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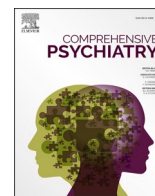
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## Stress as a mediator of brain alterations in attention-deficit hyperactivity disorder: A systematic review

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### ABSTRACT

**Objective:** Stress is a known risk factor for numerous psychopathologies, whereas evidence is lacking regarding the specific consequences of stress on the neural basis of attention-deficit hyperactivity disorder (ADHD). A systematic literature review was thus conducted to clarify the role of stress in the association between the resulting alterations of brain structure, connectivity, and function in ADHD.

**Methods:** The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identifier CRD42023379809. A systematic search of the PubMed and CINAHL databases was conducted for articles published prior to December 22nd, 2022. Retrieved literature was screened in Rayyan and data extraction was performed with respect to neuroimaging, stress exposure, and ADHD outcomes. The Quality in Prognosis Studies (QUIPS) tool was adapted based on the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidance article to assess risk of bias and quality of studies. Strength of the evidence was assessed under the guidance of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

**Results:** Screening 25,026 non-duplicate articles yielded 20 eligible studies for inclusion. Exposure to early life trauma, institutionalization, prenatal smoking or alcohol consumption, air pollution, low socioeconomic status, or low birth weight were associated with alterations in brain structure, function, and connectivity in ADHD. However, most studies did not provide strong evidence due to small sample sizes and lack of statistical approaches to determine a direct mediation of the association between stress and ADHD by neural outcomes.

**Conclusion:** This systematic review was the first to summarize evidence of structural and functional stress-associated alterations in the brain, which were found to be directly and indirectly associated with ADHD outcomes. Overall, stress requires consideration as a significant determinant of neurodevelopmental outcomes in ADHD. However, extensive further research is warranted due to little available evidence and the difficulty of obtaining clear results. In light of such a complex research question, in order to confirm findings, provide further evidence, and establish causality systematic longitudinal studies would be required. Investigating the topic may provide invaluable information when it comes to tailoring prevention and treatment strategies in ADHD, and should be pursued in order to integrate the factor of stress into a more comprehensive understanding of ADHD.

### 1. Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by display of excessive socially

disruptive behavioural characteristics such as impulsivity, inattention, and hyperactivity [1]. While the etiology of ADHD is far from being fully understood, outcomes are influenced by both genetic and environmental factors, wherein gene-environment interactions are likely to be most

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provoking in effect [2]. Recently, there has been growing recognition of the impact of environmental risk factors, particularly when experienced during earlier life periods, on ADHD outcomes [3]. Observational studies have indicated a significant positive association between exposure to various adverse events and the likelihood of developing ADHD, encompassing factors such as physical and emotional abuse, violence, neglect, dysfunctional households, and low socioeconomic status [4,5]. Additionally, children subjected to institutionalization, marked by severe neglect, exhibit an increased risk of ADHD [6–12]. Environmental pollutants and low birth weight (BW) are also identified as environmental risk factors for ADHD [13,14].

A distinct backdrop behind such environmental risk factors is that all of them are known to exert significant psychological or physiological stress on the organism [15]. Stress is a recognized determinant of various psychopathologies, including post-traumatic stress disorder (PTSD), depression, and generalized anxiety disorder [16,17]. A functional stress response is an integral part of any healthy organism, constituted by an activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis [18–20]. While the activation of the sympathetic nervous system, which causes the adrenomedullary gland to release epinephrine and norepinephrine, constitutes the “fight-or-flight” fast-acting response, the long-term stress response corresponds to the release of glucocorticoids, notably cortisol, by the HPA axis [19]. Chronic exposure to excess cortisol has been associated with stress-induced structural remodelling in the brain by causing neuronal atrophy and destruction, such that it may also be responsible for decreased brain volumes, such as described in ADHD [19,21,22]. Such chronic cortisol exposure has even been associated with ADHD-like behaviour to be exhibited in healthy individuals by leading to impairments in brain attention networks in prefrontal regions [23]. Hence, the current systematic review shall address the forthcoming research question in relation to chronic stress, in contrast to acute stress [21,24,25]. Nevertheless, the precise mechanistic effects of stress in the context of ADHD, particularly concerning neurological alterations, remain poorly understood [15]. As both stress and ADHD ultimately manifest in the brain, with findings alluding to a significant neurological basis for ADHD and stress being known to impact overall cognition and behaviour, inspecting this seems to be highly pertinent [19,22,26–28].

Despite the compelling proposal that environmental risk factors ultimately influence ADHD outcomes specifically by interfering with neurodevelopmental processes, neuroimaging studies in ADHD have hitherto mainly focused on identifying primary neurological differences between ADHD patients and healthy individuals [29,30]. Notably, the ENIGMA (Enhanced Neuroimaging Genetics Through Meta-Analysis) neuroimaging consortium mega-review, encompassing the largest ADHD sample size to date, reported overall decreased intracranial volume (ICV), atrophy in various brain structures (nucleus accumbens, amygdala, caudate, hippocampus, and the putamen), and deficits in cortical (frontal, cingulate, temporal cortex) surface area and thickness in childhood ADHD patients in comparison to healthy children [31]. Functionally, ADHD patients exhibit abnormalities in critical brain networks such as the default mode network (DMN), the frontoparietal network (FPN), and the salience network (SN), resulting in cognitive deficits, particularly in executive function skills such as decision-making, impulse control, and response inhibition [32]. Moreover, ADHD patients commonly show a delay in neurodevelopmental maturation [31,33].

While it may be challenging to differentiate whether neural alterations in ADHD patients are a consequence of environmental stress exposure or individual intrinsic neurobiological programming, neuroimaging studies would enable to go beyond mere observational associations and provide evidence for potential neural mechanisms linking the effects of stress in ADHD to shed light on this question. It is therefore the aim of this systematic review to systematically gather evidence from all published scientific literature on the neural effects in ADHD that are linked to pre- and postnatal stress. Specifically, we seek to identify

alterations in brain size, structure, connectivity, and activity that mediate the association between stress exposure and ADHD. We anticipate that stress induces both functional and structural neural impairments, potentially resembling the differences observed between ADHD patients and healthy individuals. It is also hypothesized that these changes may act as direct mediators of the stress-ADHD association. Achieving this aim may shed light on the Hypothalamic-Pituitary-Adrenal (HPA) axis as a potential therapeutic target in ADHD and lead to novel suggestions for ADHD prevention and treatment.

## 2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [34] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42023379809 [35]. Prior to defining our search strategy, scientific literature databases (including PROSPERO) were searched for published and/or ongoing systematic reviews that investigate the current research question of interest, but no such work was found. Subsequently, keywords were defined for the literature search along with the precise inclusion and exclusion criteria for studies. A narrative systematic summary was established through data synthesis following extraction of information and management of the studies. Deviations from study protocol are described in section 2.6.

### 2.1. Search strategy

The electronic databases used for our systematic search of scientific literature were PubMed (National Library of Medicine at the National Institutes of Health, Bethesda, Maryland; <http://www.ncbi.nlm.nih.gov/pubmed>) and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (<https://search.ebscohost.com>). The literature search was conducted for articles published prior to 22nd of December 2022. All retrieved literature was uploaded to Rayyan, a free-to-use online software designed for systematic review literature selection processes [36].

In order to ensure the currency of the systematic review prior to publishing, an updated literature search was conducted in PubMed on January 8th 2024 in an effort to identify any more recent and relevant studies that could contribute to the comprehensiveness of the study. As a result of no additional eligible papers having been identified, the findings and conclusions drawn from the original analysis remain unchanged.

#### 2.1.1. Search keywords

The search was conducted using keywords in three categories: ADHD, neuroimaging, and pre- or post-natal stress. Terms in each group were linked by “OR” and groups were linked with “AND”. Specifically, the following keywords were used during the literature search: “stress” OR “chronic stress” OR “long-term stress” OR “stress exposure” OR “prenatal adversities” OR “trauma” OR “childhood trauma” OR “HPA axis” OR “cortisol” OR “glucocorticoid” OR “psychological stress” OR “psychosocial stress” OR “stressful life event” OR “stressful event” OR “traumatic event” OR “early childhood stress” OR “early-life adversity” OR “prenatal stress” OR “prenatal adverse effects” OR “neonatal stress” OR “postnatal stress” OR “adverse childhood experiences” OR “ACEs” OR “maternal obesity” OR “maternal pre-eclampsia” OR “maternal smoking” OR “prenatal exposure to maternal stress” OR “peripartum adversity” OR “peripartum adverse events” OR “prenatal substance abuse” OR “maternal stress” OR “maternal depression” OR “neonatal hypoxia-ischemia” OR “postnatal adversity” OR “postnatal adverse effects” OR “socioeconomic status” OR “SES” AND “neuroimaging” OR “brain imaging” OR “neural correlate” OR “neurodevelopment” OR “neural structure” OR “brain structure” OR “brain function” OR “neurological” OR “brain scan” OR “neuroanatomical” OR “MRI” OR

“fMRI” OR “DTT” OR “EEG” OR “MEG” OR “MRS” OR “NIRS” OR “PET” OR “NIRS” OR “SPECT” AND “ADHD” OR “attention-deficit hyperactivity disorder” OR “attention deficit disorder”.

2.1.2. Inclusion and exclusion criteria

Only original peer-reviewed publications in any language were included provided that an English translation was available. Only studies performed in humans were included, with no limitations for age or gender. Studies were required to include a standardized neuropsychiatric clinical assessment in relation to ADHD in combination with any kind of neuroimaging assessment(s) and a validated exposure to long-term stress(es). ADHD assessments needed to be performed by either clinical interview or by using a validated questionnaire which followed official diagnostic criteria within the official guidelines of the Diagnostic Statistic Manual (DSM) (versions DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5) or the International Classification of Diseases (ICD) (versions ICD-9 or ICD-10) [37,38]. Stress assessments had to be performed using a validated stress assessment questionnaire or diagnostic interview. For both stress and neuropsychiatric assessments, questionnaires needed to be filled in either by subjects themselves and/or their parent (s)/caregiver(s). In case ADHD patients were diagnosed with comorbid mental illness(es), such studies were included provided that an ADHD diagnosis was the main neurodevelopmental outcome of interest. Case studies, narrative reviews, systematic reviews, and meta-analyses were excluded. The reference lists of systematic reviews and meta-analyses on the topic of interest were screened for additional articles eligible for inclusion. All animal studies were excluded. Studies where only acute

stress, such as traumatic brain injury, accidents, injury, or anaesthesia were reported on were excluded. Studies that included solely measures of ADHD symptomatology or did not assess ADHD as the main neurodevelopmental condition of interest were excluded. However, deviations from these exclusion criteria occurred and will be described in section 2.7.

2.2. Study selection

The PRISMA flowchart of the literature identification, screening, and selection processes of this systematic review is displayed in Fig. 1. A total of 26,728 papers were retrieved from Pubmed (n = 9819) and CINAHL (n = 16,909), of which 869 duplicates were removed. 25,859 were screened by title, at which stage papers were rejected due to unmatching study type or a clear appearance of an investigation regarding different topic as the systematic review focus on. Papers that passed title-screening were screened by their abstract. Papers were rejected at this stage if they did not investigate ADHD, neuroimaging, and stress in combination. Subsequently, the full texts of 259 studies were retrieved and assessed against the defined eligibility criteria. Through screening the references of these papers, 17 additional papers were found. Two articles were also found in Google Scholar (<https://scholar.google.com>). These additional 19 articles were also uploaded to the Rayyan for tracking and selection procedures. Articles were excluded in the final stage if it emerged that acute stress was studied or when not all the required outcome variables were reported. All literature selection processes were completed by two authors (KK and EG). Opinion differed

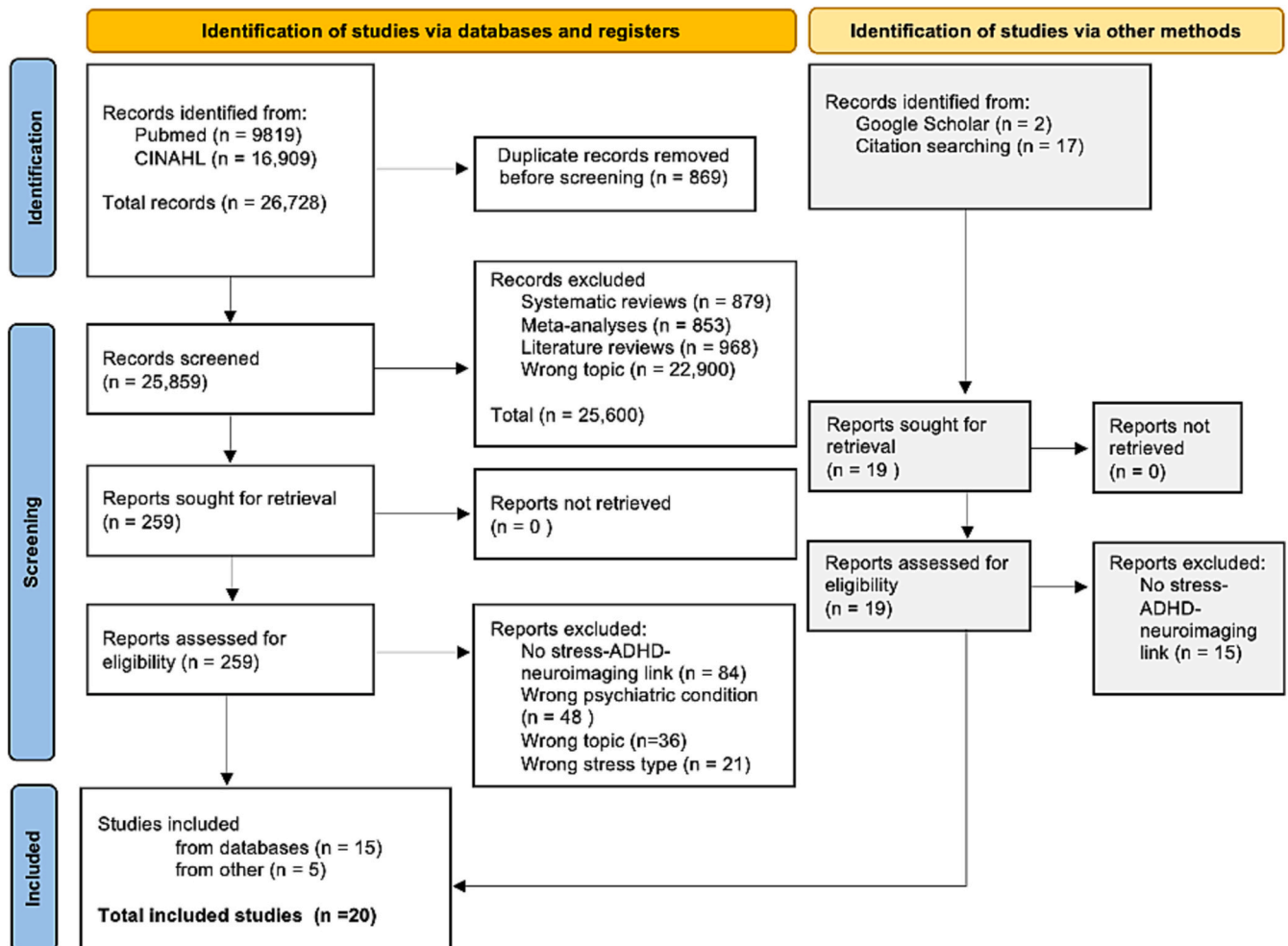


Fig. 1. PRISMA flowchart of the literature search, screening, and selection processes for qualitative analysis.

for one of the papers during the final eligibility assessment, which was resolved by a detailed analysis and discussion of the paper in question. Finally, 20 papers were eligible for inclusion in this systematic review.

### 2.3. Data extraction

Descriptive data was extracted from the 20 studies and recorded within a custom Microsoft Excel table. Simultaneously, evidence to assess study quality was gathered into an additional table for risk assessment (see [section 2.5](#)). Extracted information included the main author, year of publication, study design, data collection period, sample (location, size, groups, mean age), stress exposure (type, method of assessment, timing of assessment), neurodevelopmental assessment with regard to ADHD (method, age at assessment), neuroimaging (type, age at assessment), outcome of interest in the context of the current research question, statistical analysis, outcome association, effect sizes, and location of relevant results in the article.

### 2.4. Data synthesis

As recommended within the PRISMA guidelines, the Synthesis without Meta-analysis (SWiM) in systematic reviews reporting guideline was followed to aid in establishing a narrative synthesis of the evidence [39]. The narrative synthesis is accompanied by tables summarizing the main characteristics ([Table 1](#)), risk of bias and quality ([Table 2](#), see [section 2.5](#)), and strength of the evidence of main outcomes in all studies ([Table 3](#), see [section 2.6](#)).

### 2.5. Risk of Bias and quality assessment

The Quality in Prognosis Studies (QUIPS) tool was used to assess the quality and risk of bias in studies with respect to study population, prognostic factor measurement, measurement of confounding, outcome measurement(s), and analysis and reporting [40]. The QUIPS table was adapted to include whether a study reported on the period of data collection and the presence of a declaration of approval by an ethics committee and a statement of consent by participants. Additionally, to tailor the tool for the purposes of the current systematic review, the type, setting, validity and reliability neuroimaging methods and neuropsychiatric measurements were assessed. Stress exposure (description, setting, validity, and reliability of measurement) was considered as the prognostic factor. Risk of bias in each parameter was rated as low, medium, or high. The Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology COSMOS-E guidance letter was used to support the assessment of study methods to help avoid bias and confounding in this systematic review [41]. Additionally, an overall study quality rating was given based on the overall risk throughout all categories.

### 2.6. Strength of the evidence in individual studies

Based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, strength of the evidence was assessed in the context of specificity of the findings with respect to the association between stress exposure, neuroimaging outcome and ADHD [42].

### 2.7. Deviation from protocol

One deviation from the original study inclusion protocol occurred as to include studies that did not meet the original inclusion criteria with regard to the neuropsychiatric assessments. This can be attributed to the limited number of eligible studies that provided certified clinical diagnosis of ADHD or documented explicit and unambiguous ADHD outcomes in the participants. As a result, studies, which employed ADHD assessment questionnaires with lesser alignment to the official

diagnostic DSM/ICD guidelines and thereby yielded a non-clinical ADHD diagnosis or reported solely on ADHD symptom outcome, were also included. Additionally, studies were included which reported on ADHD outcome as part of the category of other mental disorders or externalizing disorders, or ADHD-associated facets of cognitive performance, such as inhibitory control. Occurrence of this deviation was carefully considered throughout data extraction, synthesis, and the quality assessment processes for relevant studies.

## 3. Results

In this systematic review, we summarized and critically appraised twenty studies that investigated the neural effects of various types of stressful events in relation to ADHD outcomes. A summary of the primary characteristics of these studies can be found in [Table 1](#). Among the included studies, twelve were case-control studies, while eight were cohort studies. All studies adopted a cross-sectional design for neuroimaging. Sample sizes varied from 27 [43] to 10,704 subjects [44]. Most subjects in studies were children and/or adolescents (up to 18 years old), while three studies performed neuroimaging in adult subjects [45–47], and subjects in one study were between 3 and 21 years old [48]. Subjects within the 20 studies were exposed to childhood trauma or stress [49,50] (also indicated by nomenclature i.e., Early Familial Adversity (EFA) [45], Early Life Adversity (ELA) [51], Early Life Stress (ELS) [52], Adverse Childhood Events (ACEs) [53], institutionalization [7,8,10,12,46], prenatal maternal smoking and/or alcohol consumption [47,54], “Severe Nausea and Vomiting in Pregnancy” (SNVP) [44], low BW [43,55], pre- and post-natal exposure to environmental pollutants (Polycyclic Aromatic Hydrocarbons (PAHs) and Persistent Organic Pollutants (POPs) [56–58], and growing up in families with low Socio-economic Status (SES) [48].

### 3.1. Risk of bias and quality in individual studies

A risk of bias score according to the QUIPS tool and an overall quality rating for each study was attributed on a scale of low, medium, or high risk (see [Table 2](#)) [40]. No study received an overall low quality rating, while high quality was found in eleven studies. Risk for bias regarding assessments of stress exposure was decided based on risk for retrospective recall bias and/or subjective reporting. Risk regarding ADHD outcomes was determined based on specificity and clinical relevance. High risk for bias within neuroimaging methods was assigned to studies investigating white matter (WM) structure and connectivity [49,53,55]. All studies clearly reported their findings and statistical approaches, contributing to a comprehensive and transparent assessment of the evidence.

### 3.2. Strength of the evidence in individual studies

Strength of the evidence in studies was rated in light of previous quality and bias assessments (see [Table 2](#)) as well as the specificity and the intensity of the reported outcomes relative to the effects of stress exposure in the brain in ADHD based on additional factors, as summarized in [Table 3](#) [42]. Evidence from six studies (studies of institutionalization,  $n = 4$ ; low SES status,  $n = 1$ , early trauma,  $n = 1$ ) was judged to possess the highest strength to answer the research question in this systematic review [7,8,10,45,46,48]. These studies performed an analysis of mediation by neural alterations on the association between stress exposure and ADHD-specific outcomes in medium or large sample sizes [7,8,10,46,48]. Three studies (studies of institutionalization,  $n = 1$ ; SNVP,  $n = 1$ ; low BW,  $n = 1$ ) also found a mediation by neural outcomes on the association between stress exposure and inhibitory control (small sample sizes) or externalizing disorders/psychiatric outcomes which included ADHD within medium and large sample sizes, which was rated as low to medium strength evidence [12,43,44].

Indirect evidence from nine studies (early trauma,  $n = 3$ ;

**Table 1**  
Overview of the main characteristics of the included studies (n = 20) ordered per year of publication.

Study	Location (Country)	Study design	Stress exposure, mean age at assessment	Study group(s)	Neuropsychiatric assessment, mean age at assessment	Neuroimaging method, mean age at assessment	Outcome of Interest
Skranes et al., 2007 [55]	Norway	Cross-sectional follow-up case-control study	VLBW, at birth	VLBW (n = 34, 18 females), controls (n = 47, 29 females)	ADHD-RS-IV, 15 years	MRI (DTI sequence) 15 years	WM alterations and ADHD outcomes in VLBW subjects
McLaughlin et al., 2010 [8]	Romania	Cross-sectional neuroimaging study within a longitudinal cohort	Institutionalization, n/a	IG (n = 117), control group (n = 49)	PAPA, 54 months	EEG, between 9 and 30 months	Mediation between institutionalization and ADHD symptoms by baseline EEG signals
De Zeeuw et al., 2012 [54]	The Netherlands	Cross-sectional case-control study	Prenatal exposure to smoking and alcohol, ~10 years	Unexposed (n = 132), prenatal smoking (n = 29, 3 females), prenatal alcohol consumption (n = 25, 5 females)	DISC-IV, CBCL, ~10 years	MRI, ~10 years	Structural neural alterations and ADHD as an outcome of prenatal exposure to smoking/alcohol
Slopen et al., 2012 [7]	Romania	Cross-sectional neuroimaging study within a longitudinal cohort	Institutionalization, n/a	IG (n = 136), control group (n = 72)	PAPA, 15 months	EEG, 22 months	Neural processing mediating ADHD outcome following institutionalization
Boecker et al., 2014 [45]	Germany	Cross-sectional neuroimaging study within an epidemiological cohort	EFA, 3 months	162 subjects, 94 females	MEI, SCID-I, between 2 and 15 years	EEG-fMRI, 24.4 years	Mediation of EFA and ADHD symptoms by neuronal activation
Holz et al., 2014 [47]	Germany	Cross-sectional neuroimaging study within an epidemiological cohort	Maternal smoking, WHEN	Unexposed (n = 140, 43.6% males), Smoking groups by nr. of cigarettes smoked by mother during pregnancy: 1–5 cigarettes (n = 14, 21.4% males), >5 cigarettes (n = 24, 37.5% males)	MEI, SCID-I, between 2 and 15 years	fMRI, 25 years	Mediation of prenatal maternal smoking on brain activity, ADHD outcome
Schlotz et al., 2014 [43]	United Kingdom	Cross-sectional neuroimaging study in a follow-up cohort	Low fetal growth (FG)	FG groups: low FG (n = 8), medium FG (n = 12), high FG (n = 7)	EATQ-R, unknown	MRI, 15–16 years	Association between low FG and brain volumes and ADHD, mediation of birthweight on brain volume and inhibitory control association
McLaughlin et al., 2014 [10]	Romania	Cross-sectional neuroimaging study within a longitudinal cohort	Institutionalization n/a	IG (n = 58, 28 females), controls (n = 22, 12 females).	HBQ, between 8 and 10 years	MRI, 8–10 years	Mediation of institutionalization and ADHD symptoms by variation in brain structure
Peterson et al., 2015 [57]	United States	Cross-sectional neuroimaging study in a follow-up cohort	Prenatal PAH exposure	High PAH exposure (n = 20, 9 girls), low PAH exposure (n = 20, 10 girls)	CBCL, WISC-IV, between 7 and 9 years	MRI, 7–9 years	Effects of prenatal PAH on brain morphology, processing speed, and ADHD
Pagliaccio et al., 2015 [50]	United States	Cross-sectional neuroimaging study in a longitudinal cohort	Stressful and traumatic events in childhood	107 children (54 females)	PAPA 8 years, CAPA after 8 years of age	MRI, fMRI, 7–12 years	Effect of trauma on brain function and psychiatric outcome
Park et al., 2016 [49]	South Korea	Cross-sectional case-control study	Childhood trauma	ADHD with PTE (n = 29, 26 males), ADHD without PTE (n = 25, 20 males), healthy with PTE (n = 18, 12 males), healthy without PTE (n = 23, 11 males)	K-SADS-PL, ADHD-RS-IV, ~9 years	DTI, ~9 years	PTEs-ADHD interaction with alterations in WM brain tracts
Troller-Renfree et al., 2016 [12]	Romania	Cross-sectional neuroimaging study within a longitudinal cohort	Institutionalization, n/a	IG (n = 136, 47 females), controls (n = 48, 26 females)	HBQ, 12 years	EEG, 12 years	Mediation of brain activity on association between institutionalization and externalizing behaviour or ADHD
Mortamais et al., 2017 [56]	Spain	Cross-sectional neuroimaging study within a longitudinal cohort	PAH exposure	242 children (119 girls), 8.4 years	ADHD-RS-IV, 8.4 years	MRI, 9.7 years	Relationship between PAHs exposure and BG volumes and ADHD symptoms

(continued on next page)

Table 1 (continued)

Study	Location (Country)	Study design	Stress exposure, mean age at assessment	Study group(s)	Neuropsychiatric assessment, mean age at assessment	Neuroimaging method, mean age at assessment	Outcome of Interest
Dahmen et al., 2018 [51]	Germany	Cross-sectional case-control study	ELA	Children exposed to ELA ( $n = 25$ , 50% females, 9 with ADHD diagnosis), controls ( $n = 26$ , 44% females, 5 with ADHD diagnosis)	CBCL, WASI, ~ 10.5 years	MRI, ~ 10.5 years	Association of externalizing symptoms with hippocampal volume and ELA exposure
Humphreys et al., 2019 [52]	United States	Cross-sectional cohort study	ELS	214 children (43% male)	CBCL, 11.4 years	MRI, 11.4 years	Association between structural neural alterations following ELS and ADHD
Mackes et al., 2020 [46]	Romania, United Kingdom	Cross-sectional neuroimaging study within a longitudinal study cohort	Institutionalization, n/a	IG Romanian children ( $n = 67$ , 50.7% female), controls from UK ( $n = 21$ , 38.1% female)	CBRS, 24.4 years	MRI, 24.4 years	Mediation of relationship between institutionalization and ADHD symptoms by brain volume
Wang et al., 2020 [44]	United States	Cross-sectional neuroimaging study within a prospective study cohort	SNVP	SNVP ( $n = 1496$ , 757 males, 739 females), controls ( $n = 9214$ , 4358 males, 4856 females)	CBCL, ~ 119 months	MRI, ~ 119 months	Mediation by brain area volume(s) and surface area(s) on the association between SNVP and psychiatric problems.
Machlin et al., 2020 [48]	United States	Cross-sectional neuroimaging study within epidemiological cohort	SES	ADHD ( $n = 91$ , 29.7% female), healthy controls ( $n = 783$ , 49.8% female)	NIH-TB Cognition Battery, 3–21 years	MRI, 3–21 years	Mediation of SES association with ADHD by brain structure
Hare et al., 2022 [53]	United States	Cross-sectional case-control study	ACEs	ADHD ( $n = 104$ , 74% males), healthy controls ( $n = 94$ , 67% males)	C-DISC, ~ 5.5 years	MRI, ~ 5.5 years	Impact of ACEs on brain structure in both ADHD and TD children
Sussman et al., 2022 [58]	Canada	Cross-sectional cohort study	Prenatal POP exposure	46 children (29 males)	BASC-3, 9–11 years	fMRI, 9–11 years	Association between prenatal POP exposure, neural correlates of inhibitory control and ADHD symptoms

Abbreviations: ACEs, Adverse Childhood Experiences; ADHD-RS-IV, ADHD Rating Scale-IV; BASC-3, Behavioural Assessment System for Children 3; BG, Basal Ganglia; CAPA, Child and Adolescent Psychiatric Assessment; CBCL, Child Behaviour Checklist; CBRS, Conners Comprehensive Behaviour Rating Scales; C-DISC, Computerized-Diagnostic Interview Schedule for Children; DISC-IV, Diagnostic Interview Schedule for Children Version IV; DTI, Diffusion Tensor Imaging; EEG, Electroencephalography; ELA, Early Life Adversity; ELS, Early-Life Stress; EFA, Early Family Adversity; FG, Fetal Growth; HBQ, MacArthur Health and Behaviour Questionnaire; IG, Institutionalized Group; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version; MEI, Mannheim Parent Interview; MRI, Magnetic Resonance imaging; NIH-TB Cognition Battery, NIH Toolbox Cognition Battery; PAH, Polycyclic Aromatic Hydrocarbons; PAPA, The Preschool Age Psychiatric Assessment; POP, Persistent Organic Pollutant; PTE, Potentially Traumatic Event; SCID-I, The Structured Clinical Interview for DSM-IV, German version; SES, Socioeconomic Status; SNVP, Severe Nausea and Vomiting in Pregnancy; TD, typically developing; WASI, Wechsler Abbreviated Scale of Intelligence; VLBW, Very Low Birth Weight; WISC-IV, Wechsler Scales of Intelligence for Children; WM, White Matter.

environmental pollution,  $n = 3$ ; prenatal smoking/alcohol exposure,  $n = 2$ ; low BW,  $n = 1$ ), which did not perform a mediation analysis, but in which stress exposure was separately associated with both neurological alterations and ADHD outcome was rated as low-medium to medium-high in strength [47,49,52–58].

Evidence lowest in strength was found in two studies (early life trauma,  $n = 2$ ), which considered externalizing or psychiatric disorders as outcomes in small samples and did not perform a mediation analysis [50,51].

### 3.3. The neurological impact of stress in ADHD by stress category

#### 3.3.1. Traumatic events in childhood

The highest number of included studies ( $n = 6$ ) assessed the effects of childhood trauma on brain activity and neural structure [45,49–53]. However, only Boecker et al. provided high strength evidence to answer the research question at hand, who discovered that decreased activation of the left ventral striatum (VS) during reward anticipation and increased activation of the right insula during reward delivery were associated with EFA exposure and ADHD symptoms in subjects whose mean age was 24 years old [45]. These alterations did not mediate the association between EFA and ADHD [45]. EFA was also associated with decreased neural activity of the putamen and thalamus during reward

anticipation and increased activity of the pallidum, substantia nigra, and the right posterior hippocampus during reward delivery, but not ADHD symptoms [45].

Indirect evidence was provided by three studies of early trauma. Humphreys et al. found associations of small effect sizes between larger volumes of the posterior internal capsule and the inferior temporal gyrus (ITG) in children exposed to stress, in whom these changes were also associated with increased ADHD symptoms [52]. Hare et al. observed a significant increase of small effect size in the axonal density of neurons in the corpus callosum between trauma-exposed subjects who had ADHD and those without ADHD [53]. Park et al. found that children with ADHD with trauma exposure showed significantly increased fractional anisotropy (FA) values in the left posterior limb of the internal capsule and decreased mean diffusivity (MD) values in the corpus callosum, right corona radiata, right cingulum, and right superior longitudinal fasciculus, compared to children with ADHD without trauma exposure [49]. However, no significant differences in MD and FA were found between healthy children with and without trauma exposure [49].

Two studies of early stress provided low strength evidence for alterations in structure and function of limbic structures. Dahmen et al. discovered smaller volumes in stress-sensitive hippocampal subfields in children exposed to ELA [51]. ELA was also associated with higher

**Table 2**  
Risk assessment based on the QUIPS tool in each study ordered per year of publication.

Study	Study Design	Ethics Statement	Study Population	Study Attrition	Stress Exposure	Neuro-imaging	ADHD Outcome	Study Confounding	Statistical Analysis and Reporting	Overall Quality
Skranes et al., 2017 (55)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
McLaughlin et al., 2010 (8)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow
De Zeeuw et al., 2012 (54)	Green	Green	Green	Green	Yellow	Green	Green	Green	Green	Green
Slopen et al., 2012 (7)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow
Boecker et al., 2014 (46)	Red	Green	Yellow	Green	Yellow	Green	Green	Green	Green	Yellow
Holz et al., 2014 (48)	Red	Green	Green	Green	Green	Green	Green	Green	Green	Yellow
Schlotz et al., 2014 (44)	Green	Green	Green	Green	Green	Green	Red	Green	Green	Yellow
McLaughlin et al., 2014 (10)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow
Peterson et al., 2015 (57)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Pagliaccio et al., 2015 (51)	Red	Green	Green	Green	Yellow	Green	Green	Green	Green	Green
Park et al., 2016 (50)	Green	Green	Green	Yellow	Green	Green	Green	Yellow	Green	Yellow
Troller-Renfree et al., 2016 (12)	Green	Green	Green	Green	Green	Green	Red	Green	Green	Yellow
Mortamais et al., 2017 (56)	Red	Green	Green	Green	Green	Green	Yellow	Green	Green	Green
Dahmen et al., 2018 (13)	Green	Green	Green	Green	Yellow	Green	Red	Green	Green	Yellow
Humphreys et al., 2019 (52)	Green	Green	Green	Yellow	Green	Green	Green	Green	Green	Green
Mackes et al., 2020 (13)	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Green
Wang et al., 2020 (45)	Green	Green	Green	Green	Green	Green	Red	Green	Green	Green
Machlin et al., 2020 (49)	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Green
Hare et al., 2022 (53)	Green	Yellow	Green	Yellow	Green	Green	Green	Green	Green	Yellow
Sussman et al., 2022 (58)	Red	Green	Green	Green	Green	Green	Green	Green	Green	Yellow

Colour of each cell corresponds to the either low (green), medium (yellow) or high (red) risk for bias for each study (rows) per risk parameter (columns). The final column indicates good (green), medium (yellow), or low (red) overall study quality.

symptoms of externalizing disorders, the presence of which did not explain these findings [51]. The study also performed cortisol measurements and found an association between lower diurnal cortisol with smaller hippocampal volume in the ELA-exposed subjects [51]. In Pagliaccio et al., a higher number of traumatic experiences was associated with higher activity of the amygdala in response to negative facial expressions in children [50]. This association was significantly mediated only by presence of anxiety disorder, but not externalizing disorders, which included ADHD, oppositional defiant disorder, and conduct disorder [50].

### 3.3.2. Institutionalization

Strong evidence for a mediation by structural alterations on the association between institutionalization and ADHD was found in two high quality studies. Mackes et al. discovered a significant mediation by total brain volume (TBV) and the volume of the ITG on the relationship between institutionalization and ADHD symptoms [46]. The cortical thickness of the lateral orbitofrontal cortex (OFC), insula, inferior parietal cortex, precuneus, superior temporal gyrus and sulcus, and lingual gyrus was found to mediate the association between institutionalization and ADHD symptoms of inattention and impulsivity in adolescent subjects by McLaughlin et al. in 2014 [10]. Furthermore, the cortical thickness of the supramarginal gyrus (SMG) and the fusiform gyrus mediated institutionalization and ADHD symptoms of inattention or impulsivity, respectively [10].

A mediation of the association between institutionalization and

ADHD symptoms by a neural activation pattern was also found in three studies of the BEIP cohort [7,8,12]. McLaughlin et al. 2010 discovered a mediation by reduced mid-frequency (alpha) and increased low-frequency (theta) brain activity at baseline on the association between institutionalization and ADHD symptoms [8]. Slopen et al. discovered a mediation of the association between institutionalization and ADHD symptoms by a decreased peak amplitude of the P700 signal during a task in which subjects viewed images of faces with negative emotions [7]. Troller-Renfree et al. determined a mediation by changes in error monitoring EEG signal amplitude on the association between institutionalization and externalizing behaviour [12].

### 3.3.3. Maternal risk factors

Three papers examined the neural consequences of prenatal maternal smoking and alcohol consumption, or SNP in relation to ADHD [44,47,54]. De Zeeuw et al. found a graded effect exerted by exposure to either prenatal smoking or alcohol consumption on brain volumes such that exposed children with ADHD were found to have smallest brain volumes, unexposed children with ADHD had intermediate volumes, and unexposed subjects without ADHD had the largest brain volumes [54]. These findings were of large effect sizes and also applied to the volume of the cerebellum [54]. Holz et al. who also studied prenatal smoking found decreased activity of the anterior cingulate cortex, inferior frontal gyrus (IFG), and SMG during an inhibitory control task in exposed children [47]. ADHD symptoms did not explain these differences, although higher lifetime symptoms of

**Table 3**

Main outcomes in studies and strength of the evidence (low, low-medium, medium, medium-high, or high) based on prior assessments of study quality as well as sample sizes (small, medium, or large), presence of comparison between stress-exposed(+) and un-exposed (–) groups, presence of a mediation analysis (+, yes; –, no), reported ADHD outcome, outcome associations of main findings, and reporting of effect sizes (+, yes, –, no).

Study	Stress Exposure Groups	Sample Size	Mediation analysis	ADHD Outcome	Findings	Effect Sizes	Strength of the Evidence
Skranes et al., 2007 [55]	+	Small	–	Clinical ADHD and/or ADHD symptoms	VLBW children with ADHD showed decreased FA in the external capsule, left posterior internal capsule, anterior CC, left inferior and middle fascicles compared to VLBW children without ADHD	–	Medium
McLaughlin et al., 2010 [8]	+	Medium	+	ADHD symptoms of hyperactivity and impulsivity	Decreased alpha and increased theta EEG signals were found to mediate the association between institutionalization and increased ADHD symptoms	+	High
De Zeeuw et al., 2012 [54]	+	Small	–	Clinical ADHD	Decreased TBV and decreased cerebral and cerebellar volumes were associated with both prenatal smoking and alcohol consumption and ADHD outcome	–	Medium
Slopen et al., 2012 [7]	+	Medium	+	ADHD symptoms	Amplitude of the P700 EEG signal during an emotion recognition task mediated the association between institutionalization and ADHD	+	High
Boecker et al., 2014 [45]	+	Medium	+	ADHD symptoms	Decreased activation of left VS during reward anticipation and increased activation of the right insula were associated with EFA exposure and increased ADHD symptoms.	–	High
Holz et al., 2014 [47]	–	Small	–	Lifetime ADHD symptoms	Prenatal exposure to smoking was associated with decreased activity of the ACC, IFG, SMG and higher ADHD symptoms. Neural activity was not mediated by ADHD in children exposed to prenatal smoking.	+	Low-medium
Schlotz et al., 2014 [43]	–	Small	+	Inhibitory Control	The association between BW and inhibitory control was mediated by volume of the caudate.	+	Medium
McLaughlin et al., 2014 [10]	+	Medium	+	ADHD symptoms of inattention and impulsivity	Cortical thickness of several cortical regions mediated the association between institutionalization and inattention and impulsivity	+	High
Peterson et al., 2015 [57]	–	Small	Not executed	ADHD symptoms	Decreased WM volumes were associated with PAH exposure and increased ADHD symptoms. PAH exposure was not associated with ADHD symptoms.	+	Low-medium
Pagliaccio et al., 2015 [50]	–	Small	–	Externalizing disorders	Presence of externalizing disorders did not affect association between trauma and activation of the amygdala or hippocampus.	+	Low
Park et al., 2016 [49]	+	Small	–	ADHD symptoms	Increased FA in posterior limb of internal capsule, decreased MD in CC in ADHD with PTE. No difference in healthy children with and without PTE	–	Low-medium
Troller-Renfree et al., 2016 [12]	+	Medium	+	Inattention, impulsivity, externalizing problems	Error monitoring signals moderated the association between institutionalization and symptoms of impulsivity, not attention	+	Medium
Mortamais et al., 2017 [56]	–	Medium	Not executed	ADHD symptoms	Volume of the caudate nucleus was associated with PAH exposure and ADHD symptoms. PAH exposure was not associated with ADHD symptoms.	+	Low-medium
Dahmen et al., 2018 [51]	+	Small	–	Externalizing disorder symptoms	Externalizing disorder symptoms did not explain volumetric differences in the hippocampus. ELA exposed children had decreased hippocampal volumes and increased externalizing symptoms.	–	Low
Humphreys et al., 2019 [52]	–	Medium	–	ADHD symptoms	Larger volumes of the posterior internal capsule and ITG were associated with trauma exposure and increased ADHD symptoms	+	Low-medium
Mackes et al., 2020 [46]	+	Small	–	ADHD symptoms	TBV mediated the association between institutionalization and ADHD symptoms	+	High
Wang et al., 2020 [44]	+	Large	+	Psychiatric problems	Cortical volume and SA mediated association between SNVP exposure and psychiatric problems	+	Medium
Machlin et al., 2020 [48]	+	Medium	+	ADHD outcome	Significant mediation by subcortical volumes (L, R cerebellum, right caudate) on association between SES and ADHD outcome	–	High
Hare et al., 2022 [53]	+	Medium	–	ADHD symptoms of Inattention, hyperactivity	Increased axonal density of the CC was associated with stress exposure in ADHD children, not control children	+	Medium-high
Sussman et al., 2022 [58]	–	Small	–	ADHD symptoms and inhibitory control	POP exposure was separately associated with decreased inhibitory control and ADHD symptoms	+	Medium

Abbreviations: ACC, Anterior Cingulate Cortex; ACEs, Adverse Childhood Experiences; ADHD, Attention-Deficit Hyperactivity Disorder; BW, Birth Weight; CC, Corpus Callosum; CT, Cortical Thickness; EEG, Electroencephalography; ELA, Early Life Adversity; ELS, Early-Life Stress; FA, Fractional Anisotropy; FG, Fetal Growth; IG, Institutionalized Group; IFG, Inferior Frontal Gyrus; ITG, Inferior Temporal Gyrus; L, Left; PAH, Polycyclic Aromatic Hydrocarbons; POP, Persistent Organic Pollutants; PTE, Potentially Traumatic Event; R, Right; SA, Surface Area; SES, Socioeconomic Status; SMG, Supramarginal Gyrus; SNVP, Severe Nausea and Vomiting in Pregnancy; TBV, Total Brain Volume; VLBW, Very Low Birth Weight; WM, White Matter.

ADHD were found in exposed subjects [47].

In Wang et al., smaller volume and surface area of the cingulate cortex, precuneus, superior medial prefrontal cortex mediated the association between SNVP and psychiatric problems, which included ADHD symptoms, social problems, and depression [44].

### 3.3.4. Environmental pollution

Peterson et al. and Mortamais et al. investigated the effects of pre- and postnatal exposure to air pollution, assessed by measurement of PAHs, in early school-age children [56,57]. These two PAH exposure studies had very low sample sizes, such that no expected association between PAH exposure and ADHD outcomes was found [56,57]. Neither could subsequently perform a planned mediation analysis by structural brain alterations on the association between PAH exposure and ADHD outcome [56,57]. Mortamais et al. investigated structural alterations in the basal ganglia (caudate nucleus, putamen, globus pallidus), where a significant reduction in volume of the caudate was found following postnatal PAH exposure and associated with increased ADHD symptoms [56]. Peterson et al. found that children with prenatal PAH exposure had smaller WM volumes in the prefrontal, lateral and temporal lobes of the cortex [57]. These differences were separately associated with slower processing speed and increased ADHD symptoms [57]. Indirect evidence was also provided by Sussman et al., who found that subjects prenatally exposed to POPs exhibited decreased inhibitory control, which was associated with decreased activation in the right IFC and right anterior insula [58].

### 3.3.5. Low socioeconomic status

Machlin et al., in a study which received a high quality rating within the current systematic review, investigated the effects of growing up in low status SES households in children in whom decreased volume of the left and right cerebellum, and the right caudate, mediated the association between SES and ADHD [48].

### 3.3.6. Low birth weight

Skranes et al. found that VLBW children with ADHD had significantly lower FA values especially in the external capsule and left inferior and middle fascicles [55]. Significant FA decreases in these children were also observed in the left inferior posterior capsule, anterior corpus callosum, right inferior fascicle, and the right superior fascicle [55]. Inattention symptoms were correlated with the FA of the left external capsule and the right superior and left middle fascicles [55]. However, no effect sizes were reported for these outcomes, and it was not reported whether children with ADHD in the control groups (non-VLBW) displayed similar outcomes. Schlotz et al. investigated whether structural alterations in various brain regions mediated the relationship between low BW and inhibitory control, or attention [43]. Only inhibitory control, not attention, was associated with BW in this study [43]. Of the chosen brain regions of interest, a smaller surface area of the lateral and medial OFC, right IFG, a smaller caudate volume, and increased cortical thickness of the medial OFC were associated with low BW [43]. A moderate mediation effect was discovered by decreased caudate volume on the association between low BW and inhibitory control [43].

## 4. Discussion

In this first systematic review summarizing the evidence for the neurological effects of stress in ADHD, findings suggest that exposure to stress may result in alterations in the structure and functioning of the brain which may also be mediators of the association between stress exposure and ADHD outcomes. However, the mechanisms underlying the possible mediators of stress exposure and brain structural and functional alterations in ADHD are not well understood. Further investigation into the specific mechanisms underlying these interactions would provide valuable insights into understanding the complex relationship between stress and ADHD in the brain.

The findings in this narrative systematic review suggest a potential role of structural and functional neural alterations in mediating the relationship between stress exposure and ADHD. However, drawing conclusions about causal effects of stress was limited by small sample sizes in studies and overall low study capacity to distinguish mere neurological correlates in ADHD from causal alterations due to stress exposure. Furthermore, although the critical appraisal of studies revealed sufficient quality, findings should be treated with caution due to the role of unknown factors, especially genetic ones, and high heterogeneity between studies in baseline characteristics, methodologies, and outcomes with variable strength of the evidence. Meanwhile, high heterogeneity of studies and respective outcomes is reflective of the complex etiology and manifestation of ADHD, which is indeed likely affected by a multitude of factors in a cumulative manner [22].

To address some limitations, a major limiting factor in most included studies was the absence of a mediation analysis to explore whether neural alterations moderate the effects of stress exposure on ADHD, which thereby restricted the ability to investigate a causal relationship between neural alterations and stress in ADHD. Furthermore, while the subjective reporting of stress exposure in several studies was at risk for retrospective recall bias [59], all studies were cross-sectional, thereby limiting the possibility of reporting on the effects of stress on neurodevelopment. The included studies also predominantly focused on children, reinforcing the need for future longitudinal research to assess whether stress-induced neural alterations persist into adulthood. Moreover, it is important to note that most studies did not report on differences in results between gender, despite well-described sex-specific outcomes in ADHD, pubertal status, ADHD subtype, or medication status. Indeed, only a single study examined a potential effect of medication intake by subjects, and found no differences in their results depending on whether subject who reported intake of ADHD medication were included or excluded in their analyses [10], while only 9 other included studies reported on the intake of medication by subjects [7,8,12,44,45,49,51,54,58]. The potential role of such factors in stress-related neural alterations in ADHD therefore remains an area requiring further exploration. Additionally, considering the high heritability of ADHD, it is crucial to highlight that most studies did not account for the genetic profiles of subjects related to ADHD or stress-related functions [60]. Regarding neuroimaging outcomes, in addition to small sample sizes, analysis of neuroimaging outcomes in the included studies may have been affected due to the use of different analytical software and statistical approaches [61]. Small sample sizes have been associated with low replicability, especially common in fMRI studies of children [61,62]. Furthermore, given the proclivity of ADHD patients for excessive motion, results from functional and WM neuroimaging methods should be treated with caution due to their high motion sensitivity [49,62]. It can hereby be recommended that future studies follow specific guidance to avoid confounding in psychiatric neuroimaging [63]. Finally, this systematic review mainly discussed findings which supported the assumption that the association between stress and ADHD may have a neural basis. Therefore, in future studies, especially once accumulated evidence would allow to conduct a meta-analysis, it will be important to also consider results of no effect.

Ultimately, it is essential to consider the strengths and limitations of each type of evidence and to integrate findings from multiple studies to establish robust and converging evidence for these pathways in the future. As several studies focused on an association between stress exposure, neural outcomes, and other psychiatric disorders, more research is required to distinguish ADHD-specific outcomes in those studies. Lastly, studies should consider different ADHD subtype diagnoses and aim to gather as much information as possible about the type, intensity, and duration of stress exposure.

Risk factors can be mitigated with certain approaches. For instance, environmental pollution can be considered a modifiable risk factor for ADHD. Since exposure to environmental toxins, including air pollution, has been linked to structural changes in the brain [56–58], carrying out

environmental clean-up activities may help lower the chance of developing ADHD. Performing early screening for other risk factors such as prenatal smoking, alcohol consumption, or SNVP, could help identify children with a high risk for ADHD. On the other hand, it could also be useful to investigate and promote awareness of factors that may counteract the negative effects of trauma such as parental sensitivity, improved SES, social support, cognitive stimulation, medication, and environmental enrichment [64]. Moreover, the inclusion of genetics, given the substantial heritability of ADHD, and epigenetics, which may serve as a link between stress exposure and ADHD by modulating the expression of genes implicated in neural development and the stress response, could potentially enhance the efficacy of interventions aimed at preventing and treating ADHD in children at elevated risk [65–67].

## 5. Conclusion

This systematic review provides evidence for neural alterations associated with stress, which may directly or indirectly contribute to the development or an increase of clinical ADHD or ADHD symptoms. However, a causal role of stress is difficult to establish, which, while reflective of the complexity of the multidirectional interactions between stress, the brain, and ADHD, warrants conducting further studies, especially in larger sample sizes and with a longitudinal design. Future studies should also aim to expand investigations towards a wider variety of neural outcomes and stress exposures while evaluating outcomes in a highly defined manner with respect to clinically relevant ADHD outcomes. Furthermore, genetic and molecular studies may help elucidate specific disease mechanisms involved in the neural alterations caused by stress in ADHD. Overall, stress may play a highly influential role in ADHD pathophysiology and requires consideration as a highly potent factor within the conceptualization of ADHD etiology. Furthermore, environmental risk factors for ADHD, which pose physiological stress, demand recognition as potential modifiable environmental risk factors. Raising awareness regarding the impact of these risk factors could contribute to earlier identification of individuals with high risk and allow for timely prevention and intervention strategies. Furthermore, novel treatments could be developed based on these findings and provide guidance in developing strategies to treat ADHD in patients exposed to stress.

## CRedit authorship contribution statement

**Kristin Koppelmaa:** Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristine Marie Yde Ohki:** Writing – review & editing. **Natalie Monet Walter:** Writing – review & editing. **Susanne Walitza:** Writing – review & editing, Conceptualization. **Edna Grünblatt:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Conceptualization.

## Declaration of competing interest

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