**Nicotine's long-term effects on health and its effects on epigenetics**

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*Nicotine and tobacco use have been linked to several health problems, including a higher risk of developing and progressing diseases. Cancer, immune system changes, lung and cardiovascular disease, endocrine disorders, diabetes, immune system delays, and behavioural and mental health changes are some of these challenges. A growing body of evidence indicates that nicotine-induced epigenetic changes may be involved in mediating or influencing the emergence and development of a number of harmful health outcomes. Additionally, smoking alters epigenetic signalling, which makes people more vulnerable to illnesses and mental health issues throughout their entire lives. Nicotine has an impact on epigenetic signalling, which contributes to the development of these diseases and health problems.*

1. **Introduction**

The World Health Organisation (WHO) estimates that tobacco use results in more than 8 million fatalities each year worldwide. This covers both the direct health effects of tobacco use, such as lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases, as well as the indirect consequences of secondhand smoke exposure on non-smokers. The main addictive substance in tobacco products, nicotine, contributes significantly to both the high prevalence of tobacco-related deaths and the resulting economic burden. Since nicotine is a highly addictive substance, many people find it difficult to stop using tobacco once they become dependent on it [1]. By using deceptive strategies, taking advantage of vulnerable populations, and enhancing the addictive qualities of nicotine products, the tobacco and nicotine industries have prioritised financial gains. Cigarettes have been specifically designed to make their addictiveness stronger. This is demonstrated by the presence of more than 600 chemicals, which include elements like ammonia that transform nicotine into a more potent form and filters that erroneously suggest lower health risks [2]. Internal documents from tobacco companies show that teen consumers have been the target audience for tobacco marketing for many years. These records show that the industry was aware of the developing brain's increased susceptibility to addiction. As we will see in more detail, nicotine and tobacco use during a person's formative years can be especially harmful to their physical growth and their susceptibility to diseases in later life.

Nicotine is the main psychoactive and addictive substance among the many chemicals found in tobacco products, both naturally occurring and intentionally added. The pharmacological and biological effects of nicotine are complex, just like the drug's convoluted past. As an acetylcholinergic agonist, nicotine is characterised as activating the cholinergic system. This is only partly true; however, nicotine's effects are more varied. It functions as a strong agonist at nicotinic acetylcholine receptors (nAChRs), but because of its strength, these receptors may become desensitised [3]. Because nicotine can act as both an agonist and an antagonist at nicotinic acetylcholine receptors (nAChRs), it has dual properties. The particular arrangement of subunits within these receptors' pentameric structure determines the receptors' affinity for nicotine and the consequent activation or desensitisation response. A wide variety of subunit combinations, including heteromeric and homomeric nAChRs, can be formed by the sixteen identified nAChR subunit genes found in mammals. As a result, depending on the area, type of cell, and location of the cell, the body's receptor subtype composition varies. Because of this, nicotine's effects on the body are not consistent. In fact, nicotine can behave antagonistically towards one cell type while acting as an agonist towards another, mainly as a result of receptor desensitisation. The effects of nicotine go beyond the acetylcholinergic system despite the fact that it is a nAChR agonist. It has an immediate impact on signalling via various other neurotransmitter systems. Both presynaptic and postsynaptic sites are included in the distribution of nAChRs. Dopamine, norepinephrine, serotonin, glutamate, and GABAergic neuron terminals all have presynaptic nAChRs. Because of this configuration, acetylcholine can control the release of other neurotransmitters, thereby improving the effectiveness of their signalling. Similarly, nicotine can directly stimulate the release of numerous neurotransmitters, including dopamine, as it is a more potent agonist than acetylcholine [4]. As a result, nicotine's effects on biological and behavioural systems are complex, interactive, and multifaceted, with the ability to affect different neurotransmitter pathways. This complexity could provide an explanation for nicotine's range of effects. Therefore, looking at nicotine from a different angle than just seeing it as an agonist of cholinergic signalling is necessary in order to fully understand its complex and maladaptive effects. The effects of nicotine can be both immediate and short-lived, as well as persistent and long-lived. It is possible to alter the brain, behaviour, and physiological processes in a variety of ways. These pathways cover structural changes involving the gain or loss of particular structures. Epigenetic mechanisms can also result in long-lasting changes. By controlling genetic function without altering the genetic code, epigenetics provides a pathway by which the environment, cellular factors, and even behaviour can have an impact on phenotypes. Histone modification, non-coding RNA, and DNA modification are examples of common epigenetic mechanisms [5]. Addiction, depression, developmental changes, cardiovascular disease, lung disease, and cancer are among the complex and occasionally protracted biological and behavioural effects of epigenetics. These elements are connected to tobacco and nicotine use [6].

1. **A brief introduction to epigenetics**

The protein scaffold around which DNA is wrapped is made up of histones. Nucleosomes are produced by coiling the histone-DNA structure into nucleosomes, which are then formed into chromatin fibres. To create chromosomes, these chromatin fibres are woven together. The tails of histones are still accessible and can undergo covalent modifications, which can affect the accessibility of particular DNA sections, even though chromatin is tightly wound to form chromosomes.

Methylation (of lysine or arginine), acetylation (of lysine), and phosphorylation (of serine, threonine, or tyrosine) are three popular covalent modifications. In each of these modifications, the targeted amino acid on the histone tail is given a methyl, acetyl, or phosphate group. Despite the fact that it occasionally may increase the likelihood of transcription, histone methylation is primarily linked to the silencing of genes. On the other hand, histone acetylation helps DNA unwind from histones, improving DNA accessibility and encouraging transcription. Histone phosphorylation is related to transcription and may help histone acetylation in some way [7]. Ubiquitination, sumoylation (a small ubiquitin-like modifier), ADP ribosylation, and deamination are covalent modifications of histones that have received less attention. The specific histone that is being ubiquitinated determines the complex effects of histone ubiquitination on transcription. For instance, although there are some exceptions, histone H2B ubiquitination is generally linked to transcription while histone H2A ubiquitination is associated with gene silencing. The interactions between ubiquitination, histone acetylation, and histone methylation may be the cause of this complexity. Ubiquitination is linked to both gene silencing and gene transcription because small ubiquitin-like modifier proteins can control both transcription co-activators and co-repressors [8].

Non-coding RNA (ncRNA), once viewed as unimportant, has become an essential regulator of gene expression and, as a result, a mediator of epigenetics. The classification of ncRNA variations depends on their length (less than 200 nucleotides), whether they are short or long sequences, and whether they originate from intronic or exonic regions. ncRNAs frequently contribute to the suppression of gene expression. For instance, when complementary mRNA and short non-coding RNA (ncRNA) called microRNAs (miRNAs) bind to one another, gene expression is suppressed. Long non-coding RNAs (lncRNAs), on the other hand, can inhibit gene expression by encouraging DNA methylation and histone modification. NcRNAs can, however, also activate gene expression. Some miRNAs have the ability to bind to DNA methyltransferase, which prevents DNA methylation and boosts gene expression. Additionally, lncRNAs can modify post-translational processes like splicing, mRNA translation, and protein localization by acting at gene promoters to facilitate the regulation of gene transcription. Epigenetic changes can affect biology, behaviour, and development in a variety of ways that are diverse and dynamic. The evidence indicating that interactions between nicotine/tobacco and epigenetics contribute to issues with public health will be examined in more detail in the sections that follow [9].

## Progression of epigenetics

Gene expression changes that are carefully planned and orchestrated during development give rise to structural and physiological changes. Epigenetic signalling changes have the potential to affect gene expression, and as a result, environmental factors that can change epigenetic signalling may have an effect on how development proceeds. One of these is probably nicotine, as it has been shown that exposure to it during adolescence can lead to long-term health problems. Nicotine-induced epigenetic changes in offspring are one potential mechanism by which developmental exposure to nicotine results in long-term health effects. Research comparing the DNA methylation of newborns from mothers who smoked during pregnancy to newborns from non-smoking controls provides evidence in favour of this theory [10]. The development process is typically impacted by prenatal nicotine exposure. Birth weight is linked to maternal smoking or passive smoking exposure. Developmental delays may be a result of maternal smoking's effects on the placenta's epigenetic mechanisms. Certain miRNAs (miR-16, miR-21, and miR-146a) linked to growth and development were downregulated in the placentas of mothers who had smoked in the past. While miR-16 and miR-21 remained unchanged, research on immortalised placental cell lines exposed to nicotine revealed downregulation of miR-146a. TRAF6 mRNA, which is involved in inflammatory reactions, is the target of miR-146a. This implies that miR-146a downregulation may trigger TRAF6-mediated inflammatory responses, which may exacerbate postnatal health issues because inflammation during the postnatal period can interfere with development, as is seen in lung development [11]. Foetal rats exposed to this condition provided additional proof that nicotine exposure during pregnancy causes development delays. These rats had lower levels of cholesterol and steroid hormones, both of which are essential for growth. Consequently, intrauterine growth retardation was connected to this drop in hormone levels. These rats' adrenal glands displayed increased acetoacetyl-CoA synthetase promoter region methylation, which led to decreased acetoacetyl-CoA synthetase mRNA. As a limiting element in the process, this enzyme is necessary for the synthesis of cholesterol. Thus, the acetoacetyl-CoA synthetase gene's altered DNA methylation functions as an epigenetic mechanism that might mediate the negative effects of prenatal and neonatal nicotine exposure on development [12].

* 1. *Developmental exposure and behavioural and brain changes*

Negative developmental changes can result from nicotine exposure during brain development, which is susceptible to its effects. Epigenetic changes may have an impact on some of these negative changes. According to studies done on mice, exposure to nicotine before and after birth up until postnatal day 21 changed the way cortical neurons were built and increased histone methylation. Both prenatal and postnatal nicotine exposure increased the number of dendritic spines and the complexity of the dendrites. It is important to keep in mind, though, that an excessive increase in these characteristics may not always be advantageous, especially during brain development. This is because crucial stages for processes like cell death and synaptic pruning for promoting healthy brain development [13]. Adolescence is a stage of development that is marked by quick development and significant adjustments to both behaviour and brain structure. The use of nicotine during this crucial time can have long-lasting effects on behaviour and brain function. In studies using mice, it was found that exposure to nicotine during adolescence led to changes in the hippocampal dendrite structure, increased reward sensitivity in adulthood, and learning difficulties. These long-lasting alterations in mental health and behaviour brought on by adolescent nicotine exposure may be influenced by epigenetic changes. Study showed that adolescent nicotine exposure affected the DNA methylation of adult mice's hippocampus. Further pathway analysis showed that the top gene categories most significantly impacted by adolescent nicotine exposure were those involved in chromatin remodelling [14]. This suggests that nicotine's effects on the developing brain during adolescence may be moderated by epigenetic changes.

* 1. *Drug metabolism changes caused by developmental exposure and their potential for addiction*

The likelihood of developing problems with nicotine addiction later in life is increased when people are exposed to nicotine while they are still developing. Changes in nicotine metabolism brought on by prenatal nicotine or tobacco smoke exposure are one possible mechanism contributing to this susceptibility. According to studies, nicotine metabolism in the liver was increased in neonatal and adult mice exposed to nicotine prenatally through tobacco smoke [15]. It makes sense that prenatal nicotine exposure would increase a person's risk of later developing a nicotine addiction. Evidence suggests that prenatal nicotine exposure is associated with a 5.5-fold increase in the risk of childhood tobacco use, which remains significant regardless of the mother's current tobacco use, supporting this prediction [16].

* 1. *Exposure during development and cardiovascular changes*

Congenital heart defects in newborns have been linked to pregnant women who smoke during the first trimester. Numerous studies contend that nicotine exposure during pregnancy and after birth has an impact on epigenetics, which may also play a role in these heart defects, despite the fact that other factors may also be involved. In a study using adult male rats, miRNA expression levels were elevated and cardiovascular function was altered when the rats were exposed to nicotine during the perinatal period [17]. These rats showed decreased levels of the BKCa 1 subunit in coronary arteries and increased pressure-induced vascular tone. The BKCa channels play a crucial role in controlling the blood flow and tone in the coronary arteries. It's interesting to note that adult rats exposed to perinatal nicotine had higher expression levels of the miRNA miR-181a, which binds to the BKCa 1 mRNA. This suggests that nicotine exposure during pregnancy may have an effect on cardiovascular function by altering the epigenetic tone of the coronary arteries. Higher levels of angiotensin receptors in the heart have been linked to nicotine exposure during prenatal development. Hypomethylation of the angiotensin receptor gene's promoter region was linked to this rise in angiotensin receptor expression. Because of the epigenetic upregulation brought on by nicotine exposure, the balance of angiotensin receptor signalling is altered, which may increase the activity of pathways that make people more susceptible to cardiovascular disease. Additionally, it suggests that males may be more sensitive to the cardiovascular function epigenetic effects of prenatal nicotine.

* 1. *Endocrine system changes and developmental exposure*

Throughout a person's lifespan, exposure to nicotine or tobacco smoke is associated with changes in hormone signalling. The long-lasting nature of these changes raises the possibility that epigenetic mechanisms play a role in changing endocrine function. Studies on adult rats exposed to nicotine from postnatal day 2 until postnatal day 16 showed changes in thyroid-related miRNA and mRNA expression in the liver, which lend credence to this idea [18]. According to variables like sex and differences in pre-existing health, tobacco use alters thyroid function, and the direction of these effects can lead to either hypothyroidism or hyperthyroidism. Reduced birth weight is a result of maternal smoking, which is significant because it indicates a child's future vulnerability to conditions like diabetes, obesity, and cardiovascular disease. In a different investigation, it was found that nicotine treatment decreased the expression of the steroidogenic acute regulatory protein gene in primary human foetal adrenal cortical cells as well as in cell culture [19]. The rate-limiting step in the synthesis of steroid hormones is where the steroidogenic acute regulatory protein is crucial. The gene for the steroidogenic acute regulatory protein was found to have decreased expression and increased methylation at a particular DNA promoter site. This discovery offers more proof that nicotine exposure during development alters the epigenome in ways that affect steroid hormone signalling. Early postnatal nicotine exposure altered thyroid-related signalling and was accompanied by changes in the expression of certain miRNAs. Furthermore, prenatal nicotine exposure resulted in epigenetic adjustments that impaired testicular development, increased the fetus's susceptibility to maternal glucocorticoids, and decreased testosterone levels. The reduced body weight and altered development linked to perinatal nicotine exposure are all caused by these changes taken together. Furthermore, there is proof that postnatal nicotine exposure is connected to altered expression of genes involved in pituitary gland development.

* 1. *Developmental exposure and changes in immune function*

According to a study, nicotine exposure during pregnancy has been found to affect how well the immune system functions. Separate studies found that prenatal nicotine exposure alters the immune and thymus functions in mice. Prenatal nicotine exposure in female mice resulted in a reduced immune response to stressors at day 42 after birth [20]. At postnatal day 49 in these female mice, this change in the immune response was accompanied by an increase in thymocyte apoptosis. Further research showed that nicotine increased the *Fas* apoptotic pathway and decreased methylation in the Fas promoter region in thymic primary cell culture. Additionally, in thymic primary cells, nicotine increased the expression of TET2 (*tet methylcytosine dioxygenase 2*). DNA demethylation is known to involve TET2, a protein. Hence, the study suggests that prenatal nicotine exposure negatively affects immune function through epigenetic modifications that regulate cell death in the thymus.

1. **Developmental exposure and epigenetics**

Epigenetics is highly sensitive to environmental factors because it plays a critical role in mediating important changes in gene expression during development. Nicotine stands out among these substances as having a negative effect on growth. The idea that developmental exposure to nicotine or cigarette smoke may increase the likelihood of susceptibility to different diseases and disorders throughout life is supported by growing evidence. Numerous changes occur in biological processes and cell signalling as a result of nicotine. However, new research indicates that epigenetic changes may partially mediate or influence the negative effects on the predisposition to developmental diseases. Numerous studies have pinpointed specific epigenetic alterations connected to nicotine or cigarette smoke exposure during development. In neonates exposed to smoking, DNA methylation was found to be altered in genes linked to cancer (AHRR, MEG3), Alzheimer's Disease (FRMD4A), diabetes (GALNT2), and neural development (CNTNAP2). Many of these changes persisted into adolescence. Additionally, miRNA changes related to inflammation (miR-146a), thyroid function (miR-224 and miR-383), and cardiovascular function (miR-181a) were observed. Furthermore, developmental nicotine exposure led to DNA methylation alterations in genes related to cardiovascular function (Gata4 and Tbx5), nicotine metabolism (Cyp2a5), and lung development (PPARγ). p66shc, a gene involved in apoptosis, and Mef2c, a gene associated with cortical development, both showed altered histone methylation patterns. It is astounding how many different biological systems and processes are affected by the epigenetic changes brought on by exposure to tobacco smoke and nicotine during development. These changes have the potential to be harmful to one's health. This emphasises how urgent it is to stop children from being exposed to nicotine and tobacco products during their development in order to improve their overall health and quality of life.

1. **Adult exposure and unfavourable results**

The negative effects of smoking on health are well known, but recent research on the epigenetic changes brought on by nicotine in adults and how this affects health outcomes reveals that nicotine's effects are extensive, complex, and may be influenced by epigenetic changes. According to research, nicotine can serve as a gateway drug, promoting the onset of substance abuse and addiction to other drugs. These effects are connected to modifications in histone acetylation and DNA methylation in addiction-related brain regions. Adult nicotine exposure also affects the methylation and function of the brain's cortical and hippocampal regions, which are essential for cognition and mental health. Smoking is linked to lung disease as well, and nicotine-related epigenetic changes may contribute to this since smokers' lung tissue was found to have altered levels of miRNA linked to oxidative stress and inflammation. Additionally, smokers' immune cells exhibited changes in miRNA levels linked to tumorigenesis and apoptosis, raising the possibility of an elevated risk of cancer and arthritis. Smoking history was linked to changes in AHRR methylation, and epigenetic analyses of smokers and electronic cigarette users revealed hypomethylation of LINE-1, a cancer marker. The expression of AHRR is also influenced by developmental nicotine exposure, which is related to poor cancer outcomes. In a renal carcinoma cell line, nicotine was also discovered to change the methylation of histones. Collectively, these results imply that the susceptibility and development of disease may be influenced by nicotine's epigenetic targets. Additionally, they draw attention to the possibility of concentrating on epigenetic targets as a component of therapeutic research to address the negative effects of nicotine exposure on health.**Top of Form**

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**Summary**

Tobacco and nicotine have had a profound effect on humanity, and it is increasingly clear that these effects also include epigenetic alterations that can affect development and increase the risk of disease and unfavourable outcomes. Gene expression changes that are precise are crucial for development, and because epigenetics controls this process, outside influences can interfere with development with potentially harmful effects. One such external agent with the potential to cause such disruptions is nicotine. Numerous epigenetic alterations have been linked to perinatal exposure to nicotine and tobacco smoke. The DNA methylation of genes in the offspring has been linked to changes in maternal smoking, with effects on conditions like cancer, Alzheimer's disease, addiction, diabetes, and neural development. These alterations in DNA methylation raise the possibility that prenatal nicotine exposure may have an impact on development and raise the risk of contracting various diseases. Smoking during pregnancy has also been linked to altered miRNA signalling that affects the inflammatory response. Lower birth weights and impaired lung development are both known to be linked to inflammation, and both have been linked to early exposure to nicotine and tobacco. In summary, the evidence shows that nicotine and tobacco can leave persistent epigenetic alterations that disrupt development and raise vulnerability to illnesses and negative changes. Understanding these effects is essential for formulating mitigation plans for the negative effects of nicotine exposure during critical developmental stages. Epigenetics are significantly impacted by nicotine and tobacco use and exposure, which results in negative health effects. Overall, studies on nicotine's effects on the epigenome have helped us better understand the subtleties of epigenetic signalling and how to use this knowledge to treat disease and promote health. The development of focused interventions and therapies to lessen the harmful effects of nicotine and tobacco exposure could be influenced by this information.

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