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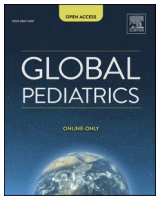

Effects of adolescent psychoactive substance exposure: Developmental vulnerability and long-term pathophysiology outcomes

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ABSTRACT

Background: Adolescence is a critical neurodevelopmental period characterized by heightened vulnerability to psychoactive substance exposure. The increasing prevalence of cannabis use among young people, together with persistent misconceptions regarding its safety, raises important public health concerns.
Objective: This scoping review aims to summarize current evidence on the biological and clinical consequences of psychoactive substance exposure during adolescence, with a focus on developmental vulnerability and long-term pathophysiological effects.
Methods: A Narrative literature review was conducted using PubMed/MEDLINE, Scopus, and Web of Science databases, focusing on studies published in English from 2000 to 2026. Evidence from experimental, clinical, epidemiological, and review studies was included, prioritizing high-quality research such as longitudinal cohort studies, systematic reviews, meta-analyses, and clinical guidelines.
Results: Adolescence is characterized by ongoing maturation of brain structures involved in executive function, impulse control, and emotional regulation, with increased sensitivity of the endocannabinoid system. Exposure to cannabis during this period is associated with alterations in neurotransmission, synaptic plasticity, and neurodevelopmental trajectories, with potential long-term effects on cognition and mental health. Respiratory consequences include airway inflammation, impaired mucociliary function, and increased risk of chronic bronchitic symptoms, while cardiovascular effects involve sympathetic activation, endothelial dysfunction, and potential increased risk of acute ischemic events, although evidence remains partly inconsistent due to confounding factors. Endocrine effects include disruption of hypothalamic–pituitary–gonadal and stress axis function, with possible implications for reproductive health, metabolic regulation, and stress responsivity. Environmental and psychosocial factors, including peer influence, availability, and perceived risk, strongly modulate initiation and persistence of use.
Conclusions: Psychoactive substance use during adolescence represents a significant public health challenge due to the interaction between biological vulnerability and environmental exposure. Although some neurobiological changes may be partially reversible, early exposure may result in persistent functional consequences. Pediatricians play a central role in prevention through early education, screening, and brief interventions, supported by multidisciplinary and community-based strategies aimed at reducing adolescent substance use and promoting healthy development.

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Introduction

Adolescence is a complex developmental period characterized by profound neurobiological, psychosocial, and behavioral changes. This vulnerable phase is associated with increased risk-taking behaviors and experimentation with psychoactive substances, representing a significant public health concern worldwide.[1]

The traditional distinction between "soft" and "hard" drugs is not based on a standardized pharmacological classification and lacks clear criteria. Terminology in the field of addiction is often imprecise, with terms that can be inconsistent or misleading. Currently, the labels "soft" and "hard" drugs largely reflect historical, legal, and sociocultural perceptions of harm associated with different substances.[2,3]

The term "soft drugs" is generally used to describe substances perceived as less harmful, typically associated with a lower risk of physical dependence, reduced acute toxicity, and a lower likelihood of fatal overdose. These substances commonly include tobacco and alcohol, and, according to some classifications, caffeine (for which substance use disorder is recognized in ICD-10), cannabis (e.g., marijuana and hashish), and certain mild hallucinogens such as lysergic acid diethylamide (LSD) and psilocybin, although their classification remains context-dependent.

Cannabis is the most widely used illicit substance among adolescents worldwide, with approximately 20% of U.S. high school students reporting use in the past month and nearly 37% reporting lifetime use.[4] Although prevalence has declined from peak levels observed in the late 1990s, cannabis use continues to affect millions of adolescents, with evolving patterns that include increased consumption of high-potency products and the use of vaping devices[5,6]

In contrast, the term "hard drugs" has traditionally been used to describe substances with a high potential for addiction, significant toxicity, and increased risk of overdose. These include opioids (e.g., heroin, fentanyl, morphine), stimulants (e.g., cocaine, crack cocaine, methamphetamine), certain hallucinogens, and central nervous system depressants (e.g., gamma-hydroxybutyric acid, anxiolytics/hypnotics, and high-dose benzodiazepines).

Contemporary literature emphasizes that this dichotomous classification is overly simplistic and not scientifically robust. Even substances traditionally considered "soft," such as cannabis, can have significant adverse health effects, particularly during adolescence.[2,3,7]

Furthermore, legal psychoactive substances such as alcohol and nicotine should be fully integrated into this framework, given their high prevalence among adolescents and their well-established association with dependence and substantial physical and mental health consequences.[8] This narrative review aims to summarize current evidence on the biological and clinical consequences of psychoactive substance exposure during adolescence, with a focus on developmental vulnerability and long-term pathophysiological effects.

Methods

This narrative review was designed to summarize and critically evaluate current evidence regarding the biological and clinical consequences of psychoactive substance exposure during adolescence, a developmental period characterized by heightened neurobiological vulnerability. The review aimed to integrate findings across multiple domains, including neurodevelopmental, cardiovascular, respiratory, and endocrine outcomes, with a focus on long-term pathophysiological effects.

A structured literature search was conducted across three major electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The search encompassed studies published from January 2000 through February 2026 to capture both foundational and contemporary research. Search strategies were adapted for each database using controlled vocabulary (e.g., MeSH terms) and free-text keywords. Core search terms included combinations of "adolescence," "adolescent brain development," "psychoactive substances," "substance use," "cannabis," "alcohol," "nicotine," "stimulants," "neurodevelopment," "cardiovascular effects," "respiratory effects," "endocrine effects," and "long-term outcomes." Boolean operators (AND, OR) were used to refine the search and ensure comprehensive coverage.

Eligibility criteria were defined a priori. Included studies comprised original research articles (both observational and interventional), systematic reviews, meta-analyses, and clinical guidelines published in English. Particular emphasis was placed on high-quality evidence, including longitudinal cohort studies that assessed long-term outcomes, randomized controlled trials (where available), and consensus statements or position papers from recognized international scientific and medical organizations. Preclinical studies were considered when they provided mechanistic insights relevant to human adolescent development.

Studies were excluded if they focused exclusively on adult populations without retrospective assessment of adolescent exposure, lacked relevance to biological or clinical outcomes, or addressed substance use solely from a sociological or behavioral perspective without physiological correlates. Case reports and small case series were generally excluded unless they highlighted rare but clinically significant outcomes.

Following the initial database search, titles and abstracts were screened for relevance. Full-text articles were subsequently reviewed for inclusion based on the predefined criteria. To enhance completeness, additional references were identified through manual screening of the bibliographies of key articles and relevant reviews (snowballing technique).

Given the narrative nature of this review, a formal risk-of-bias assessment or quantitative meta-analysis was not performed. Instead, the selection and synthesis of evidence were guided by the authors' clinical and research expertise. Studies were qualitatively evaluated based on methodological rigor, sample size, consistency of findings, and relevance to adolescent populations. When conflicting evidence was identified, priority was given to studies with stronger designs and larger cohorts.

The findings were synthesized thematically, with results organized according to major physiological systems and types of psychoactive substances. This approach was chosen to provide a comprehensive, integrative, and clinically meaningful overview of the current state of knowledge, while also identifying gaps in the literature and areas for future research.

Epidemiology of psychoactive substance use

Substance use during adolescence represents a significant public health concern. Approximately 43.5% of individuals aged 15–17 years report lifetime exposure to at least one psychoactive substance.[9] In the United States, about 7.9% of adolescents aged 12–17 years report use of an illicit substance within the previous month, and nearly half have experimented with such substances by the end of high school.[10)]

Cannabis

Cannabis is the most commonly used illicit substance among adolescents and often represents the initial substance of use for approximately two-thirds of individuals who initiate substance use. In contrast, more than one in four adolescents report that their first exposure involves a prescription medication used for nonmedical purposes, most frequently opioid analgesics.[11]

In Italy, lifetime prevalence of cannabis use among adolescents is estimated at approximately 30%, followed by cocaine (5%) and hallucinogens (2%), while heroin remains the least commonly used substance.[12]

Multiple factors contribute to the initiation and progression of substance use during adolescence. Individual risk factors include sensation-

seeking behavior, conduct problems, poor academic performance, and low perceived risk of harm.[13–15] Reported motivations for use include relaxation (73%), stress relief (44%), and coping with anxiety or depressive symptoms (40%), while approximately half of adolescents also report experimentation or recreational use as primary drivers.[16]

A study by Liakoni et al. involving 1139 Swiss secondary school students (mean age 17.1 years) found that 9.2% reported substance use for cognitive enhancement and 6.2% for recreational purposes. Prescription medications—particularly methylphenidate—were more frequently used for cognitive enhancement, whereas cannabis and alcohol were the most commonly used substances for recreational purposes and were also sometimes used for cognitive enhancement. Cannabis was perceived as effective, and most users expressed willingness to use it again.[17)] These findings suggest that substance use for cognitive enhancement begins before university, underscoring the need for early preventive interventions.

Environmental influences include substance availability, permissive social norms, family history of substance use, and exposure to adverse childhood experiences.[13,18] Interpersonal factors—particularly peer substance use and parental attitudes—are among the strongest predictors of adolescent use patterns.[14,19]

Alcohol use

Alcohol remains one of the most prevalent psychoactive substances used during adolescence and represents a major contributor to global morbidity and mortality in this age group. Early initiation of alcohol consumption is associated with an increased risk of developing alcohol use disorder (AUD) later in life, as well as a range of neurocognitive and behavioral consequences.

From a neurobiological perspective, alcohol interferes with ongoing brain maturation, particularly affecting the prefrontal cortex and hippocampus—regions involved in executive function, memory, and emotional regulation. Adolescent alcohol exposure has been shown to disrupt synaptic pruning and myelination, leading to impairments in learning, attention, and decision-making. Functional neuroimaging studies have demonstrated alterations in neural connectivity and reduced gray matter volume in adolescents with heavy or binge drinking patterns.

Alcohol also modulates key neurotransmitter systems, including gamma-aminobutyric acid (GABA), glutamate, and dopamine pathways. These effects contribute not only to acute intoxication but also to long-term alterations in reward processing and increased vulnerability to addiction. Importantly, adolescents appear more sensitive to the rewarding effects of alcohol and less sensitive to its sedative effects, a combination that may promote higher consumption and risk-taking behaviors.

Beyond neurological effects, alcohol use is associated with significant systemic consequences. Acute risks include injuries, violence, and risky sexual behaviors, while chronic use may lead to liver dysfunction, metabolic disturbances, and cardiovascular alterations. Furthermore, alcohol consumption during adolescence is strongly associated with co-occurring mental health disorders, including depression, anxiety, and suicidality.

Nicotine and tobacco use

Nicotine exposure during adolescence, primarily through cigarette smoking and increasingly through electronic nicotine delivery systems (ENDS), poses substantial risks to both brain development and long-term health. Adolescents are particularly vulnerable to nicotine addiction due to heightened neuroplasticity and increased sensitivity of the mesolimbic dopaminergic reward system.

Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are widely distributed in the developing brain. Activation of these receptors during adolescence can lead to long-lasting changes in synaptic plasticity, neural circuitry, and gene expression. These neuroadaptations may impair cognitive functions such as attention, memory, and impulse control, while also increasing susceptibility to other substance use disorders—a phenomenon often described as the "gateway effect."

Emerging evidence indicates that nicotine exposure may also exacerbate underlying psychiatric conditions, including anxiety disorders, depression, and attention-deficit/hyperactivity disorder (ADHD). Moreover, early nicotine use has been associated with increased risk of polysubstance use, including cannabis and alcohol.

From a respiratory standpoint, traditional cigarette smoking is well known to cause airway inflammation, reduced lung growth, and increased risk of chronic respiratory diseases. Although e-cigarettes are often perceived as safer alternatives, they are not without risk. Vaping aerosols contain potentially harmful substances, including ultrafine particles, volatile organic compounds, and heavy metals, which may induce oxidative stress and inflammatory responses in the respiratory epithelium.

Cardiovascular effects of nicotine include increased heart rate, elevated blood pressure, endothelial dysfunction, and early vascular damage. These changes may contribute to the early development of atherosclerosis and increase long-term cardiovascular risk.

Prescription drug misuse

The nonmedical use of prescription medications among adolescents is an emerging and concerning trend, often underestimated compared with illicit substance use. Commonly misused medications include opioid analgesics, central nervous system stimulants (e.g., methylphenidate, amphetamines), benzodiazepines, and sedative-hypnotics.

Prescription drug misuse in adolescence is frequently driven by diverse motivations, including recreational use, self-medication for untreated mental health conditions, and cognitive or academic performance enhancement. This latter phenomenon is particularly relevant in high-pressure academic environments, where stimulants are used to improve concentration and productivity.

Opioid misuse poses a particularly high risk due to its association with respiratory depression, overdose, and progression to illicit opioid use. Even short-term exposure during adolescence may increase the likelihood of long-term misuse and dependence. Neurobiologically, opioids act on the endogenous opioid system, altering reward processing and reinforcing drug-seeking behaviors.

Stimulant misuse can lead to adverse cardiovascular effects, including tachycardia, hypertension, and arrhythmias, as well as psychiatric symptoms such as anxiety, agitation, and, in severe cases, psychosis. Chronic misuse may disrupt normal dopaminergic signaling and contribute to long-term alterations in motivation and reward sensitivity.

Benzodiazepine misuse is associated with sedation, cognitive impairment, and risk of dependence, particularly when combined with other central nervous system depressants such as alcohol. Polysubstance use is common in this context and significantly increases the risk of adverse outcomes, including overdose.

Importantly, access to prescription medications often occurs through family members or peers, highlighting the role of environmental and social factors. This underscores the need for improved prescribing practices, secure medication storage, and targeted educational interventions.

Integration and clinical implications

Alcohol, nicotine, and prescription drug misuse frequently co-occur with cannabis use, contributing to patterns of polysubstance use that amplify health risks. These substances share common neurobiological pathways, particularly involving dopaminergic reward circuits, and may exert synergistic effects on brain development and behavior. Given their high prevalence and accessibility, these substances should be systematically addressed in pediatric practice. Routine screening, early

identification of risk factors, and brief interventions remain essential components of prevention strategies. In addition, addressing underlying mental health conditions and psychosocial stressors is critical to reducing substance use initiation and progression.

Effects on different body systems

Neurological effects

The adolescent brain undergoes substantial maturation, particularly within the hippocampus and prefrontal cortex—regions responsible for executive function, decision-making, planning, and impulse control. During this developmental window, the endocannabinoid system plays a critical role in neuronal maturation, rendering the adolescent brain particularly vulnerable to exogenous cannabinoids such as delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis.[20,21]

THC exerts its effects primarily through CB1 receptors, disrupting the finely regulated balance of glutamatergic and GABAergic neurotransmission. These alterations can impair synaptic plasticity, memory processing, and cellular energy metabolism, ultimately affecting cognitive function.[22]

Evidence supports a dose-dependent relationship between frequency of use and the severity of adverse outcomes.[22,23] Early onset of use and exposure to high-potency products are associated with an increased risk of psychiatric conditions, including depression, suicidality, and psychotic disorders.[24]

Longitudinal neuroimaging studies have demonstrated that adolescent exposure is associated with structural alterations in the hippocampus and prefrontal cortex.[25] In addition, THC exposure during this critical developmental period may induce long-lasting changes in brain function through epigenetic mechanisms, particularly involving genes related to synaptic plasticity.[21] These effects appear to be especially pronounced during adolescence, reflecting the heightened vulnerability of the developing brain, characterized by ongoing neurodevelopment and elevated CB1 receptor density.[25,26]

Chronic exposure during adolescence has been linked to persistent alterations in prefrontal cortical function and dopaminergic signaling,[21] which may contribute to long-term deficits in sustained attention, working memory, and verbal intelligence, as well as reduced social functioning and altered emotional regulation.

Importantly, emerging evidence suggests that some neurobiological changes associated with cannabis exposure may not persist into adulthood and may be at least partially reversible. This finding underscores the importance of early identification and timely intervention strategies.[20]

Respiratory effects

Cannabis smoking exerts significant respiratory effects through mechanisms similar to those associated with tobacco smoke exposure. Combustion produces smoke containing particulate matter, carcinogens, and toxic compounds, including tar, nitric oxide, ammonia, hydrogen cyanide, and aromatic amines.[27,28] Although individuals who use cannabis typically consume fewer joints than cigarette smokers consume cigarettes, they often employ deeper inhalation and prolonged breath-holding. This results in approximately fourfold greater tar deposition per joint compared with a single cigarette. Numerous studies have demonstrated that chronic exposure is associated with large airway inflammation, characterized by squamous cell hyperplasia, loss of ciliated epithelium, vascular proliferation, submucosal edema, and goblet cell hyperplasia.[27,29]

Increased airway resistance, lung hyperinflation, and respiratory symptoms—such as cough, wheezing, and sputum production—have also been reported.[30] The Canadian Users of Cannabis Smoke (CANUCK) study demonstrated that cannabis smoking is associated with dysregulated immune responses in the airway epithelium, including increased type 2 immune signaling, reduced type 17 responses, and elevated expression of the MUC5AC mucin gene.[31)] Clinically, this translates into symptoms consistent with chronic bronchitis and asthma, including cough, sputum production, wheezing, and dyspnea.[27,29]

In contrast to tobacco smoke, cannabis inhalation has also been shown to exert acute bronchodilatory effects, a phenomenon historically exploited in the management of asthma since the 19th century.[32] These effects are primarily mediated by THC and have been observed in both healthy individuals and patients with asthma.[33]

Cross-sectional studies report relatively modest and variable effects on lung function, including slight reductions in the FEV_1/FVC ratio and increases in forced vital capacity (FVC), suggesting a nonlinear dose–response relationship. At low to moderate levels of exposure, lung function may appear preserved or even slightly increased, possibly reflecting a "stretch effect" due to deep inhalation. However, at higher levels of exposure, these effects plateau or reverse, particularly for FEV_1.[28,34]

Imaging studies indicate that heavy exposure is associated with emphysema and ventilation defects, suggesting structural lung damage beyond reversible inflammation.[31] Additionally, heavy use has been linked to bullous lung disease and spontaneous pneumothorax, although causality remains uncertain. These complications may be related to increased intrathoracic pressure from deep inhalation and prolonged breath-holding, which can promote alveolar rupture, particularly in susceptible individuals.[35,36]

While tobacco smoking is a well-established cause of lung cancer, the association between cannabis smoking and lung cancer remains inconclusive. Cannabis smoke contains mutagenic compounds, and airway biopsies have demonstrated precancerous changes similar to those observed with tobacco exposure. However, epidemiological evidence is inconsistent. For instance, a large Canadian cohort study reported a twofold increased risk of lung cancer among heavy users over a 40-year follow-up, whereas a meta-analysis of case–control studies found no significant association after adjustment for confounding factors such as tobacco use.[37–39]

Finally, although vaping is often perceived as a safer alternative, its long-term respiratory effects remain unclear. Vaping aerosols may contain harmful substances, including ammonia and heavy metals, with potential toxic and carcinogenic effects.[40]

Cardiovascular effects

The relationship between cannabis use and cardiovascular disease remains controversial, although an increasing body of evidence suggests a potential association with adverse events such as arrhythmias, myocardial infarction (MI), and stroke.

Acute exposure to THC is associated with tachycardia, transient increases in blood pressure, and enhanced sympathetic nervous system activity, which may increase myocardial oxygen demand and predispose to vasospasm.[41–44] In addition, THC has been shown to exert pro-inflammatory and prothrombotic effects, promoting platelet activation, aggregation, and endothelial dysfunction.[41]

The combination of increased myocardial oxygen demand and reduced oxygen supply—partly due to elevated carboxyhemoglobin levels resulting from combustion—can create a supply–demand mismatch, potentially triggering myocardial infarction.[43,44]

Some studies have also reported structural and functional cardiac alterations, including reductions in end-diastolic volume, stroke volume index, ejection fraction, and left ventricular ejection time.[41,43] However, interpretation of these findings is complicated by the presence of multiple confounding factors commonly associated with cannabis use, including tobacco and alcohol consumption, poor sleep, unhealthy lifestyle behaviors, and concomitant use of other substances.[42,43]

Despite these limitations, several studies have identified an increased risk of acute cardiovascular events, particularly within the first hours

following exposure. Myocardial infarction, atrial fibrillation, and ischemic stroke have been reported, with the highest risk occurring within the first two hours and a mean onset of approximately five hours after use.[42,44]

Emerging evidence in pediatric populations has also described cases of myocardial ischemia related to coronary vasospasm following the use of synthetic cannabinoids, which are becoming increasingly prevalent.[41–44]

Endocrine effects

In parallel with cardiovascular research, increasing attention has been directed toward the endocrine effects of cannabis, largely due to the widespread distribution of cannabinoid receptors within the hypothalamic–pituitary axis and peripheral endocrine organs, including the adrenal glands, gonads, pancreas, and adipose tissue.[45–47]

Both animal and human studies have demonstrated that acute exposure can alter hypothalamic–pituitary signaling, often resulting in increased secretion of adrenocorticotropic hormone (ACTH) and cortisol. Consequently, exposure during adolescence may lead to persistent alterations in cortisol regulation, potentially impairing stress-response mechanisms and increasing vulnerability to subsequent substance use.[46–48]

Cannabis use has also been associated with suppression of gonadotropin-releasing hormone (GnRH), leading to downstream reductions in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormonal changes may adversely affect reproductive function. In females, they may impair follicular development, ovulation, and corpus luteum function, potentially reducing fecundability and negatively influencing outcomes in assisted reproduction. In males, evidence suggests impaired spermatogenesis, reduced sperm motility, and possible decreases in testosterone levels.[46]

Sexual function appears to be both dose- and duration-dependent: while acute use may transiently enhance libido, chronic use has been associated with erectile dysfunction and other sexual disturbances.[45–47]

In addition, emerging evidence indicates that the endocannabinoid system plays a role in metabolic regulation, influencing appetite, energy balance, lipid metabolism, and insulin sensitivity.[46]

The role of pediatrician as a central figure in reducing adolescent substance use

Adolescent vulnerability to psychoactive substance use is shaped by a complex interplay of individual and environmental factors. The widespread perception of cannabis as a harmless substance represents a significant public health concern. Therefore, it is essential to support adolescents not only in addressing physical health needs but also in promoting their social and emotional development.

Pediatricians are often the first healthcare professionals with whom adolescents establish a continuous and trusting relationship, placing them in a pivotal position within adolescent care. They play a central role across the prevention–intervention–treatment continuum in addressing substance use. Their responsibilities extend beyond treatment to include prevention, early identification, and timely intervention in health risk behaviors.[48]

Current clinical practice guidelines from the American Academy of Pediatrics and other major organizations provide clear, evidence-based recommendations.[49–51]

First, in primary prevention, pediatricians should promote access to evidence-based family and community programs from early childhood, encourage healthy lifestyles, and provide clear, age-appropriate information about the risks associated with substance use. A nonjudgmental communication style is essential. Confidential consultations with adolescents, combined with appropriate family involvement, can enhance communication and strengthen protective factors such as self-esteem, decision-making skills, and resilience.[49,51]

Second, screening and early detection are critical. Validated tools such as the CRAFFT questionnaire are recommended for routine use to identify at-risk adolescents before progression to substance use disorders.[49–52] Early identification is particularly important given evidence suggesting that some substance-related neurobiological changes may be partially reversible, underscoring the value of timely intervention.[20]

Third, in brief intervention, pediatricians should employ motivational interviewing techniques for adolescents who screen positive, including those who do not meet criteria for a substance use disorder. Brief interventions delivered within integrated care settings have been shown to reduce substance use and improve engagement with treatment services.[49,52]

Fourth, referral to specialized services is essential when indicated. This includes collaboration with addiction specialists, child and adolescent mental health professionals, schools, and social services, ensuring a comprehensive and multidisciplinary approach to care.

Beyond clinical practice, pediatricians also play a key role in promoting school- and community-based prevention initiatives and advocating for policies that improve access to prevention and treatment services.[50]

Research gaps and future directions

Despite substantial advances in understanding the effects of adolescent psychoactive substance exposure, several critical gaps remain that limit the ability to draw definitive conclusions and inform targeted interventions.

Long-Term reversibility of neurobiological changes

One of the most important unresolved questions concerns the extent to which substance-induced neurobiological alterations during adolescence are reversible. While emerging evidence suggests that some changes in brain structure and function—particularly those related to cannabis exposure—may partially recover following sustained abstinence, findings remain inconsistent and highly dependent on factors such as age at onset, duration and intensity of use, and co-occurring substance exposure.

Longitudinal studies with extended follow-up into adulthood are limited, and many existing investigations are constrained by small sample sizes, short observation periods, and inadequate control for confounding variables. In particular, it remains unclear whether observed improvements reflect true neurobiological recovery or compensatory mechanisms. Future research should prioritize large-scale, prospective cohort studies integrating neuroimaging, cognitive assessments, and biomarker analyses to better characterize trajectories of recovery and identify potential windows for intervention.

Vaping-specific effects

The rapid rise in the use of electronic nicotine delivery systems and cannabis vaping devices among adolescents represents a significant and evolving public health challenge. Despite their widespread perception as safer alternatives to traditional smoking, the long-term health effects of vaping remain poorly understood.

Current evidence is limited by the heterogeneity of devices, variability in chemical composition of aerosols, and rapidly changing product formulations. Preliminary studies suggest that vaping may expose users to harmful substances, including ultrafine particles, heavy metals, and volatile organic compounds, which can induce oxidative stress, inflammation, and potential endothelial dysfunction. However, the long-term respiratory, cardiovascular, and neurodevelopmental consequences of these exposures—particularly during adolescence—are largely unknown.

Additionally, the higher bioavailability of certain substances (e.g., nicotine salts, high-potency THC formulations) delivered through

vaping devices may increase the risk of dependence and adverse outcomes. There is a critical need for standardized exposure assessment, longitudinal data, and mechanistic studies to clarify the specific risks associated with vaping compared with traditional routes of administration.

Sex differences in vulnerability and outcomes

Sex- and gender-related differences in the effects of psychoactive substance exposure during adolescence remain underexplored and insufficiently characterized. Biological differences, including hormonal fluctuations, sex-specific patterns of brain development, and variations in pharmacokinetics and pharmacodynamics, may influence susceptibility to both acute and long-term effects. Preliminary evidence suggests that females may exhibit greater vulnerability to certain neuropsychiatric outcomes, such as anxiety and depression, in association with substance use, while males may demonstrate higher rates of externalizing behaviors and substance use disorders. In addition, sex hormones may interact with the endocannabinoid and dopaminergic systems, potentially modulating the effects of substances such as cannabis and nicotine.

However, many studies do not stratify results by sex, limiting the ability to draw meaningful conclusions. Future research should systematically incorporate sex- and gender-based analyses, including consideration of hormonal status, to better understand differential risk profiles and to inform the development of tailored prevention and treatment strategies.

Addressing these gaps is essential to advancing the field and improving clinical and public health responses. A more nuanced understanding of reversibility, vaping-related risks, and sex-specific vulnerabilities will enable the development of targeted, evidence-based interventions aimed at reducing the burden of adolescent substance use and its long-term consequences.

Conclusions

The increasing prevalence of cannabis use among adolescents, coupled with its widespread perception as a harmless substance, represents a significant public health concern. Adolescents are particularly vulnerable due to ongoing neurodevelopment and heightened endocannabinoid system activity, which increases sensitivity to delta-9-tetrahydrocannabinol (THC). Importantly, some cannabis-related neurobiological alterations may be partially reversible if identified and addressed early, underscoring the importance of timely intervention. Environmental and social factors further amplify this risk: permissive contexts characterized by easy availability, peer influence, and low perceived harm significantly increase the likelihood of initiation and continued use.

A comprehensive understanding of the interplay between biological vulnerability and environmental influences is essential for the development of effective prevention strategies (summary Table 1). In this context, pediatricians play a central role through early education, routine screening, and targeted brief interventions. Finally, the promotion of evidence-based prevention programs involving families, schools, and communities is crucial to reduce adolescent substance use and to support healthy developmental trajectories.

CRediT authorship contribution statement

Pietro Ferrara: Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Francesca Scaltrito:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Maria Pastore:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Ida Giardino:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Sara Cannito:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Ignazio Cammisa:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Gregorio Serra:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Giovanni Corsello:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Margherita Zona:** Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization.

Declaration of competing interest

Francesca Scaltrito, under her responsibility as corresponding author and on behalf of the other co-Authors releases the following declarations:

All Authors equally contributed to the conceptualization, data curation, investigation, methodology, supervision, writing and validation of the original draft, its review and editing. a. the manuscript has not been and will not be submitted in the current form to any other journal while it is under consideration by Global Pediatrics. b. the Authors do not have any potential conflict of interest, real or perceived. c. No generative artificial Intelligence tools were used to develop and complete the manuscript. d. The Authors have seen and approved the final version of the manuscript.

The corresponding Author, Francesca Scaltrito declare that NO honorarium, grant, or other form of payment was given to anyone to

Table 1
Summary of system-specific effects of adolescent psychoactive substance exposure.

SYSTEM	SUBSTANCE(S)	KEY EFFECTS	STRENGTH OF EVIDENCE	POTENTIAL REVERSIBILITY
Neurological	*Cannabis, Alcohol, Nicotine, Stimulants*	*Altered synaptic plasticity, impaired memory and executive function, changes in brain structure (hippocampus, prefrontal cortex), increased risk of psychiatric disorders (depression, psychosis)*	*Strong (longitudinal studies, neuroimaging, meta-analyses)*	*Partial – some recovery with abstinence, especially with early cessation*
Respiratory	*Cannabis (smoked/vaped), Nicotine (cigarettes, e-cigarettes)*	*Airway inflammation, chronic bronchitic symptoms, impaired mucociliary clearance, possible emphysema (heavy use), vaping-related epithelial injury*	*Moderate (observational studies, some longitudinal data)*	*Partial – improvement after cessation, but structural damage may persist in heavy users*
Cardiovascular	*Cannabis, Nicotine, Stimulants*	*Tachycardia, hypertension, endothelial dysfunction, increased risk of arrhythmias and acute ischemic events*	*Moderate (observational data, limited causal inference)*	*Unclear – some acute effects reversible; long-term impact not well established*
Endocrine	*Cannabis, Alcohol*	*Disruption of HPA axis, altered cortisol regulation, suppression of reproductive hormones (GnRH, LH, FSH), potential effects on fertility and metabolism*	*Limited–Moderate (animal + human studies)*	*Uncertain – depends on duration and timing of exposure*
Mental Health	*Cannabis, Alcohol, Nicotine, Prescription drugs*	*Increased risk of anxiety, depression, suicidality, substance use disorders, impaired emotional regulation*	*Strong (epidemiological and longitudinal studies)*	*Variable – early intervention improves outcomes*
Cognitive/ Behavioral	*All substances*	*Impaired attention, learning, decision-making, increased risk-taking and poor academic performance*	*Strong*	*Partial – may improve with abstinence, but deficits can persist*

produce the manuscript.

Finally, the undersigned Author states under his responsibility that each author listed on the manuscript has seen and approved the submission of this final version of the manuscript and takes full responsibility for the manuscript.

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