THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 6

REVIEW ARTICLE

Improving the medical assessment of young people with ADHD: Genetic, psychosocial or metabolic issues? (II)

Anne-Isabelle Dionne, M.D., IFMCP[a] & Joël Monzée, Ph.D.[a*]

[a]Institut du développement de l'enfant et de la famille, Quebec, Canada

[*]joel.monzee@institutdef.ca

OPEN ACCESS

PUBLISHED
30 June 2025

CITATION
Dionne, A.I. and Monzée, J., 2025. Improving the medical assessment of young people with ADHD: Genetic, psychosocial or metabolic issues? (II). Medical Research Archives, [online] 13(6). https://doi.org/10.18103/mra.v13i6.6535

DOI
https://doi.org/10.18103/mra.v13i6.6535

ISSN
2375-1924

ABSTRACT

A good understanding of the origin of symptoms is essential to ensure the optimization of therapeutic treatments. This article proposes a critical re-evaluation of both confounding and risk factors associated with attention deficit hyperactivity disorder to avoid over-diagnosis and over-medication as currently observed in Quebec. We provide an in-depth analysis of the nutritional, metabolic, digestive, respiratory and behavioral factors that may contribute to the onset and persistence of symptomatology resembling attention deficit hyperactivity disorder (ADHD), traditionally classified as a neurodevelopmental disorder of genetic origin. Emerging evidence suggests that the symptomatology may result from a multifactorial dysregulation affecting dopaminergic and noradrenergic pathways. It is essential to consider the critical role of nutrition in neurotransmitter synthesis, as deficiencies in amino acids, vitamins, minerals, and essential fatty acids may significantly compromise executive and attentional functions. Among the vulnerability factors, particular attention should be given to the long-term impact of childhood malnutrition on cognitive performance. Optimal therapeutic management of attention deficit hyperactivity disorder (ADHD) also requires evaluating its symptomatology within the broader continuum of metabolic dysfunction, including insulin resistance, glycemic variability, sedentarity and pediatric obesity. These imbalances affect neuroinflammation, neuronal energy production, and neurotransmitter synthesis. In this context, it is relevant to explore the role of the gut microbiota and intestinal permeability in the emergence of symptoms associated with attention-deficit/hyperactivity disorder (ADHD). This includes examining the potential benefits of elimination diets and the behavioral effects of food dyes and additives, thereby highlighting the importance of a personalized, patient-centered approach. Finally, sleep-disordered breathing in children, which has multiple causes, is also common among children with attention deficit hyperactivity disorder and can exacerbate neurocognitive symptoms. To ensure optimal therapeutic direction, it is therefore recommended to evaluate nutritional, metabolic, digestive, respiratory and behavioural factors before making a diagnosis of attention deficit hyperactivity disorder and initiate a treatment. All in all, mental health should not be considered as an isolated entity, but as the expression of a neuro-metabolic imbalance modulated by lifestyle habits on which it is possible to act effectively.

Keywords: children, adolescents, ADHD, psychostimulants, metabolic assessment, clinical ethics

Introduction

There is a growing number of psychostimulant prescriptions for young people aged 0 to 26 years in European and North American countries, despite ongoing uncertainty about the origins of ADHD. A first article[1] , together with this second companion article provide a comprehensive overview of the various clinical hypotheses that should be considered during the diagnostic process to better guide therapeutic decisions. Given the significant heterogeneity of the symptoms included under the ADHD diagnosis and the continuous increase in its prevalence and psychostimulant prescriptions over the past 20 years[2], several concerns have been raised about the lack of rigor in the diagnostic process. A frequent clinical oversight involves the failure to differentiate between genuine neurodevelopmental ADHD of genetic origin and ADHD-like presentations secondary to personal adversity, psychosocial stressors, or underlying vulnerability factors — some of which may have a metabolic basis. Careful evaluation of these elements is essential to ensure a well-targeted therapeutic approach[1].

To distinguish between patients with ADHD and those presenting with ADHD-like symptoms, clinicians must engage in a thorough differential diagnostic process[1,3]. Unfortunately, such a rigorous assessment is often overlooked, partly due to the strong emphasis on genetic factors in the current conceptualization of ADHD[4,5]. Of course, several genes have been identified as factors that increase the risk of developing ADHD. Moreover, the relative risk (RR) increased by 4.0~5.4 within families, whereas there was a certain correlation in dizygotic (0.39-0.91) and monozygotic (0.68-0.81) twins[6]. Offspring of parents diagnosed with ADHD exhibit a relative risk (RR) of 6.87 for developing the condition, compared to children of parents without ADHD[7]. Finally, the absolute proportion of ADHD in children of parents with ADHD is very high, reaching 41.5% in boys and 25.1% in girls when both parents are affected[8]. This theory may misdirect treatment when symptoms stem from psychological or psychosocial factors. In that sense, comprehensive evaluation is essential to distinguish ADHD from ADHD-like presentations.

In this article, we explore other factors to take into account, as they could either amplify the intensity of ADHD symptoms or trigger ADHD-like behaviors. Clinical experience indicates that potential metabolic disorders should be assessed prior to prescribing psychostimulants, as these may obscure underlying chronic conditions or exacerbate physiological dysfunctions beyond the behavioral domain.

Clinical and ethical issues

Although ADHD is defined as a genetically based disorder, it is important to recognize that phenotypes—more readily observable than genotypes—are strongly influenced by environmental factors. Classical genetics relies on phenotypic expression to infer gene function or chromosomal anomalies; thus, caution is warranted before attributing ADHD solely to hereditary origins[1,9]. Also, epigenetic processes can be modulated by neuroendocrine and biochemical homeostasis, which in turn regulates the expression of genes implicated in numerous conditions traditionally viewed as hereditary[10].

Despite a sustained rise in psychostimulant prescriptions among students, it should be remembered that 60-80% of patients have side effects that can disrupt appetite, sleep, digestion, generate tics, headaches, irritability, anxiety and restlessness[2,11]. Prolonged use of psychostimulants may also increase risk of cardiovascular disease[12]. The doctor must therefore find the right balance between pharmacotherapy to reduce the impact of a disorder and the side effects that sometimes lead to other diseases. However, this dilemma becomes irrelevant when a genetic neurodevelopmental disorder like ADHD is mistakenly conflated with another condition or with transient difficulties, which may arise from family, social, or school contexts that naturally trigger behavioral responses, or from nutritional, metabolic or inflammatory issues (ADHD-like)[1].

The difficulty in identifying the underlying causes of symptom heterogeneity complicates the diagnostic process and can compromise clinical decision-making, leading to the inappropriate prescription of psychostimulants in individuals with ADHD-like, but not true ADHD presentations. It is therefore essential to establish a differential diagnosis that considers both developmental and psychosocial domains, while also evaluating potential metabolic factors, in order to optimize the therapeutic

approach for each patient. In other words, medication is a tool, but it should not be considered without an thorough assessment of the underlying causes of the neurochemical disturbance affecting attentional processes or impulsivity regulation.

Nutritional issues

Biochemically, ADHD is thought to be the consequence of an alteration in the function and balance of several neurotransmitters that can affect the executive functions of the brain, including dopamine and norepinephrine[13]. It is therefore necessary to go back to the basics of physiology to remember that dopamine comes from the conversion of phenylalanine obtained in food or from the transformation of L-tyrosine made from phenylalanine or also found in food. Then, it is hydroxylated to L-DOPA using iron and BH4, whose regeneration is mediated by the active form of folate (5-MTHF) as essential co-factors to the enzyme tyrosine hydroxylase. Finally, vitamin B6 (P5P) and zinc are required to enable the activity of the dopamine-producing enzyme DOPA-decarboxylase, but also to effectively modulate its action in the synaptic space. Norepinephrine is synthesized through the action of the enzyme dopamine β-hydroxylase, which requires vitamin C and copper as its principal cofactors. This neurotransmitter synthesis is mediated by the efficient production of ATP by the mitochondria of neuronal cells, where magnesium and B vitamins in optimal amounts are indispensable as co-factors for key enzymes for energy production. Finally, these neurotransmitters must, after reuptake, be adequately metabolized and recycled by enzymes that fall under several B vitamins to ensure their optimal functioning.

Given this biochemical cascade, the quality of the diet and the integrity of digestive functions may significantly influence the severity of symptoms associated with ADHD. Composed of 100 billion neurons and trillions of synaptic connections, the brain requires 20 to 25% of the body's metabolic demand[14]. Moreover, the synthesis of neurotransmitters involved in emotional regulation, cognitive organization, and attentional processes depends on the conversion of essential amino acids absorbed during digestion—since the body cannot synthesize them—through enzymatic reactions that require vitamin- and mineral-based cofactors to function effectively. It is therefore evident that an imbalance in the availability of essential amino acids, vitamins, and minerals may compromise neurotransmitter synthesis and, consequently, negatively impact mental health.

Child malnutrition influences the determinants of mental health in adulthood. Eighty individuals who suffered from protein-energy malnutrition (PEM) in their first year of life were assessed 40 years later. Compared to control-subjects, they had lower levels of education, lower employment rates, and reduced incomes[15]. In addition, 48/80 showed symptoms of ADHD. Subsequently, 55/80 subjects were evaluated by near-infrared spectroscopy to measure brain activity. They showed significant alterations in resting brain activity compared to the control group[16].

Let's not forget that essential amino acids must be consumed in a diet that is diversified in terms of protein sources. Absorbed efficiently, they are direct precursors to the synthesis of the various neurotransmitters ensuring healthy cognitive function (e.g., phenylalanine, tryptophan)[17,18]. Lower levels of some of these amino acids essential to produce neurotransmitters are observed in ADHD patients, suggesting that this deficient nutritional state may be related to the pathology or, presumably, trigger cases of ADHD-like[19].

There appears to be a correlation between dietary habits and nutritional biochemical status and ADHD or ADHD-like clinical profiles. Then to explore this association, 432 children (6-12 years) divided into two groups, with or without symptoms of ADHD, but matched by age, sex and place of residence were examined[20]. After documenting their lifestyle habits, blood concentrations of polyunsaturated fatty acids (PUFAs), zinc, iron, and magnesium were measured. First, ADHD subjects generally consumed more sweets and sugary drinks, but fewer fruits and fewer vegetables. Second, they had lower levels of omega-3 PUFAs, zinc, and iron compared to controls. Third, unhealthy eating habits negatively influence biochemical nutritional status, while also being correlated with increased symptom intensity. These findings underscore the critical role of a nutrient-rich, balanced diet in supporting the regulation of attentional processes and motor impulse control in young patients—both as a therapeutic intervention to improve clinical outcomes and as a preventive strategy to mitigate symptom severity

Despite common assumptions, malnutrition remains underestimated in developed countries, particularly when assessed through markers of cellular function and micronutrient status. While it is considered as a determinant of health, it is overlooked in the diagnosis process of ADHD. Beyond the socioeconomic challenges faced by some families, it is important to recognize that food overprocessing compromises nutritional quality, leading to a disconnect between caloric intake and micronutrient adequacy[21]. Indeed, the consumption of ultra-processed foods is associated with a decrease in the intake of fiber, vitamins and essential minerals while increasing the intake of sugar, processed carbohydrates and poor-quality fats[22]. The decline in nutritional quality contributes to a form of malnutrition marked by excessive caloric intake coupled with insufficient essential nutrients, a condition that predisposes individuals to obesity, type 2 diabetes, hypertension, and other chronic diseases[23].

At the micronutrient level, it has also been observed that children with ADHD have significantly lower serum levels of zinc and magnesium compared to neurotypical children[24,26]. Considering that these minerals are essential to support neurotransmitter synthesis and regulation reactions, it seems that optimizing trace element levels is beneficial in reducing ADHD symptoms[27,28]. Meta-analyses have revealed that serum ferritin levels were significantly lower in children with ADHD and that there was a significant correlation between iron deficiency and the severity of ADHD symptoms. The effect of iron supplementation in ADHD children with ferritin was <30ng/mL was found to be beneficial in reducing symptoms. Similar observations were made for deficient and supplemented children, even though they were also treated pharmacologically[29].

The same trend can be observed for certain vitamins, which are largely involved in the metabolism of neurotransmitters, thus regulating multiple brain functions involved in attention, focus and executive functions. Vitamin D and several B vitamins (e.g. B6, B9 and B12) seem to be more deficient in children with ADHD[30,31]. In the event of a deficiency, supplementation therefore becomes interesting to improve children's cognitive skills, especially in vitamin B6 and magnesium[32]. In addition, vitamin D3 supplementation, combined with neurofeedback methods, revealed favorable electrophysiological results in children with ADHD while significantly increasing serum vitamin D levels[33].

A meta-analysis of 16 clinical studies involving 1719 participants divided according to their psychiatric diagnosis (ADHD, depression, PTSD, autism, dementia-related behavioural deficits, antisocial behaviour) highlights the effectiveness of multivitamin supplements[34]. For the ADHD/ADHD-like population, an improvement in overall functioning and a reduction in inattention symptoms are observed. The results were more robust with formulations containing a broad spectrum of vitamins and minerals, although more studies are needed to formally issue clinical recommendations.

What's more, omega-3 fatty acid supplementation is associated with a modest, but significant, reduction in ADHD symptoms[35]. Considering that 60% of the dry weight of the human brain is made up of essential fatty acids, its consumption is essential in the critical period of brain development during gestation and early childhood. They also act as messengers by participating in the synthesis and functions of brain neurotransmitters, as well as those of immune system molecules[36]. Neuronal membranes contain phospholipid reserves for the synthesis of specific lipid messengers in response to neuronal stimulation or injury, but also to provide neuroprotection[37]. Studies show that the intake of omega-3 fatty acids -e.g. alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)- is often insufficient in children. For example, a study found that only 61% of Canadian children (4-8 years old) achieve adequate ALA intake, while 22% meet DHA and EPA intake[38]. In addition, the NHANES survey shows that replacing traditional Omega-3-rich vegetable oils with oils rich in oleic acid disrupts the intake of essential fatty acids in children, potentially leading to a risk of deficiency[39].

Metabolic syndrome

In recent years, a decline in metabolic health has been observed among young populations. Analysis of data from the Global Burden of Disease Study (1990 to 2021) showed a significant increase in disability-adjusted life years (DALYs) attributable to metabolic risk factors in subjects aged 15 to 39 years. The main risk factors were high body mass index (BMI) and high fasting blood glucose, with increases of 84.2% and 53.6%, respectively[40].

Canadian studies have also found the same abnormalities in our children in body weight, BMI, fasting blood sugar and/or glycated hemoglobin[41-43]. These studies show metabolic decline, which raises concerns about negative impacts on the physical and mental well-being of our youth. As there is a two-way interaction between physical and mental well-being, metabolic imbalances could contribute to the increased burden of psychiatric disorders and, in turn, also impair metabolic health[44,45]. These observations therefore warrant caution when considering a psychiatric diagnosis without first evaluating the integrity of key physiological systems, as is often the case in individuals diagnosed with ADHD.

Insulin resistance occurs when cells in the body become less sensitive to the action of insulin, a key hormone in regulating glucose metabolism allowing it to enter cells, resulting in high levels of insulin in the blood. This is often the result of a diet high in refined carbohydrates, compounded by a sedentary lifestyle, and further aggravated by insufficient sleep and chronic stress. Insulin resistance is present in adults with unhealthy lifestyle habits, but also in young people, as the consumption of ultra-processed foods has increased significantly over the past two decades, contributing to rising rates of childhood obesity and insulin resistance[46,47]. Young Americans now eat almost 67% of their total energy from these foods, which is associated with poor diet quality and excessive calorie intake, leading directly to a state of insulin resistance[48].

Insulin resistance is a common feature of various metabolic disorders, including type 2 diabetes, obesity, and hypertension. It may also extend to the central nervous system, resulting in cerebral insulin resistance—a condition in which neurons, particularly in the prefrontal cortex, lose their ability to efficiently utilize glucose, a substrate critical to their function[49]. Cognitive symptoms of insulin resistance include deficits in verbal episodic memory, executive function, auditory attention, word comprehension, and verbal fluency, as well as progressive brain atrophy in specific regions[50-53]. Insulin resistance also promotes chronic inflammation, characterized by the production of pro-inflammatory cytokines such as TNF-α and IL-6, which in turn activate inflammatory signaling pathways within the brain. This activation leads to an increased production of reactive oxygen species (ROS), causing oxidative stress. Oxidative stress damages mitochondria, impairing their capacity to generate ATP and promoting the overproduction of reactive oxygen species (ROS), thereby establishing a vicious cycle of mitochondrial dysfunction and sustained oxidative stress [54,55].

Dysfunctional mitochondria in neurons, especially in the prefrontal cortex, impair the production of ATP needed for neuronal processes, including neurotransmitter synthesis. Dopamine and norepinephrine, synthesized from tyrosine and phenylalanine via ATP-dependent processes, have their production decreased due to the induced mitochondrial dysfunction[56]. In addition, the increase in the activity of monoamine oxidases (MAO A and B) in a context of cerebral insulin resistance accelerates the degradation of dopamine, thereby exacerbating the neurotransmitter deficiency[56]. It is therefore interesting to note that the decrease in dopamine and norepinephrine in the prefrontal cortex may have resulted from the phenomenon of neuroinflammation observed in the context of metabolic dysfunction and seems to be closely associated with deficits in attention and executive functions, characteristic of ADHD[57].

In addition, the consumption of ultra-processed foods is associated with a decrease in attentional skills and an increase in impulsivity. Empirical evidence indicates that diets high in refined sugars and low-quality fats are associated with an increased risk of ADHD symptom manifestation, whereas diets rich in fruits and vegetables appear to exert a protective effect[58,59]. Consuming ultra-processed foods over long periods of time can also disrupt the gut microbiota, which is linked to metabolic alterations and ADHD symptoms[60]. These results suggest that promoting healthy lifestyle habits among students, by optimizing their diet, could reduce the frequency of behaviours associated with ADHD.

The prevalence of obesity is approximately 40% higher in students with untreated ADHD compared to their peers without ADHD[61]. The symptoms of ADHD are frequently associated with somatic conditions such as sleep disorders, autoimmune diseases, and metabolic disorders such as type 2 diabetes and hypertension. These conditions also appear on the continuum of metabolic dysfunction and insulin resistance[62,63]. Although the association does not establish causality, it is noteworthy that the pathophysiological

mechanisms underlying these conditions appear to be closely related. This highlights the need for clinicians to consider them carefully when managing young patients suspected of having ADHD.

Another metabolic disturbance associated with a diet high in refined carbohydrates is the marked fluctuation in blood glucose levels, particularly in individuals who have developed insulin resistance as a result of lifestyle factors[64]. Transient hyperglycemia is often followed by a drastic drop in blood sugar because of excessive insulin secretion. When this process occurs repeatedly, it diminishes cellular receptor sensitivity for insulin and, when coupled with impaired glucagon secretion—as seen in reactive hypoglycemia—may lead to cognitive dysfunction[65]. Experimentally induced acute hypoglycemia in humans also causes a significant deterioration of attentional abilities, although non-verbal intelligence is preserved[66]. Neuroglycopenic symptoms of hypoglycemia (e.g., confusion, behavioral changes, inattention, impaired working memory) may mimic the symptoms of ADHD[67,68]. Since many children eat breakfast with ultra-processed, carbohydrate-rich foods, clinicians should consider the effects of fluctuating blood sugar levels during the day. If insulin resistance gradually develops, there is a risk that the prescription of psychostimulants may mask early symptoms of dysglycemia, delaying detection until metabolic dysfunction is more advanced and potentially less reversible.

Sedentary lifestyle

Only 19% of students meet current physical activity guidelines, a deficiency that may contribute to a range of adverse health outcomes[69]. One contributing factor to this trend is the increased number of hours spent in front of screens, which has also been correlated with the severity of ADHD symptoms[70]. Consequently, cardiorespiratory endurance among students declined significantly between 1986 and 2012[71]. Reduced cardiorespiratory fitness in childhood has been linked to a higher risk of developing ADHD symptoms during adolescence[72]. On the other hand, physical activity can prevent and decrease the intensity of ADHD in students[73]. Through their anti-inflammatory properties and influence on neurotransmitter regulation, physical activity-based interventions have demonstrated significant improvements in executive functions among students diagnosed with ADHD—particularly in inhibitory control, working memory, and cognitive flexibility[74]. While some are more effective than others, all forms of physical activity improve executive function and reduce ADHD symptoms[75]. Moderate to vigorous exercise, especially aerobic activities, are associated with a reduction in the intensity of inattention and impulsive behaviours[76]. Promoting healthy lifestyle habits should therefore be considered an integral component of both preventive and therapeutic strategies aimed at reducing the risk or frequency of behaviors associated with ADHD, as is the case for other metabolic disorders

Intestinal microbiome

Now recognized for its essential role in health, the microbiome is made up of billions of microorganisms residing on the skin, as well as in the urogenic and intestinal tracts. This complex and dynamic ecosystem fulfills various vital functions such as, e.g., fiber digestion, vitamin synthesis, immune system modulation, and protection against pathogens. In addition, the bacteria present in the gut participate in the synthesis of neurotransmitters or their precursors[77].

An imbalance of the microbiota, or dysbiosis, occurs when the diversity and richness of beneficial microorganisms in the gut are altered, due to an unbalanced or ultra-processed diet, excessive intake of antibiotics or non-steroidal anti-inflammatory drugs, as well as chronic stress, among other factors.[78,79]. In the case of dysbiosis, pathogenic bacteria proliferate and cause adverse health effects[80]. However, it appears that hyperactive and impulsive children show significant alterations in their gut microbiota[81]. These alterations influence the production of neurotransmitters and their precursors thereby directly impacting the gut-brain axis[82]. Studies point to correlations, but there is no established causality yet. Further research is needed to identify targeted interventions on the gut microbiota that may help restore its balance and potentially reverse neurocognitive symptoms. However, treatment plans should include an evaluation of the appropriateness and potential efficacy of probiotic supplementation in alleviating certain debilitating symptoms associated with ADHD[83].

Also, the observation of gut dysbiosis is often associated with the presence of a leaky gut, i.e. an

alteration in the integrity of the junctions between the cells of the intestinal epithelium. Under normal conditions, the thight jonctions prevent the translocation of microbes, toxins, and undigested food particles into the bloodstream, thereby protecting against the development of low-grade systemic inflammation[84]. The inflammatory responses associated with increased intestinal permeability (leaky gut) may contribute to the development of digestive disorders, cardiometabolic diseases, autoimmune conditions, and psychiatric disorders[85]. Indeed, the production of pro-inflammatory cytokines secondary to gut dysbiosis and leaky gut is likely to affect the permeability of the blood-brain barrier, neuronal mitochondrial function and interfere with the synthesis of dopamine and norepinephrine. As a result, these mecanisms can disrupt the regulation of attention, concentration and impulsivity[86].

The leaky gut is also associated with a greater likelihood of food reactivity. These reactions are typically non-IgE-mediated[87]. They can create extra-digestive symptoms due to the secondary inflammatory reaction that extends far beyond the gastrointestinal system[88]. As part of a supervised elimination diet, many children showed an improvement in their physical and mental symptoms, including a decrease in ADHD symptoms[89,90]. However, dietary interventions aimed at reducing antigenic load elicit variable responses across individuals, with some showing little to no clinical improvement. In fact, a cohort of 28 children with ADHD was followed over 3.5 years while undergoing a four-week elimination diet excluding common allergens — such as gluten, dairy, soy, eggs, and nuts — , followed by a gradual reintroduction phase or permanent elimination if symptoms reappeared[91]. It appears that 64% of the children responded favourably and 40% saw a decrease in ADHD symptoms. The benefits were observable for several years for 30% of the children, especially if they did not use psychostimulants. These findings suggest that an oligo-antigenic diet, followed by personalized nutritional guidance, may represent a complementary therapeutic option for reducing the risk or severity of ADHD symptoms, regardless of whether pharmacological treatment is used.

Finally, artificial additives and flavorings warrant greater attention, as they may exacerbate ADHD symptoms or contribute to the manifestation of ADHD-like presentations[92]. This is because synthetic food dyes bind to proteins in various food environments, forming complexes digested by proteolytic enzymes. However, this binding can block the active sites needed for enzymatic hydrolysis, reducing protein digestibility[93]. Thus, dietary restriction protocols—including those eliminating synthetic food dyes—may lead to a modest reduction in ADHD symptoms; however, it is estimated that approximately 8% of children with ADHD display sensitivity to these additives[94]. Therefore, the exclusion of artificial food colorings may significantly reduce ADHD symptoms, particularly in individuals identified as having food sensitivities.[95]. Consequently, it is plausible that heightened sensitivity to food additives may trigger ADHD-like symptoms, a possibility that should be carefully considered prior to establishing a psychiatric diagnosis in children

It remains unclear whether dysbiosis or increased intestinal permeability directly contributes to the onset of ADHD-like symptoms through inflammatory and neurochemical pathways, or whether these factors merely exacerbate existing ADHD symptoms. Regardless, clinicians should try to identify and eliminate specific dietary triggers in children and adolescents with ADHD symptoms to reduce possible neuroinflammation in young patients. Any preventive or therapeutic intervention should be individualized and supported by close clinical monitoring. It is important to recall the considerable heterogeneity in both the causes and the severity of ADHD and ADHD-like symptoms. Young patients affected by dysbiosis may experience greater improvement from targeted interventions than those whose microbial composition remains within a healthy balance. While the personalized elimination diet is not necessarily a solution for all students affected by problems with concentration, hyperactivity or impulsivity, it could provide both preventive or curative benefits.

Sleep and Airway Integrity

The quality and duration of sleep influence various aspects of cognitive and physical health in children and adolescents. It has been shown to improve cognitive performance, academic functioning, mental health, and reduce behavioral problems in school-aged children[96,97]. Additionally, sleep quality is important to optimize the secretion of

growth hormone, which is closely linked to the deep phases of sleep[98]. Consequently, sleep disruptors may amplify the intensity of symptoms associated with neurodevelopmental disorders, including ADHD[99], or trigger an ADHD-like presentation.

The severity of ADHD symptoms in children may correlate with the severity of sleep disorders, including sleep-disordered breathing such as obstructive sleep apnea (OSA)[100,101]. This condition hinders airflow through the airways during sleep and causes a state of hypoxia, which disrupts the integrity of deep sleep phases. A prospective study of 40 children with ADHD showed that 62.5% were at high risk for sleep apnea following an orthodontic examination[102]. Conversely, approximately 30% of children with sleep apnea also present with ADHD symptoms, and this incidence increases with age[100]. Moreover, children with ADHD and a high risk of sleep-disordered breathing were significantly more likely to exhibit behavioral problems, hyperactivity, and attention deficits compared to children at low risk for such disorders[103].

Common nighttime symptoms of obstructive sleep apnea in children include snoring, excessive sweating, nightmares, bedwetting, restless sleep, mouth breathing, and observed apneas or labored breathing during the night. Other signs may include hyperextension of the neck during sleep or bruxism, indicating an increased effort to open the airways. Daytime symptoms may include poor concentration, behavioral or mood disturbances, morning headaches, and excessive daytime sleepiness[104]. Untreated sleep apnea can therefore lead to neurocognitive dysfunction and behavioral disorders that may be misdiagnosed as ADHD, highlighting the importance of evaluating and addressing sleep-disordered breathing before making an ADHD diagnosis and initiating medication.

Obesity is a major risk factor for the development of sleep apnea, affecting 45% of children with this condition[105]. Enlarged tonsils and adenoids are also a frequent cause of airway obstruction and sleep apnea, and their severity correlates with the manifestation of ADHD symptoms[100]. Furthermore, neurocognitive symptoms often improve after adenoidectomy and tonsillectomy[106]. This surgical procedure also restores nocturnal growth hormone pulsatility and improves growth in children suffering from sleep apnea caused by tonsillar and/or adenoidal hypertrophy[107].

Chronic nasal congestion caused by enlarged tonsils and adenoids, recurrent colds, or poorly controlled chronic environmental or seasonal allergies can obstruct airflow through the nasal passages, forcing the child to breathe through the mouth most of the time. This may lead to chronic ADHD-like symptoms secondary to the development of sleep apnea. Indeed, mouth breathing in children is associated with OSA due to the reduced pharyngeal space caused by tongue and jaw collapse into the airway[108]. This condition can simultaneously have significant consequences on craniofacial development[108].

Insufficient jaw development caused by mouth breathing and modern dietary patterns —such as the consumption of processed or ultra-processed foods, precooked meals, or foods low in fiber, pureed, or requiring minimal chewing— can understimulate the muscles required to maintain the structural integrity of the airways. These phenomena are associated with a rising frequency of craniofacial abnormalities, which are also linked to sleep apnea[109,110]. Reduced jaw size leads to less space for proper tooth alignment and increases the risk of malocclusion, sometimes requiring orthodontic treatment. Children with ADHD often present with more severe malocclusions, which supports the hypothesis that sleep-disordered breathing contributes to ADHD symptoms[111], or may induce an ADHD-like syndrome in children with these conditions by disrupting sleep integrity.

To properly distinguish children with true ADHD from those with ADHD-like symptoms, it is essential to evaluate craniofacial anatomy, breathing patterns, and sleep quality as part of the comprehensive assessment process. This ensures an adequate treatment plan and helps reduce symptom severity. It is important to note that none of these phenomena are considered in standard psychometric testing. However, a differential diagnosis could take into account these various contributing factors to explain the increasing prevalence of ADHD-like presentations, which are too often confused with true neurodevelopmental disorders.

Conclusion

It is important to recognize that while the definition of ADHD includes a genetic component, there is substantial heterogeneity in the manifestation of symptoms. To avoid confusion between ADHD

and ADHD-like presentations, a thorough differential diagnosis must account for multiple parameters before confirming a neurodevelopmental disorder. The example of Quebec[1,2] unfortunately illustrates the risks for children and adolescents of an evaluation process based on questionnaires and other psychometric tests that do not take into account vulnerability factors, lifestyle habits, or possible problems related to food, additives, microbiota and sleep-disordered breathing. We have explored potential causes of ADHD-like presentations, which should be considered alongside familial, academic, and psychosocial vulnerability factors in order to effectively guide patient management. To this effect, the available data suggest that clinicians should take the time to assess nutritional, metabolic, digestive and respiratory health as well as dietary lifestyle habits that contribute to the emergence of ADHD-like symptoms or increase physiological sensitivity in ADHD patients. Even when the use of psychostimulants is temporarily justified, their long-term use may carry risks, particularly if the pharmacological suppression of symptoms masks early indicators of underlying metabolic disorders. Given the involvement of multiple pathophysiological mechanisms in the emergence of ADHD symptoms, personalized patient management is essential to identify and address potential ADHD-like triggers. It is therefore essential that the treatment plan assess all lifestyle habits and the quality of the family, social and school environment before assuming that the neurological disorder is of genetic origin. While further research is needed to better understand the causes underlying the heterogeneity of clinical profiles in ADHD and to develop tailored therapeutic protocols, it remains essential—both medically and ethically—that clinicians take the time to conduct a comprehensive diagnostic assessment that accurately reflects the patient's true difficulties, particularly in children and adolescents.

Disclosure Statement Statement:

The authors or immediate family members have no potential conflicts of interest for the findings presented, nor has any funding source influenced the content of this article.

Funding Statement:

None.

Acknowledgements:

None.

References:

1. Monzée J, Dionne AI. Improve the medical assessment of young people with ADHD: Clinical and Ethical Issues from the Quebec Experience, *ESMED* (Submitted).

2. Monzée J. Evolution of psychotropic medication prescription in young people: reflection from the Quebec experience. *Psychotherapy and Psychosomatics*. 2025;94(1):8–14.

3. MSSS-MEES, *Protocole: trouble de déficit de l'attention avec ou sans hyperactivité*, 2019.

4. Deng MG, Zhou X, Li X, Liu J. Identification of Risk Genes for Attention-Deficit/Hyperactivity Disorder During Early Human Brain Development. J Am Acad *Child Adolesc Psychiatry*. 2024;S0890-8567(24)01976–2.

5. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet*. 2006;15(14):2276–84.

6. A. Kirley. Scanning the genome for attention deficit hyperactivity disorder. In D. Gozal D.(ed.). *Attention deficit hyperactivity disorder: from gene to patients*. Humana Press Inc., 2005.

7. Chen MH, Pan TL, Huang KL et al. Coaggregation of Major Psychiatric Disorders in First-Degree Relatives of Individuals With Attention-Deficit/Hyperactivity Disorder: A Nationwide Population-Based Study. *J Clin Psychiatry*. 2019;80(3):1812371.

8. Solberg BS, Hegvik TA, Halmøy A et al. Sex differences in parent-offspring recurrence of attention-deficit/hyperactivity disorder. *J Child Psychol Psy*chiatry. 2021;62(8):1010–1018.

9. Monzée J. Neuropsychologie et généticisation: limites scientifiques et éthiques. In Hervé Ch et al.(dir.). *Généticisation et responsabilités*. Dalloz. 2008:53–78.

10. Peedicayil J. The Role of Epigenetics in the Pathogenesis and Potential Treatment of Attention Deficit Hyperactivity Disorder. *Curr Neuropharmacol*. 2022;20(9):1642–1650.

11. Storebø OJ, Pedersen N, Ramstad E et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - Assessment of adverse events in non-randomised studies. *Cochrane Database Syst Rev*. 2018; 5(5):CD012069.

12. Zhang L, Li L, Andell P et al. Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases. *JAMA Psychiatry*. 2024;81(2):178–187.

13. Charney DS, Nestler EJ. Neurobiology of mental illness, Oxford PU, 2004.

14. Yu Y, Herman P, Rothman DL et al. Evaluating the gray and white matter energy budgets of human brain function. *J Cereb Blood Flow Metab*. 2018;38(8):1339–1353.

15. Galler JR, Bryce C, Waber DP et al. Socioeconomic outcomes in adults malnourished in the first year of life: a 40-year study. *Pediatrics.* 2012;130(1):e1–7.

16. Roger K, Vannasing P, Tremblay J et al. Early childhood malnutrition impairs adult resting brain function using near-infrared spectroscopy. *Front Hum Neurosci.* 2024;17:12874–88.

17. Fernstrom JD, Fernstrom MH. Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. *J Nutr*. 2007;137(6-Suppl 1):1539S–1547S.

18. Roth W, Zadeh K, Vekariya R, Ge Y, Mohamadzadeh M. Tryptophan Metabolism and Gut-Brain Homeostasis. *Int J Mol Sci*. 2021;22(6):2973.

19. Bornstein RA, Baker GB, Carroll A et al. Plasma amino acids in attention deficit disorder. *Psychiatry Res*. 1990;33(3):301–6.

20. Wang LJ, Yu YH, Fu ML et al. Dietary Profiles, Nutritional Biochemistry Status, and Attention-Deficit/Hyperactivity Disorder: Path Analysis for a Case-Control Study. *J Clin Med.* 2019;8(5):709.

21. Martini D, Godos J, Bonaccio M et al. Ultra-Processed Foods and Nutritional Dietary Profile: A Meta-Analysis of Nationally Representative Samples. *Nutrients*. 2021;13(10):3390.

22. Moubarac JC, Batal M, Louzada ML et al. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite*. 2017;108:512–520.

23. Liu J, Steele EM, Li Y, Karageorgou D et al. Consumption of Ultraprocessed Foods and Diet Quality Among U.S. Children and Adults. *Am J Prev Med*. 2022;62(2):252–264.

24. Skalny AV, Mazaletskaya AL, Ajsuvakova OP et al. Serum zinc, copper, zinc-to-copper ratio, and other essential elements and minerals in children with attention deficit/hyperactivity disorder (ADHD). *J Trace Elem Med Biol*. 2020;58:126445.

25. Huang YH, Zeng BY, Li DJ et al. Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;90:134–141.

26. Tinkov AA, Mazaletskaya AL, Ajsuvakova OP et al. ICP-MS Assessment of Hair Essential Trace Elements and Minerals in Russian Preschool and Primary School Children with Attention-Deficit/Hyperactivity Disorder (ADHD). *Biol Trace Elem Res*. 2020;196(2):400–409.

27. Tseng PT, Cheng YS, Yen CF et al. Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):788.

28. Wang Y, Huang L, Zhang L et al. Iron Status in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. *PLoSOne*. 2017;12(1):e0169145.

29. Pongpitakdamrong A, Chirdkiatgumchai V, Ruangdaraganon N et al. Effect of Iron Supplementation in Children with Attention-Deficit/Hyperactivity Disorder and Iron Deficiency: A Randomized Controlled Trial. *J Dev Behav Pediatr*. 2022;43(2):80–86.

30. Prades N, Varela E, Flamarique I et al. Water-soluble vitamin insufficiency, deficiency and supplementation in children and adolescents with a psychiatric disorder: a systematic review and meta-analysis. *Nutr Neurosci*. 2023;26(2):85–107.

31. Bala KA, Doğan M, Kaba S et al. Hormone disorder and vitamin deficiency in attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs). *J Pediatr Endocrinol Metab*. 2016;29(9):1077–82.

32. Mousain-Bosc M, Roche M, Polge A et al. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. I. Attention deficit hyperactivity disorders. *Magnesium research*. 2006;19(1):46–52.

33. Mirhosseini H, Maayeshi N, Hooshmandi H et al. The effect of vitamin D supplementation on the brain mapping and behavioral performance of children with ADHD: a double-blinded randomized controlled trials. *Nutritional Neuroscience*. 2023;27:566–76.

34. Johnstone JM, Hughes A, Goldenberg JZ et al. Multinutrients for the Treatment of Psychiatric Symptoms in Clinical Samples: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2020;12(11):3394.

35. Sonuga-Barke EJ, Brandeis D, Cortese S et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psy*chiatry. 2013;170(3):275–89.

36. Chang CY, Ke DS, Chen JY. Essential fatty acids and human brain. *Acta Neurol Taiwan*. 2009;18(4):231–41.

37. Bazan NG. Lipid signaling in neural plasticity, brain repair, and neuroprotection. *Mol Neurobiol*. 2005;32(1):89–103.

38. Madden SM, Garrioch CF, Holub BJ. Direct diet quantification indicates low intakes of (n-3) fatty acids in children 4 to 8 years old. *J Nutr*. 2009;139(3):528–32.

39. Belury MA, Raatz S, Conrad Z. Modeled Substitution of Traditional Oils with High-Oleic Acid Oils Decreases Essential Fatty Acid Intake in Children. *Am J Clin Nutr*. 2022;115(4):1180–1188.

40. Zhou XD, Chen QF, Targher G et al. Global burden of disease attributable to metabolic risk factors in adolescents and young adults aged 15-39, 1990-2021. *Clin Nutr*. 2024;43(12):391–404.

41. Leone M, Bui HT, Kalinova E et al. Updating normative cross-sectional values and secular trends in body mass, body height and body mass index among Québec children and adolescents. *Can J Public Health*. 2023;114(4):629–641.

42. Rodd C, Feely A, Dart A, Sharma A, McGavock J. Biological and socioeconomic determinants of prediabetes in youth: an analysis using 2007 to 2011 Canadian Health Measures Surveys. *Pediatr Res*. 2018;84(2):248–253.

43. Harnois-Leblanc S, Van Hulst A, Ybarra M et al. Natural history and determinants of dysglycemia in Canadian children with parental obesity from ages 8-10 to 15-17 years: The QUALITY cohort. *Pediatr Diabetes*. 2022;23(3):274–285.

44. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. *Dialogues Clin Neurosci*. 2018;20(1):63–73.

45. Cheon SY, Song J. Neuropsychiatric Abnormalities in Metabolic Disturbances: Interplay of Adipokines and Neurotransmission. *Mol Neurobiol*. 2025;5. doi:10.1007/s12035-025-04797-6.

46. Neri D, Martínez-Steele E, Khandpur N, Levy R. Associations Between Ultra-processed Foods Consumption and Indicators of Adiposity in US Adolescents: Cross-Sectional Analysis of the 2011-2016. National Health and Nutrition Examination Survey. *J Acad Nutr Diet*. 2022;122(8):1474–1487.

47. Tagi VM, Chiarelli F. Obesity and insulin resistance in children. *Curr Opin Pediatr.* 2020;32(4):582–88.

48. Wang L, Martínez Steele E, Du M et al. Trends in Consumption of Ultraprocessed Foods Among US Youths Aged 2-19 Years, 1999-2018. *JAMA*. 2021;326(6):519–30.

49. Cui Y, Tang TY, Lu CQ, Ju S. Insulin Resistance and Cognitive Impairment: Evidence From Neuroimaging. *J Magn Reson Imaging*. 2022;56(6):1621–49.

50. Laws SM, Gaskin S, Woodfield A et al. Insulin resistance is associated with reductions in specific cognitive domains and increases in CSF tau in cognitively normal adults. *Sci Rep*. 2017;7(1):9766.

51. Menon AJ, Selva M, Sandhya G et al. Understanding the link between insulin resistance and cognition: a cross-sectional study conducted in an urban, South Indian cohort. *Acta Diabetol*. 2025.doi:10.1007/s00592-025-02483-6.

52. Ekblad LL, Rinne JO, Puukka PJ et al. Insulin resistance is associated with poorer verbal fluency performance in women. *Diabetologia*. 2015; 58(11):2545–53.

53. Willette AA, Xu G, Johnson SC et al. Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. *Diabetes Care*. 2013;36(2):443–9.

54. Corona JC. Role of Oxidative Stress and Neuroinflammation in Attention-Deficit/Hyperactivity Disorder. *Antioxidants (Basel)*. 2020;9(11):1039.

55. Vázquez-González D, Carreón-Trujillo S, Alvarez-Arellano L et al. A Potential Role for Neuroinflammation in ADHD. *Adv Exp Med Biol*. 2023;1411:327–56.

56. Kleinridders A, Cai W, Cappellucci L et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc Natl Acad Sci USA*. 2015;112(11):3463–8.

57. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. *Pharmacol Biochem Behav*. 2019;182:22–34.

58. Del-Ponte B, Quinte GC, Cruz S et al. Dietary patterns and attention deficit/hyperactivity disorder (ADHD): A systematic review and meta-analysis. *J Affect Disord*. 2019;252:160–73.

59. Yan W, Lin S, Wu D et al. Processed Food-Sweets Patterns and Related Behaviors with Attention Deficit Hyperactivity Disorder among Children: A Case-Control Study. *Nutrients*. 2023;15(5):1254.

60. Jung TH, Hwang HJ, Han KS. Correlation of attention deficit hyperactivity disorder with gut microbiota according to the dietary intake of Korean elementary school students. *PLoSOne*. 2022;17(9):e0275520.

61. Hampl SE, Hassink SG, Skinner AC et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics*. 2023;151(2):e2022060640.

62. Chen Q, Hartman CA, Haavik J et al. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *PLoSOne*. 2018; 13(9):e0204516.

63. Libutzki B, Neukirch B, Reif A, Hartman CA. Somatic burden of attention-deficit/hyperactivity disorder across the lifecourse. *Acta Psychiatr Scand*. 2024;150(2):105–17.

64. Dimova R, Chakarova N, Del Prato S, Tankova T. The Relationship Between Dietary Patterns and Glycemic Variability in People with Impaired Glucose Tolerance. *J Nutr*. 2023;153(5):1427–38.

65. Færch K, Vistisen D, Pacini G et al. Insulin Resistance Is Accompanied by Increased Fasting Glucagon and Delayed Glucagon Suppression in Individuals With Normal and Impaired Glucose Regulation. *Diabetes*. 2016;65(11):3473–81.

66. McAulay V, Deary IJ, Ferguson SC, Frier BM. Acute hypoglycemia in humans causes attentional dysfunction while nonverbal intelligence is preserved. *Diabetes Care*. 2001;24(10):1745–50.

67. Verhulst CEM, Fabricius TW, Nefs G et al. Consistent Effects of Hypoglycemia on Cognitive Function in People With or Without Diabetes. *Diabetes Care*. 2022;45(9):2103–10.

68. Lin SY, Lin CL, Hsu WH et al. Association of attention deficit hyperactivity disorder with recurrent hypoglycemia in type 1 diabetes mellitus. *Pediatr Diabetes*. 2019;20(2):189–96.

69. ISQ. Enquête québécoise sur l'activité physique et le sport (EQAPS) 2018-2019. Published Augustus 6, 2020; Accessed April 15, 2025. https://statistique.quebec.ca/fr/enquetes/realisees

/enquete-quebecoise-sur-lactivite-physique-et-le-sport-eqaps-2018-2019.

70. van Egmond-Fröhlich AW, Weghuber D, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with physical activity, media time, and food intake in children and adolescents. *PLoSOne*. 2012;7(11):e49781.

71. Fühner T, Kliegl R, Arntz F et al. An Update on Secular Trends in Physical Fitness of Children and Adolescents from 1972 to 2015: A Systematic Review. *Sports Med*. 2021;51(2):303–20.

72. Muntaner-Mas A, Ortega FB, Femia P et al. Low cardiorespiratory fitness and obesity for ADHD in childhood and adolescence: A 6-year cohort study. *Scand J Med Sci Sports.* 2021;31(4):903–13.

73. Wu X, Ohinmaa A, Veugelers PJ. The Influence of Health Behaviours in Childhood on Attention Deficit and Hyperactivity Disorder in Adolescence. *Nutrients*. 2016;8(12):788.

74. Song Y, Fan B, Wang C, Yu H. Meta-analysis of the effects of physical activity on executive function in children and adolescents with attention deficit hyperactivity disorder. *PLoSOne*. 2023; 18(8):e0289732.

75. Zhu F, Zhu X, Bi X et al. Comparative effectiveness of various physical exercise interventions on executive functions and related symptoms in children and adolescents with attention deficit hyperactivity disorder: A systematic review and network meta-analysis. *Front Public Health*. 2023;11:1133727.

76. Pujalte GGA, Narducci DM, Smith MS et al. Athletes With Attention-Deficit/Hyperactivity Disorder: Position Statement of the American Medical Society for Sports Medicine. *Clin J Sport Med*. 2023;33(3):195–208.

77. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res*. 2018;1693:128–33.

78. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. *Cell Mol Life Sci.* 2017;74(16):2959–77.

79. Zhang H, Wang Z, Wang G et al. Understanding the Connection between Gut Homeostasis and Psychological Stress. *J Nutr*. 2023;153(4):924–39.

80. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. *Cell Mol Life Sci.* 2017;74(16):2959–77.

81. Gkougka D, Mitropoulos K, Tzanakaki G et al. Gut microbiome and attention deficit/hyperactivity disorder: a systematic review. *Pediatr Res*. 2022; 92(6):1507–19.

82. Gurow K, Joshi DC, Gwasikoti J, Joshi N. Gut Microbial Control of Neurotransmitters and Their Relation to Neurological Disorders: A Comprehensive Review. *Horm Metab Res*. 2025. doi:10.1055/a-2536-1421.

83. Nahidi M, Soleimanpour S, Emadzadeh M. Probiotics as a Promising Therapy in Improvement of Symptoms in Children With ADHD: A Systematic Review. *J Atten Disord.* 2024;28(8):1163–72.

84. Martel J, Chang SH, Ko YF et al. Gut barrier disruption and chronic disease. *Trends Endocrinol Metab*. 2022;33(4):247–65.

85. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol.* 2021;21(11):739–51.

86. Lewis N, Villani A, Lagopoulos J. Gut dysbiosis as a driver of neuroinflammation in attention-deficit/hyperactivity disorder: A review of current evidence. *Neuroscience*. 2025;569:298–321.

87. Poto R, Fusco W, Rinninella E et al. The Role of Gut Microbiota and Leaky Gut in the Pathogenesis of Food Allergy. *Nutrients*. 2023;16(1):92.

88. Su KW, Shreffler WG, Yuan Q. Gastrointestinal immunopathology of food protein-induced enterocolitis syndrome and other non-immunoglobulin E-mediated food allergic diseases. *Ann Allergy Asthma Immunol*. 2021;126(5):516–23.

89. Meyer R, Cianferoni A, Vazquez-Ortiz M. An update on the diagnosis and management of non-IgE-mediated food allergies in children. *Pediatr Allergy Immunol.* 2025;36(3):e70060.

90. Pelsser LM, Frankena K, Toorman J, Rodrigues Pereira R. Diet and ADHD, Reviewing the Evidence: A Systematic Review of Meta-Analyses of Double-Blind Placebo-Controlled Trials Evaluating the Efficacy of Diet Interventions on the Behavior of Children with ADHD. *PLoS One*. 2017;12(1):e0169277.

91. Walz G, Blazynski N, Frey L et al. Long-Term Effects of an Oligoantigenic Diet in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) on Core Symptomatology. *Nutrients*. 2022;14(23):5111.

92. Cook PS, Woodhill JM. The Feingold dietary treatment of the hyperkinetic syndrome. *Med J Aust*. 1976;2(3):85–8, 90.

93. Saeed S. Investigations of In vitro Digestibility of Proteins Bound to Food Colors. *J of pharmacy and nutrition sciences*. 2011;1:34–40.

94. Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder

or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *J Am Acad Child Adolesc Psychiatry*. 2012;51(1):86–97.

95. Sonuga-Barke EJ, Brandeis D, Cortese S et al. European ADHD Guidelines Group. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry*. 2013;170(3):275–89.

96. Astill RG, Van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. *Psychol Bull*. 2012;138(6):1109–38.

97. El-Sheikh M, Philbrook LE, Kelly RJ et al. What does a good night's sleep mean? Nonlinear relations between sleep and children's cognitive functioning and mental health. *Sleep*. 2019;42(6):zsz078.

98. Van Cauter E, Plat L. Physiology of growth hormone secretion during sleep. J Pediatr. 1996;128(5/2):S32–7.

99. Bruni O, Breda M, Mammarella V et al. Sleep and circadian disturbances in children with neurodevelopmental disorders. *Nat Rev Neurol*. 2025;21(2):103–20.

100.Wu J, Gu M, Chen S, Chen W et al. Factors related to pediatric obstructive sleep apnea-hypopnea syndrome in children with attention deficit hyperactivity disorder in different age groups. *Medicine*. 2017;96(42):e8281.

101.Prajsuchanai T, Tanphaichitr A, Hosiri T et al. Prevalence of high-risk for obstructive sleep apnea in attention deficit hyperactivity disorder children referred to psychiatry clinic and impact on quality of life. *Front Psychiatry*. 2022;13:926153.

102. Alessandri-Bonetti A, Guglielmi F, Deledda G et al. Malocclusions, Sleep Bruxism, and Obstructive Sleep Apnea Risk in Pediatric ADHD Patients: A Prospective Study. *J Atten Disord*. 2024; 28(6):1017–23.

103.Kim KM, Lim MH, Ha M, Kwon HJ. Associations Between Sleep-Disordered Breathing and Behavioral and Cognitive Functions in Children With and Without Attention-Deficit/Hyperactivity Disorder. *J Acad Consult Liaison Psychiatry.* 2022;63(3):234–43.

104.Mukherjee S, Patel SR, Kales SN et al.; American Thoracic Society ad hoc Committee on Healthy Sleep. An Official American Thoracic Society Statement: The Importance of Healthy Sleep. Recommendations and Future Priorities. *Am J Respir Crit Care Med.* 2015;191(12):1450–8.

105.Hampl SE, Hassink SG, Skinner AC et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics.* 2023;151(2):e2022060640.

106.Sedky K, Bennett DS, Carvalho KS. Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: a meta-analysis. *Sleep Med Rev.* 2014;18(4):349–56.

107.Nieminen P, Löppönen T, Tolonen U et al. Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics.* 2002;109(4):e55.

108.Juliano ML, Machado MA, deCarvalho et al. Polysomnographic findings are associated with cephalometric measurements in mouth-breathing children. *J Clin Sleep Med.* 2009;5(6):554–61.

109.Bozzini MF, Di Francesco RC. Managing obstructive sleep apnoea in children: the role of craniofacial morphology. *Clinics.* 2016;71(11):664–6.

110.Sabuncuoglu O. Understanding the relationships between breastfeeding, malocclusion, ADHD, sleep-disordered breathing and traumatic dental injuries. *Med Hypotheses*. 2013;80(3):315–20.

111.Roy A, Ferraz Dos Santos B, Rompré P, Nishio C. Dental malocclusion among children with attention deficit hyperactivity disorder. *Am J Orthod Dentofacial Orthop*. 2020;158(5):694–9.

