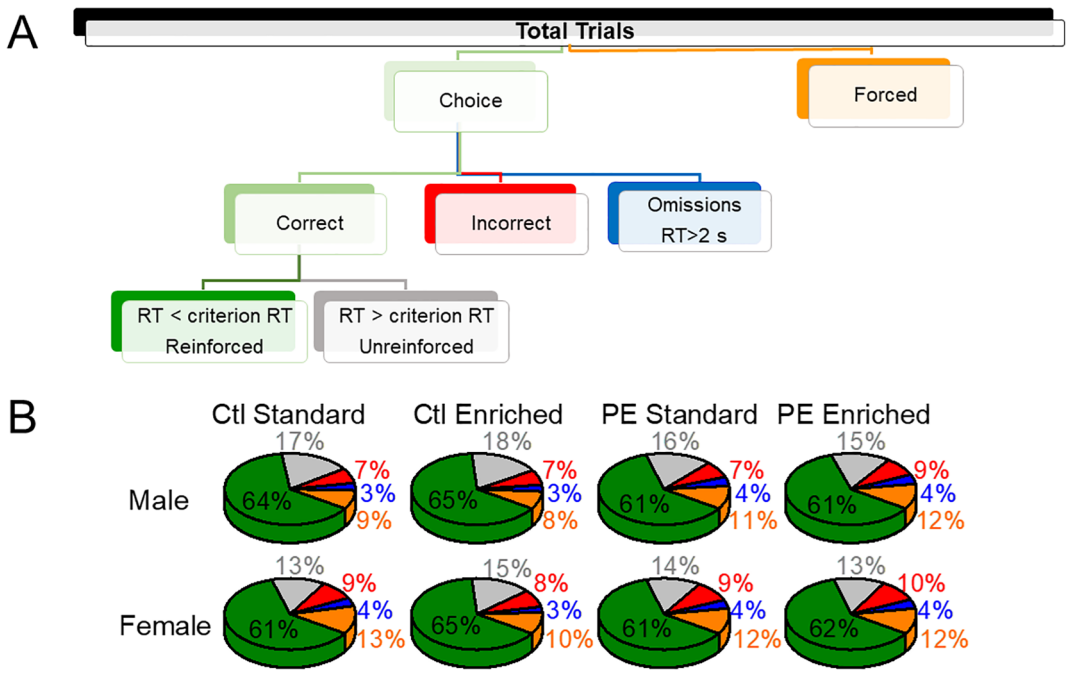

FIGURE 1
The trial composition of the 2-choice reaction time (2-CRT) task. The upper panel depicts the composition of all trials **(A)**. The lower panel depicts the portions of each trial type **(B)**. Prenatal treatment (control; PE), postnatal rearing conditions (standard; environmental enrichment), or sex (male; female) did not impact the proportions of different trial types.

(Table 1). In addition, the greater body weight of PD 1 was observed in males compared to females regardless of prenatal treatment (t86 = 2.48, p<0.05; (Table 1)The results showed that PE did not lead to major teratogenic effects.

Effects of PE, sex, and enriched environment on trial performance

The compositions of trials are depicted in Figure 1. We examined the effects of PE and rearing conditions on trial composition with a focus on choice trials, forced trials, and reinforced trials. Males performed more trials than females, which is consistent with previous studies (5). In addition, male and female control rats reared in the enriched condition performed more choice trials than rats in the standard condition (Figure 2A). Such an effect was not observed in PE rats reared in the enriched condition (three-way way ANOVA with litter as the nested factor, prenatal treatment, postnatal rearing condition, sex; litter effect: F46,101 = 3.99, P<0.01; main effect of sex: F1, 101 = 19.43, P<0.01; interaction effect of prenatal treatment and rearing conditions F1,101 = 17.41, P<0.01; planned comparison: male or female: control stand *vs* control enriched, P<0.001, Figure 2A). The effects were caused by control rats in the enriched condition escalated more in their choice trials soon after the session started and sustained such escalation for a long duration. This effect was more prominent in males (Figure 2).

We also examined the proportion of forced trials (% forced trials) as an index of possible learning deficits and found male PE rats showed greater % forced trials than controls in both standard and enriched conditions, suggesting rigidity or inability to switch to the correct choice (three-way ANOVA with litter as the nested factor, litter effect, F46,101 = 1.59, P<0.05; interaction effect of prenatal treatment and sex, F1,101 = 6.16, P<0.05; planned comparison: male: control *vs* PE, P<0.05, Figure 2). To understand the efficiency of getting rewards across groups, we analyzed the proportion of (%) reinforced trials and found no group differences. However, male and female control rats reared in the enriched condition obtained more rewards than control rats reared in the standard condition. This effect was not observed in PE rats. In addition, male rats performed more reinforced trials than females (three-way ANOVA with litter as the nested factor, litter effect, 46,101 = 4.00, P<0.001, main effect of sex, F1, 101 = 18.49, P<0.001, interaction effect of prenatal treatment and rearing condition, F1,101 = 17.40, P<0.001, planned comparison: male control: standard *vs* enriched conditions, P<0.001, female control: standard *vs* enriched condition, P<0.001, Figure 2). The increased number of reinforced trials in control rats reared in the enriched condition was due to an overall increase in the number of total choice trials.

Environmental enrichment altered the pattern of reaction time by increasing initiation time and decreasing movement time

We analyzed three RT parameters: total RT, initiation time, and movement time to understand the speed of responding. Medians instead of means were used for these RT parameters due to their skewed distributions in each rat. The RT parameters were not influenced by hold time, which was not used as an independent variable. We did not find any group differences in total RT. Interestingly, we found the initiation time was increased in male and female control and PE rats reared in the enriched condition. In addition, initiation time was decreased in female rats compared to males (three-way ANOVA, prenatal treatment, rearing condition, sex; main effect of prenatal treatment, F1,147 = 3.93, P<0.05; main effect of rearing condition, F1,147 = 142.54, P<0.01, main effect of sex, F1,147 = 5.70, P<0.05; Figure 3). In contrast, movement time was decreased in both male and female control and PE rats reared in the enriched condition (three-way ANOVA with litter as the nested factor, litter effect, F46, 101 = 2.20, P<0.001, main effect of postnatal treatment, F1,101 = 67.62, P<0.001, Figure 3).

Environment enrichment decreased action impulsivity in both control and PE rats

Action impulsivity was evaluated by premature initiations and false alarms. In previous studies, we observed that both parameters were exacerbated with increased cognitive load (i.e. increased hold

TABLE 1 Birth outcome of control and prenatal ethanol-exposed litters.

	Control: 20 litters 11 Std & 9 Enriched (mean ± SEM)	PE: 22 litters 13 Std & 9 Enriched (mean ± SEM)	*P*-Value
Litter Size	13.90 ± 0.49	13.05 ± 0.39	0.18
Number of Male Pups	6.50 ± 0.44	7.05 ± 0.39	0.38
Number of Female Pups	7.40 ± 0.49	6.00 ± 0.37	<0.05
Pup weight on Postnatal Day 1			
Average Weight (g)	6.50 ± 0.14	6.63 ± 0.09	0.45
Average Male Weight (g)	6.68 ± 0.15	6.76 ± 0.09	0.66
Average Female Weight (g)	6.34 ± 0.14	6.44 ± 0.12	0.56

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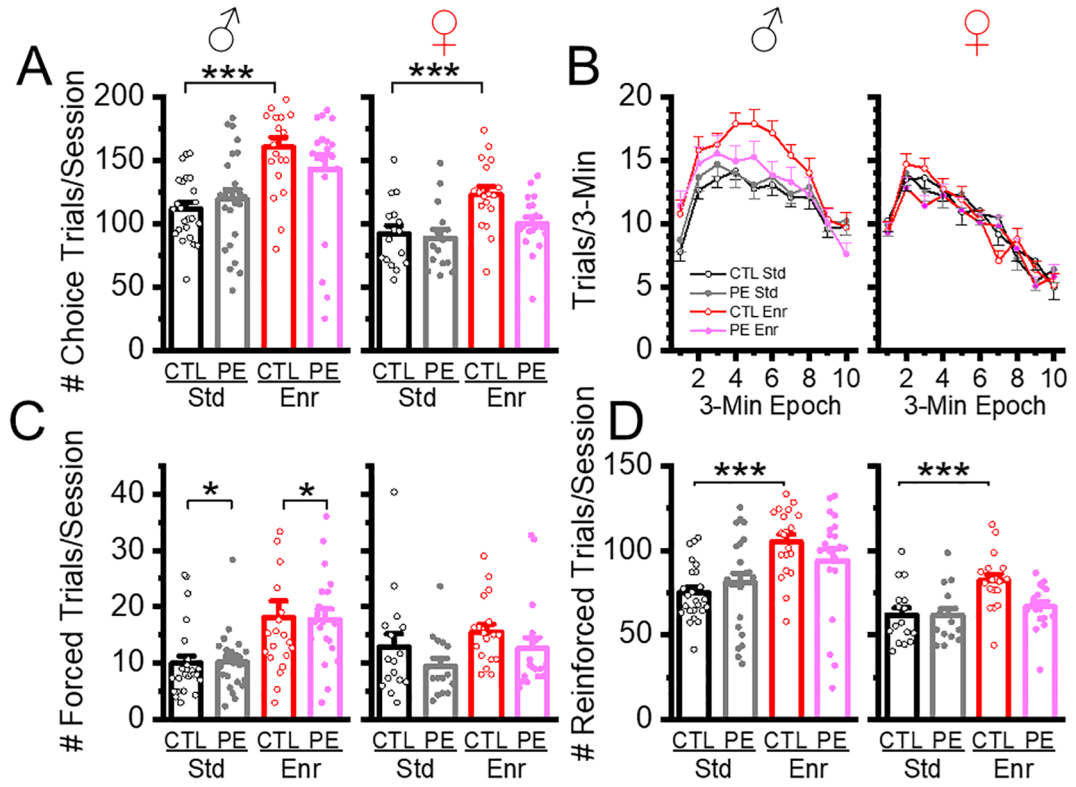

FIGURE 2
Environmental enrichment increased the number of trials in control and PE rats of both sexes. Rearing in the enriched environment increased the number of choice trials/sessions in control rats of both sexes but not in PE rats **(A)**. Such an effect was more prominent in males, shown as a persistent escalation of trials soon after the session started **(B)**. Environmental enrichment also increased the number of forced trials in male control and PE rats **(C)** and led to more reinforced trials in control, but not PE rats of both sexes **(D)**. *P< 0.05, ***P< 0.001.

time). The analyses were performed by dichotomizing the trials with hold times<4 s and > 4 s (5, 7). In addition, these events rarely occur when the hold time is<= 1 s. Therefore, in the present study, data analyses were performed in trials with a hold time >1 &< 4 s and > 4 s, corresponding to low and high cognitive load, respectively. To simplify the analyses and avoid high levels of factorial ANOVA, we first compared the control and PE rats reared in the standard condition, followed by analyzing the effects of environmental enrichment. We also analyzed the time for completing each trial (trial completion time) to understand how action impulsivity could impact the efficiency of completing each trial. We found premature initiations, false alarms, and trial completion time increased as hold time increased in all groups of rats. Therefore, we did not report the main effect of hold time in ANOVAs.

In trials with hold time< 4, increased premature initiation was found in PE rats in the standard condition. Sex effect was also observed. Females showed more premature initiation than males (three-way mixed-design ANOVA with litter as a nested factor, prenatal treatment, sex, hold time; litter effect, $F_{50,101} = 1.00$, $P<0.01$, interaction effect of prenatal treatment and hold time, $F_{8,808} = 2.96$, $P<0.01$, interaction effect of sex and hold time, $F_{8,808} = 3.52$, $P<0.05$, planned comparison: female control *vs* PE, $P = 0.06$. Figure 4). In trials with hold time > 4 s, premature initiations were increased in PE rats reared in the standard condition. Female rats also showed more premature initiation than male rats (three-way mixed-design ANOVA with litter as the nested factor: prenatal treatment, sex, hold time; litter effect $F_{50,101} = 2.07$, $P<0.01$; main effect of sex, $F_{1,101} = 5.05$, $P< 0.05$; interaction effect of prenatal treatment and hold time, $F_{5, 505} = 6.20$, $P< 0.001$; planned comparison: females: control *vs* PE, $P<0.01$, Figure 4).

We analyzed the effect of the enriched condition on premature initiation. We first examined the effect in trials with hold time< 4 s and found rearing in the enriched condition decreased premature initiations in both control and PE rats. Female rats had more premature initiations than males (in control rats: three-way mixed-design ANOVA, rearing condition, sex, hold time; interaction effect of postnatal treatment, sex, and hold time, $F_{8,592} = 2.32$, $P<0.05$; planned comparison: male control: standard *vs* enriched: $P = 0.09$, females control: standard *vs* enriched, $P< 0.01$; in PE rats: three-way mixed ANOVA with litter as a nested factor: rearing condition, sex, hold time; litter effect, $F_{24,49} = 2.04$, $P<0.05$, interaction effect of hold time and postnatal treatment, $F_{8,392} = 9.92$, $P< 0.001$, interaction effect of hold time and sex, $F_{8,392} = 3.79$, $P< 0.001$, planned comparison: male PE: standard *vs* enriched, $P<0.001$, female PE: standard *vs* enriched, $P< 0.05$, Figure 4). We next examine the enrichment effect in trials with hold time > 4 s. Rearing in the enrichment condition decreased premature initiation in control (three-way mixed

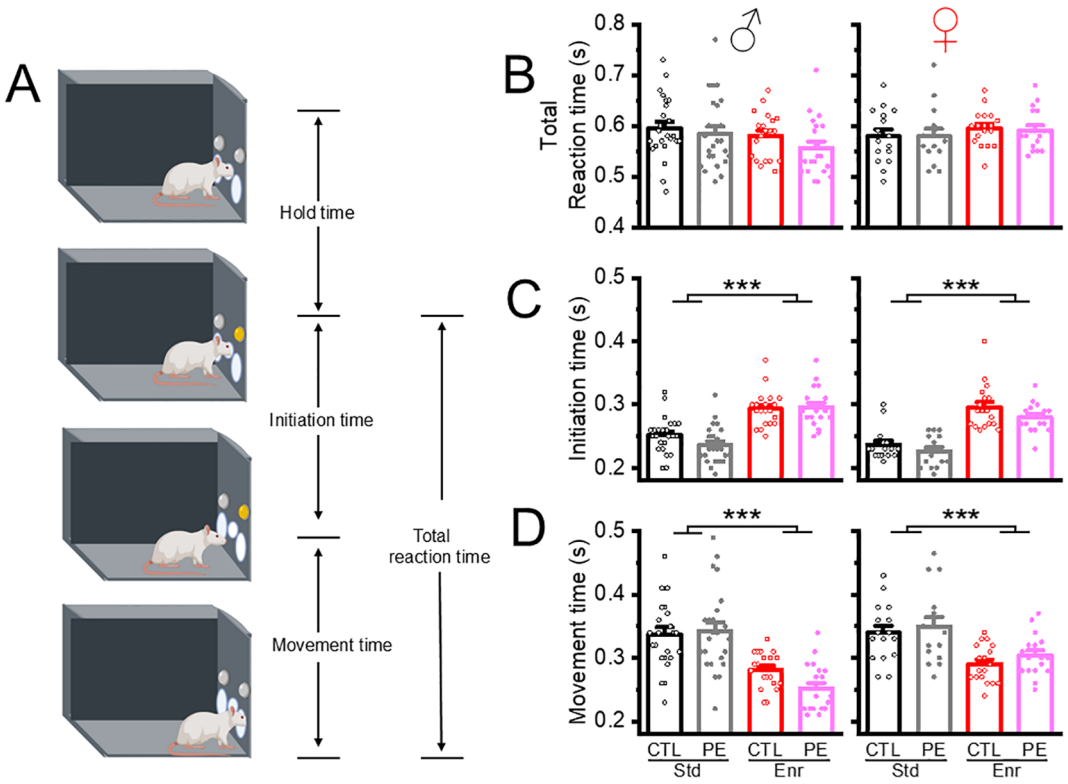

FIGURE 3
Environmental enrichment altered the reaction time (RT) pattern by increasing initiation time and decreasing movement time. The reaction time consists of two components: initiation time and movement time **(A)**. There were no group differences in total reaction time **(B)**. The initiation time was increased while the movement time was decreased in control and PE rats of both sexes reared in the enriched environment **(C, D)**. *** P< 0.001.

ANOVA, rearing condition, sex, hold time; interaction effect of postnatal treatment and hold time, F5, 370 = 6.23, P< 0.001; plan comparison: males control: standard *vs* enriched condition, P<0.05; female control: standard *vs* enriched condition, P< 0.01, Figure 4) and PE rats (three-way mixed ANOVA with litter as a nested factor, rearing condition, sex, hold time, litter effect, F24,49 = 2.04, P<0.05, interaction effect of postnatal treatment, sex and hold time, F5, 245 = 5.77, P< 0.001; plan comparison: males control: standard *vs* enriched P<0.001; female control: standard *vs* enriched, P=0.07 of both sexes, Figure 4).

We next analyzed false alarms, which took place less frequently than premature initiation. In the standard rearing condition, no PE effects were found when hold time was either< 4 s or > 4 s. The only effect found was increased false alarms in female PE rats compared to male PE rats (three-way mixed ANOVA, prenatal treatment, sex, hold time, hold time< 4 s: interaction effect of sex and hold time, F5, 250 = 2.89, P< 0.05; plan comparison: PE: male *vs* female: P<0.01; hold time > 4 s: interaction effect of sex and hold time, 5,375 = 5.16, P<0.001; planned comparison: PE: male *vs* female: P<0.05, Figure 5). We next examined the effect of the enriched condition. In control rats, in trials with hold time< 4 s, we did not find an enrichment effect. Only sex effect was found (Three-way ANOVA, postnatal treatment, sex, hold time, interaction effect of sex and hold time, F8,592 = 2.16, P<0.05, Figure 5) In trials with hold time > 4 s, we found false alarms were reduced in the enriched condition in females (Three-way ANOVA, postnatal treatment, sex, hold time; interaction effect of postnatal treatment, sex, and hold time, F5,260 = 2.45, P<0.05; planned comparison: female: standard *vs* enriched, P=0.07, Figure 5). In PE rats, in trials with hold time< 4 s, we found enrichment increased the false alarms in females (Three-way ANOVA: postnatal condition, sex, hold time, interaction effect of postnatal conditions, sex and hold time, F8,392 = 3.01, P< 0.01, planned comparison; female standard *vs* enriched P<0.001, Figure 5). No group differences were found in PE rats with trial time > 4 s. Overall, no major PE or enrichment effects were found in FA.

Environment enrichment decreased trial completion time in both control and PE rats

Next, we analyzed the trial completion time. In the standard condition, we did not find any PE effects for hold time< 4 s or > 4 s. We did find female rats show longer trial completion time (Three-way ANOVA, prenatal treatment, sex, hold time; hold time<4: interaction effect of prenatal treatment, sex, and hold time, F8,600 = 3.46, P< 0.001, planned comparison, PE: male *vs* female, P=0.06; hold time > 4 s: interaction effect of prenatal treatment, sex, and hold time; F5,375 = 2.75, P<0.05; planned comparison: control: male *vs* female, P=0.06, PE: male *vs* female, P< 0.05, Figure 6). This

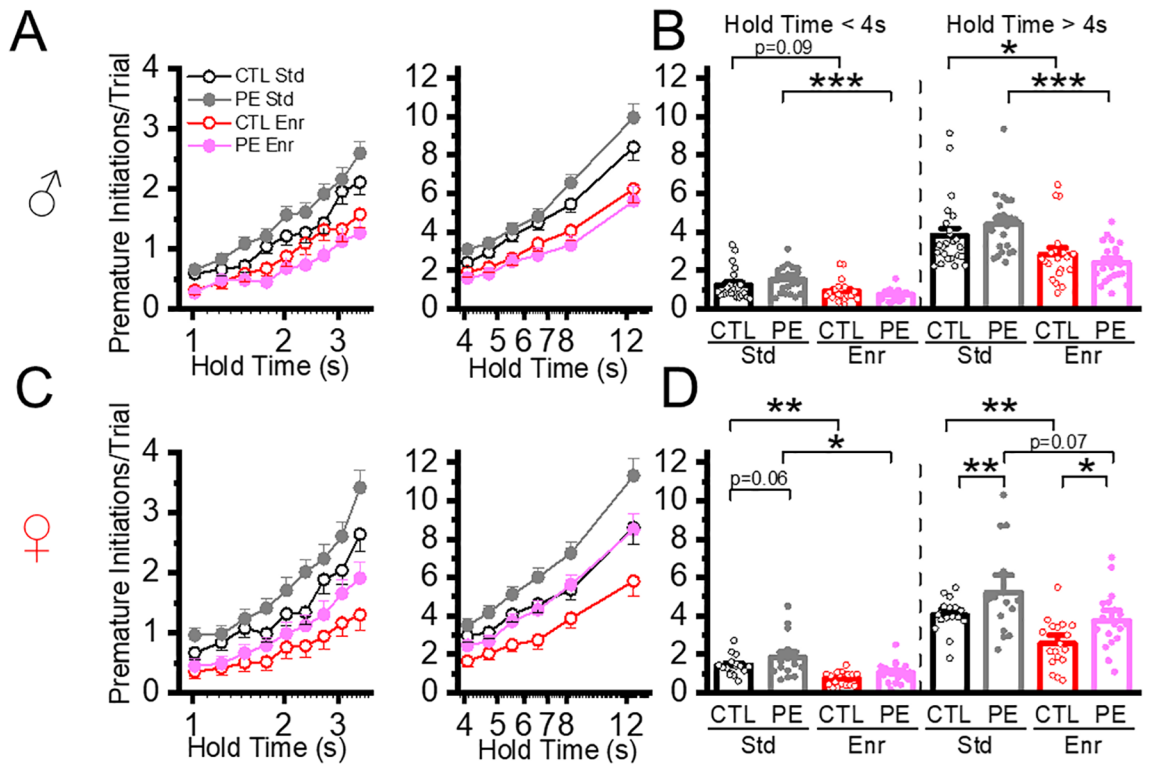

FIGURE 4
Environment enrichment decreased action impulsivity measured by premature initiations in both control and PE rats. Action impulsivity was measured by premature initiations/trial during hold time. The data was analyzed at low and high cognitive loads (hold time< 4 s and hold time > 4 s). Environmental enrichment reduced premature initiations/trials in male control and PE rats at both low and high cognitive loads **(A, B)**. Similar effects were observed in female rats **(C, D)**. Increased premature initiations/trial were also observed in female PE compared to controls but not male rats **(C, D)**. *P< 0.05, **P< 0.01, ***P< 0.001.

result revealed that longer trial completion time could be the reason for reduced trial number in females.

We next analyzed how rearing in the enriched condition could impact trial completion time. In control rats withhold time< 4 s, we did not observe an enrichment effect. Again, female rats had longer trial completion time (Three-way ANOVA with litter as the nested factor: prenatal treatment, sex, hold time; litter effect, $F_{22,52} = 2.16$, $P<0.05$; interaction effect of prenatal treatment, sex, and hold time, $F_{8,416} = 2.57$, $P<0.01$; planned comparison: control: male *vs* female, $P<0.05$; PE: male *vs* female: $P< 0.05$, Figure 6). In control rats withhold time > 4 s, we observed decreased trial completion time in the enriched condition in both sexes (three-way ANOVA, prenatal treatment, sex, hold time; main effect of sex, $F_{1,74} = 8.77$, $P<0.01$, interaction effect of rearing condition and hold time, $F_{5,370} = 13.20$, $P<0.001$; planned comparison: male: standard *vs* enriched, $P< 0.001$; female: standard *vs* enriched, $P<0.001$; standard: male *vs* female, $P=0.07$, enriched: male *vs* female, $P<0.05$, Figure 6). In PE rats withhold time< 4 s, we observed decreased trial completion time in males reared in the enriched condition (Three-way ANOVA with litter as a nested factor: prenatal treatment, sex, hold time; litter effect, $F_{20,49} = 1.80$, $P<0.05$; interaction effect of rearing condition, sex, and hold time, $F_{8,392} = 2.19$, $P<0.05$; plan comparison: male: standard *vs* enriched, $P<0.01$, Figure 6). In PE rats withhold time > 4 s, we observed decreased trial completion time in both male and female rats in the enriched condition (Three-way ANOVA with litter as a nested factor: prenatal treatment, sex, hold time; litter effect, $F_{20,49} = 2.34$, $P<0.01$; interaction effect of rearing condition, sex, and hold time, $F_{5,245} = 3.22$, $P<0.01$; plan comparison, male: standard *vs* enriched, $P< 0.001$, female: standard *vs* enriched, $P<0.001$, Figure 6). Taken together, the enrichment condition was effective in decreasing trial completion time in both sexes.

Environmental enrichment decreased lapses of attention in both control and PE rats

We have used % incorrect trials and % omissions over choice trials to evaluate lapses of attention (5, 7). In male but not female rats, we found an increase in % incorrect trials in PE rats compared to controls reared in either standard or enriched conditions. No effects of environmental enrichment were found (three-way ANOVA with litter as the nested factor: prenatal treatment, rearing condition, sex; litter effect, $F_{46,101} = 2.05$, $P<0.01$; interaction effect of prenatal treatment and sex $F_{1,101} = 4.81$, $P<0.05$; planned comparison: male standard condition: control *vs* PE, $P=0.08$; male enriched condition: control *vs* PE, $P=0.08$, Figure 7). We next examined % omissions. No PE or rearing condition effects were found in either male or female rats (Figure 7).

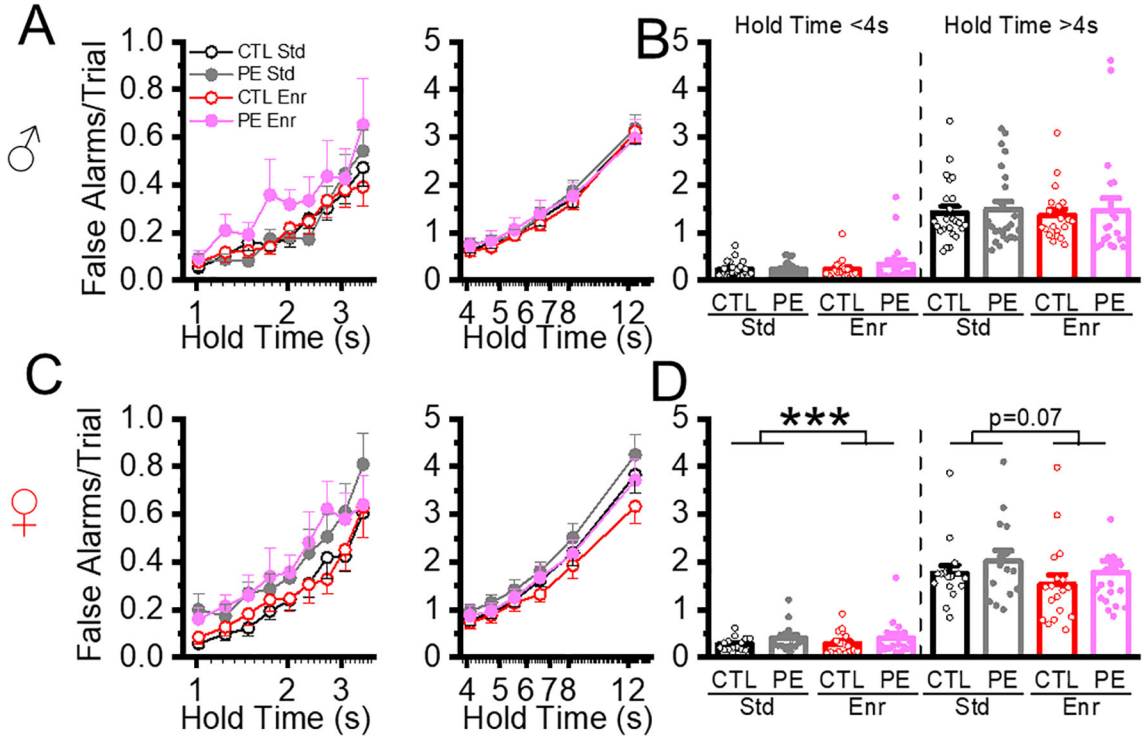

FIGURE 5
Environment enrichment did not alter action impulsivity measured by false alarms. Action impulsivity was measured by false alarms/trial at low and high cognitive load (hold time< 4 s and hold time > 4 s). We did not find a PE effect on rats reared in the standard condition **(A-D)**. Environmental enrichment reduced the false alarms/trial females with low and high cognitive load **(C, D)**. ***P< 0.001.

Lapse of attention can also be accessed by extremely large RTs, which causes positive skewness of the RT distribution (5, 7). We did not find hold times affected RTs. Therefore, all trials from each rat were used to calculate the skewness. The results showed that PE increased the skewness in females but not males in the standard condition. Enrichment decreased the skewness in both sexes (three-way ANOVA with litter as the nested factor: prenatal treatment, rearing condition, sex; litter effect, $F1,46 = 1.722$, $P< 0.05$; main effect of rearing condition $F1, 101 = 5.30$, $P< 0.05$; interaction effect of prenatal treatment and sex, $F1,101 = 4.561$, $P< 0.05$; planned comparison, female PE: standard *vs* enriched, $P< 0.01$, male PE: standard *vs* enriched condition: $P<0.05$, Figure 8).

We next analyzed the skewness in initiation time. Increased skewness was observed in females compared to males. In addition, the enrichment condition decreased the skewness in PE, but not control rats of both sexes (three-way ANOVA: prenatal treatment, rearing condition, sex; main effect of sex, $F1,101 = 3.34$, $P<0.05$; interaction effect of prenatal treatment and rearing condition, $F1,101 = 8.18$, $P< 0.01$; planned comparison: male PE: standard *vs* enriched condition, $P <0.05$, female PE: standard *vs* enriched condition: $P<0.001$, Figure 8)

Movement skewness was also analyzed. We did not find any group differences (Figure 8). The result shows initiation time skewness is contributing to the RT skewness.

Discussion

The results of the present study show that rearing in an enriched environment from early development to adulthood increases the efficiency of obtaining rewards and alters the responding patterns of RT. Importantly, rearing in the enriched environment ameliorates PE-induced attention deficits, including increased action impulsivity and lapses of attention. Some of the enrichment effects are sex-dependent and observable in control rats. Taken together, rearing in an enriched environment exerts multiple beneficial effects on attentional control and task efficiency.

We have not found a PE effect on trial performance in rats reared under standard conditions. However, we find rearing in the enriched environment leads to increased choice trials in control rats of both sexes, leading to the acquisition of more reinforcers. Interestingly, this effect is not observed in PE rats reared in the enriched environment. The effect in control animals is more prominent in male than female rats, which shows a substantial escalation of trial numbers after the session starts. Increased trial numbers have also been reported in rats with environmental enrichment in a previous study (47). Such an effect cannot be attributed to more correct trials or shorter RT, which are not altered. One likely contributor to this effect is reduced action impulsivity (premature initiations), resulting in shorter trial

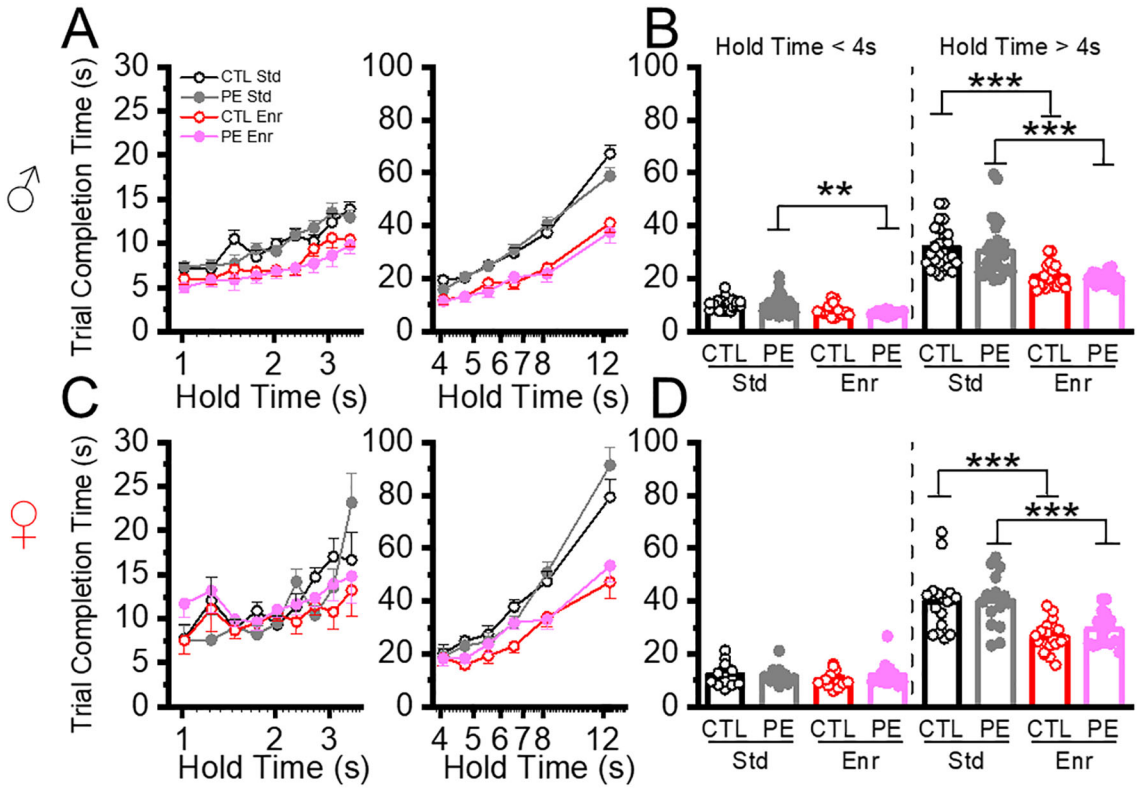

FIGURE 6
Environmental enrichment reduced trial completion time. The duration to complete each trial was analyzed at low and high cognitive load conditions (hold time< 4 s and hold time > 4 s). Environmental enrichment reduced trial completion time in male PE rats when cognitive load was low (**A, B** left panels) and females **(C, D)** control and PE rats when the cognitive load was high. **P<0.01, ***P< 0.001.

completion time, which allows more time for the rats to perform additional trials. However, reduced premature initiations and trial completion time are observed in both control and PE rats reared in the enriched environment, which does not explain why the number of choice trials is only increased in control but not PE rats. Another likely reason is increased motivation for rewards in control enriched rats. This possibility is supported by the observation that environmental enrichment increases motivation and sensitivity toward natural rewards and influences task performance (48). These motivational factors could be confounded by PE, leading to a lack of increase in choice trials in PE rats reared in the enriched environment. Our previous studies show PE leads to disruption of the midbrain dopaminergic system support this possibility. More studies are required to examine this possibility.

Altered RT structure in rats is observed in rats reared in the enriched environment. First, neither PE nor environmental enrichment impacts the median total RT, which is the sum of initiation time and movement time. In a previous study, reduced RT has been reported in rats with environmental enrichment in a reaction time task (47). The discrepancy between Ishiwari et al. and the present study could be due to differences in data analysis and experimental paradigms. In Ishiwari et al, mean RT instead of median RT is used. Because of the skewed distribution of RT, we use median RT to better represent the RT in each animal. Second, the reaction time task in Ishiwari et al. does not involve choice. Third, the enrichment paradigm in Ishiwari et al. starts only after weaning. An interesting observation from the present study is that control and PE rats of both sexes reared in the enriched environment show slower initiation time and faster movement time. The cause of this effect is unclear. It is apparent that movement deficits are not the contributing factor because rats reared in the enriched environment show faster movement time. On the other hand, reduced action impulsivity could contribute to slower initiation time. There is a clear association between reduced initiation time and premature initiation in rats reared in the enriched condition. Furthermore, the initiation time in the present study is similar to the RT measured before motor responses in clinical studies, which report an association between RT and anxiety. Faster RT is linked to higher anxiety and less caution (49). On the other hand, environmental enrichment has also been reported to improve caution in a rat model of ADHD (50). We have found that rearing in an enriched environment significantly reduces anxiety in both control and PE rats (20). Therefore, the reduced initiation time in rats reared in the enriched environment could be due to increased caution and reduced anxiety. The faster movement time in rats reared in the enriched condition is also consistent with increased caution and preparedness. Taken together, environmental enrichment leads to a different phenotype in reaction time, probably due to increased caution and decreased anxiety.

We have observed that PE leads to increased action impulsivity indicated by augmented premature initiations, an effect that is more

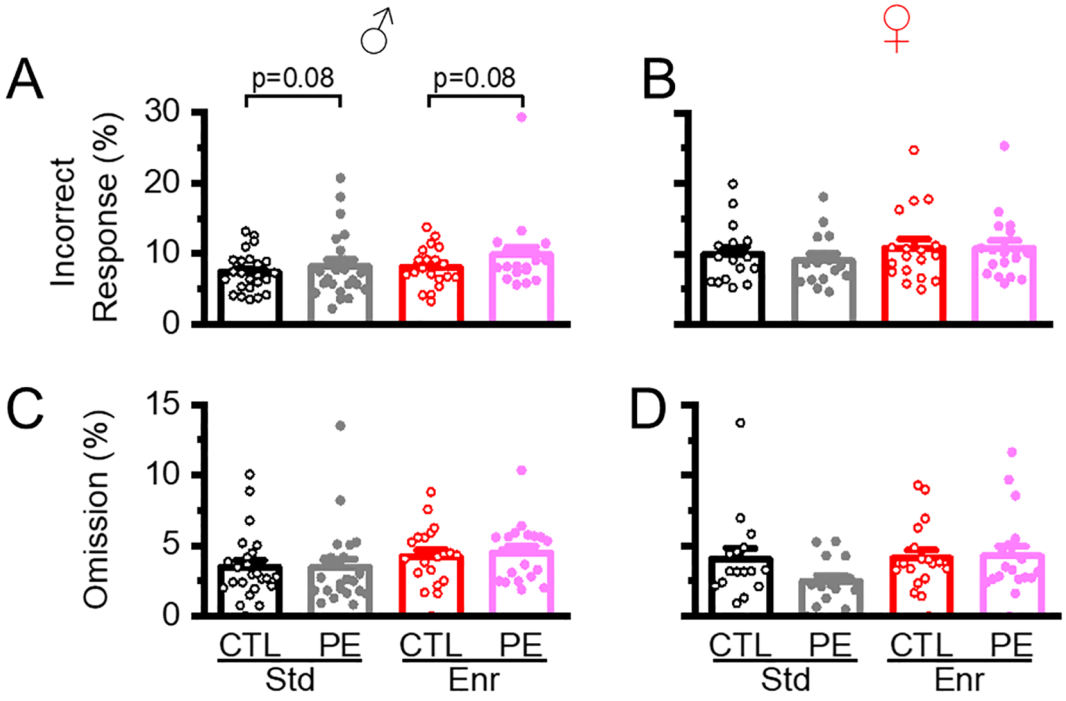

FIGURE 7
Environment enrichment did not impact lapses of attention reflected by incorrect responses or omissions. The percent incorrect response was increased in male PE rats reared in either standard or enriched condition **(A)**. No other PE or environmental enrichment effect was observed **(B-D)**.

obvious when the cognitive load (hold time) is increased. The action impulsivity or impulsive action describes the lack of ability to control unwanted motor behavior (51, 52). Increased action impulsivity is associated with decreased inhibitory control, a key symptom of ADHD (51). We find that action impulsivity is reduced in both control and PE rats reared in the enriched environment. This effect could be a major factor leading to reduced trial time because time is not wasted on premature initiations during hold time and the interruptions within each trial. The current literature regarding environmental enrichment effects on impulsivity/inhibitory control is limited and mixed due to the following reasons. First, impulsivity is a complex construct. In preclinical studies, the two components of impulsivity, action impulsivity, and choice impulsivity involved in the decision-making process, are investigated. Environmental enrichment has been shown to reduce action impulsivity in an early study (53). On the other hand, more recent studies have shown that environmental enrichment increases action impulsivity in rodents (40) or has no effects on birds (54). The discrepancy could be caused by variability in the enrichment paradigms, age/duration of enrichment, and/or species used. In rodents, a more complex environment after weaning is associated with a reduction in action impulsivity (53, the present study), while limited environmental complexity or duration is associated with no change or increased impulsivity (40, 53) The enrichment paradigm used in the present study is comprehensive. It starts after birth (PD 2) with a short maternal separation procedure aiming at increasing maternal behavior before weaning, followed by complex housing providing social, novelty, and activity enrichment throughout the behavioral training and testing period. This approach is used because evidence shows the additive beneficial effects of neonatal handling and complex housing (39). At the present time, it is unclear how different perspectives or ages of enrichment impact action impulsivity in PE rats. Future studies are required. The information will provide critical translational information for intervention strategies for FASD.

We use the skewness of RT distribution caused by large RTs as a major index for deficits in sustained attention. We find PE leads to increased lapses of attention in female PE rats, in addition, environmental enrichment reduces the skewness of RT distribution in PE rats of both sexes but not in control rats. These results indicate that environmental enrichment can ameliorate deficits in sustained attention caused by PE. This observation is consistent with another preclinical study showing environmental enrichment could reduce inattention and improve sustained auditory attention in a rat model of ADHD using Lister Hooded rats (50).

Other than reducing attention deficits reported in the present study, evidence from preclinical studies shows multiple beneficial effects of environmental enrichment. For example, environmental enrichment can reduce emotional reactivity, enhance learning and memory, improve habituation, and increase motivation (48, 55). Using the same environmental enrichment paradigm in the present study, we demonstrated similar beneficial effects in control and PE animals. We show rearing in the enriched condition decreases anxiety and addiction risk to drugs of abuse and facilitates habituation to sensory stimuli (20, 21, 41). Among the behavioral effects of environmental enrichment, decreased anxiety could be the

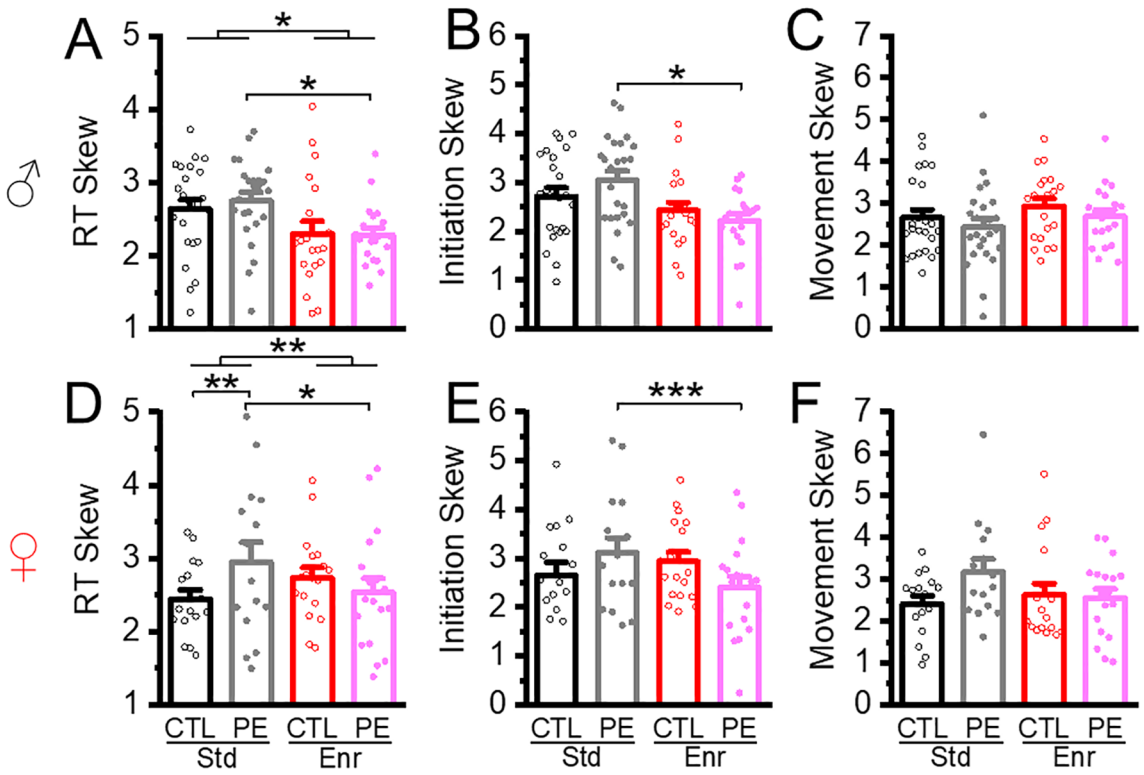

FIGURE 8
Environmental enrichment reduced the deficits in lapses of attention in PE rats. Prenatal ethanol exposure led to deficits in lapses of attention, which was reflected as increased skewness in total reaction time in female PE rats **(D)**. Environmental enrichment reduced deficits in lapses of attention reflected in total reaction time in male control and PE rats of **(A)** and female PE rats **(D)**. Environmental enrichment also decreased the skewness of initiation time in PE rats of both sexes **(B, E)**. No group differences in the skewness of movement time were found **(C, F)**. *P< 0.05, **P< 0.01, ***P< 0.001.

major moderator of attention deficits and reaction time. Previous studies, including those from our laboratory, report that PE leads to increased trait anxiety in rats (20, 24, 56–60) while reduced anxiety is observed in both control and PE rats reared in the enriched environment, resulting in no group differences (20). Indeed, previous studies have shown that environmental enrichment can effectively reduce stress and corticosterone levels (61). On the other hand, long-lasting anxiety and increased cortisol levels are associated with worse outcomes for many neurodevelopmental diseases, even in those with genetic contributions, such as ADHD (55). The inhibitory control is impacted by chronic stress (62–64). Anxiety and attention deficits, or ADHD, have a strong association in the clinical literature (25). However, the causal relationship is not clear. To understand if anxiety could exacerbate attention deficits, we have exposed rats to chronic unpredictable stress during adolescence to generate persistent trait anxiety in adulthood (26). The results show increased action impulsivity in both male and female rats, while the exacerbation of sustained attention is only observed in female rats. These observations support that anxiety could exacerbate attention deficits, and reduced anxiety in rats reared in the enriched environment may mediate, at least in part, reduced attention deficits shown in the present study. Evidence from clinical literature also supports that anxiety could impact attention deficits. Specifically, anxiety is shown to increase impulsivity, decrease the efficacy of attentional control, and impair executive function (65, 66). Specifically, Anxiety impairs inhibitory control when there are threat-related stimuli.

Although clinical studies examining environmental enrichment on ADHD symptoms are limited. Recent reviews describe that warm and sensitive parental-child interaction is negatively correlated with ADHD symptoms, and physical activity could decrease ADHD symptoms (1, 67). On the other hand, an adverse home environment is positively correlated with ADHD symptoms (1). These results show that other than genetic factors, environmental factors can clearly modulate ADHD symptoms. The results from the present study support the modulatory role of postnatal environmental factors in attention deficits by showing rearing in an enriched environment throughout development can reduce attention deficits in both control and PE rats. Clinical studies often advise that children with ADHD or FASD should be placed in an environment with limited stimuli due to their easily aroused nature and habituation deficits to environmental changes. However, it has been suggested that the externalization behaviors in ADHD are caused by under-stimulation rather than over-stimulation (48). The results from the present study support that a complex, enriched, rather than simple environment during development

ameliorates ADHD-like symptoms in FASD. A complex, enriched environment also ameliorates multiple other deficits in FASD such as increased addiction risk and anxiety, as well as habituation deficits. Currently, there is a lack of effective medications for FASD (14, 16). Environmental enrichment should be considered as an important intervention strategy for FASD.

The present study focuses on the impact of positive environmental factors on ADHD-like symptoms in FASD. Other than alcohol exposure, individuals with FASD also encounter many adverse prenatal and postnatal environmental factors, such as maternal stress and undernutrition, as well as early life adversity. It is unclear to what extent these negative environmental factors contribute to deficits observed in FASD. Limited preclinical studies suggest that adverse postnatal environments can worsen emotional dysfunctions and inflammation caused by PE (57, 68). Future studies using well-designed animal models are needed to clarify the role of these negative environmental factors to cognitive/behavioral deficits in FASD. The results could provide additional insights into the intervention strategy for FASD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Institutional Animal Care and Use Committee of the University at Buffalo. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

RW: Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. CM: Data curation, Methodology, Writing – review & editing. AL: Formal Analysis, Methodology, Writing – review & editing. KH: Data curation, Formal Analysis, Methodology, Writing – review & editing. JR: Conceptualization, Formal Analysis, Methodology, Resources, Software, Writing – review & editing. SH-D: Formal Analysis, Methodology, Supervision, Writing – review & editing. R-YS: Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Associations between anxiety and working memory components in clinically evaluated children with and without ADHD

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Theoretical models describe working memory difficulties as risk factors and/or outcomes of anxiety in children, but the current evidence base is surprisingly mixed. Understanding the nature of the working memory/anxiety relation is complicated by the multi-component nature of each of these constructs. Consideration of the co-occurrence of anxiety with attention-deficit/hyperactivity disorder (ADHD) is also imperative given that ADHD is associated with large magnitude working memory impairments. The current study addressed these considerations using bifactor modeling to evaluate associations between latent estimates of working memory and anxiety subcomponents. The carefully-phenotyped sample included N=340 children between the ages of 8 and 13 (M = 10.31, SD = 1.39; 144 female participants), with an oversampling of children with ADHD (n=197). Results showed that domain-general anxiety was associated with worse phonological short-term memory (r = -.22, p = .01), but not central executive working memory or visuospatial short-term memory. Domain-specific anxiety factors (cognitive worry, physiological arousal) did not uniquely predict any of the short-term/working memory components. Further, multigroup analysis indicated that the magnitude and significance of these relations were comparable for both children with and without ADHD. Our findings did not support unique relations between domain-specific cognitive worry/physiological arousal and instead implicated domain-general common anxiety in difficulties with phonological short-term memory. Further research will be needed to replicate findings using this approach across additional measures and performance metrics, while continuing to account for the high co-occurrence between anxiety and ADHD.

KEYWORDS

working memory, anxiety, ADHD, worry, anxious arousal

Introduction

Working memory is an executive function that involves the active, top-down manipulation of information held in short-term memory through interrelated functions of updating, dual-processing, and temporal/serial reordering (1). Working memory is crucial to development and has been associated with a wide range of behavioral and functional outcomes, such as academic (2), social (3), and occupational (4) functioning. Further, working memory has been found to be associated with various forms of psychopathology in children (5), including anxiety, a highly prevalent form of internalizing problems in childhood characterized by a variety of symptoms including worry, fear, avoidance, vigilance, and hyperarousal (6–8). As a result, understanding the nature of, and the processes underlying, working memory's relation to anxiety has the potential to provide essential insights into the interplay between neurocognitive, behavioral, and emotional functioning in pediatric populations. However, characterizing the relations between working memory and anxiety is complicated given the multi-component structure of working memory (9) and multidimensional nature of anxiety (10). Additionally, anxiety frequently co-occurs with attention-deficit/hyperactivity disorder (ADHD; 11), a neurodevelopmental disorder characterized by inattention and hyperactivity/impulsivity (6) that has been linked with large magnitude impairments in working memory (12, 13). As a result, co-occurring ADHD is also an important variable to consider when evaluating these working memory and anxiety relations. Building on prior work, the current study is the first to fractionate the working memory system into its component processes (i.e., central executive, phonological short-term memory, visuospatial short-term memory; defined below) and examine their relations with theoretically motivated dimensions of anxiety (i.e., cognitive worry, physiological arousal) using a latent variable approach. These relations will also be examined while accounting for ADHD in a large and well-characterized sample of clinically evaluated children.

Anxiety and working memory

Working memory deficits have been proposed to be an outcome of (14), risk factor for (7), and/or reciprocally related to (15, 16) anxiety symptoms. In general, the mechanisms by which anxiety may be related to impaired working memory are theorized to be a combination of top-down and bottom-up cognitive processes (15). At the bottom-up level, greater anxiety is related to worse filtering efficiency (16, 17) due to prioritization of threat-related cues (e.g., worry thoughts or external stimuli; 14, 16). From a top-down perspective, there is competition for cognitive resources and interference between anxiety-related and task-related processes (16). This competition is evidenced by similar neural circuitry involved in both working memory and anxiety (18), which reduces bandwidth for both storing and processing task-relevant information (1, 14). In a reciprocal fashion, depleted attentional control resources then make it difficult to disengage from cognitive processes of anxiety (i.e., worry thoughts), which subsequently results in increased dual-processing working memory demands (1, 15, 19). However, others have argued that anxiety may also serve a motivational function that potentially offsets the negative effects of anxiety on working memory (20). Theoretical work suggests that increased motivation results in individuals compensating for impaired attentional control through greater recruitment of cognitive resources and increased effort (14, 21).

Prior work examining working memory and anxiety in children and adolescents has yielded mixed results. Some studies have found increased anxiety to be related to worse working memory (16, 22–24), and others have found no effect (25) or even the opposite relation (26–28). The mixed literature is highlighted in varying meta-analytic studies with several methodological differences such as examining anxiety dimensionally (i.e., continuum of severity) versus categorically (i.e., diagnostic categories). One meta-analysis found a small overall relation between greater dimensional levels of anxiety and reduced working memory capacity (d = -0.33; 16), whereas another found no relation (25). When examining anxiety categorically, the most recent meta-analysis found a small effect in the opposite direction such that better working memory accuracy was found among anxiety disorder groups compared to control groups (d = 0.38; 27), a finding that was also demonstrated in a recent empirical study controlling for ADHD status (28). Taken together, relations between anxiety and working memory are likely impacted by multiple factors, such as symptom severity and clinical significance, as well as the multicomponent nature of both anxiety and working memory.

A primary limitation that may contribute to these disparities is that previous studies have typically examined relations based on a single measure of working memory. Use of a single task significantly limits our ability to infer construct-level associations (16) because the majority of variance in any single neurocognitive test is attributable to process(es) other than the specific executive function of interest (29). Additionally, a large body of evidence indicates that working memory is not a unitary construct (for review, see 30). An influential framework of working memory with significant empirical support proposed by Baddeley (9) suggests that working memory may be broken down into three components. First, the *central executive* is responsible for operating on the information stored in short-term memory, hence the "working" part of working memory. Central executive processes include reordering and updating stimuli held in short-term memory, as well as maintaining relevant information in the forefront of memory while performing a secondary, cognitively demanding task (i.e., dual-processing) (1). In addition to the central executive, Baddeley (9) proposed two temporary storage and rehearsal, or short-term memory, systems: the visuospatial sketchpad (visuospatial short-term memory) and the phonological loop (phonological short-term memory). The *visuospatial short-term memory* component is responsible for visual and spatial information, whereas the *phonological short-term memory* component is responsible for language-based verbal information. These three components of working memory are both functionally and anatomically distinct (9, 31). However, single tests cannot measure just one working memory component because the central executive requires information to operate on (i.e.,

information from phonological and visuospatial short-term memory systems), and at least some central executive processes are evoked even by simple span/short-term memory tasks (9, 29). An additional short-term storage component, the episodic buffer, was added to the model more recently to account for bound, cross-modality information (32). The episodic buffer was not investigated in the current study in order to examine modality-specific processes but will be an important component to consider in future studies.

Dimensions of anxiety and components of working memory

Despite extensive research on overall relations between anxiety and working memory, the specific processes and systems that might be driving or masking these relations cannot be determined because, to our knowledge, no studies have examined the multidimensional/multi-component relations between anxiety and working memory components at a latent variable level (16). However, theoretical models generally posit that difficulties in the domain-general central executive are driving the hypothesized working memory/anxiety relations (14, 16) due to anxiety negatively affecting attentional control (33). Specifically, Moran (16) found similar magnitude relations between anxiety and performance on visuospatial (d = -0.41) and phonological (d = -0.34) working memory tasks in a large meta-analysis of both adult and child samples. Based on this similarity, Moran (16) posited that overall anxiety was likely to be associated with the variance shared between visuospatial and phonological working memory tasks (i.e., domain-general central executive).

In contrast, others have argued that the short-term memory stores are implicated in specific, separable dimensions of anxiety (20, 34): physiological arousal and cognitive worry (35–37). *Physiological arousal* (i.e., anxious arousal) refers to somatic symptoms and arousal such as hypervigilance, increased heart rate, sweating, dizziness, and somatic tension (35). *Cognitive worry* (i.e., anxious apprehension) on the other hand refers to worry and rumination about negative events that may happen in the future (35). Some evidence suggests that arousal may be uniquely associated with visuospatial memory tasks and worry may be uniquely associated with phonological memory tasks (20, 38). The importance of examining these two dimensions of anxiety and their relations with working memory has been highlighted (39). For example, evidence suggests that physiological arousal and engagement with visuospatial memory tasks involve similar right prefrontal and right posterior parietal brain regions (i.e., asymmetric dependency). It is hypothesized these shared brain regions result in disruption of visuospatial short-term memory processes due to competition for limited neural resources (20, 34). Similarly, worry and engagement with phonological memory tasks both involve regions in the prefrontal cortex and left-hemisphere verbal processing circuits that may lead to competition for cognitive resources (20, 36). Notably however, worry may be more readily regulated than arousal by top-down processes when needed to meet the demands of high cognitive load tasks (20, 40). Despite overlap in reliance on certain prefrontal systems between physiological arousal/visuospatial tasks and cognitive worry/phonological tasks, there is also evidence for engagement of separable shared systems between the two pairs (20, 41). Although these studies reflect methodological refinements including differentiating between anxiety dimensions and assessing multiple working memory modalities, no studies have fractionated performance on multiple working memory tests into the central executive, and visuospatial and phonological short-term memory subsystems.

Based on this evidence, Moran (16) proposed a model in which greater anxiety is related to impairments in each of the three working memory components. Specifically, the model proposes that common anxiety (i.e., shared variance between arousal and worry) predicts domain-general attentional control (i.e., central executive working memory), whereas variance specific to worry and arousal predict phonological and visuospatial short-term storage capacity, respectively. Importantly, however, Moran (16) called for studies to examine these hypotheses within the same study because the conclusions were based on inferences from comparisons across different studies. Given the emphasis on distinct dimensions of anxiety in the literature, the shared variance between arousal and worry (common anxiety) is not clearly defined, but could represent temperamental characteristics, attentional biases, or aspects of emotion regulation and cognitive control that are shared between these constructs (42–44). The Moran (16) review emphasized the need for a latent-variable approach to isolate unique variance associated with each construct of this model, a method that had not been used in studies prior to their meta-analysis or since then, to our knowledge. Indeed, Gustavson and Miyake (39) highlighted the importance of taking the multifaceted nature of both working memory and anxiety into account when investigating and characterizing the relation between working memory and anxiety. This is the approach taken in the current study.

Co-occurring anxiety and ADHD

In addition to the need for increased specificity in examining relations between the subcomponents of both working memory and anxiety, accounting for the role of co-occurring psychopathology is also important (27). In particular, anxiety commonly co-occurs with ADHD (11), as approximately 25% of children with ADHD have co-occurring anxiety and vice versa (11, 45). The comorbidity of anxiety and ADHD presents a critical consideration for understanding relations between anxiety and working memory given that working memory difficulties are very common in ADHD (31). Estimates suggest that the majority of children with ADHD have a deficit in this area (i.e., 65-85%; 12, 13, 31, 46).

Research using latent variable methods suggests that working memory impairments in ADHD are largely driven by deficits in the central executive, rather than the two short-term memory storage systems (1, 31). For example, Kofler et al. (31) found that the central executive, but neither of the short-term memory systems, was uniquely associated with ADHD symptom severity. However,

although short-term memory deficits do not appear to underlie ADHD symptomology (31), there is nonetheless evidence that children with ADHD demonstrate greater visuospatial than phonological short-term memory impairments. Findings further suggest that phonological short-term memory tends to be intact in most children with ADHD (31, 47, 48). Overall, experimental and theoretical work has implicated central executive working memory deficits as a causal factor in ADHD symptom expression (e.g., 49, 50). Thus, examining the role of co-occurring ADHD in the relations between working memory and anxiety is critical, particularly when examining these associations in pediatric populations.

Interestingly, theoretical work predicts that anxiety is related to working memory impairment above and beyond what can be accounted for by ADHD (21, 22, 51). However, empirical studies that have specifically taken ADHD diagnostic status or symptoms into account when evaluating the relations between anxiety and working memory in youth have yielded highly mixed results (22, 28, 52–54). Importantly, however, none of these studies were able to consider the multi-component nature of working memory or the multiple dimensions of anxiety (16). In addition, to our knowledge, the majority of these studies used tests that have been criticized for poor construct validity and are likely better tests of short-term memory and/or gross neuropsychological functioning rather than working memory (for reviews, see 29, 30, 55). Given that the ADHD and anxiety literatures have both emphasized the importance of these methodological considerations, addressing these limitations is crucial to advancing our understanding of the associations between the multidimensional/multi-component anxiety and working memory constructs. Further, the extent to which these hypothesized anxiety/working memory relations are also detectable in children with co-occurring ADHD remains an open empirical question that the current study is well positioned to address.

Current study

Taken together, previous research paints a mixed picture regarding the association between anxiety and working memory, including evidence for small impairments or small strengths in working memory for children with greater anxiety, or no association between the two. The mixed literature may be accounted for by several proposed mechanisms that are evaluated in the current study, including the multiple components of working memory, multiple dimensions of anxiety, and the high rates of co-occurrence between pediatric anxiety and ADHD.

First, as recommended by Moran (16), bifactor modeling based on eight indicators from two criterion working memory tests (each with 4 distinct memory load conditions) was employed to obtain latent estimates of the domain-general central executive, as well as domain-specific phonological and visuospatial short-term storage systems (e.g., 31, 48). This method was used to address concerns about the limited interpretability of single 'working memory' tasks as reflecting specific cognitive processes (16, 34). Second, the current study evaluated the extent to which latent estimates of the physiological arousal and cognitive worry manifestations of anxiety, as well as the variance shared between the two (i.e., common anxiety), have differential associations with each of the three working/short-term memory components. Lastly, given the high co-occurrence between anxiety and ADHD, and the well-documented working memory deficits in children with ADHD (e.g., 31), the current study examined whether any detected working memory/anxiety associations differed between children with versus without ADHD.

We hypothesized that greater common anxiety would be associated with impairments in the domain-general central executive (16). We also expected that higher levels of cognitive worry would be associated with impaired phonological short-term memory and greater physiological arousal symptoms would be associated with worse visuospatial short-term memory (16, 20, 34). No specific hypotheses regarding whether these relations differ for children with versus without ADHD were offered given the paucity of prior research. However, differential associations in children with versus without ADHD seem most likely between anxiety components and central executive working memory given evidence of larger central executive working memory deficits in ADHD compared to short-term memory functioning (31).

Method

Participants

The sample included 340 children between the ages of 8 and 13 years (M = 10.31, SD = 1.39; 144 female participants: Table 1) from the Southeastern U.S. recruited through community resources for participation in a clinical research study of the neurocognitive mechanisms underlying pediatric attention and behavior problems. The Florida State University IRB approved the study prior to and throughout data collection, and parents and children gave informed consent/assent. Sample ethnicity consisted of 229 White Non-Hispanic or Latino (67%), 46 Black or African American (13%), 37 multiracial (11%), 23 Hispanic or Latino (7%), and 5 Asian (2%) children. None of the children presented with gross neurological, sensory, or motor impairment; non-stimulant medications that could not be withheld for testing; or history of seizure disorder, psychosis, or intellectual disability.

Group assignment

Children and caregivers completed a comprehensive psychoeducational evaluation that included detailed parent semi-structured clinical interviewing using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS; 56). The K-SADS (2013 Update) facilitates differential diagnosis according to symptom onset, course, duration, quantity, severity, and impairment in children and adolescents based on DSM-5 criteria (6). Its psychometric properties are well established, including interrater agreement of .93 to 1.00, test-retest reliability of .63 to 1.00,

and concurrent (criterion) validity between the K-SADS and psychometrically established parent rating scales (56). This semi-structured clinical interview was supplemented with parent and teacher rating scales from the Behavior Assessment System for Children (BASC-2/3; 57) and ADHD Rating Scale for DSM-IV/5 (ADHD-4/5; 58). Our standard assessment battery also included norm-referenced child internalizing disorder screeners, and additional standardized measures were administered clinically as needed to inform differential diagnosis and accurate assessment of comorbidities (e.g., semi-structured child clinical interviews, additional testing). A psychoeducational report was provided to caregivers; participating children selected a small toy (≤$5) from a prize box.

Children that met all of the following criteria were included in the ADHD group (n = 197): (1) DSM-5 diagnosis of ADHD combined (n = 132), inattentive (n = 57), hyperactive/impulsive (n = 6), or other-specified (n = 2) presentation by the directing clinical psychologist and multidisciplinary team based on the K-SADS and differential diagnosis considering all available clinical information indicating onset, course, duration, and severity of ADHD symptoms consistent with the ADHD neurodevelopmental syndrome; (2) borderline/clinical elevations on at least one parent and one teacher ADHD subscale (i.e., >90th percentile); and (3) current impairment based on parent-report. Children with any current ADHD presentation specifiers were eligible given the instability of ADHD presentations (e.g., 59). Several children with ADHD also met criteria for common comorbidities based on this comprehensive psychoeducational evaluation, including 67 anxiety disorder (34%), 12 depression (6%), 17 oppositional-defiant disorder (9%)[1], and 18 autism spectrum disorder (9%). To improve generalizability given that comorbidity is the norm rather than the exception for children with ADHD (60), these children were retained in the sample. Further, 50 children with ADHD (25%) met diagnostic criteria for a learning disorder. 47 children (24%) with ADHD were prescribed psychostimulant medication, which was withheld >24 hours for neurocognitive testing.

The non-ADHD group comprised 143 consecutive case control referrals who did not meet ADHD criteria and included both neurotypical children and children with psychiatric disorders other than ADHD. The non-ADHD group was deliberately recruited to include children who were, and were not, diagnosed with clinical disorders other than ADHD to control for the presence of these diagnoses in the ADHD group. This allows us to draw stronger conclusions about processes implicated in ADHD specifically as opposed to processes that may appear to be impaired in ADHD due to the confounding influence of co-occurring conditions. Thus, participants in this group included neurotypical children (57%) and children with anxiety (31%), depressive (8%), and autism spectrum (10%) disorders. Neurotypical children had normal developmental histories and nonclinical parent/teacher ratings and were recruited through community resources. 10 children without ADHD (7%) met diagnostic criteria for a learning disorder. The ADHD and non-ADHD groups did not differ significantly in the proportion of children with clinical disorders other than ADHD (anxiety, depression, ASD; p >.56); however, the ADHD group had higher proportions of ODD and learning disorder as expected (p<.001).

96 non-ADHD participants underwent identical evaluations to the ADHD group. Due to funding constraints, the remaining 47 non-ADHD participants (33%) completed abbreviated evaluations that included parent BASC-3 and ADHD-RS-5, a 1 to 2-subtest IQ screener (described below), and detailed developmental, medical, educational, and psychiatric histories. Neurotypical children that received the abbreviated evaluation did not differ from the full evaluation neurotypical subgroup in terms of child-reported anxiety symptoms, age, IQ, SES, and sex (all p>.07).

Procedure

Children completed the working memory tasks as part of a larger battery of neurocognitive testing that involved 1–2 sessions of approximately three hours each. All tasks were counterbalanced to minimize order effects. Children received brief breaks after each task and preset longer breaks every 2–3 tasks to minimize fatigue. For all testing, performance was monitored at all times by the examiner, who was stationed just outside of the testing room (out of the child's view) to provide a structured setting while minimizing performance improvements associated with examiner demand characteristics (61).

Measures

Socioeconomic status and global intellectual functioning

Hollingshead SES was estimated based on caregiver(s)' education and occupation (62). In addition, children were administered either a 4-subtest (full evaluation) or a 1–2 subtest (abbreviated battery) Short-Form of the WISC-V (63, 64).

Working memory tasks

The Rapport et al. (65) computerized phonological and visuospatial working memory test and administration instructions are identical to those described in Kofler et al. (13). Reliability and validity evidence includes high internal consistency (α = .82-.97; 66); 1- to 3-week (r = .76-.90; 67) and 10-week (r = .73-.84; 30) test-retest reliability; and expected magnitude relations with working memory updating and complex span tasks (r = .61-.69; 68). Each working memory test consisted of six trials at each set size (3–6 stimuli/trial), administered in randomized/unpredictable order as recommended (e.g., 69), yielding 24 total trials per task. Five practice trials were administered before each task (80% correct required).

For the *phonological working memory task*, children were presented with a series of jumbled numbers and a capital letter. The letter never appeared in the first or last position of the sequence to

1 As recommended in the K-SADS, oppositional-defiant disorder (ODD) was diagnosed only with evidence of multi-informant/multi-setting symptoms.

TABLE 1 Sample and demographic variables.

Variable	ADHD		Non-ADHD		Cohen's *d*	*p*	Possible Range	Obtained Range		Skewness		Kurtosis	
	(*N*=197)		(*N*=143)										
	M	*SD*	*M*	*SD*				ADHD	Non-ADHD	ADHD	Non-ADHD	ADHD	Non-ADHD
Sex (%Male/Female)	63/37		50/50		–	0.02	–	–	–	–	–	–	–
Ethnicity (% B/A/W/H/M)	16/0/69/6/9		10/4/65/8/14		–	0.016	–	–	–	–	–	–	–
Age	10.12	1.39	10.57	1.34	0.33	0.003	8.10-13.50	8.10-13.34	8.29-13.37	0.58	0.37	-0.75	-0.83
SES	47.53	10.16	46.79	12.16	-.07	0.544	11-66	21-66	11-66	-0.5	-0.57	-0.33	-0.03
IQ	101.36	14.9	105.89	12.9	0.32	0.003	73-151	73-138	73-151	0.06	0.06	-0.7	0.64
ADHD Symptoms													
BASC-2/3 Parent ATT T-Score	68.58	6.97	56.71	10.83	-1.35	<.001	10-120	48-86	36-81	-0.4	0.15	0.55	-0.78
BASC-2/3 Parent HYP T-Score	69.45	12.61	56.12	11.49	-1.1	<.001	10-120	42-102	38-91	0	0.92	-0.37	0.83
Anxiety													
Diagnosis (%Yes/No)	34/66		31/69		–	0.623	–	–	–	–	–	–	–
MASC-2 Self-Report Total T-Score	55.84	10.63	54.54	9.66	-0.13	0.249	40-90	40-87	40-81	0.43	0.17	-0.28	-0.74
Working Memory Task Performance													
Phonological Set Size 3	2.62	0.44	2.83	0.24	0.58	<.001	0-3	1.32-3.00	1.83-3.00	-1.2	1.72	0.69	2.71
Phonological Set Size 4	3.19	0.66	3.66	0.34	.85	<.001	0-4	1.17-4.00	2.70-4.00	-0.7	-0.89	-0.05	-0.05
Phonological Set Size 5	3.55	0.92	4.27	0.63	0.9	<.001	0-5	.82-5.00	2.20-5.00	-0.4	-1.23	-0.22	1.1
Phonological Set Size 6	3.13	1.18	3.98	1.15	0.73	<.001	0-6	.33-5.67	.90-6.00	-0.24	-0.55	-0.43	-0.18
Visuospatial Set Size 3	1.92	0.66	2.4	0.48	0.8	<.001	0-3	.17-3.00	.83-3.00	-0.59	-1.07	-0.25	1.09
Visuospatial Set Size 4	2.31	0.91	3.04	0.71	0.87	<.001	0-4	.17-4.00	.83-4.00	-0.25	-0.83	-0.69	0.21
Visuospatial Set Size 5	2.38	1.04	3.21	0.97	0.81	<.001	0-5	.33-4.83	.50-5.00	0.2	-0.4	-0.83	-0.35
Visuospatial Set Size 6	2.13	1.03	3.16	1.14	0.96	<.001	0-6	.33-5.18	.67-5.67	0.81	-0.09	0.48	-0.62

A, Asian; ATT, Attention Problems; B, Black or African American; BASC-2/3, Behavior Assessment Scale for Children, 2nd or 3rd edition; H, Hispanic or Latino; HYP, Hyperactivity; IQ, WISC-V short-form IQ score, fluid reasoning index score, or one-subtest screener; MASC-2, Multidimensional Anxiety Scale for Children, 2nd edition; M, Multiracial; SES, Hollingshead SES total score; W, White Non-Hispanic or Latino. Cohen's d effect sizes are interpreted as small = .20; medium = .50; large = .80.

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minimize potential primacy and recency effects and was counterbalanced across trials to appear an equal number of times in the other serial positions (i.e., position 2, 3, 4, or 5). Children were instructed to verbally recall numbers in order from smallest to largest, and to say the letter last (e.g., 4H62 is correctly recalled as 246H). For the *visuospatial working memory task*, children were shown nine squares arranged in three offset vertical columns. A series of 2.5 cm diameter dots (3, 4, 5, or 6) were presented sequentially in one of the nine squares during each trial, such that no two dots appeared in the same square on a given trial. All dots presented within the squares were black with the exception of one red dot that was counterbalanced across trials to appear an equal number of times in each of the nine squares, but never presented as the first or last stimulus to minimize potential primacy and recency effects. Children reordered the dot locations (black dots in serial order, red dot last) and responded on a modified keyboard. Partial-credit unit scoring (i.e., stimuli correct per trial) was used to index overall working memory performance as recommended (70), computed separately for the phonological and visuospatial working memory tests. Higher scores reflect better working memory.

Anxiety symptoms

The *Multidimensional Anxiety Scale for Children* 2nd Edition Self-Report (MASC-2; 71) was completed by children to assess symptoms related to anxiety disorders. Child self-reported anxiety was utilized as our primary indicator of anxiety due to prior work demonstrating that child report of anxiety appears to show greater associations with neurocognitive functions than parent report (54, 72) and appears to be more sensitive to early symptom emergence than parent report (73). The MASC-2 consists of 50 items (4-point Likert scale) and has demonstrated high internal consistency (α=.92) and 1- to 4-week test-retest reliability (r=.89; 71). Higher raw scores reflect greater quantity/severity of anxiety symptoms.

Given our goal of assessing two dimensions of anxiety (i.e., cognitive worry and physiological arousal), we examined the MASC-2 item pool to determine if there was a sufficient number of items falling into each subdomain. The 10 items on the Obsessions and Compulsions scale were excluded given that Obsessive-Compulsive and Related Disorders are now classified separately from Anxiety Disorders in the DSM-5 and DSM-5-TR. To this end, the remaining 40 items were judged to fall into one of four categories using an empirically driven rational approach (48, 74). After reviewing definitions of cognitive worry and physiological arousal from the published literature (35–37), the 7 judges (CM, FG, EC, SC, MT, JO, MG) independently determined whether each item reflected (1) cognitive worry, (2) physiological arousal, (3) both, or (4) neither/unclear. Items judged to belong to each category are shown in Table 2. Fleiss' kappa was computed to test the interjudge reliability of our classification of each item into these categories (75) using the R functions fleissm.kappa (from package irr; 76). Fleiss' kappa for more than two raters (77) indicated substantial agreement between raters, κ = .77, p <.001. Internal consistency for the rationally-derived physiological arousal and cognitive worry subdomains was acceptable in the current sample (ω=.81-.84, α=.78-.80).

Descriptively, 11 items each were judged to fall in the cognitive worry and physiological arousal categories, 1 item was judged to fall in both categories, and 17 items were judged to fall in neither of the categories. There was 100% agreement for 26 of the 40 items. Of the remaining items, 6 of 7 judges (86%) agreed for 5 items, and 5 of 7 judges (71%) agreed for 6 items. These minor discrepancies were resolved via consensus by the first and senior authors (CM, MK) based on category definitions derived from prior literature. Finally, there were 3 items with low agreement (Table 2), which we therefore classified as Neither/Unclear.

Bifactor models

Bifactor modeling was used to build latent estimates of the domain-general and domain-specific components of both anxiety and working memory. The current study followed recommendations for bifactor models by Eid et al. (78). As required to properly fit the bifactor models and interpret the general factors, one or more indicators must load onto the general factor but not onto any specific factor (79). These indicators are called 'reference facets' or 'reference domains' and define the meaning of the general factor (i.e., common anxiety, central executive working memory). The general factors were modeled as uncorrelated with each specific factor, and the specific factors were modeled as uncorrelated with each other, based on the assumption that two distinct sources of variance contribute to an individual's score on any given item/trial (i.e., variance attributable to the general factor and to a specific factor). This method allows for maximal discrimination between constructs in our bifactor models to provide reliable variance attributable to both domain-general (common anxiety; central executive working memory) and domain-specific (cognitive worry and physiological arousal; phonological and visuospatial short-term memory) processes (78).

Anxiety

The anxiety bifactor-(S-1) model was selected to build latent estimates of domain-general common anxiety and two domain-specific anxiety dimensions (cognitive worry and physiological arousal) based on the evidence reviewed above. To that end, the 22 MASC-2 items described above were modeled to all load onto a general factor (i.e., common anxiety) and a subset of 11 items each loaded onto the specific factors (i.e., cognitive worry, physiological arousal). Additionally, a total score of the 17 MASC-2 items that were judged to be neither cognitive worry or physiological arousal was created and served as the reference facet to define the meaning of the general factor (in this case, common anxiety). See Figure 1 for a visual depiction of the anxiety bifactor-(S-1) model.

Working memory

The working memory bifactor-(S·I-1) model was selected to build latent estimates of the domain-general central executive working memory and the two domain-specific short-term memory systems (phonological, visuospatial) based on the

TABLE 2 Item-level judgments for hypothesized cognitive worry and physiological arousal factor structure.

Paraphrased Item Content	Cognitive Worry/ Anxious Apprehension	Physiological Arousal/ Anxious Arousal	Both	Neither/ Unclear	Inter-judge Agreement (K = 7)	Mean (SD)	Skewness (SE)	Kurtosis (SE)
3. worry about people laughing	X				100%	1.36 (1.13)	0.20 (0.13)	-1.34 (0.26)
4. scared when parents go away	X				86%	1.29 (1.11)	0.26 (0.13)	-1.28 (0.26)
7. going away to camp scares me	X				100%	0.83 (1.05)	0.95 (0.13)	-0.46 (0.26)
10. afraid other kids will make fun	X				100%	1.18 (1.14)	0.44 (0.13)	-1.24 (0.26)
14. getting called on in class	X				100%	0.96 (1.08)	0.68 (0.13)	-0.93 (0.26)
16. afraid people will think I'm stupid	X				100%	0.85 (1.09)	0.93 (0.13)	-0.57 (0.26)
22. worry what people think of me	X				100%	1.11 (1.10)	0.47 (0.13)	-1.16 (0.26)
29. doing something stupid or embarrassing	X				100%	1.32 (1.13)	0.22 (0.13)	-1.34 (0.26)
30. scared riding in car/bus	X				71%	0.37 (0.74)	2.00 (0.13)	3.21 (0.26)
32. nervous to perform in public	X				86%	1.66 (1.21)	-0.21 (0.13)	-1.52 (0.26)
33. scared of bad weather, the dark, heights, animals, or bugs	X				86%	1.26 (1.10)	0.32 (0.13)	-1.23 (0.26)
1. tense/uptight		X			100%	1.09 (0.87)	0.28 (0.13)	-0.80 (0.26)
6. trouble getting breath		X			100%	0.81 (0.93)	0.84 (0.13)	-0.37 (0.26)
8. shaky/jittery		X			100%	1.02 (0.92)	0.47 (0.13)	-0.74 (0.26)
12. dizzy/faint feelings		X			100%	0.80 (0.97)	0.92 (0.13)	-0.31 (0.26)
15. jumpy		X			100%	1.34 (1.14)	0.21 (0.13)	-1.37 (0.26)
18. pains in chest		X			100%	0.82 (0.92)	0.81 (0.13)	-0.37 (0.26)
24. heart races/skips beats		X			100%	0.70 (0.86)	0.99 (0.13)	0.03 (0.26)
27. restless/on edge		X			86%	1.04 (1.08)	0.58 (0.13)	-1.01 (0.26)
31. sick to my stomach		X			100%	1.02 (0.97)	0.48 (0.13)	-0.89 (0.26)
34. hands shake		X			100%	0.83 (0.95)	0.85 (0.13)	-0.36 (0.26)
37. hands feel sweaty/cold		X			100%	1.03 (1.06)	0.60 (0.13)	-0.95 (0.26)
2. asks for permission				X	100%	2.31 (0.84)	-1.10 (0.13)	0.53 (0.26)
5. eyes open for danger				X	71%	1.99 (1.07)	-0.57 (0.13)	-1.05 (0.26)
9. stay near mom/dad				X	100%	2.04 (0.97)	-0.60 (0.13)	-0.77 (0.26)

(Continued)

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TABLE 2 Continued

Paraphrased Item Content	Cognitive Worry/ Anxious Apprehension	Physiological Arousal/ Anxious Arousal	Both	Neither/ Unclear	Inter-judge Agreement (K = 7)	Mean (SD)	Skewness (SE)	Kurtosis (SE)
11. obey parents and teachers				X	100%	2.49 (0.82)	-1.67 (0.13)	2.16 (0.26)
13. check things out first				X	100%	1.78 (1.02)	-0.39 (0.13)	-0.96 (0.26)
17. light on at night				X	100%	1.23 (1.24)	0.37 (0.13)	-1.51 (0.26)
19. avoids going places without family				X	86%	1.39 (1.06)	0.12 (0.13)	-1.20 (0.26)
20. feels strange, weird, or unreal				X	43%	0.67 (0.92)	1.21 (0.13)	0.41 (0.26)
21. do things other people will like				X	100%	1.67 (1.04)	-0.33 (0.13)	-1.04 (0.26)
23. avoids watching scary movies/ T.V. shows				X	100%	1.56 (1.20)	-0.11 (0.13)	-1.52 (0.26)
25. stay away from things that upset me				X	71%	2.03 (1.06)	-0.74 (0.13)	-0.75 (0.26)
26. sleep next to someone in family				X	100%	1.20 (1.13)	0.39 (0.13)	-1.26 (0.26)
28. do everything exactly right				X	100%	1.94 (1.01)	-0.65 (0.13)	-0.65 (0.26)
35. make sure things are safe				X	71%	1.91 (1.02)	-0.52 (0.13)	-0.90 (0.26)
36. trouble asking kids to play				X	71%	0.98 (1.15)	0.69 (0.13)	-1.05 (0.26)
38. shy				X	71%	1.39 (1.07)	0.10 (0.13)	-1.23 (0.26)
39. trouble making up mind				X	57%	1.44 (1.11)	0.03 (0.13)	-1.35 (0.26)
40. upset over thought of getting sick			X		43%	0.81 (0.98)	0.94 (0.13)	-0.30 (0.26)
Internal Consistency	ω=.84; α=.80	ω=.81; α=.78	–	ω=.74; α=.71				

Consensus judgments across 7 judges of items from the MASC-2 as reflecting (1) cognitive worry/anxious apprehension, (2) physiological arousal/anxious arousal, (3) both, or (4) neither/unclear. Item content is paraphrased. The 10 items on the Obsessions and Compulsions scale were excluded. Descriptive statistics of each item for the current sample are also depicted.

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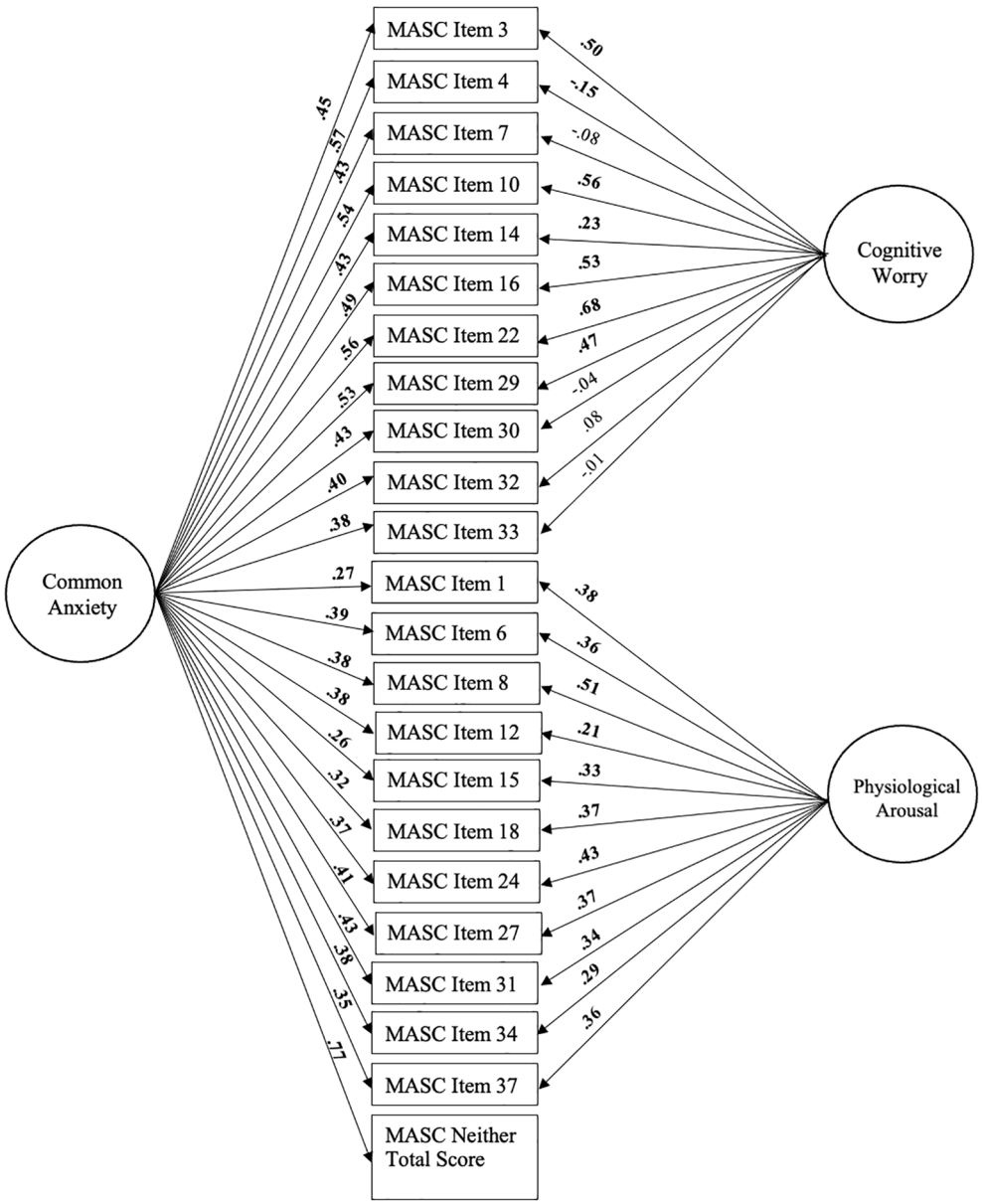

FIGURE 1
Bifactor-(S-1) model of common anxiety (general factor), and cognitive worry and physiological arousal (specific factors). Standardized loadings are shown. Significant loadings are bolded (all p<.05). Age, sex, and SES are controlled for but not depicted for clarity.

Baddeley (9) model. In this model, shared variance across working memory tasks with different stimulus modalities (i.e., phonological vs. visuospatial) is attributed to domain-general working memory central executive, whereas unique variance associated with each task is attributed to a domain-specific short-term memory system (i.e., phonological and visuospatial 'storage/rehearsal' subsystems; for review, see 31).

The working memory bifactor-(*S*·I-1) model used identical procedures as Kofler et al. (31). All 8 indicators (visuospatial and phonological memory set sizes 3, 4, 5, 6) were modeled to load onto the general factor (i.e., central executive working memory) and a subset of indicators were also modeled to load onto a specific short-term memory factor (i.e., phonological or visuospatial). To ensure that the general factor reflected domain-general central executive working memory, we selected 2 reference facets: one phonological and one visuospatial (80). Following Kofler et al. (31), we chose set size 3 from both tasks given that central executive demands remain relatively constant despite increasing set size (9, 49)[2]. See Figure 2 for a visual depiction of the working memory bifactor-(*S*·I-1) model.

2 Use of different set size reference facets did not change the pattern and interpretation of results from the bifactor model based on a subset of the current sample (31).

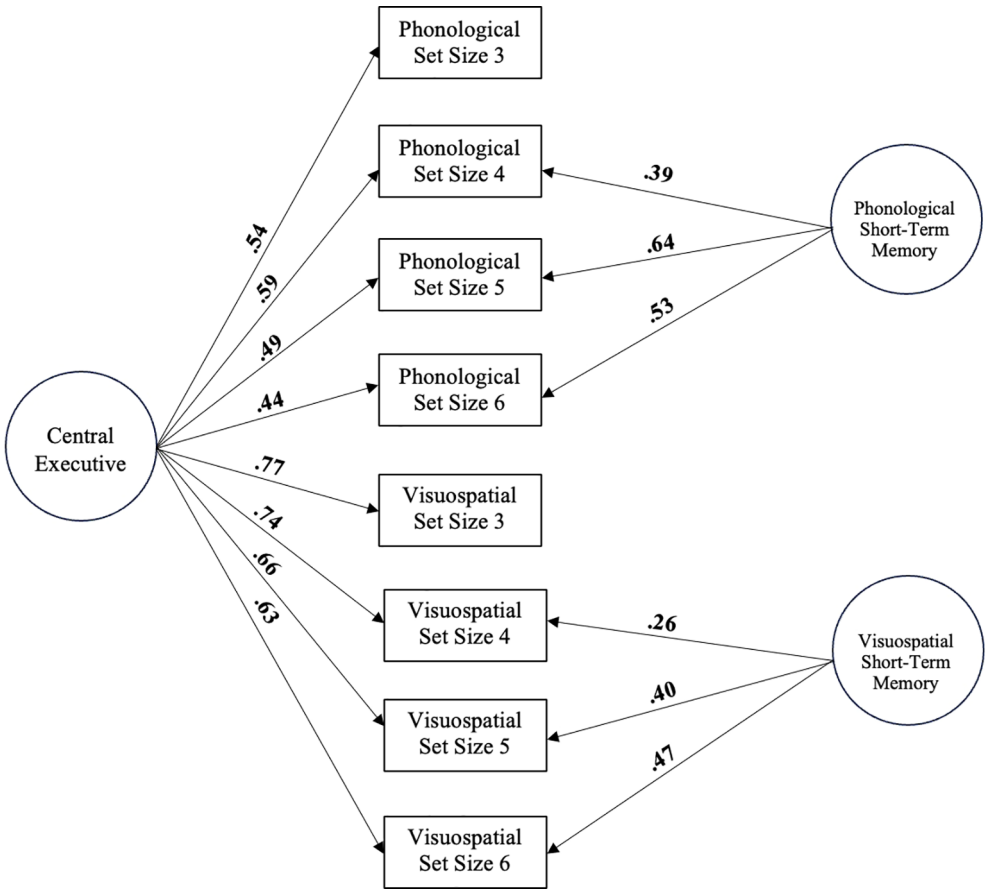

FIGURE 2
Bifactor-(S-I-1) model of central executive working memory (general factor) and short-term memory (phonological and visuospatial specific factors). Standardized loadings are shown. Significant loadings are bolded (all p<.001). Age, sex, and SES are controlled for but not depicted for clarity.

Transparency and openness

We report how we determined our sample size, all data exclusions (if any), all manipulations, and all study measures. The study was not pre-registered; however, all measure inclusion/exclusion decisions and analytic plans were made *a priori*, prior to accessing the data. A complete correlation matrix is included to allow replication (Supplementary Table 1); data/code are available upon reasonable request by emailing the corresponding author. Data were analyzed via structural equation modeling (SEM) using the R package lavaan (81) as implemented in JASP v0.18.3 and R v4.3.3.

Data analysis overview

Age, sex, and SES were included as covariates in all models. First, the anxiety and working memory bifactor models were built that both included a general factor (common anxiety; central executive working memory), as well as specific factors (cognitive worry and physiological arousal; phonological and visuospatial short-term memory). Model fit was evaluated by comparing these models to 1-factor anxiety and 1-factor working memory models with no specific factors.

Next, we used structural equation modeling to determine if there were differential associations across anxiety dimensions with the three working memory processes. We created a structural model including each anxiety component (i.e., common anxiety, cognitive worry, and physiological arousal) and each working memory component (i.e., central executive, visuospatial and phonological short-term memory) and evaluated correlations between the factors.

Finally, we examined the extent to which any detected relations between anxiety and working memory components differed for children with versus without ADHD using multigroup analysis. In other words, we tested whether the model fit was significantly degraded when the covariances between the anxiety and working/short-term components were constrained to equality across the ADHD and non-ADHD groups by comparing the fit between the constrained and unconstrained models using the chi-square difference test ($\Delta\chi 2$). Lower chi-square values indicate the preferred model (82).

For all confirmatory models, absolute and relative fit were tested. Adequate model fit is indicated by comparative fit index (CFI) and Tucker-Lewis index (TLI) ≥.90, and root mean square

error of approximation (RMSEA) ≤.10. For the working memory and anxiety bifactor measurement models, omega total (ω), omega subscale (ωs), explained common variance, and the percentage of uncontaminated correlations were also computed. Omega total (ω) and omega subscale (ωs) index the reliability of the general factor (working memory central executive, common anxiety) and specific factors (phonological and visuospatial short-term memory, cognitive worry and physiological arousal) by providing estimates of the proportion of variance attributable to sources of common and specific variance, respectively; values >.70 are preferred (83). Explained common variance (ECV) indicates the proportion of reliable variance explained by each factor. The percentage of uncontaminated correlations (PUC) is used to assess potential bias from forcing unidimensional data into a multidimensional (bifactor) model. When general factor ECV >.70 and PUC >.70, bias is considered low and the instrument can be interpreted as primarily unidimensional (i.e., the increased complexity of the bifactor structure is likely not warranted; 84). Construct replicability (H) values >.80 suggest a well-defined latent variable that is more likely to be stable across studies (85).

Power analysis

A series of Monte Carlo simulations were run using the package *simsem* (86) in R (version 4.3.3) to estimate the power of our proposed bifactor models according to the steps outlined in Bader et al. (87). For the proposed working memory bifactor model, we hypothesized general factor loadings (i.e., central executive) of .60 and specific factor loadings (i.e., phonological and visuospatial short-term memory) of .40 based on studies using a subset of the current study's sample (31, 88). Given these parameters and our sample size of n = 340, 5,000 simulations indicated that there was an acceptable convergence rate (99.46%), negligible relative bias (below .03 for all loadings and explained common variance), and very high power to detect significant parameters (above .98 for all loadings).

For the anxiety bifactor model, we hypothesized general factor loadings (i.e., common anxiety) of .60 and specific factor loadings (i.e., cognitive worry and physiological arousal) of .30 based on previous work using similar analyses with child anxiety measures (89–91). Given these parameters and our sample size of n = 340, 5,000 simulations indicated that there was an acceptable convergence rate (97.68%), negligible relative bias for all loadings and explained common variance (below .03), and high power to detect significant parameters (above .93 for all loadings).

Power to detect correlations above r = .30 between the two bifactors was then estimated using the R package *semPower* (92) given the highly mixed literature regarding anxiety and working memory (22, 28, 52–54). Given the hypothesized bifactor parameters specified above, α-level of .05, and power (1-β) ≥ .80, a sample size of 331 is required to detect correlations above r = .30 between the two bifactors. Thus, our sample of n=340 is powered to detect clinically relevant associations between components of the working memory and anxiety bifactor models.

Results

Preliminary analyses

All raw data were screened for univariate outliers, defined as values three standard deviations above or below the mean for the ADHD and non-ADHD groups separately. Outliers were corrected to the next most extreme value in the sample (0.30% and 0.12% of data points affected for ADHD and non-ADHD groups, respectively). Missing data were imputed using expectation maximization based on all available data and were determined to be missing completely at random (Little's MCAR test: χ^2 = 1014.30, p >.99). This affected 0.20% of data points. Sample demographics are shown in Table 1. Parent ADHD ratings were significantly higher for the ADHD relative to non-ADHD group as expected. The ADHD and non-ADHD groups did not significantly differ from one another on child report of anxiety symptoms. In contrast, the non-ADHD group was slightly older (M=10.57 vs. 10.12; p=.003), less likely to be male (p=.01), and had slightly higher IQ scores (M=105.89 vs. 101.36; p=.004), but did not differ from the ADHD group in terms of SES. IQ was not included as a covariate based on compelling statistical, methodological, and conceptual rationale against covarying IQ when investigating cognitive processes in ADHD (93), and because IQ appears to reflect, in part, an outcome rather than a cause of executive function/cognitive control abilities (e.g., 94). In other words, covarying IQ would preclude conclusions regarding executive functioning/cognitive control by fundamentally changing our primary predictor variables, and remove significant variance associated with our predictors and outcomes of interest (93).

Primary analyses

Bifactor measurement models

Anxiety bifactor model

First, we created a 1-factor anxiety measurement model in which all 22 cognitive worry and physiological arousal indicators, and the total score variable comprised of items that were classified as falling in neither of these categories, loaded significantly onto the domain general anxiety factor (β = .31-.71, all p <.001). However, this model did not show adequate fit (Table 3). Next, we built the anxiety bifactor (S-1) model by adding the cognitive worry and physiological arousal specific factors to the 1-factor measurement model. This model included the domain-general anxiety (general factor) and the domain-specific cognitive worry and physiological arousal factors (specific factors). As shown in Figure 1, all 22 items loaded significantly onto the general factor (all p <.001), and all 11 physiological arousal items loaded significantly onto their hypothesized factor (all p <.01). The cognitive worry items showed more variability, with four items not significantly loading onto the cognitive worry specific factor (see Figure 1). This indicates that these four items (7, 30, 32, 33) do not measure cognitive worry (no true score variance on cognitive worry) after controlling for

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TABLE 3 Model fit statistics.

Model	CFI	TLI	RMSEA (90% CI)	SRMR	χ^2 [df]	$\Delta\chi^2$ [df]	ω	ωs	ECV	PUC	H
Bifactor Measurement Models											
Anxiety Single Factor	.71	.68	.07 (.07-.08)	.07	850.20 [296] p <.001	–	–	–	–		–
Anxiety Bifactor	.93	.92	.04 (.03-.05)	.04	393.50 [268] p <.001	456.70 [28] p <.001	.89	.84 (CW) .79 (PA)	.60 (CA) .21 (CW) .19 (PA)	.57	.87 (CA) .71 (CW) .64 (PA)
WM Single Factor	.83	.78	.13 (.11-.14)	.07	263.52 [41] p <.001	–	–	–	–	–	–
WM/STM Bifactor	.95	.90	.08 (.07-.10)	.04	98.59 [29] p <.001	164.93 [12] p <.001	.88	.78 (PH) .82 (VS)	.70 (CE) .19 (PH) .11 (VS)	.68	.85 (CE) .56 (PH) .36 (VS)
Anxiety ➔ WM/STM Model											
	.93	.92	.04 (.03-.04)	.05	696.11 [472] p <.001	–	–	–	–	–	–
ADHD/Non-ADHD Multigroup Models											
Unconstrained	.89	.87	.05 (.04-.05)	.06	1279.36 [944] p <.001	–	–	–	–	–	–
Constrained	.89	.87	.05 (.04-.05)	.06	1289.36 [953] P <.001	10.01 [9] p = .35	–	–	–	–	–

CFI, comparative fit index; ECV, explained common variance; H, construct replicability; PUC, percentage of uncontaminated correlations; RMSEA, root mean square error of approximation; SRMR; STM, short-term memory; TLI, Tucker-Lewis Index; WM, working memory; ω, omega total; ωs, omega subscale; CA, common anxiety; CE, central executive; CW, cognitive worry; PA, physiological arousal; PH, phonological short-term memory; VS, visuospatial short-term memory.

their association with general anxiety (80). As noted below, study results were unchanged in sensitivity analyses that removed these four items.

This model showed excellent fit and model fit was significantly improved relative to the 1-factor anxiety measurement model ($\Delta\chi2$ [28] = 456.70, p <.001). The proportion of uncontaminated correlations and explained common variance were both <.70, supporting the multidimensionality of the data (PUC = .57, ECV = .60; 84, 85). Reliability was high for the general factor (ω = .89) and both specific factors (ωs = .79 – .84). Thus, the anxiety bifactor-(*S*-1) model was retained for subsequent analyses. Of note however, construct replicability (H) values for the specific factors were lower than recommended values (Table 3), highlighting the importance of additional studies utilizing these methods.

WM/STM bifactor model

We then created a 1-factor working memory measurement model in which all 8 indicators loaded significantly onto the domain general working memory factor (β = .51-.77, all p <.001). However, this model did not show adequate fit (Table 3). Next, we built the working/short-term memory bifactor (S·I-1) model by adding the visuospatial and phonological short-term memory specific factors to the 1-factor measurement model. As shown in Figure 2, this model included the domain-general central executive (general factor) and the domain-specific phonological short-term memory and visuospatial short-term memory factors (specific factors). This model showed excellent fit, all indicators loaded significantly onto their hypothesized factors (all p <.001), and model fit was significantly improved relative to the 1-factor working memory measurement model ($\Delta\chi2$ [12] = 164.93, p <.001). The proportion of uncontaminated correlations and explained common variance were both less than or equal to .70, supporting the multidimensionality of the data (PUC = .68, ECV = .70; Rodriquez et al., 2016; 85). Reliability was high for the general factor (ω = .88) and both specific factors (ωs = .76 – .85). Thus, the working/short-term memory bifactor-(S·I-1) model was retained for subsequent analyses. As with the anxiety bifactor model, construct replicability (H) values for the specific factors were lower than recommended values (Table 3) and indicate the need for additional studies measuring and evaluating these constructs.

Structural model: associations between anxiety and WM/STM components

We then created the structural model with the three anxiety components and three short-term/working memory components (see Figure 3). The model showed excellent fit as shown in Table 3. Results indicated that greater common anxiety was significantly associated with worse phonological short-term memory (r = -.22, p = .01), but not central executive working memory (r = .14, p = .10) or visuospatial short-term memory (r = -.16, p = .18). Cognitive worry and physiological arousal were not significantly associated with any of the short-term/working memory components (all p >.36).

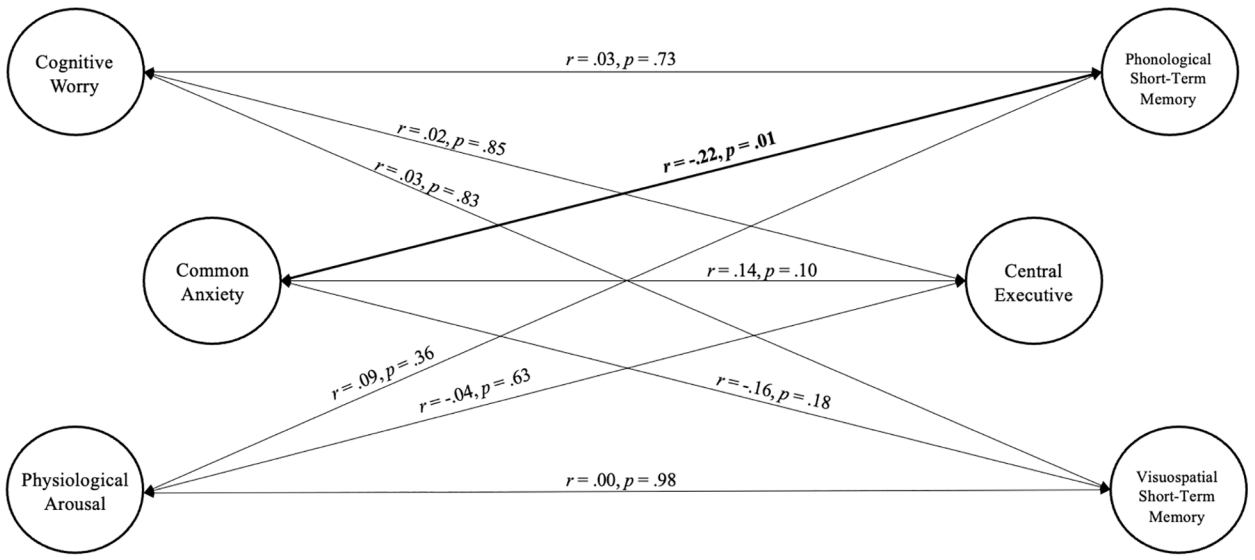

FIGURE 3
Correlations between bifactor-(S-1) model of common anxiety (general factor), and cognitive worry and physiological arousal (specific factors), and bifactor-(S·I-1) model of central executive working memory (general factor) and short-term memory (phonological and visuospatial specific factors). Age, sex, and SES are controlled for but not depicted for clarity.

ADHD/Non-ADHD multigroup analysis

Finally, we repeated the model above using a multigroup model (ADHD, Non-ADHD) to test the extent to which the results hold for children with and without ADHD. The unconstrained multigroup model resulted in fit indices slightly below adequate levels (Table 3; CFI = .89, TLI = .87, RMSEA = .05). Model fit was similar across the ADHD (CFI = .89, TLI = .87, RMSEA = .05) and non-ADHD groups (CFI = .90, TLI = .88, RMSEA = .05). Constraining the covariances to be equal for both groups did not significantly worsen the overall model fit ($\Delta\chi 2$ [9] = 9.72, p = .37), indicating that cognitive worry, physiological arousal, and common anxiety were associated approximately equally with each of the short-term/working memory components for both children with ADHD and without ADHD.

For completeness, we also conducted tests for metric and scalar invariance, which are reported in the Supplementary Materials (see Supplementary Appendix A). Briefly, there was evidence for scalar invariance, but only partial metric invariance due to minor differences across groups in loadings for specific phonological set sizes that did not impact the pattern or interpretation of results. Comparison of group means on the latent variables indicated that the ADHD group demonstrated worse central executive working memory (d=1.03, p <.001), as well as phonological and visuospatial short-term memory (d=.73, p <.001; d=.66, p = .002, respectively), abilities relative to the non-ADHD group. The groups did not differ on any of the anxiety factors (all p >.30).

Sensitivity analyses

Overall, our primary findings indicate that cognitive worry and physiological arousal were not associated with any of the working/short-term memory components, but greater common anxiety was associated with worse phonological short-term memory. Next, we conducted sensitivity analyses to probe the extent to which the pattern of results reported above was impacted by our *a priori* decisions to (a) include age, sex, and SES as covariates and (b) retain the four MASC-2 items that failed to load onto the cognitive worry factor. First, we repeated the primary analyses without including age, sex, and SES as covariates. The model continued to demonstrate good fit (CFI = .94, TLI = .93, RMSEA = .04). Greater common anxiety continued to be significantly associated with worse phonological short-term memory (r = -.26, p = .005) and all other relations remained non-significant. Next, we repeated the primary analyses after removing the four items that failed to load onto the cognitive worry domain (CFI = .94, TLI = .93, RMSEA = .04). Consistent with the primary analyses, greater common anxiety continued to significantly predict worse phonological short-term memory (r = -.22, p = .01) and all other relations were non-significant.

Discussion

The current study evaluated several possible explanations for the mixed findings regarding associations between anxiety and working memory in children, including the multi-component nature of working memory, multiple dimensions of anxiety, and high co-occurrence between pediatric anxiety and ADHD. Bifactor modeling was used to establish latent estimates of domain-general (central executive working memory; common anxiety) and domain-specific (phonological and visuospatial short-term memory; cognitive worry and physiological arousal) working/short-term memory and anxiety. Structural models were then used to evaluate relations between the latent factors, with sensitivity analyses probing the impact of our oversampling of children with ADHD, selection of

covariates, and decision to retain non-significant items in the anxiety bifactor model. Overall, the current study suggests that greater common anxiety is associated with moderately lower phonological short-term memory (r = -.22 to -.26). In contrast – and inconsistent with our hypotheses and theoretical models (16) – cognitive worry and physiological arousal were not uniquely associated with any of the working/short-term memory components.

Interestingly, we found that it is the variance shared between cognitive worry and physiological arousal (i.e., common anxiety) that significantly predicts difficulties in phonological short-term memory. This finding extends prior work that found working memory impairments in children with greater anxiety (22–24) and indicates that the phonological short-term memory storage system may be particularly vulnerable to disruption by anxiety-related thoughts, feelings, and behaviors. That is, greater anxiety may interfere with the temporary storage of phonological information in a variety of ways including competition for neural resources and interference from anxiety-related processes (16), increased dual-processing demands (1, 15), and depleted filtering efficiency (14, 17).

By using bifactor modeling to parse apart the primary components of the working memory/short-term memory system, we were able to address the possibility that prior findings of relations between anxiety and performance on phonological or visuospatial working memory tasks were driven by the central executive rather than either short-term memory system specifically. Our results contrast with the model of working memory and anxiety proposed by Moran (16), in which cognitive worry is related to phonological working memory and physiological arousal is related to visuospatial working memory, whereas domain-general central executive is associated with domain-general common anxiety. Inconsistent with this hypothesis, the latent cognitive worry and physiological arousal factors did not significantly predict any of the latent short-term/working memory components in the current study. Further, our finding that anxiety is related specifically to reduced phonological short-term memory stands in contrast with theoretical models suggesting that the central executive should be most vulnerable to the effects of anxiety (14, 16, 33). That is, we did not find evidence that anxiety is associated with the attentional control processes that are part of the central executive components of working memory (1, 9), but rather the more basic capacity to temporarily store phonological information. The phonological short-term memory system has been found to be more dissociable from central executive working memory processes than the visuospatial system (9, 95), further emphasizing that anxiety may be interfering with processes other than attentional control. Past work has suggested that worry may interfere with phonological storage due to verbal rumination creating dual-processing demands and competition for neural resources (14, 20, 36). While consistent with the current findings, previous studies have been unable to fractionate anxiety and working memory into their component parts. Thus the extent to which prior findings can specifically inform our understanding of cognitive worry and physiological arousal may be limited given their shared variance as demonstrated herein.

These results also contrast with studies suggesting unique associations with each of these anxiety dimensions (20, 34, 39). Interestingly, however, the current findings are consistent with the meta-analytic results from Moran (16), which did not find empirical support for unique predictions from specific domains. This finding was interpreted at the time to be attributable to methodological limitations of the included studies. In light of the current findings, however, it appears likely that specific anxiety subcomponents may not be associated with specific working memory subcomponents – at least for clinically evaluated children. For example, Gustavon and Miyake (39) examined both worry and physiological arousal with separate measures, leaving the possibility that anxiety characteristics shared across these two domains may best account for associations with working memory. Similarly, experimental manipulations of threat-induced anxiety, such as those used by Shackman et al. (34) and Vytal et al. (20) provide a useful paradigm for evaluating causal effects of anxiety in the moment but face similar challenges in parsing apart what is shared versus unique between the anxiety dimensions.

Interpreting what the shared variance between cognitive worry and physiological arousal represents is challenging because most literature focuses on characteristics that distinguish the two anxiety dimensions rather than on their commonality (20, 35, 36, 96, 97). However, some research has proposed temperamental characteristics as cutting across the domains, particularly avoidance temperament or behavioral inhibition (44). These temperaments reflect a tendency toward inhibited behavior that is guided by the possibility of a negative event (98). Consistent with this hypothesis, many of the MASC-2 items judged to reflect neither physiological arousal nor cognitive worry reflected avoidance behaviors and the sum of these items served as the reference facet. As a result, it seems reasonable to conclude that our anxiety general factor reflects avoidance/inhibition, which is a common component of anxiety that is present in both cognitive worry and physiological arousal (44, 99, 100). Research focusing on neural regions that are involved in both cognitive worry and physiological arousal has also provided insight into shared processes between the two dimensions. For example, Castagna and colleagues (42) found that greater cortical thickness in neural regions associated with perceived salience of threat stimuli and cognitive control aspects of emotion regulation was related to high levels of both cognitive worry and physiological arousal. Similarly, a study utilizing event-related potentials as a metric for neural processing found that individuals with elevated physiological arousal and cognitive worry both showed an attentional bias to emotional stimuli (43). These shared neural correlates suggest that heightened processes related to regulation and/or appraisal may be common to both cognitive worry and physiological arousal. Future research will be needed to further characterize domain-general anxiety given our findings that features of anxiety common to both cognitive worry and physiological arousal appear to be implicated in phonological short-term memory processes.

The current study indicated that there were no significant differences in the relations between anxiety and working/short-term memory components for children with versus without ADHD. That is, common anxiety, cognitive worry, and physiological arousal were associated approximately equally with each of the short-term/working memory components for both groups. Thus, our results do not support the hypothesis that anxiety may further

impair working memory abilities above and beyond ADHD (21, 22, 51). By the same token, our results were also not in line with the opposite hypothesis that anxiety may buffer against executive function deficits in ADHD through increased effort, greater recruitment of cognitive resources, and/or increased cortical arousal (21, 22, 101–103). Instead, our findings add to this mixed body of literature and suggest that even when anxiety and working memory are fractionated into domain-general and domain-specific components, children with and without ADHD do not exhibit differential associations among these constructs. The mixed literature regarding anxiety and working memory in pediatric ADHD spans a variety of operational definitions of anxiety (e.g, 22, 28, 102, 104) including varied measurement and informant. However, it will be important for future studies to evaluate if the present study results using child self-report of anxiety to fractionate anxiety into multiple components extend to parent report of child anxiety given additional substantive information provided by multiple informants about child psychopathology and high frequency of informant discrepancies (105).

Consistent with prior literature (31, 46), children with ADHD exhibited large magnitude impairments in central executive working memory relative to children without ADHD, whereas visuospatial and phonological short-term memory deficits were larger than expected based on prior literature (12, 31, 47). In contrast, the ADHD and non-ADHD groups did not differ in their levels of cognitive worry, physiological arousal, or domain-general anxiety. However, these results likely reflect, at least in part, our recruitment strategy that emphasized inclusion of clinical controls in addition to typically developing children. Indeed, these results suggest that our recruitment strategy was successful because the two groups did not differ in their anxiety levels, which is consistent with the relatively equal proportion of anxiety diagnoses across groups (approximately one-third of children in each group were diagnosed with an anxiety disorder). Future research with larger samples of neurotypical children as a separate comparison group would provide more clarity regarding the extent to which there may be higher levels of specific dimensions of anxiety in children with ADHD compared to the general population (106). Of course, such an approach would ideally be considered in the context of the limited generalizability of 'pure' ADHD groups given that co-occurring conditions are the norm rather than the exception for these children (60).

Limitations and future directions

The current study has several strengths, including a large, carefully phenotyped sample of children, bifactor modeling to fractionate domain-general and domain-specific components of anxiety and working memory, and the ability to account for the potential impact of the common co-occurrence between ADHD and anxiety. At the same time, the following limitations should be considered when interpreting results. First, the need to fractionate domain general and domain specific factors was highlighted by the poor fit of the single factor working memory and anxiety models, good fit for the bifactor models, and evidence supporting the multidimensionality of both item sets. Further, every latent factor was comprised of at least three significant indicators and showed high reliability. However, the construct replicability (H) values for the specific factors fell below optimal levels, suggesting that future studies may benefit from including additional items when modeling these constructs. Relatedly, our operationalization of cognitive worry and physiological arousal was constrained to the item pool from the MASC-2, which was not developed specifically to measure these dimensions and thus may not have fully captured all aspects of these constructs. Future studies would benefit from developing/utilizing measures designed to specifically differentiate anxiety-related arousal versus worry and/or include a broader sampling of items.

In addition, the current study evaluated trait anxiety, whereas other studies have examined anxiety experienced during the cognitive tasks themselves (i.e., state anxiety; 20, 34). Thus, it is possible that our findings would have differed if we had used an anxiety induction experiment. However, meta-analytic evidence has suggested that relations between anxiety and executive functions do not differ significantly when based on state (induced) versus trait anxiety (16, 25). Nonetheless, future studies may benefit from dual dissociation designs that systematically manipulate working memory demands and state anxiety levels to provide further clarification about the nature and directionality of any detected relations between subcomponents of working memory and anxiety. Studies evaluating both state and trait anxiety in the context of the multicomponent nature of both anxiety and working memory are also needed to determine the mechanisms that may be underlying these relations. For example, Gustavson and Miyake (39) outline two possibilities that may underlie any observed relations between anxiety and working memory: a) the trait effects of anxiety may actually be the result of state anxiety processes elicited during the working memory tasks, or b) cognitive processing may actually differ based on trait-level variability in anxiety.

The current study utilized bifactor modeling to fractionate working memory into component factors across two separate tasks. Central executive working memory, phonological and visuospatial short-term memory, were modeled as uncorrelated to allow for maximal discrimination between each of these constructs (78) due to the study's aim to examine unique associations between working memory components and multiple dimensions of anxiety. However, given that these distinct processes work in conjunction with one another on any given working/short-term memory task (9), extension of the current findings to additional working memory tasks and performance metrics is needed to further evaluate the robustness of working memory/anxiety relations. We used working memory tasks that assessed reordering processes. In addition to reordering, models of central executive working memory have also highlighted continuous updating and dual-processing (1, 107). Future research utilizing working memory tasks that assess these additional processes are needed to determine if results from the current study extend beyond tasks engaging reordering processes. Additionally, performance on our working memory tests is based on accuracy (i.e., stimuli correct per trial), whereas it is possible that working memory efficiency (i.e., response speeds) may be more

vulnerable to the effects of anxiety than working memory accuracy (14, 39) due to the motivational effects of anxiety (108). That is, individuals with high anxiety may put forth increased effort to compensate for reduced working memory capacity, resulting in slower but just as accurate performance (14, 108). Similarly, it is also possible that different levels of anxiety may facilitate rather than impair working memory processing, although this may be unlikely given a recent, relatively large study that tested this hypothesis in a subset of the current sample and did not find support for a curvilinear relation between anxiety and working memory (28).

Conclusion

Taken together, the current study found that higher levels of domain-general anxiety – but not domain-specific components of anxiety including cognitive worry and physiological arousal – are associated with reduced phonological short-term memory abilities. In contrast, none of the anxiety factors were associated with central executive working memory or visuospatial short-term memory. Given that this was the first study to fractionate both working memory and anxiety into their primary components, these results suggest that prior findings linking anxiety with working memory difficulties may be driven specifically by the interfering effects of anxiety on the temporary storage of phonological information. Interestingly, this pattern was observed equally for children with and without ADHD, suggesting that the findings were not driven by our oversampling for children with ADHD and are not specific to children who have difficulties with working memory as is commonly observed in ADHD samples (12, 13, 31, 46). For practitioners, these findings suggest that the presence of anxiety should be carefully considered when selecting and interpreting neuropsychological testing batteries, as features of anxiety that cut across both cognitive worry and physiological arousal may specifically disrupt short-term memory capacity for verbal information. Similarly, parents and teachers working with children experiencing various forms of anxiety may need to provide visual aids and break down tasks when information is presented verbally, as these children are likely to experience disruptions to their short-term ability to remember this information.

Data availability statement

The data/code will be made available on emailing the corresponding author, without undue reservation.

Ethics statement

The studies involving humans were approved by Florida State University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

CM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. FG: Investigation, Visualization, Writing – review & editing. EC: Visualization, Writing – review & editing. SC: Visualization, Writing – review & editing. MT: Visualization, Writing – review & editing. JO: Data curation, Writing – review & editing. MG: Data curation, Writing – review & editing. SH: Investigation, Project administration, Writing – review & editing. MK: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

MK holds a patent for neurocognitive interventions that target central executive working memory and inhibitory control. These interventions were not used in the current study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2025.1536942/full#supplementary-material

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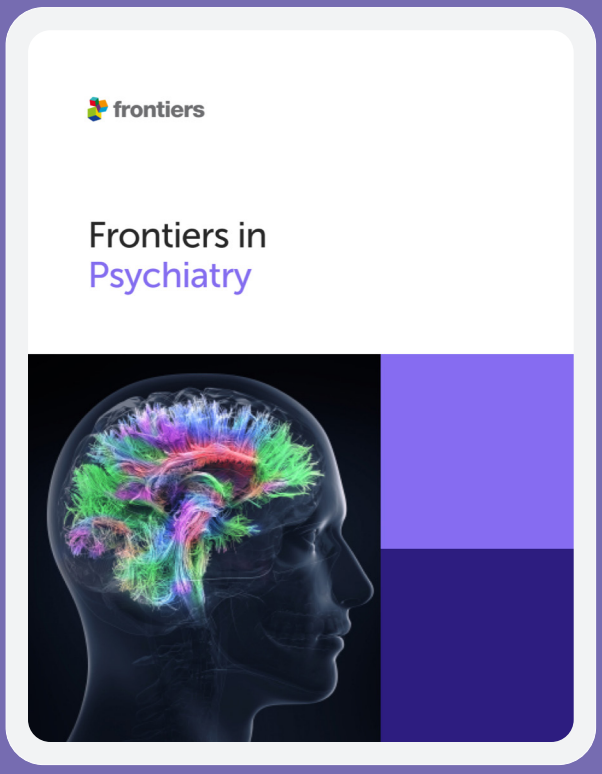

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