



The First 1000 Days of Life and the Risk of Future Drug Consumption

Saeid Mirzaei ¹, Nadia Oroomieei ¹ and Nouzar Nakhaee ^{2,*}

¹Non-communicable Diseases Research Center, Bam University of Medical Sciences, Bam, IR Iran

²Health Services Management Research Center Institute for Futures Studies in Health, Kerman University of Medical Sciences, 7616913555, Kerman, IR Iran

*Corresponding author: Health Services Management Research Center Institute for Futures Studies in Health, Kerman University of Medical Sciences, 7616913555, Kerman, IR Iran. Tel: +98-3431325829, Email: nakhaeen@gmail.com

Received 2022 February 12; Revised 2022 April 30; Accepted 2022 May 14.

Abstract

Context: The first 1000 days of life last from the beginning of pregnancy to the age of two, a unique step that shapes the basis for a person's health over their lifetime. Numerous studies have indicated the relationship between one's first 1000 days of life and the consequent adverse outcomes in adulthood. However, to the extent that we have reviewed it, not a single study has shown the relationship between various aspects of an individual's first 1000 days of life and the probability of drug consumption in adult life. Hence, the primary purpose of this narrative review was to understand the role of the first 1000 days of life on vulnerability to drug abuse later in life.

Evidence Acquisition: This article is a narrative review that has identified the role of the first 1000 days of life on susceptibility to substance abuse later in life. The articles were extracted from valid databases, including PubMed, Scopus, Science Direct, Web of Science, and Embase.

Results: Various significant research has pointed to the mother's distress and anxiety during pregnancy through embryonic planning, influencing the planning of the hypothalamic-pituitary-adrenal (HPA) axis and epigenetic changes. The intestinal microbiota is a part of a complex link named the microbiota-gut-brain axis that can affect drug abuse through the variety and number of intestinal microbiota. On the other hand, a mother's drug consumption during pregnancy can function as chronic stress by affecting the enteric nervous system (ENS), which activates the concurrent axis of HPA and dopamine pathways by changing the reward circuit and the subsequent increase in drug abuse. The results indicated that various factors, such as exposure to adverse childhood experiences (ACEs), parental separation, and attachment insecurity, increase the probability of drug abuse in adulthood. Nevertheless, the quality of nurturing care during the first 1000 days of life and the mother's warm relationship with children may hinder the increase in addiction in society.

Conclusions: The first 1000 days of one's life are a crucial and delicate stage. If these days are tainted with unpleasant events, the various mechanisms can reduce a person's resilience to drug abuse in later life. How the first 1000 days of an infant's life and the quality of this period, such as prenatal stress, substance use during pregnancy, ACEs, maternal-infant bonding, maternal separation (MS), and intestinal microbiota, can affect drug abuse in the future. As a result, focusing on the first 1000 days of life is critical to adapting prevention strategies. Health policymakers can design suitable entries during pregnancy and early childhood to reduce the probability of drug abuse.

Keywords: The First 1000 Days, Drug Abuse, Adverse Childhood Experiences, Object Attachment, Environmental, Maternal Deprivation

1. Context

Drug abuse is a pervasive worldwide problem. According to 2016 statistics, six percent of the world's population between the ages of 15 and 64 probably smoked once in their lifetime (1). The U.S. Food and Drug Administration (FDA) defines drug abuse as "the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect" (2). Global statistics show that 35 million people are drug addicts, 11.8 million people inject drugs, and the preva-

lence of AIDS is 13.1%. One hundred forty-eight countries reported injecting drugs, while 120 countries reported HIV infections among this population (3). Given the adverse physical, mental, psychological, and social consequences of drug abuse for countries, identifying the causes and evidence-based policymaking by governments can be effective in preventing the occurrence of drug abuse (4).

Numerous studies have been conducted on the factors that predict the risk of substance abuse (5, 6). One of the factors evaluated in these studies concerns the initial 1000 days of life (7). The first 1000 days of life begin from preg-

nancy to when a child is two years old. This unique stage is fundamental for optimum health, nerve growth, and development throughout life (8). Various studies referred to the relationship between the first 1000 days of life and the harmful consequences in adulthood. For example, maternal stress during pregnancy affects long-term health outcomes in children, including stress and low self-esteem (9). However, no investigation has mentioned any aspects of the first 1000 days of life and the future drug abuse. The main objective of this narrative review is to present scientific evidence to demonstrate the effect of the unpleasant events on the first 1000 days of life, such as maternal separation (MS), maternal-infant bonding, adverse childhood experiences (ACEs), substance use during pregnancy, prenatal stress, and one's future drug abuse. Therefore the present study aimed to indicate the relevance of the first 1000 days of life and the risk of future drug abuse.

2. Evidence Acquisition

This article is a narrative review that identifies the role of the first 1000 days of life on vulnerability to addiction later in life. The articles were extracted from valid databases, including PubMed, Scopus, Science Direct, Web of Science, and Embase. Due to the nature of the study, no sampling was performed, and studies involving the first 1000 days of life and drug use were reviewed. Keywords included: First 1000 days, drug abuse, adverse childhood experiences, maternal bonding, maternal separation, and other similar keywords.

Conventional content analysis was used in the analysis of the data. The related sections of the articles were studied separately by two team researchers, and the content was extracted. Disputes were discussed in a meeting with the research team.

3. Results

3.1. The Effect of Prenatal Stress

For the first time, Baker have referred to the fetal origins of adult disease (10). When the fetus in the womb is exposed to unpleasant events, one may expect an increase in disease risk in adulthood (11). One of those unpleasant events is maternal anxiety and stress during pregnancy (12).

Many studies have examined the harmful impact of a mother's anxiety and stress during pregnancy and its adverse effect on children over the long term (13). It is, to some extent, related to maternal stress hormones like cortisol, which are fundamental to the neural development of

the fetus; nevertheless, high exposure to these stress hormones can harm the fetal hypothalamus-pituitary-adrenal axis (HPA) (14). The HPA axis has a ubiquitous influence on vital regulatory systems such as the immune system, microbiome, and autonomic nervous system (15).

Exposure to stress during pregnancy and childbirth through embryonic planning affects animal behavior in three fields: learning disabilities, increased anxiety and depressive behaviors, and increased sensitivity to drug abuse (16).

When exposed to stress, rodent offsprings showed higher sensitivity to a broader range of drugs like amphetamines, methamphetamines, ethanol, morphine, and cocaine (17).

Most studies focus on the relationship between stress during pregnancy and the HPA axis in children with fetal anxiety (18). Epigenetic changes such as DNA methylation influence gene expression and suppression. It can last for generations and even reach generations of grandchildren (19). Also, DNA methylation is found in children whose grandmothers have experienced violence during pregnancy (20).

3.2. The Effect of Microbiota

The microbiota composition of the digestive system in adulthood is shaped in the early years of life. They are sensitive to environmental factors like childbirth, breastfeeding or bottle-feeding, diet, medicine like antibiotics, and exposure to viral, bacterial infections, and stress (21). The relationship between the intestine and brain was first introduced at the beginning of the twentieth century when terms like autointoxication and intestinal toxemia described how toxins derived from the intestine affected mental health (22). Studies have referred to the change of intestinal microbiota in patients suffering from mental illnesses like depression. Clinical evidence implies a change in the diversity of microbiota and its complexity in patients with autism, schizophrenia, and attention deficit disorder, as well as mood disorders including bipolar disorder, anxiety, stress, and depression, and disorders associated with neuroinflammation, including Alzheimer's and Parkinson's (23, 24).

Scientific research has shown the mutual effect of the intestinal tract through microbiota and the brain. Some researchers even consider the intestine as the second brain. Moreover, microbiota usage has effectively cured psychiatric disorders (25).

Another study demonstrated that psychosocial stress in pregnancy might adversely influence children through microbiota (26). There was also a relationship between a mother's stress and anxiety during the pregnancy and a

less varied meconium microbiota community with fewer Enterococcaceae in the offspring (27).

Many studies investigated the relationship between intestinal microbiota and CNS through the intestinal-brain axis and have introduced a mechanism by which these microbes affect the host (26). Mostly, drug consumption is accompanied by dysbiosis intestinal microbiota (an imbalance in bacterial colonies of the gastrointestinal system) (28), and these changes may influence the creation and maintenance of addiction by changing the signals between the intestine and the brain (26). In this case, probiotic intervention is introduced as a new type of substance use disorder treatment (29). Recent evidence showed that probiotics significantly cure other mental disorders like anxiety and depression (26).

3.3. The Effect of Substance Use During Pregnancy

Several animal studies have paid enough attention to the danger of increasing the risk of drug abuse in children whose mothers consumed drugs during pregnancy. For instance, being exposed to morphine before birth is accompanied by increased cocaine and heroin in adult rats (30).

Considerable evidence has been found in human beings that can indicate that if a fetus is exposed to drug abuse by its mother, the risk of the child, at last, becoming an addict is high (31). The onset of drug abuse in children is highly related to exposure to a mother's consumption of nicotine and alcohol during pregnancy (32).

Moreover, several studies have focused on the response of cortisol in children being exposed to drug consumption (33-35). As a neural biological mechanism, chronic stress and dysfunction of the HPA axis have been stimuli to drug consumption and addiction disorders. Pieces of evidence have proved that the malfunction of the parasympathetic nervous system and the basic cortisol level at the age of eleven are all indicators of the period of exposure of fetuses to drug use (36).

Many investigations on animal and human beings identified drug-addicted children exposed to prenatal drug use. Additionally, clinical studies showed that pre-birth drug consumption would predict higher cortisol levels in later life (37).

Overall, numerous studies have presented enough evidence that being exposed to drug consumption before birth is a significant risk factor that would predict changes in the HPA axis and susceptibility to drug abuse in adulthood (38).

3.4. The Effect of Adverse Childhood Experiences

Adverse childhood experiences (ACEs) describe traumatic events that some people suffer during childhood

(39). Adverse childhood experiences include physical, emotional, and sexual abuse or neglect. Their life may be filled with parenting problems, domestic violence, parental divorce, and drug and alcohol abuse by a household member (40). Frequent activation of the stress response system during childhood and the lack of interaction with sympathetic adults can strongly influence the regulation of the neuroendocrine system, immune system and metabolism, and social and emotional development, leading to poor health conditions (41).

Results showed that there exists a substantial and concurrent relationship between being exposed to psychological, physical, or sexual abuse as a child and family dysfunction as a child and also the occurrence of high-risk behaviors in adulthood, such as suicide attempts, alcoholism, drug abuse, and multiple sexual partners (42, 43). Studying the relationship between ACEs and illicit drug abuse showed that ACEs would increase the likelihood of drug abuse by two to four times, and those who have experienced more than five ACEs will have five to seven times more likely to the illicit drug abuse (44).

Moreover, studies demonstrated that physical and psychological abuse would increase the possibility of marijuana and alcohol consumption among youth (45) and waterpipe smoking (46).

3.5. The Effect of Maternal-Infant Bonding

According to Bowlby's attachment theory, whenever the child feels in danger, it will seek to be close to its primary caregiver. In an ideal situation, parents will calm children down and give them a sense of safety (47). This feeling of safety or the "basis of safety" will assist the children's primary attachment experience. They will adjust their feelings and take an essential step toward appropriate strategies in the event of fear or anxiety (48).

Evidence showed that a child's secure attachment to a mother significantly prevents drug abuse. On the other hand, insecure attachment is a risk factor for substance abuse in later life (49). While many studies have referred to insecure attachment and drug abuse among children, few studies have focused on how children's attachment to parents affects substance abuse (44). One study noted the mediation role of emotional dysregulation in insecure attachment and addiction. Emotional dysregulation refers to deficits in awareness, perception, and acceptance of emotions and the ability to manage emotional experiences (50). Emotional regulation may occur through adaptive tools such as social support, but it may also happen through maladaptive tools such as engaging in addictive behaviors. One of the theories in the field of addiction considered coping with negative emotions as a motivational

factor in drug use initiation, and various studies emphasized this relationship in the way that those who have an unsafe attachment style have less ability to regulate emotions relative to others with secure attachment style (51). Consequently, those with an insecure attachment style use addictive behaviors as a pathologic strategy to regulate emotions and attachment needs (50). MacLean noted that drug abuse replaces a secure attachment style and helps addicts modify self-regulatory responses (52). Addiction can be considered a transition where "emotional bonds" are replaced by "addictive bonds" to self-regulate. Hence, considering addiction as a sign of relationship trauma during the early years of life, drug abuse can be viewed as an attempt to self-regulate, adapt, self-care, and create a feeling similar to secure attachment through drug abuse (53).

Negative self-perceptions failed relationships with others, and distorted worldviews through distorted perception lenses can lead to attachment problems (41). Attachment behaviors resulting from the failed bond and intimacy of the child and caregivers in early childhood (insecure attachment style) may ultimately lead to addiction while representing past traumas as a defense strategy (53). Despite the persistent effects of insecure attachments throughout life, many highlighted that attachment styles are not permanent and can evolve for a lifetime (53). The protective role of the child's caregivers is vital. Furthermore, parent-child attachment appeared to be a significant factor in protecting adolescents from addiction (41). Therefore, it seems that insecure attachments, especially attachment anxiety and emotion dysregulation, are essential psychological characteristics that increase the risk of drug abuse (38).

3.6. The Effect of Maternal Separation

Most mammals spend their childhood in close contact with their mothers. Maternal separation (MS) is a stress factor during childhood, and it is defined as the termination of the continuity of the mother-child relationship once the relationship is established (54).

Experimental studies regarding MS mainly use animal samples, while human samples are retrospectively studied. Evidence implied that rats with MS had the self-administration of morphine, cocaine, ethanol, and amphetamine (55).

Increasing the length of MS has also increased the use of drugs and alcohol in rats (54). Treating rats with selective serotonin reuptake inhibitors decreased drug consumption in rats with a more extended MS (56). Another study showed that MS rats were more prone to alcohol consumption (57). However, those rates with MS but enough handling had less consumption of cocaine (56). It is implied that a baby's reaction to MS and its level of care is

critical and can cause changes in neuroanatomy and neurochemistry (58). MS is mainly caused by changes in a mother's caring levels and not necessarily her total separation (56). Analyzing the effect of MS on the children's spiritual, physical, and social aspects, one should be aware that living in a calm environment without the stress and having a kind and compassionate caregiver can alleviate the harmful effect of MS (59). In addition, the consequences of MS were related to age, duration of separation, type of separation, and gender of the child (60). For example, studies have shown that males are more vulnerable to alcohol abuse due to the experience of MS in childhood than females (61). On the other hand, having a mother is not enough, and the fact that the baby is the victim of maternal harassment is also very detrimental (54, 62).

4. Conclusions

In conclusion, this can be inferred that adverse events in the first 1000 days of one's life can lead to neurobehavioral problems later in life. If this vulnerable period of human development is tainted with unpleasant incidents, it may diminish a person's resiliency to drug consumption in later life. Thus, while developing social prescriptions to prevent drug abuse in society, we should take these stages seriously. Health policymakers can reduce the potential for drug abuse by designing appropriate interventions during pregnancy and early childhood.

Acknowledgments

This article is approved by the Bam University of Medical Sciences, and the authors would appreciate Bam University of Medical Sciences.

Footnotes

Authors' Contribution: The overall design of the study, Nadia Oroomie, Saeid Mirzaei, Nouzar Nakhaee; Data collection activities, Nouzar Nakhaee, Saeid Mirzaei; Analysis and conceptualization of the manuscript, Nadia Oroomie, Saeid Mirzaei, Nouzar Nakhaee; Writing the original manuscript draft, Nadia Oroomie, Nouzar Nakhaee; Review and editing of subsequent manuscript drafts, Saeid Mirzaei, Nadia Oroomie, Nouzar Nakhaee. All authors read the manuscript and approved the final version of the manuscript.

Conflict of Interests: The authors declare no conflict of interests.

Funding/Support: The authors of this article have not received any funding.

References

- United Nations Office on Drugs and Crime. *World Drug Report*. Vienna, Austria: United Nations Office on Drugs and Crime; 2018, [cited 2022]. Available from: <https://www.unodc.org/wdr2018>.
- Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Assessment of Abuse Potential of Drugs: Guidance for Industry*. Maryland, USA: Center for Drug Evaluation and Research (CDER); 2017.
- United Nations Office on Drugs and Crime. *World drug report 2019*. Vienna, Austria: United Nations Publication; 2019.
- Mirzaei S, Yazdi-Feyzabadi V, Mehrolhassani MH, Nakhaee N, Oroomie N. Setting the policy agenda for the treatment of substance use disorders in Iran. *Harm Reduct J*. 2022;19(1):27. doi: [10.1186/s12954-022-00612-w](https://doi.org/10.1186/s12954-022-00612-w). [PubMed: 35292060]. [PubMed Central: PMC8922872].
- Bystrova K, Ivanova V, Edhborg M, Matthiesen AS, Ransjo-Arvidson AB, Mukhamedrakhimov R, et al. Early contact versus separation: effects on mother-infant interaction one year later. *Birth*. 2009;36(2):97-109. doi: [10.1111/j.1523-536X.2009.00307.x](https://doi.org/10.1111/j.1523-536X.2009.00307.x). [PubMed: 1949802].
- Schindler A, Broning S. A Review on Attachment and Adolescent Substance Abuse: Empirical Evidence and Implications for Prevention and Treatment. *Subst Abus*. 2015;36(3):304-13. doi: [10.1080/08897077.2014.983586](https://doi.org/10.1080/08897077.2014.983586). [PubMed: 25424652].
- Iranpour A. How to "Immunize" Children against Drug and Alcohol Abuse. *Addict Health*. 2021;13(3):205-6. doi: [10.2212/AH.V13I3.308](https://doi.org/10.2212/AH.V13I3.308).
- Nawi AM, Ismail R, Ibrahim F, Hassan MR, Manaf MRA, Amit N, et al. Risk and protective factors of drug abuse among adolescents: a systematic review. *BMC Public Health*. 2021;21(1):2088. doi: [10.1186/s12889-021-11906-2](https://doi.org/10.1186/s12889-021-11906-2). [PubMed: 34774013]. [PubMed Central: PMC8590764].
- Juan J, Yang H. Early life 1000 days: opportunities for preventing adult diseases. *Chin Med J (Engl)*. 2021;135(5):516-8. doi: [10.1097/CM9.0000000000001920](https://doi.org/10.1097/CM9.0000000000001920). [PubMed: 34967791]. [PubMed Central: PMC8920419].
- Luckett T, Newton-John T, Phillips J, Holliday S, Giannitrapani K, Powell-Davies G, et al. Risk of opioid misuse in people with cancer and pain and related clinical considerations: a qualitative study of the perspectives of Australian general practitioners. *BMJ Open*. 2020;10(2). e034363. doi: [10.1136/bmjopen-2019-034363](https://doi.org/10.1136/bmjopen-2019-034363). [PubMed: 32071185]. [PubMed Central: PMC7044941].
- No Authors Listed. ACOG Committee Opinion No. 757: Screening for Perinatal Depression. *Obstet Gynecol*. 2018;132(5):e208-12. doi: [10.1097/AOG.0000000000002927](https://doi.org/10.1097/AOG.0000000000002927). [PubMed: 30629567].
- Barker DJ. The developmental origins of adult disease. *J Am Coll Nutr*. 2004;23(6 Suppl):588S-95S. doi: [10.1080/07315724.2004.10719428](https://doi.org/10.1080/07315724.2004.10719428). [PubMed: 15640511].
- Brines J, Rigourd V, Billeaud C. The First 1000 Days of Infant. *Healthcare (Basel)*. 2022;10(1):106. doi: [10.3390/healthcare10010106](https://doi.org/10.3390/healthcare10010106). [PubMed: 35052270]. [PubMed Central: PMC8775982].
- Buffa G, Dahan S, Sinclair I, St-Pierre M, Roofigari N, Mutran D, et al. Prenatal stress and child development: A scoping review of research in low- and middle-income countries. *PLoS One*. 2018;13(12). e0207235. doi: [10.1371/journal.pone.0207235](https://doi.org/10.1371/journal.pone.0207235). [PubMed: 30592715]. [PubMed Central: PMC6310253].
- Rosin S, Xia K, Azcarate-Peril MA, Carlson AL, Propper CB, Thompson AL, et al. A preliminary study of gut microbiome variation and HPA axis reactivity in healthy infants. *Psychoneuroendocrinology*. 2021;124(2):105046. doi: [10.1016/j.psyneuen.2020.105046](https://doi.org/10.1016/j.psyneuen.2020.105046). [PubMed: 33254059]. [PubMed Central: PMC8121098].
- Vazquez V, Girois B, Dauge V. Maternal deprivation specifically enhances vulnerability to opiate dependence. *Behav Pharmacol*. 2006;17(8):715-24. doi: [10.1097/FBP.0b013e3280116e6f](https://doi.org/10.1097/FBP.0b013e3280116e6f). [PubMed: 17110797].
- Deroche V, Piazza PV, Casolini P, Maccari S, Le Moal M, Simon H. Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. *Brain Res*. 1992;598(1-2):343-8. doi: [10.1016/0006-8993\(92\)90205-n](https://doi.org/10.1016/0006-8993(92)90205-n).
- Horn SR, Roos LE, Berkman ET, Fisher PA. Neuroendocrine and immune pathways from pre- and perinatal stress to substance abuse. *Neurobiol Stress*. 2018;9:140-50. doi: [10.1016/j.jynstr.2018.09.004](https://doi.org/10.1016/j.jynstr.2018.09.004). [PubMed: 30450380]. [PubMed Central: PMC6236513].
- Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. 2008;3(2):97-106. doi: [10.4161/epi.3.2.6034](https://doi.org/10.4161/epi.3.2.6034). [PubMed: 18536531].
- Serpeloni F, Radtke K, de Assis SG, Henning F, Natt D, Elbert T. Grandmaternal stress during pregnancy and DNA methylation of the third generation: an epigenome-wide association study. *Transl Psychiatry*. 2017;7(8). e1202. doi: [10.1038/tp.2017.153](https://doi.org/10.1038/tp.2017.153). [PubMed: 28809857]. [PubMed Central: PMC5611722].
- Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends Mol Med*. 2014;20(9):509-18. doi: [10.1016/j.molmed.2014.05.002](https://doi.org/10.1016/j.molmed.2014.05.002). [PubMed: 24956966].
- Taylor VH. The microbiome and mental health: Hope or hype? *J Psychiatry Neurosci*. 2019;44(4):219-22. doi: [10.1503/jpn.j90110](https://doi.org/10.1503/jpn.j90110). [PubMed: 31245969]. [PubMed Central: PMC6606431].
- Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, et al. Gut Microbiota is Altered in Patients with Alzheimer's Disease. *J Alzheimers Dis*. 2018;63(4):1337-46. doi: [10.3233/JAD-180176](https://doi.org/10.3233/JAD-180176). [PubMed: 29758946].
- Bedarf JR, Hildebrand F, Coelho LP, Sunagawa S, Bahram M, Goeser F, et al. Erratum to: Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. *Genome Med*. 2017;9(1):61. doi: [10.1186/s13073-017-0451-z](https://doi.org/10.1186/s13073-017-0451-z). [PubMed: 28662719]. [PubMed Central: PMC5492116].
- Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*. 2016;352(6285):565-9. doi: [10.1126/science.aad3369](https://doi.org/10.1126/science.aad3369). [PubMed: 27126040]. [PubMed Central: PMC5240844].
- Russell JT, Zhou Y, Weinstock GM, Bubier JA. The Gut Microbiome and Substance Use Disorder. *Front Neurosci*. 2021;15:725500. doi: [10.3389/fnins.2021.725500](https://doi.org/10.3389/fnins.2021.725500). [PubMed: 34531718]. [PubMed Central: PMC8439419].
- Loughman A, Ponsonby AL, O'Hely M, Symeonides C, Collier F, Tang MLK, et al. Gut microbiota composition during infancy and subsequent behavioural outcomes. *EBioMedicine*. 2020;52:102640. doi: [10.1016/j.ebiom.2020.102640](https://doi.org/10.1016/j.ebiom.2020.102640). [PubMed: 32062351]. [PubMed Central: PMC7016366].
- Franzin M, Stefancic K, Lucafo M, Decorti G, Stocco G. Microbiota and Drug Response in Inflammatory Bowel Disease. *Pathogens*. 2021;10(2). doi: [10.3390/pathogens10020211](https://doi.org/10.3390/pathogens10020211). [PubMed: 33669168]. [PubMed Central: PMC7919657].
- Slattery J, MacFabe DF, Frye RE. The Significance of the Enteric Microbiome on the Development of Childhood Disease: A Review of Prebiotic and Probiotic Therapies in Disorders of Childhood. *Clin Med Insights Pediatr*. 2016;10:91-107. doi: [10.4137/CMPed.S38338](https://doi.org/10.4137/CMPed.S38338). [PubMed: 27774001]. [PubMed Central: PMC5063840].
- Ramsey NF, Niesink RJ, Van Reea JM. Prenatal exposure to morphine enhances cocaine and heroin self-administration in drug-naïve rats. *Drug Alcohol Depend*. 1993;33(1):41-51. doi: [10.1016/0376-8716\(93\)90032-1](https://doi.org/10.1016/0376-8716(93)90032-1).
- Barry JM, Birnbaum AK, Jasin LR, Sherwin CM. Maternal Exposure and Neonatal Effects of Drugs of Abuse. *J Clin Pharmacol*. 2021;61 Suppl 2:S142-55. doi: [10.1002/jcpb.1928](https://doi.org/10.1002/jcpb.1928). [PubMed: 34396555].
- Lester BM, Andreozzi L, Appiah L. Substance use during pregnancy: time for policy to catch up with research. *Harm Reduct J*. 2004;1(1):5. doi: [10.1186/1477-7517-1-5](https://doi.org/10.1186/1477-7517-1-5). [PubMed: 15169566]. [PubMed Central: PMC419718].
- Ahmadi Sarbarzeh P, Karimi S, Jalilian M, Mosafer H. Depression,

Anxiety, Stress and Social Isolation in Hepatitis Patients. *SciMed J.* 2020;2(4):225-33. doi: [10.28991/SciMedJ-2020-0204-5](https://doi.org/10.28991/SciMedJ-2020-0204-5).

34. Arab Rahmatipour M, Ebadollahi-Natanzi A, Arab-Rahmatipour G. Letter to the Editor: Prevention of Depression and Psychological Stress by Studying Book in Quarantine Conditions of COVID-19. *SciMed J.* 2020;2(3):182-3. doi: [10.28991/SciMedJ-2020-0203-7](https://doi.org/10.28991/SciMedJ-2020-0203-7).

35. Aki BD, Lamprey E, Hembah SN, Oibiokpa OM, Tachin TR. Covid-19 Lockdown: Psychological Implications on Life Quality. *Journal of Human, Earth, and Future.* 2020;1(2):78-86. doi: [10.28991/hef-2020-01-04](https://doi.org/10.28991/hef-2020-01-04).

36. Conradt E, Lagasse LL, Shankaran S, Bada H, Bauer CR, Whitaker TM, et al. Physiological correlates of neurobehavioral disinhibition that relate to drug use and risky sexual behavior in adolescents with prenatal substance exposure. *Dev Neurosci.* 2014;36(3-4):306-15. doi: [10.1159/000365004](https://doi.org/10.1159/000365004). [PubMed: [25033835](https://pubmed.ncbi.nlm.nih.gov/25033835/)]. [PubMed Central: [PMC4476628](https://pubmed.ncbi.nlm.nih.gov/PMC4476628/)].

37. Barrocas J, Vieira-Santos S, Paixão R. Parenting and drug addiction: A psychodynamic proposal based on a multifactorial perspective. *Psychonaal Psychol.* 2016;33(1):161-78. doi: [10.1037/a0037344](https://doi.org/10.1037/a0037344).

38. Piazza PV, Le Moal M. The role of stress in drug self-administration. *Trends Pharmacol Sci.* 1998;19(2):67-74. doi: [10.1016/s0165-6147\(97\)01115-2](https://doi.org/10.1016/s0165-6147(97)01115-2).

39. Hughes K, Ford K, Kadel R, Sharp CA, Bellis MA. Health and financial burden of adverse childhood experiences in England and Wales: a combined primary data study of five surveys. *BMJ Open.* 2020;10(6). e036374. doi: [10.1136/bmjjopen-2019-036374](https://doi.org/10.1136/bmjjopen-2019-036374). [PubMed: [32513892](https://pubmed.ncbi.nlm.nih.gov/32513892/)]. [PubMed Central: [PMC7282338](https://pubmed.ncbi.nlm.nih.gov/PMC7282338/)].

40. Mirzaei S, Safizadeh H, Oroomie N. [Comparative Study of Social Determinants of Health Models]. *Iran J Epidemiol.* 2017;13(3):222-34. Persian.

41. Kalmakis KA, Chandler GE. Health consequences of adverse childhood experiences: a systematic review. *J Am Assoc Nurse Pract.* 2015;27(8):457-65. doi: [10.1002/2327-6924.12215](https://doi.org/10.1002/2327-6924.12215). [PubMed: [25755161](https://pubmed.ncbi.nlm.nih.gov/25755161/)].

42. Snyder SM, Smith RE. Do physical abuse, depression, and parental substance use influence patterns of substance use among child welfare involved youth? Substance use misuse. *Subst Use Misuse.* 2015;50(2):226-35. doi: [10.3109/10826084.2014.966845](https://doi.org/10.3109/10826084.2014.966845). [PubMed: [25338287](https://pubmed.ncbi.nlm.nih.gov/25338287/)].

43. Casanueva C, Stambaugh L, Urato M, Fraser JG, Williams J. Illicit Drug Use From Adolescence to Young Adulthood Among Child Welfare-Involved Youths. *J Child Adolesc Subst Abuse.* 2013;23(1):29-48. doi: [10.1080/1067828x.2012.735514](https://doi.org/10.1080/1067828x.2012.735514).

44. Strathearn L, Mertens CE, Mayes L, Rutherford H, Rajhans P, Xu G, et al. Pathways Relating the Neurobiology of Attachment to Drug Addiction. *Front Psychiatry.* 2019;10:737. doi: [10.3389/fpsyg.2019.00737](https://doi.org/10.3389/fpsyg.2019.00737). [PubMed: [31780957](https://pubmed.ncbi.nlm.nih.gov/31780957/)]. [PubMed Central: [PMC6857543](https://pubmed.ncbi.nlm.nih.gov/PMC6857543/)].

45. Kristman-Valenti AN, Brown EC, Herrenkohl TI. Child physical and sexual abuse and cigarette smoking in adolescence and adulthood. *J Adolesc Health.* 2013;53(4):533-8. doi: [10.1016/j.jadohealth.2013.06.003](https://doi.org/10.1016/j.jadohealth.2013.06.003). [PubMed: [2387801](https://pubmed.ncbi.nlm.nih.gov/2387801/)]. [PubMed Central: [PMC3783597](https://pubmed.ncbi.nlm.nih.gov/PMC3783597/)].

46. Naghavi M, Nakhaee N. Associations between Childhood Abuse, Resilience, Mindfulness, and Waterpipe Smoking: Implications for Cessation Interventions. *J Smok Cessat.* 2021;2021:6648779. doi: [10.1155/2021/6648779](https://doi.org/10.1155/2021/6648779). [PubMed: [34429784](https://pubmed.ncbi.nlm.nih.gov/34429784/)]. [PubMed Central: [PMC8356016](https://pubmed.ncbi.nlm.nih.gov/PMC8356016/)].

47. Benakappa AD. Breastfeeding in the first hour of birth: Science and skills. *Karnataka Paediatr J.* 2021;35(2):72-5. doi: [10.25259/KPJ_20_2020](https://doi.org/10.25259/KPJ_20_2020).

48. Meulewaeter F, De Pauw SSW, Vanderplasschen W.母爱, Substance Use Disorders and Intergenerational Trauma Transmission: An Attachment-Based Perspective. *Front Psychiatry.* 2019;10:728. doi: [10.3389/fpsyg.2019.00728](https://doi.org/10.3389/fpsyg.2019.00728). [PubMed: [31681040](https://pubmed.ncbi.nlm.nih.gov/31681040/)]. [PubMed Central: [PMC6813727](https://pubmed.ncbi.nlm.nih.gov/PMC6813727/)].

49. Fairbairn CE, Briley DA, Kang D, Fraley RC, Hankin BL, Ariss T. A meta-analysis of longitudinal associations between substance use and interpersonal attachment security. *Psychol Bull.* 2018;144(5):532-55. doi: [10.1037/bul0000141](https://doi.org/10.1037/bul0000141). [PubMed: [29494194](https://pubmed.ncbi.nlm.nih.gov/29494194/)]. [PubMed Central: [PMC5912983](https://pubmed.ncbi.nlm.nih.gov/PMC5912983/)].

50. Liese BS, Kim HS, Hodgins DC. Insecure attachment and addiction: Testing the mediating role of emotion dysregulation in four potentially addictive behaviors. *Addict Behav.* 2020;107:106432. doi: [10.1016/j.addbeh.2020.106432](https://doi.org/10.1016/j.addbeh.2020.106432). [PubMed: [32330652](https://pubmed.ncbi.nlm.nih.gov/32330652/)].

51. Poole JC, Kim HS, Dobson KS, Hodgins DC. Adverse Childhood Experiences and Disordered Gambling: Assessing the Mediating Role of Emotion Dysregulation. *J Gambl Stud.* 2017;33(4):1187-200. doi: [10.1007/s10899-017-9680-8](https://doi.org/10.1007/s10899-017-9680-8). [PubMed: [28258336](https://pubmed.ncbi.nlm.nih.gov/28258336/)].

52. MacLean PD. *The triune brain in evolution: Role in paleocerebral functions*. New York, USA: Springer Science & Business Media; 1990. 672 p.

53. Iyengar U, Rajhans P, Fonagy P, Strathearn L, Kim S. Unresolved Trauma and Reorganization in Mothers: Attachment and Neuroscience Perspectives. *Front Psychol.* 2019;10:110. doi: [10.3389/fpsyg.2019.00110](https://doi.org/10.3389/fpsyg.2019.00110). [PubMed: [30761051](https://pubmed.ncbi.nlm.nih.gov/30761051/)]. [PubMed Central: [PMC6363675](https://pubmed.ncbi.nlm.nih.gov/PMC6363675/)].

54. Delavari F, Sheibani V, Esmaeili-Mahani S, Nakhaee N. Maternal Separation and the Risk of Drug Abuse in Later Life. *Addict Health.* 2016;8(2):107-14. [PubMed: [27882208](https://pubmed.ncbi.nlm.nih.gov/27882208/)]. [PubMed Central: [PMC5115644](https://pubmed.ncbi.nlm.nih.gov/PMC5115644/)].

55. Lewis CR, Staudinger K, Scheck L, Olive MF. The Effects of Maternal Separation on Adult Methamphetamine Self-Administration, Extinction, Reinstatement, and MeCP2 Immunoreactivity in the Nucleus Accumbens. *Front Psychiatry.* 2013;4:55. doi: [10.3389/fpsyg.2013.00055](https://doi.org/10.3389/fpsyg.2013.00055). [PubMed: [23785337](https://pubmed.ncbi.nlm.nih.gov/23785337/)]. [PubMed Central: [PMC3683635](https://pubmed.ncbi.nlm.nih.gov/PMC3683635/)].

56. Moffett MC, Vicentie A, Kozel M, Plotsky P, Francis DD, Kuhar MJ. Maternal separation alters drug intake patterns in adulthood in rats. *Biochem Pharmacol.* 2007;73(3):321-30. doi: [10.1016/j.bcp.2006.08.003](https://doi.org/10.1016/j.bcp.2006.08.003). [PubMed: [16962564](https://pubmed.ncbi.nlm.nih.gov/16962564/)]. [PubMed Central: [PMC2692348](https://pubmed.ncbi.nlm.nih.gov/PMC2692348/)].

57. Bertagna NB, Favoretto CA, Rodolpho BT, Palombo P, Yokoyama T, Righi T, et al. Maternal separation stress affects voluntary ethanol intake in a sex-dependent manner. *Front Physiol.* 2021;2054.

58. Wang D, Levine JLS, Avila-Quintero V, Bloch M, Kaffman A. Systematic review and meta-analysis: effects of maternal separation on anxiety-like behavior in rodents. *Transl Psychiatry.* 2020;10(1):174. doi: [10.1038/s41398-020-0856-0](https://doi.org/10.1038/s41398-020-0856-0). [PubMed: [32483128](https://pubmed.ncbi.nlm.nih.gov/32483128/)]. [PubMed Central: [PMC7264128](https://pubmed.ncbi.nlm.nih.gov/PMC7264128/)].

59. Gustafsson L, Ploj K, Nylander I. Effects of maternal separation on voluntary ethanol intake and brain peptide systems in female Wistar rats. *Pharmacol Biochem Behav.* 2005;81(3):506-16. doi: [10.1016/j.pbb.2005.03.016](https://doi.org/10.1016/j.pbb.2005.03.016). [PubMed: [15927243](https://pubmed.ncbi.nlm.nih.gov/15927243/)].

60. Rees SL, Steiner M, Fleming AS. Early deprivation, but not maternal separation, attenuates rise in corticosterone levels after exposure to a novel environment in both juvenile and adult female rats. *Behav Brain Res.* 2006;175(2):383-91. doi: [10.1016/j.bbr.2006.09.013](https://doi.org/10.1016/j.bbr.2006.09.013). [PubMed: [17081629](https://pubmed.ncbi.nlm.nih.gov/17081629/)].

61. Roman E, Ploj K, Nylander I. Maternal separation has no effect on voluntary ethanol intake in female Wistar rats. *Alcohol.* 2004;33(1):31-9. doi: [10.1016/s0741-8329\(04\)00077-1](https://doi.org/10.1016/s0741-8329(04)00077-1).

62. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, et al. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A.* 2011;108(7):2693-8. doi: [10.1073/pnas.1010076108](https://doi.org/10.1073/pnas.1010076108). [PubMed: [21262822](https://pubmed.ncbi.nlm.nih.gov/21262822/)]. [PubMed Central: [PMC3041102](https://pubmed.ncbi.nlm.nih.gov/PMC3041102/)].