Prevention Science (2024) 25 (Suppl 2):S316–S336
https://doi.org/10.1007/s11121-022-01398-w

Childhood Physical Health and Attention Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Modifiable Factors

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Accepted: 30 June 2022 / Published online: 10 August 2022

Abstract

Although neurobiologic and genetic factors figure prominently in the development of attention deficit/hyperactivity disorder (ADHD), adverse physical health experiences and conditions encountered during childhood may also play a role. Poor health is known to impact the developing brain with potential lifelong implications for behavioral issues. In attempt to better understand the relationship between childhood physical health and the onset and presence of ADHD symptoms, we summarized international peer-reviewed articles documenting relationships between a select group of childhood diseases or health events (e.g., illnesses, injuries, syndromes) and subsequent ADHD outcomes among children ages 0–17 years. Drawing on a larger two-phase systematic review, 57 longitudinal or retrospective observational studies (1978–2021) of childhood allergies, asthma, eczema, head injury, infection, or sleep problems and later ADHD diagnosis or symptomatology were identified and subjected to meta-analysis. Significant associations were documented between childhood head injuries, infections, and sleep problems with both dichotomous and continuous measures of ADHD, and between allergies with dichotomous measures of ADHD. We did not observe significant associations between asthma or eczema with ADHD outcomes. Heterogeneity detected for multiple associations, primarily among continuously measured outcomes, underscores the potential value of future subgroup analyses and individual studies. Collectively, these findings shed light on the importance of physical health in understanding childhood ADHD. Possible etiologic links between physical health factors and ADHD are discussed, as are implications for prevention efforts by providers, systems, and communities.

Keywords Attention deficit/hyperactivity disorder · Meta-analysis · Childhood physical health · Pediatrics · Head injuries · Sleep problems · Infections · Allergies

Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental condition of childhood, with 8% of all US children ages 3–17 years estimated to have a current diagnosis (Bitsko et al., 2022). This represents a substantial portion of the population with a chronic condition characterized by impulsivity, hyperactivity, and inattentiveness often requiring specific support services and medications for comprehensive care (Wolraich et al., 2019), amounting to significant economic impact (Doshi et al., 2012). Although many individuals with ADHD can function adaptively, particularly with appropriate therapies and supports, the condition's symptoms can present considerable challenges addressable through prevention, treatment, and support (Sonuga-Barke & Halperin, 2010; Wolraich et al., 2019).

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Treatment for child and adolescent ADHD typically includes supporting positive behaviors and addressing comorbid medical and psychological conditions, such as adolescent substance use (Wolraich et al., 2019). From a clinical standpoint, screening and management of ADHD can be both time and resource intensive, requiring familiarity with known risk factors and treatment guidelines. This is further complicated by the fact that, although children possess remarkable resilience, they are vulnerable to developmental disruptions. Attentional abilities are honed throughout childhood and are key for managing the neural processes that allow for the acquisition of skills, knowledge, and appropriate social, academic, and adaptive functions (Claussen et al., 2021; Hanania & Smith, 2010). Children with delays or deficits in these areas may experience adverse outcomes, including rejection by peers, academic challenges, and behavioral issues (Faraone et al., 2021).

The development of ADHD is likely to involve a combination of multiple environmental and genetic factors that individually may have small effects (Faraone et al., 2021), Although the heritability of ADHD is established, factors at multiple ecological levels can also affect neurodevelopmental outcomes and are likely more amenable through medical and public health intervention (Jensen, 2000; Nigg, 2018). Thus, calls have been made to better characterize plausible risk factors in order to better apportion resources that might enhance the condition's diagnosis, prevention, and treatment (Narad et al., 2018; Quach et al., 2018; Sonuga-Barke & Halperin, 2010). One set of factors that may be relevant are health experiences and conditions during childhood, particularly as efforts to identify and manage ADHD symptoms often involve healthcare providers and systems (Wolraich et al., 2019). Certain early-life experiences that typically come to the attention of healthcare providers could be opportune for intervention to prevent direct morbidity and mortality, as well as for possible auxiliary benefits for ADHD.

The literature points to several childhood physical health factors shown to be associated with ADHD symptom onset and severity, such as injuries (Adeyemo et al., 2014; Narad et al., 2018), infectious disease (Mora et al., 2020), nutritional status (Curtis & Patel, 2008), atopic conditions such as allergies, eczema, and asthma (Cortese et al., 2018; Miyazaki et al., 2017; van der Schans et al., 2017), sleep problems (Mehta et al., 2019; Weiss et al., 2015), and healthcare-related exposures, such as corticosteroid use (Crowther et al., 2016). A firm understanding of the etiology explaining these associations remains elusive (Faraone & Larsson, 2019), with evidence to date positing that the pathogenesis of ADHD reflects the range of mechanisms through which blood oxygen, blood flow, and injury or inflammation can impact the systemic immune and neuroendocrine systems (Allred et al., 2017; Verlaet et al., 2014). Effectively, such insults could impact the central nervous system, possibly in regions governing executive function (Buske-Kirschbaum et al., 2013), motor activity (Teicher et al., 2000), or temporal information processing (Toplak et al., 2006). Individual factors are unlikely to trigger ADHD symptom onset alone, and ADHD subtypes do not necessarily correlate with consistent pathophysiologic profiles (Poelmans et al., 2011; Wallis et al., 2008).

In the absence of obvious genetic or pathophysiologic mechanisms to serve as intervention targets, focusing on potentially modifiable child health experiences with reliable associations to ADHD could represent more proximal levers for improving population health (Fagan et al., 2019; Halperin et al., 2012). Thus, the present paper provides meta-analytic results to determine whether certain child physical health factors are associated with subsequent ADHD symptoms and diagnosis.

Methods

This paper leverages a larger set of meta-analyses of potential risk factors for ADHD in childhood. The review protocol of the full set of meta-analyses, which was not previously registered, is described in Bitsko et al. (2022). The same literature search and analytic methods were followed in each paper, to allow for comparisons of results across as well as within papers. We positioned the present paper to target physical health conditions or experiences that can be encountered in utero or during childhood. Other papers report on experiences specific to pregnancy or childbirth Bitsko et al. (2022), chemical or environmental exposures Dimitrov et al. (under review), or caregiver characteristics and behaviors Claussen et al. (2022), Maher et al. (under review), Robinson et al. (2022). Here we highlight methodological details pertinent to "childhood physical health factors," defined as health conditions, experiences, or healthcare-related exposures that occur in individuals aged 0 to 17 years. We specifically focused on factors for which literature suggests a potential association with ADHD, ultimately including the eight child physical health factors for which there was a sufficient body of published studies that met eligibility criteria: allergies, asthma, corticosteroid use, eczema, head injuries, infections, malnutrition, and sleep problems.

Our systematic review focused on non-experimental studies in which the risk factor of interest took place at least 6 months prior to assessing the ADHD outcome (i.e., longitudinal or retrospective studies). The systematic review was first conducted in 2014, using a bottom-up search approach covering terms for ADHD symptomatology or diagnosis and known or suspected risk factors, and a top-down approach including terms for ADHD symptomatology or diagnosis

and terms identifying studies of risk. Search strings used in the initial bottom-up approach included terms for infection, bacteria, virus, fungus, protozoa, malnutrition, sleep, and injury; terms for allergies, asthma, eczema, and corticosteroids were identified in the top-down phase (see Bitsko et al., 2022 and Appendix 1). This process yielded 208 potentially eligible childhood physical health articles garnered from directed searches and iterative reference mining. A secondary review of titles and abstracts was then completed, excluding 144 articles. Articles were excluded if they had overlapping populations, no relevant exposure or outcome measurements, no control group, adult study sample, or reporting concurrent measurements of exposure and outcome. The remaining 64 articles then underwent full text review, further excluding 18 articles that did not contain the necessary data for the analyses. In 2021, to account for papers that had been published in the interim, we conducted a secondary follow-up search applying identical terms and criteria from the 2014 review. Papers published from 2014 to January 2021 were reviewed using the same criteria, yielding 11 additional articles for a total of 57 (Fig. 1). Several articles contained multiple eligible outcomes or study populations, resulting in 69 total effect sizes.

Only factors with at least three effect sizes from individual studies for a given ADHD outcome were included in reported analyses see Bitsko et al. (2022). Corticosteroids and malnutrition were excluded due to an insufficient number of eligible studies. Random-effects models were used to estimate weighted, pooled effect sizes accounting for the variation in effect size between studies. These calculations were conducted and presented separately for studies in which the results were reported using continuous (e.g., means and standard deviations, correlations) vs. dichotomous (e.g., raw counts, odds ratios) outcomes. Correlation coefficients (CC) were calculated for continuous statistics, and odds ratios (OR) were calculated for dichotomous statistics. Details on how articles with multiple study populations, effect sizes, or measures of the outcome were handled to ensure independence of observations in each analysis are described in Bitsko et al. (2022). Heterogeneity of effect

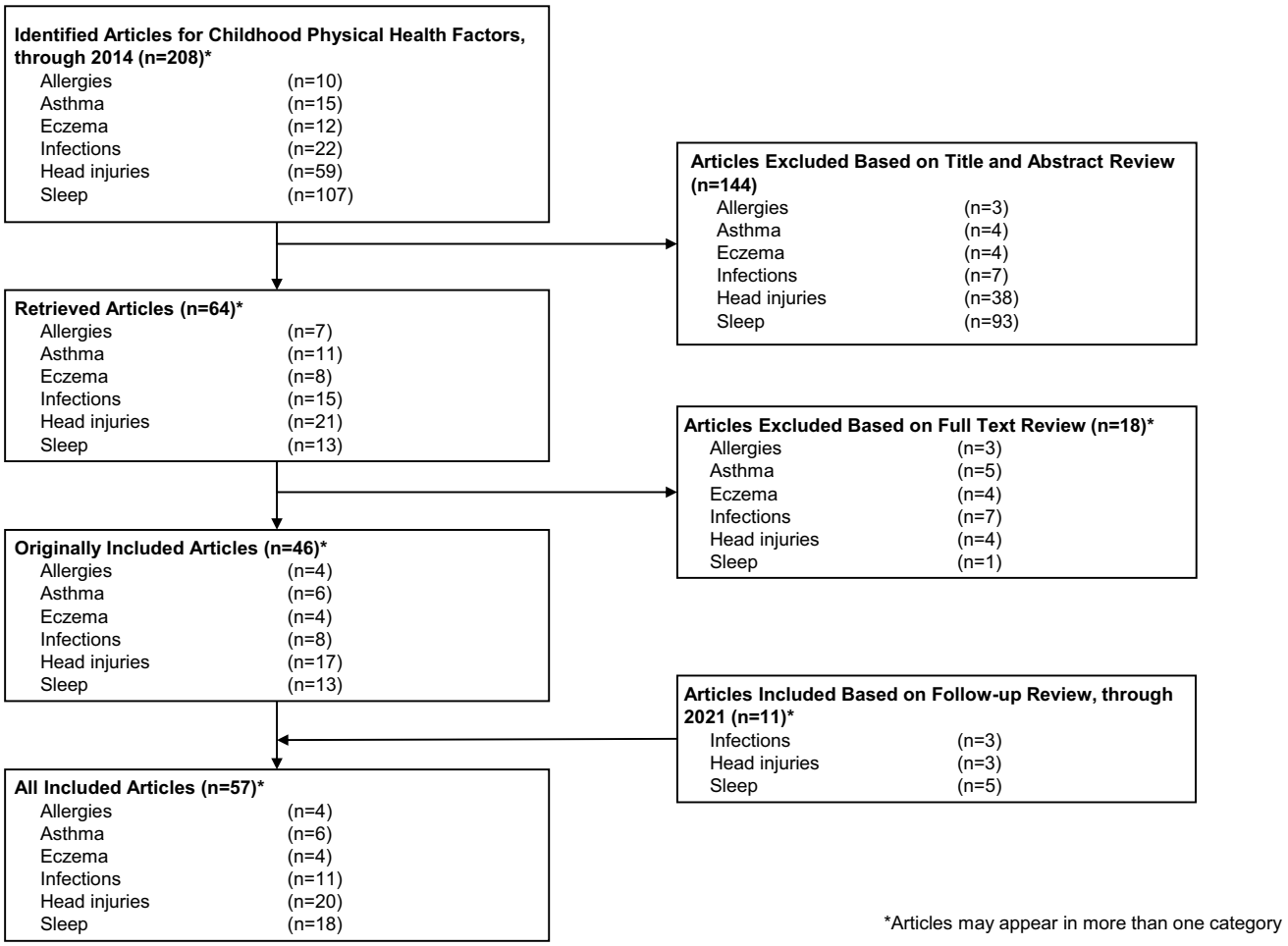

Fig. 1 Flowchart of triage process for inclusion/exclusion of articles identified for meta-analytic review of childhood physical health risk factors for attention

sizes across studies was assessed using Cochran's Q statistic (DerSimonian & Laird, 1986).

For the current meta-analysis, articles on allergies (i.e., type I hypersensitivity reactions) could have included different clinical presentations such as allergic rhinitis, conjunctivitis, or sinusitis (Mahr & Sheth, 2005). Studies on eczema also included investigations in which the alternate term, atopic dermatitis, was used. Studies on childhood infection included pediatric exposures to infectious agents in utero or postnatally. For studies on childhood head injuries, we examined two separate subsets: studies that investigated head injury experiences relative to other bodily injuries (e.g., burns) and studies that examined head injuries relative to normal, healthy controls. Head injuries refer to any mechanical or traumatic injury to a child's head and could have included events ranging from concussions (i.e., mild traumatic brain injury) to more severe traumatic brain injuries (Haarbauer-Krupa et al., 2018). Sleep problems included any descriptions of childhood challenges with sleep duration, quality, or consistency.

Results

The 57 included studies were published from 1978 to 2021, with nearly half (47%) published since 2010. Studies represented 253,423 distinct children across 20 countries spanning Asia, Australia, Europe, and the Americas. The USA was the most commonly represented country ($n=16$). The identified risk factors were allergies ($n=4$), asthma ($n=6$), eczema ($n=4$), infections ($n=11$), head injuries ($n=20$), and sleep problems ($n=18$). Notably, three studies contained effect sizes for multiple factors; these investigations assessed allergy and eczema with either asthma or childhood infections. We depict study characteristics in Table 1, and forest plots with effect sizes and 95% confidence intervals (CIs) in Appendix 2.

Effect sizes (ORs and CCs) from random-effects models with heterogeneity findings are described below and in Table 2. For six risk factors, we had sufficient studies to calculate weighted effect sizes when examining any ADHD outcomes (i.e., across studies that used diagnosis, inattention, or hyperactivity/impulsivity, from here on referred to as ADHD overall). There were fewer factors with the requisite number of studies to examine risk based on ADHD diagnosis (two factors), inattention (two factors), or hyperactivity/impulsivity (four factors) as a separate set. The strength of association between factors and continuous ADHD outcomes ranged from 0.12 (95% CI: 0.06, 0.18; sleep with ADHD overall) to 0.36 (95% CI: 0.25, 0.47; head injuries relative to normal controls with ADHD overall). For dichotomous outcomes, significant effect sizes ranged from 1.67 (95% CI: 1.23, 2.27; head injuries relative to other injuries with ADHD diagnosis) to 3.25 (95% CI: 1.61, 6.53; infections with ADHD overall).

Results by Factor

Several factors typically described as atopic conditions were examined in the current analysis, specifically allergies, eczema, and asthma. Drawing on four eligible studies with dichotomously reported results, childhood allergies were associated with greater odds for subsequent ADHD overall (capturing both symptoms and diagnoses; OR: 1.71, 95% CI: 1.24, 2.37), with no significant heterogeneity detected. We did not observe a statistically significant pooled measure of association between asthma and ADHD within the seven studies with sufficient data, whether defined by dichotomous effect sizes of ADHD overall ($k=4$), continuous effect sizes of ADHD overall ($k=3$), or continuous effect sizes for hyperactivity/impulsivity symptoms ($k=3$). However, for asthma, significant heterogeneity was observed among continuously reported effect sizes in the ADHD overall and hyperactivity/impulsivity analyses. There was no statistically significant association between eczema or atopic dermatitis and dichotomous ADHD overall ($k=4$), nor was there significant heterogeneity. Forest plots of effect sizes are found in the supplemental materials.

Among investigations on childhood infections, eligible studies demonstrated that infection was associated with greater odds for ADHD overall measured dichotomously ($k=9$; OR: 3.25, 95% CI: 1.61, 6.53). The association of infections and dichotomous effect sizes for ADHD diagnosis ($k=4$) and hyperactivity/impulsivity symptoms ($k=3$) did not reach statistical significance. Studies reporting continuous effect sizes evidenced positive associations between childhood infections and later ADHD overall ($k=4$; CC: 0.16, 95% CI: 0.06, 0.26). Of note, all infection and ADHD risk factor analyses demonstrated significant heterogeneity except for the dichotomous ADHD diagnosis effect size analysis.

For head injuries, 20 studies were assessed, the most studies for any of the risk factors we evaluated. Studies comparing head injuries to other injuries evidenced significantly higher odds for ADHD, whether defined based on ADHD overall ($k=10$; OR: 1.89, 95% CI: 1.35, 2.67) or diagnosis ($k=7$; OR: 1.67, 95% CI: 1.23, 2.27). Head injuries were also positively associated with continuous effect sizes for ADHD, for ADHD overall ($k=13$; CC: 0.27, 95% CI: 0.13, 0.41), inattention symptoms ($k=9$; CC: 0.31, 95% CI: 0.11, 0.51), and hyperactive/impulsive symptoms ($k=5$; CC: 0.21, 95% CI: 0.11, 0.31). Similarly, for the studies comparing head injuries to normal controls, head injury was significantly associated with all dichotomous and continuous effect sizes we were able to examine. Greater summary odd ratios for ADHD overall ($k=8$; OR: 2.13, 95% CI: 1.40, 3.25) and

Table 1 Characteristics of 57 studies included for meta-analytic review of childhood physical health risk factors for attention deficit/hyperactivity disorder (ADHD)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Anderson et al. (1998)	Childhood head injuries	36	8–14	89.0	Inattention (Code Transmission)[S]	Clinical, case–control research study of children with TBI history and without (Australia)	Medical diagnosis of child TBI
Anderson et al. (2005)	Childhood head injuries	42	7.3–7.9	64.6	ADHD symptoms (Continuous Performance Task)[S]	Clinical, case–control research study of children with TBI history and without (Australia)	Medical documentation of child TBI
Babikian et al. (2011)	Childhood head injuries	190	11.9–12.8	46.0–64.0	Inattention (Span of Apprehension Test)[S]	Clinical, case–control research study of children with TBI history and without (USA)	Medical documentation of child TBI
Bennett and Haggard (1999)	Childhood infections	9278/9283 [a]	10	52.0	ADHD symptoms (RCBQ)[S]	Birth cohort study (BCS70; UK)	Retrospective parent report of suspected or confirmed child middle ear infection (hearing problems with purulent ear discharge)
Bilenberg et al. (2011)	Childhood infections	332	4–18	63.9	ADHD symptoms (SDQ)[P]	Twin registry (Danish Twin Registry; Denmark)	IgG antibody testing of postnatal blood samples
Bonuck et al. (2012)	Sleep	9007	4–7	51.5	Hyperactivity (SDQ)[P]	Birth cohort study (ALSPAC; UK)	Retrospective parent report of child snoring, apnea, and mouth breathing
Bussing et al. (1995)	Asthma	7152	5–17	50.3–62.1	Hyperactivity (BPI)[P]	Nationally representative cross-sectional survey (NHIS-CH; USA)	Retrospective parent report of child asthma presence and asthma suffering
Calam et al. (2005)	Asthma	9555	11–17	50.1	Hyperactivity (SDQ)[P,T,S]	Cross-sectional survey (UK NMHS; UK)	Retrospective parent report of child asthma presence
Campbell et al. (1978)	Sleep	41	4.5–7.5	85.2	Hyperactivity (CQ)[P]	Longitudinal study recruited from private practice pediatricians (Canada)	Retrospective parent report of babies' sleep requirements and sleep regularity
Carpena et al. (2020)	Sleep	3343	11	48.8	Diagnosis (DAWBA)[P]	Prospective cohort study recruited from hospitals after childbirth (Pelotas; Brazil)	Parent report of restless sleep
Catroppa et al. (2007)	Childhood head injuries	34	9.6–10.4	62.9	Inattention (code transmission)[S]	Clinical, case–control research study of children with TBI history and without (Australia)	Medical diagnosis of child TBI
Chervin et al. (2005)	Sleep	229	2–17	54.3	Hyperactivity (CQ)[P]	Prospective cohort study recruited from general pediatrics clinics (USA)	Retrospective parent report of child snoring, sleepiness, and sleep-disordered breathing

Table 1 (continued)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Fay et al. (1994)	Childhood head injuries	30	9–19	n/a	Hyperactivity (CBCL)[P]	Clinical, case–control research study of children with TBI history and without (USA)	Medical diagnosis of child TBI
Ganesalingam et al. (2006)	Childhood head injuries	130	6–11	71.0	Inattention (TEA-Ch)[C]	Clinical, case–control research study of children with TBI history and without (USA)	Medical documentation of child TBI
Gau et al. (2008)	Childhood infections	258	4–16	59.0	ADHD symptoms (CQ)[P,T]	Clinical, case–control research study of children with enterovirus 71 central nervous system infection and without (Taiwan)	Confirmation of enterovirus 71 infection by serological, immunological, or viral culture and evidence of central nervous system involvement
Genuneit et al. (2014)	Eczema	770	6–11	50.1	Diagnosis (parent report)	Prospective cohort study of mothers presenting to deliver babies in OB/GYN department (Germany)	Retrospective parent report of child symptoms for atopic eczema
Gregory et al. (2004)	Sleep	4387	7	n/a	Hyperactivity (SDQ)[P]	Birth cohort study (TEDS; UK)	Retrospective parent report of child sleep problems
Gurevitz et al. (2014)	Sleep	116	7.77–8.17	67.2	Diagnosis (DSM-IV)	Clinical, case–control research study of children with ADHD and without (Israel)	Medical records indicating child sleep problems or recurrent awakenings
Hadzic et al. (2017)	Childhood infections	120	7.6	66.5	Diagnosis (DSM-IV)	Clinical, case–control retrospective study of children with or without meningitis (Bosnia and Herzegovina)	Medical records of hospital treatment for meningitis
Hagerman and Falkenstein (1987)	Childhood infections	51	6–13	88.0	Hyperactivity (CQ)[P,T] or diagnosis (DSM-III)	Clinical sample of children referred for hyperactivity or school failure (USA)	Medical or parent documentation of child recurrent otitis media
Hak et al. (2013)	Allergies; childhood infections; eczema	4420	9.6	100.0	Diagnosis (NHS READ)	Nationally representative case–control research study (UK GPRD; UK)	Medical records indicating child atopic disorders (including asthma), atopic dermatitis, allergic rhinitis, and allergies
Hawley et al. (2004)	Childhood head injuries	93	5–15	69.2	Inattention (questionnaire)[P]	Clinical, case–control research study of children with TBI and without (UK)	Retrospective parent report of child TBI experience

Table 1 (continued)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Hersher (1978)	Childhood infections	794	7–13	90.9	Hyperactivity (clinic assessment)[P,T]	Clinical sample of children referred for behavioral problems (USA)	Medical records indicating child otitis media
Huhdanpää et al. (2019)	Sleep	689	5	52.8	Hyperactivity and Inattention (FTF and SDQ)[P]	Prospective birth cohort study of families attending maternity clinics (child sleep; Finland)	Prospective parent report of sleep problems (including short sleep)
Jaspers et al. (2013)	Sleep	1664	11.09–16.26	47.8	ADHD symptoms (CBCL)[P]	Prospective cohort study of children who contacted specialty mental health services (TRAILS; the Netherlands)	Retrospective parent report of child sleep problems
Keenan et al. (2008)	Childhood head injuries	60,972	2–10	51.2	Diagnosis (NHS READ)	Retrospective cohort study from primary care practice records (HIND; UK)	Medical records indicating child head injury
Keenan et al. (2018)	Childhood head injuries	219	9	63.8	Hyperactivity (SDQ)[P] and ADHD symptoms (CBCL)[P]	Prospective clinical sample of children attending pediatric trauma centers (USA)	Medical records indicating child head injury
Kortesoja et al. (2020)	Sleep	3703	17	48.8	Hyperactivity (SDQ)[S]	Prospective population cohort study of children in metropolitan secondary schools (MetLoFin; Finland)	Self-report of sleep problems (difficulty falling asleep or night waking)
Kramer et al. (2008)	Childhood head injuries	13	6–9	53.8	Inattention (TEA-Ch; CBCL)[S,P]	Prospective cohort study of children with TBI from tertiary hospitals (USA)	Medical diagnosis of child TBI coupled with imaging or GCS data indicating TBI
Massagli et al. (2004)	Childhood head injuries	1959	10–15	62.0	Hyperactivity (medical record; ICD-9)	Prospective cohort study of children from children receiving care from a large health plan (USA)	Medical diagnosis of child TBI
Max et al. (1997)	Childhood head injuries	112	9.88–10.13	83.9	Diagnosis (DSM-III)	Clinical sample of children admitted to inpatient psychiatry unit (USA)	Medical documentation of child TBI
Max et al. (2004)	Childhood head injuries	121	10.92–11.64	64.4	Diagnosis (K-SADS; DSM-III)	Prospective and retrospective cohort study of children with and without TBI (USA)	Medical documentation of child TBI
McKinlay et al. (2002)	Childhood head injuries	814	10–13	n/a	Inattention (CQ/RCBQ; DSM-III)[P]	Birth cohort study (CHDLS; New Zealand)	Medical diagnosis of child TBI

Table 1 (continued)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Mogensen et al. (2011)	Asthma	1812	13–14	49.2	ADHD symptoms (DSM-IV)[P]	Prospective cohort study of twins (TCHAD; Swedish)	Retrospective parent report of child asthma
O'Callaghan et al. (2010)	Sleep	3368	5–14	51.7	Inattention (CBCL)[P]	Birth cohort study (MUSP; Australia)	Retrospective parent report of child sleep problems
Perfect et al. (2013)	Sleep	179	13.2	46.9	ADHD symptoms (BASC)[P]	Prospective cohort study of children with sleep-disordered breathing (TuCASA; USA)	Home-based polysomonography and retrospective parent report of child snoring
Plourde et al. (2018)	Childhood head injuries	51	14.3	48.0	ADHD symptoms (SDQ)[S]	Clinical, case–control research study of children with concussions or orthopedic injuries (Canada)	Medical documentation and parent report of child concussion
Pohlabeln et al. (2017)	Childhood infections	13,355	2–11.9	50.6	Diagnosis (parent report)	Prospective multi-center cohort study in eight European countries (IDEFICS; Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, and Sweden)	Retrospective parent report of child infection in first 4 weeks after birth
Sasaluxnanon and Kaewpornsawan (2005)	Childhood infections	241	6–12	88.0	Diagnosis (DSM-IV)	Clinical, case–control research study of children with ADHD and without (Thailand)	Retrospective parent report of child central nervous system infection
Schachar et al. (2004)	Childhood head injuries	91	5–17	56.8	ADHD symptoms (CBCL)[P]	Prospective cohort study of children with TBI and without (CJCCS; China)	Retrospective parent report of child TBI
Segalowitz and Lawson (1995)	Childhood head injuries	1091/196 [b]	16.8/17.8	43.0/56.0	Diagnosis (self- report)	Community cohort study, high school sample (Canada)	Retrospective self-report of head injury
Simola et al. (2014)	Sleep	470	7–11	50.4	Inattention (CBCL)[P]	Cross-sectional survey of children sampled from demographic register (Finland)	Retrospective parent report of child sleep disturbances and daytime tiredness
Smedje et al. (2001)	Sleep	635	6–8	52.9	Hyperactivity (SDQ)[P]	Cross-sectional survey (Sweden)	Retrospective parent report of child sleep–wake behavior
Suwan et al. (2011)	Allergies; asthma; eczema	80	5–15	77.5	Diagnosis (DSM-IV)	Clinical, case–control research study of children with allergies (Thailand)	Medical history and skin prick test for allergy, asthma, eczema

Table 1 (continued)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Thaler et al. (2012)	Childhood head injuries	50	12.7	80.0	ADHD symptoms (BASC)[T]	Clinical, case–control research study of children with ADHD and without (USA)	Child presenting for neuropsychological evaluation, with imaging or other diagnostic evidence showing brain damage
Thunström (2007)	Sleep	50	5.5	59.3	Diagnosis (DSM-IV)	Cross-sectional survey (Sweden)	Retrospective parent report of child sleep characteristics
Touchette et al. (2007)	Sleep	1492	6	n/a	ADHD symptoms (questionnaire)[P]	Prospective cohort study of children born in province (QLSCD; Canada)	Retrospective parent report of child sleep duration and daytime sleepiness
Tsai et al. (2013a)	Allergies	183	6–16	62.3	ADHD symptoms (SNAP-IV)[P]	Clinical, case–control research study of children with epilepsy and without (Taiwan)	Retrospective parent report diagnosed child allergies
Tsai et al. (2013b)	Allergies; asthma; eczema	23,460	0–18	77.9	Diagnosis (ICD-9-CM and DSM-IV)	Case–control research study of children receiving care from public health plan using insurance records (LHID; Taiwan)	Medical diagnosis of allergic conjunctivitis, allergic rhinitis, asthma, or atopic dermatitis
Wang et al. (2019)	Sleep	1557	5	n/a	Inattention (CBCL)[P]	Pregnancy community cohort study (Raine Study; Australia)	Parent report of sleep problems
Wang et al. (2016)	Childhood infections	28,556	9	52.7	Diagnosis (ICD-9-CM)	Retrospective, population-based cohort study using insurance records (LHID; Taiwan)	Medical documentation of group A streptococcal (GAS) infections
Wetherington et al. (2010)	Childhood head injuries	51	3	57.3	Inattention (CBCL)[P]	Prospective cohort study of children with TBI and without (USA)	Medical documentation of child TBI
Williams and Sciberras (2016)	Sleep	3461	8–9	51.3	ADHD symptoms (SDQ)[P] and diagnosis (parent report)	Longitudinal population cohort study, infant cohort (LSAC; Australia)	Parent report of sleep problems
Williamson et al. (2008)	Childhood infections	120	2.5–5	51.7	ADHD symptoms (CBCL)[P]	Clinical sample of children seen in hospital and private dental clinics (USA)	Children classified as having sufficient dental caries to warrant dental restoration under general anesthesia
Yang et al. (2016)	Childhood head injuries	52,080	5.6	60.9	Diagnosis (ICD-9-CM)	Retrospective, population-based cohort study using insurance records (LHID; Taiwan)	Medical documentation of child TBI

Table 1 (continued)

Study	Risk factors	Sample size	Age at outcome measurement (years)	Male (%)	ADHD measurement (Method)	Study design (country)	Physical health factor measurement
Yuksel et al. (2008)	Asthma	100	7–12	57.0	ADHD symptoms (CQ)[P]	Case–control research study of children with asthma and without (Turkey)	Medical diagnosis of child asthma
Zuckerman et al. (1987)	Sleep	56	3	47.0	Hyperactivity (BSQ)[P]	Prospective cohort study of children with sleep problems and without (UK)	Retrospective parent report of child night wakenings and maternal sleep disruption

ADHD attention deficit/hyperactivity disorder, *ALSPAC* Avon Longitudinal Study of Parents and Children, *BASC* Behavior Assessment System for Children, *BCS70* 1970 British Cohort Study, *BPI* behavior problem index, *BSQ* Behavioral Screening Questionnaire, *CBCL* Child Behavior Checklist, *CHDLS* Christchurch Health and Development Longitudinal Study, *CJCCS* China Jintan Child Cohort Study, *CRS-R* Conners' Rating Scale-Revised, *CQ* Conners' Questionnaire, *DAWBA* Development and Well-Being Assessment, *DSM-III* Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, *FTF* Five-to-Fifteen Questionnaire, *GCS* Glasgow Coma Scale, *HIND* Health Improvement Network Database, *ICD-9* International Classification of Diseases, 9th revision, *IgG* immunoglobulin G antibody, *K-SADS* Kiddie Schedule for Affective Disorders and Schizophrenia, *LHID* Longitudinal Health Insurance Database, *LSAC* Longitudinal Study of Australian Children—Infant Cohort, *MetLoFin* Metropolitan Longitudinal Finland Group, *MUSP* Mater-University of Queensland Study of Pregnancy and its Outcomes, *NHIS-CH* National Health Interview Survey on Child Health, *NHIRD* National Health Insurance Research Database, *OB/GYN* Obstetrics and gynecology, *PSQ* Pediatric Sleep Questionnaire, *NHS READ* UK National Health Service Read Codes, *QLSCD* Quebec Longitudinal Study of Child Development, *RCBQ* Rutter Children's Behaviour Questionnaire, *SDQ* Strengths and Difficulties Questionnaire, *SNAP-IV* Swanson, Nolan, and Pelham Rating Scale, 4th edition, *TEA-Ch* Test of Everyday Attention for Children, *TEDS* Twins Early Development Study, *TBI* traumatic brain injury, *TRAILS* TRacking Adolescents' Individual Lives Survey, *TCHAD* Twin study of Child and Adolescent Development, *TuCASA* Tucson Children's Assessment of Sleep Apnea Study, *UK NMH* UK Nationwide Mental Health Survey, *UK GPRD* UK General Practice Research Database

[a] Dichotomous and continuous outcomes were available for the same sample, but some cases had missing data

[b] Two separate subsamples were included in the study and analyzed separately

[P] Parent report

[T] Teacher report

[S] Self report

Table 2 Meta-analysis and heterogeneity results for studies examining childhood physical health risk factors for attention deficit/hyperactivity disorder (ADHD)

Risk factor	Most common risk factor definition	Outcome type	Overall		Diagnosis only		Inattention		Hyperactivity/impulsivity	
			Sample size (studies)	Pooled ES (95% CI)	Sample size (studies)	Pooled ES (95% CI)	Sample size (studies)	Pooled ES (95% CI)	Sample size (studies)	Pooled ES (95% CI)
Allergies	Medical documentation of childhood allergy or allergic reaction (e.g., rhinitis, conjunctivitis)	Dichotomous	28,143 (4)	OR: 1.71 (1.24, 2.37)*	—	—	—	—	—	—
Asthma	Parent report of childhood asthma	Dichotomous	34,907 (4)	OR: 1.71 (0.85, 3.46)	—	—	—	—	—	—
		Continuous	16,807 (3)	CC: 0.15 (−0.02, 0.32)**	—	—	—	—	16,807 (3)	CC: 0.13 (−0.04, 0.30)**
Eczema	Medical documentation of childhood eczema or atopic dermatitis	Dichotomous	28,730 (4)	OR: 1.47 (0.99, 2.16)	—	—	—	—	—	—
Infections	Parent report of childhood infection or infectious exposure	Dichotomous	57,078 (9)	OR: 3.25 (1.61, 6.53)*,**	46,572 (4)	OR: 1.45 (0.97, 2.17)	—	—	11,573 (3)	OR: 5.00 (0.98, 25.58) **
		Continuous	9988 (4)	CC: 0.16 (0.06, 0.26)*,**	—	—	—	—	—	—
Head injuries (vs. other injuries)	Medical documentation of child traumatic brain injury	Dichotomous	116,765 (10)	OR: 1.89 (1.35, 2.67)*,**	114,663 (7)	OR: 1.67 (1.23, 2.27)*	—	—	—	—
		Continuous	1751 (13)	CC: 0.27 (0.13, 0.41)*,**	—	—	1360 (9)	CC: 0.31 (0.11, 0.51)*,**	377 (5)	CC: 0.21 (0.11, 0.31)*
Head injuries (vs. normal controls)		Dichotomous	64,564 (8)	OR: 2.13 (1.40, 3.25)*,**	62,462 (5)	OR: 1.96 (1.26, 3.05)*	—	—	—	—
		Continuous	1314 (10)	CC: 0.36 (0.25, 0.47)*,**	—	—	1157 (7)	CC: 0.32 (0.11, 0.53)*,**	158 (4)	CC: 0.29 (0.13, 0.45)*
Sleep problems	Parent report of childhood sleep problems or patterns	Dichotomous	15,523 (12)	OR: 2.50 (1.67, 3.75)*	—	—	6198 (5)	OR: 2.92 (1.40, 6.09)*	3051 (5)	OR: 2.50 (1.41, 4.42)*
		Continuous	22,385 (7)	CC: 0.12 (0.06, 0.18)*,**	—	—	—	—	—	—

ES effect size, *CI* confidence interval, *OR* odds ratio, *CC* correlation coefficient

* $p < 0.05$ for random-effects model pooled effect size; ** $p < 0.05$ for Cochran's Q statistic for heterogeneity

ADHD diagnosis ($k=5$; OR: 1.96, 95% CI: 1.26, 3.05) were estimated for children with head injuries in comparison to healthy counterparts. Statistically significant unit increases in continuous effect sizes for ADHD overall ($k=10$; CC: 0.36, 95% CI: 0.25, 0.47), inattentive symptoms ($k=7$; CC: 0.32, 95% CI: 0.11, 0.53), and hyperactive/impulsive symptoms ($k=4$; CC: 0.29, 95% CI: 0.13, 0.45) were also observed. For both sets of head injury studies, we detected significant heterogeneity for the studies on dichotomous and continuous ADHD overall and inattentive symptoms. For this risk factor, there were four studies that used cognitive tests of attentional abilities as the outcome, rather than more conventional indicators of ADHD symptomology. As a test of robustness of our results, we also calculated effects sizes for the continuous overall and continuous inattention symptoms analyses without those four studies (Anderson et al., 1998, 2005; Babikian et al., 2011; Catroppa et al., 2007). The pattern of results did not change. Absent those four studies, head injuries were positively associated with continuous effect sizes for ADHD overall and for inattention symptoms (data not shown).

Sleep problems were associated significantly with ADHD overall, inclusive of dichotomous ($k=12$; OR: 2.50, 95% CI: 1.67, 3.75) and continuous ($k=7$; CC: 0.12, 95% CI: 0.06, 0.18) effect sizes. Experiencing issues with sleep duration or quality was associated with greater odds for later inattentive ($k=5$; OR: 2.92, 95% CI: 1.40, 6.09) and hyperactive/impulsive ($k=5$; OR: 2.50, 95% CI: 1.41, 4.42) symptoms. Among these studies on sleep, only the subset of continuous effect sizes of ADHD overall was found to have significant heterogeneity.

Discussion

This meta-analytic review provides a systematic assessment of select child physical health factors and their longitudinal association with ADHD, reflecting international, primary evidence across 43 years. Statistically significant pooled estimates with at least one measure of ADHD were observed for allergies, infections, head injuries, and sleep problems, suggesting that these health experiences may be ADHD risk factors. The findings address gaps in the literature by focusing only on studies where risk factors precede diagnosis or symptom onset, although this paper does not address, nor disprove, the possibility that risk factor-ADHD relationships also operate in the opposite direction. Possible mechanisms, discussed further below, include factors that are causal contributors to ADHD, are coincident outcomes with ADHD from a separate underlying factor, increase the likelihood of symptom or diagnosis identification, or lead to other exposures or experiences that increase ADHD risk. This review points to varied opportunities for tailored environmental or medical intervention and prevention efforts that can address these risks.

We found that when aggregating across available ADHD outcomes (i.e., ADHD overall), allergies, infections, head injuries (examined against both other injuries and healthy controls), and sleep problems were significantly associated with later ADHD. For risk factors with sufficient studies to examine more narrowly defined ADHD outcomes, head injury (both subsets) was the only factor significantly correlated with subsequent ADHD diagnosis. For inattentive and hyperactive/impulsive symptoms, head injury (both subsets) and sleep problems emerged as significantly and positively associated. Notably, effect sizes of larger magnitude were observed for head injuries, infections, and sleep problems compared to other factors. For example, sleep problems were associated with almost 3 times the odds of later inattention symptoms. For head injuries and sleep problems, significant effect sizes held for outcomes irrespective of the way ADHD was measured (diagnosis, by inattentive or hyperactive/impulsive symptom, or overall; Table 2). These patterns may imply that particular attention could be accorded to these risk factors by researchers, clinicians, and systems. On balance, this finding may reflect greater quantity of study invested in these areas, potentially yielding larger samples factoring into effect size calculations.

Overall, findings exhibit consistency with research showing that ADHD is associated with a range of child health experiences (Cortese et al., 2018; Mehta et al., 2019; Miyazaki et al., 2017). Twin studies make clear that the development of ADHD has substantial genetic roots, but its etiology likely reflects a multifactorial interaction between genetic and environmental factors that impact the condition's ultimate expression (Demontis et al., 2019; Faraone & Larsson, 2019). Although researchers have proposed that advances in epigenetics will pave new insights for primary and secondary prevention (Faraone & Larsson, 2019; Nigg, 2018; Wallis et al., 2008), efforts to identify common genetic markers for ADHD remain nascent (Demontis et al., 2019). While we await progress in that area, our findings support the general notion in previous literature that injuries, insults, and inflammation affecting the developing brain can result in lasting functional consequences for behavior and attention (Dutil et al., 2018; Faraone et al., 2021; Leffa et al., 2019). Whether such impacts represent moderators between intrinsic neurophysiologic or genetic susceptibility and ADHD severity, or direct influences on the brain's development, requires further inspection and may vary by risk factor (Halperin et al., 2012; Nigg, 2018). Below we explore findings by factor along with plausible mechanisms, sources of heterogeneity, and linkages to intervention.

Interpretation by Factor

Allergies, Asthma, and Eczema

We identified studies focusing individually on allergies, asthma, and eczema, as well as several that examined these factors in tandem (Suwan et al., 2011; Tsai et al., 2013b), in line with these conditions often being classified together as atopic diseases. Childhood allergies were associated with higher odds for ADHD overall, based on studies that varied in methodology such as binary determinations of allergy presence via medical record or diagnostic code documentation (Hak et al., 2013; Tsai et al., 2013b), positive skin prick tests for particular allergens (Suwan et al., 2011), or parent report of child diagnosis (Tsai et al., 2013a). In contrast, studies on eczema and asthma did not reveal significant associations with later ADHD outcomes. Generally, these findings partially echo previous hypotheses that pro-inflammatory mechanisms, particularly histamine-driven pathways at play in atopic diseases, could play a role in the etiology of ADHD (Miyazaki et al., 2017; Pelsser et al., 2009). Inflammatory processes may contribute to excess oxidative stress that supersedes individuals' ability to mount antioxidant defenses (Joseph et al., 2015).

Our findings contrast some prior research on allergic rhinitis (Schmitt et al., 2010), asthma (Chen et al., 2014; Cortese et al., 2018; Joseph et al., 2015; Mogensen et al., 2011; Schmitt et al., 2010), and eczema (Schmitt et al., 2010), which may reflect study design and measurement characteristics or the complex gene-environment interactions of atopic conditions (Nieto et al., 2014). Specifically, some of the previous studies focused on associations rather than focusing analyses on the direction of the association with atopic diseases as risk factors for ADHD (Cortese et al., 2018; Schmitt et al., 2010), whereas Chen et al. (2014) examined atopic disease as a single outcome rather than for specific conditions. As such, a classic public health approach to risk factor avoidance can be difficult to apply for atopic diseases. Children who have insufficient exposure to allergenic stimuli as well as those with excessive exposures both bear risk for atopic disease (Hamelmann et al., 2008; Tulic et al., 2011), and atopy often waxes and wanes over the developmental course. It may be that an epidemiologic nadir exists between over- and under-exposure to allergens for optimal population health, inclusive of ADHD (Hamelmann et al., 2008). Modification of indoor environmental agents, such as tobacco smoke, may help limit allergic sensitization and asthma, although the strength of evidence on how particular exposures correlate with atopic manifestations has been heterogeneous (Kanchongkittiphon et al., 2015; Nieto et al., 2014). Similarly, dietary modification has been proposed as an approach to influence behavioral issues in some children through limiting potential hypersensitivity mechanisms, though evidence is mixed (Verlaet et al., 2014), and there is more evidence for a negative impact of generally unhealthy diets than specific foods (Faraone et al., 2021). Additional research would help clarify when, for whom, and at what level atopic disease prevention could benefit ADHD-related processes.

Infections

Findings on childhood infections were mixed, and significant heterogeneity was found for multiple analyses. Although we opted to combine studies into this broad category in order to inform public health actions, we recognize that bacterial, viral, and other microbial agents exert their effects through a range of molecular or pathophysiologic pathways (see Jensen, 2000; Mora et al., 2020; Verlaet et al., 2014). In the current review, definitions for infection ranged from reports of symptoms or syndromes (viral exanthems, otitis media, dental caries) to speciated bacterial or viral infections (streptococcus, pneumococcus, enterovirus). Aggregating studies with diverse means of classifying infection (e.g., caregiver report, infectious processes determined based on laboratory data) may have contributed to mixed findings.

Another possible explanation is that the mechanisms linking microbial infection to ADHD symptoms may primarily be driven by insults to the developing brain, particularly dopaminergic and neurotransmitter systems (Akaltun et al., 2019; Millichap, 2008); thus, infections that do not interact with the nervous system may not be expected to evidence these associations. Further, we could not systematically evaluate the extent (i.e., local vs. systemic), developmental phase, nor length of the infection which would have implications for the likelihood of nervous system involvement and impairment. Because infections represent one of the most common experiences of childhood (Weintraub, 2015), future research can delineate this further with attention to the timing, course, and pathogenic/immunologic profile of particular infections. Early prevention and treatment of infections, particularly those with established neurophysiologic mechanisms (e.g., group A streptococcal infection; Mora et al., 2020), could improve child health outcomes, but subgroup effects on ADHD remain to be fully understood.

Head Injuries

Across all outcomes examined and regardless of control group used, our meta-analysis revealed that earlier head injury was associated with later markers of ADHD. Coupled with research that has helped elucidate temporality of the association (Adeyemo et al., 2014; Asarnow et al., 2021; Biederman et al., 2015), our findings lend support to the

hypothesis that such traumas lead to subsequent ADHD. Given that longitudinal studies have helped establish that children who have ADHD are prone to accidents or injuries (Biederman et al., 2015; Liou et al., 2018), as well as experience more severe impairment when they do sustain head injuries (Bonfield et al., 2013; Levin et al., 2007), head injuries and ADHD may operate in a bidirectional manner. We also address the concern raised in previous work that comparing children's head injuries to those with other injuries may over-estimate the true relationship strength (Biederman et al., 2015), as we observed a significant association even among the subset of studies relying on normal controls.

Head injury studies employed a range of means for operationalizing the presence of traumatic head injuries, including medical diagnoses (e.g., Catroppa et al., 2007), parent report (e.g., Hawley et al., 2004), and medical record documentation (e.g., Max et al., 2004). However, further details such as injury severity (e.g., concussion vs. severe TBI), determination methods (e.g., clinical diagnosis vs. brain imaging), or anatomic location were typically not available. Such features may explain heterogeneity observed, particularly among continuous effect sizes, and their inclusion in future work could add insights to research and practice. For example, impairments to the brain's prefrontal cortex have been implicated in both ADHD and traumatic brain injuries (Levin et al., 2007), and prevention efforts might benefit from enhanced understanding of the circumstances surrounding these traumas. For now, interventions at multiple socio-ecological levels including concussion education, school return-to-play policies, and state car seat laws are being implemented and tested (Yang et al., 2017), and may be reasonable actions to address the immediate and long-term neurodevelopmental morbidity related to such events.

Sleep Problems

We found consistent associations between sleep difficulties and all outcomes examined, building upon a body of correlational and experimental studies showing how sleep affects executive function. This research highlights the complex interplay between sleep and ADHD, suggesting that sleep issues and ADHD may emerge jointly from common neurobiological pathways (e.g., melatonin and dopamine metabolism), influence one another bidirectionally, or a combination thereof (Mehta et al., 2019; Weiss et al., 2015). For example, poor arousal regulation due to ADHD may lead both to daytime inattention and hyperactivity and also present difficulties for sleep–wake cycles (Touchette et al., 2007; Weiss et al., 2015).

There is some difficulty in inferring directionality or mechanisms of the relationship, as the 18 studies in this category examined sleep irregularities in varying ways (e.g., sleep disordered breathing, disruptive sleep patterns, daytime sleepiness). These problems may reflect anatomic, psychosocial (e.g., irregular bedtime), or neurologic differences between children and yield behavioral difficulties through mechanisms such as hypoxemia (Bonuck et al., 2012; Mehta et al., 2019). As above, they may also contribute to the heterogeneity observed in this category for continuous ADHD overall. Future analyses could pinpoint the effect of different types of sleep issues, the influence of which may also vary over the course of development (Huhdanpää et al., 2019). Interventions could target specific problems, such as surgical approaches for sleep disordered breathing (Chervin et al., 2005), as well as behavioral approaches for disruptive sleep patterns or short sleep durations (Rigney et al., 2018). These approaches are part of evidenced-based behavior therapy for ADHD including parent training (Wolraich et al., 2019) and providing access may address sleep as well as overall functioning.

Implications for Providers and Systems

This paper provides insight into the importance of children's physical health for later ADHD symptoms, with distinct relevance for healthcare providers and systems. Clinicians serving children who have experienced allergies, head injuries, infections, or sleep problems can consider monitoring for inattentive, impulsive, or hyperactive symptoms (Claussen et al., 2021; Cortese et al., 2018; Millichap, 2008). Providers could help distinguish whether behavioral symptoms reflect the emergence of primary ADHD or possible reactions to underlying chronic disease or stress (Meldrum et al., 2012; Pliszka and American Academy of Child and Adolescent Psychiatry [AACAP] Workgroup on Quality Issues, 2007). Such an approach may promote more timely ADHD evaluation, diagnosis, and intervention for a subset of children who may otherwise be missed. It may also be reasonable for families of children with ADHD or who exhibit its core symptoms to be advised about the conditions identified herein, particularly in light of other studies documenting bidirectional risk factor-ADHD associations (Liou et al., 2018; Quach et al., 2018). Providers can consider evaluating for and addressing co-occurring conditions that might elicit or aggravate difficulties with attention or self-regulation as part of their ADHD management and counseling (Wolraich et al., 2019). Pediatric integrated behavioral health models represent one path for attending to both the medical and psychological service needs of affected children (Brundage et al., 2021; So et al., 2019).

At the public health level, findings suggest that efforts by health, education, and social service systems to assess for, and support children with, ADHD could benefit from knowledge about their health history (Pliszka and AACAP Work Group on Quality Issues, 2007; Claussen et al., 2021). Public health stakeholders might improve ADHD morbidity through deploying prevention strategies targeting risk factors, such as

concussion prevention policies (Yang et al., 2017), or their social and structural determinants. Focusing on children disproportionately impacted by both physical health conditions and ADHD, such as those in low-income families (Brown, 2010; Danielson et al., 2018), may help advance health equity. Further, universal public health actions can be considered to improve population outcomes, even though contributing processes for each risk factor may vary. For example, delayed school start times (Weiss et al., 2015) can improve children's sleep at the population level, even if individual children have issues rooted in neurological, psychosocial, anatomical, or multifactorial etiologies (Rigney et al., 2018). For some factors, additional study would help inform the design of optimal and equitable prevention approaches. Meaningful population-wide impact for any of these risk factors will likely benefit from incorporating both universal and targeted prevention (Dodge, 2020; Fagan et al., 2019).

Finally, in addition to mitigating risks, systems could consider promoting protective factors that might buffer children—particularly those already affected by health conditions—from developing or exacerbating ADHD symptoms. For example, strategies to support children's cognitive enrichment or physical activity may promote structural and functional neurodevelopment to affect the trajectory of behavioral symptoms (Halperin et al., 2012). This approach may be particularly salient for those factors where a linear relationship between exposure and health status is less clear, in which case universal primary prevention may not be advisable (e.g., allergies; Hamelmann et al., 2008). Ultimately, preventing the developmental processes leading to ADHD may be more resource efficient, as long-term medication and behavioral treatments, once indicated, can be difficult for families to access and maintain (So et al., 2019; Wolraich et al., 2019). As knowledge about ADHD prevention strategies grows, concurrent system efforts to expand access to ADHD treatment and supports remain nonetheless vital.

Limitations

Despite numerous strengths similar to those described in Robinson et al. (2022), this meta-analytic review has limitations. First, child health factors can be related to other variables, such as perinatal Bitsko et al. (2022) or chemical factors Dimitrov et al. (under review), that might mediate or moderate relationships observed. For example, adverse prenatal experiences can contribute to stress-related neuroendocrine immune activation in children with genetic predisposition to ADHD, thereby creating a window of vulnerability for children exposed to additional insults such as head injury (Allred et al., 2017). Second, we were able to examine only a select group of child health risks for which there were adequate data. Future research could examine other factors we initially considered, such as malnutrition and corticosteroids (Tsai et al., 2018; Verlaet et al., 2014), or other insults to the developing nervous system (e.g., brain tumors; Hardy et al., 2018). Furthermore, for factors with relatively fewer included studies (e.g., allergies, asthma, eczema) and with large variations in sample size, additional research may identify significant associations. Relatedly, as with all studies based on published literature, these results cannot be assumed to generalize beyond the populations in the included studies. Third, the absence of significant findings for certain factors may reflect methodological limits rather than lack of an empirical relationship. Fourth, we could not evaluate the timing (e.g., early vs. middle childhood infections) or severity (e.g., frequency of head injuries) of risk factor exposures, nor time-to-event outcomes. This is a notable challenge, as both child health experiences and ADHD are developmentally sensitive (Rice & Barone, 2000; Sonuga-Barke & Halperin, 2010). We cannot exclude the possibility that child health experiences and ADHD symptoms occurred contemporaneously, even if assessment or formal diagnosis of ADHD took place at a later timepoint than exposure assessment (Asarnow et al., 2021). Additionally, recent research has shown shared genetic risk for ADHD and somatic conditions, suggesting that these disorders may be different manifestations of similar genotypes rather than causal risk factors (Brikell et al., 2021; Garcia-Argibay et al., 2022); additional research is needed to further understand these relationships. Further complicating matters, certain conditions like allergies can emerge and recede over time precluding straightforward temporal inferences. Additional investigation into the role of chronicity, timing, and severity can guide more precise prevention and diagnostic efforts.

Finally, we observed significant heterogeneity for several risk factors examined, especially with continuous outcomes, suggesting variability in the magnitude or direction of estimates from individual studies (see Table 2). This result may be unsurprising, as we did not limit our meta-analyses based on key elements that may lead to heterogeneity, such as differences in measures of risk, severity of exposures, or other study design characteristics. For instance, although factors were grouped together conceptually, exposures within individual studies may confer risk for ADHD via distinct mechanisms (e.g., different pathways of microbial pathogenesis under "childhood infections") or might operate only above a certain threshold. Relatedly, exposures we conceived of as separate factors (e.g., "allergies" and "asthma") may in reality share a common etiologic pathway toward ADHD, such as oxidative stress (Joseph et al., 2015). Heterogeneity seen across multiple factors suggests that these effect sizes should be interpreted cautiously and explored for possible subgroup or outlier effects. Undertaking these additional analyses herein was considered, but such efforts could have rendered several factors with insufficient effect sizes to produce

pooled estimates. Overall, study decisions were guided by a public health approach to child development, recognizing that identification of ADHD correlates can help inform key focal areas for intervention (Fagan et al., 2019). In using random-effects models, our meta-analysis offers a statistically conservative initial profile of select risk factors' associations, laying the groundwork for future study.

Conclusion

Drawing upon data from a quarter-million children over four decades, we identified childhood physical health risk factors associated with increased likelihood of later ADHD symptoms or diagnosis. This work expands the scope of previous evidence syntheses by focusing on antecedent health experiences, considering both ADHD diagnosis and constituent symptoms, and applying identical methods to examine multiple plausible risk factors simultaneously. Systems and healthcare providers may be well positioned to influence ADHD outcomes by considering these preventable, and sometimes treatable, health issues, such as childhood head injuries and sleep problems. Available clinical and public health strategies (e.g., screening tools, educational programs, policies) that identify or ameliorate physical health risk factors may foster neurodevelopmental health for children and their families.

Appendix 1

Search terms used for meta-analytic review of childhood physical health risk factors for attention deficit/hyperactivity disorder (ADHD).

Component	Search terms
Attention deficit/hyperactivity disorder (ADHD) related terms	((("attention deficit") OR ("hyperactivity disorder*") OR ("deficit hyperactiv*") OR ("ADHD") OR ("deficit disorder*") OR ("minimal brain dysfunction") OR ("minimal brain damage") OR ("MBD") OR ("brain injured child syndrome*") OR ("hyperactive child syndrome*") OR ("hyperactive syndrome*") OR ("impulse disorder*") OR ("hyperkinetic disease") OR ("hyperkinetic syndrome*") OR ("hyperkinetic reaction of childhood")) OR (("ADD" AND (disorder OR attention OR hyperactiv*))) OR (("attention problem*") OR ("inattenti*") OR ("hyperactiv*") OR ("hyperkines*")))
Child health terms	AND ((("nutrition*") OR ("deficienc*") OR ("iron") OR ("ferritin") OR ("transferrin") OR ("anemia") OR ("copper") OR ("zinc") OR ("magnesium") OR ("polyunsaturated fatty acids") OR ("fatty acid*") OR ("folate") OR ("nutritional surplus*") OR ("fat") OR ("sugar*") OR ("sodium") OR ("food additive*") OR ("food color additive*") OR ("food color*") OR ("FD&C Yellow") OR ("FD&C Red") OR ("preservatives") OR ("sodium benzoate") OR ("diet") OR ("IgG") OR ("western diet") OR ("malnutrition") OR ("electronic*") OR ("television") OR ("TV") OR ("video game*") OR ("screen time") OR ("sleep") OR ("built environment") OR ("nature") OR ("green space") OR ("physical activity") OR ("exercise") OR ("injury") OR ("infection*") OR ("bacteria*") OR ("viral") OR ("virus") OR ("fungus") OR ("fungal") OR ("protozoa*")))

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11121-022-01398-w.

Acknowledgements We thank Lu (Mary) Meng, PhD, and Jaleal Sanjak, PhD, for support creating forest plots; and Katherine McGowan, BA, and Kayla Saadeh, MPH for support conducting literature searches. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Funding The work presented here was completed through an Interagency agreement between the CDC and the General Service Administration (13-FED-1303304). The work was completed under GSA Order Number ID04130157 to Gryphon Scientific, LLC, titled "*Identifying Public Health Strategies with Potential for Reducing Risk for Attention Deficit/Hyperactivity Disorder*." This project was also supported in part by an appointment to the Research Participation Program at the CDC, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and CDC.

Declarations

Ethics Approval Not applicable. This study includes analyses of data previously published in the literature.

Consent to Participate Not applicable. This study includes analyses of data previously published in the literature.

Conflict of Interest All authors declare that they have no conflict of interest.

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* indicates study that was included for meta-analysis

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