**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, cardiovascular disease, cancer, immune system modifications, lung illness, immune system delays, endocrine diseases, and changes in mental health Diabetes and behavioural issues are two of these issues. A growing body of evidence indicates that nicotine-induced epigenetic changes may be involved in mediating or influencing the emergence and development of several 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) reports that tobacco use causes more than 8 million deaths globally each year. This covers both the direct health effects of tobacco use, such as chronic obstructive pulmonary disease (COPD), lung cancer, 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]. The tobacco and nicotine businesses have prioritised financial advantages by employing misleading techniques, exploiting vulnerable groups, and strengthening the addictive properties of nicotine products. 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.

 Among the various compounds contained in tobacco products, both naturally occurring and artificially added, nicotine is the most psychotropic and addictive molecule. Nicotine's pharmacological and biological impacts are complicated, just like the drug's convoluted past. Nicotine, as an acetylcholinergic agonist, stimulates the cholinergic system. This is only partially correct; the impacts of nicotine are more diversified. It is a powerful agonist at nicotinic acetylcholine receptors (nAChRs), however due to its potency, these receptors may become desensitised. [3]. Because nicotine can serve as both an agonist and antagonist at nAChRs, it has dual properties. The 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 may be antagonistic to one cell type while behaving as an agonist to another, owing to receptor desensitisation. Despite being a nAChR agonist, nicotine has effects that extend beyond the acetylcholinergic system. It has an immediate impact on signalling via various other neurotransmitter systems. Both presynaptic and postsynaptic sites are included in the distribution of nAChRs. Norepinephrine, dopamine, glutamate, serotonin, 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, because nicotine is a stronger agonist than acetylcholine, it may directly trigger the release of several neurotransmitters, including dopamine [4]. As a result, nicotine has complex, interacting, and multidimensional impacts on biological as well as behavioural systems, with the capacity to alter several neurotransmitter pathways. This complexity could provide an explanation for nicotine's range of effects. To completely appreciate nicotine's complex and deleterious consequences, it must be seen from a different perspective than just as an activator of cholinergic signalling. 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 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 capable of covalent transformation modifications, which can affect the accessibility of DNA sections, even though chromatin is tightly wound to form chromosomes.

Acetylation, methylation, and phosphorylation are three popular covalent modifications. Each of these changes involves the addition of acetyl, methyl, or phosphate group to the specific amino acid on the histone tail. Even though 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]. Sumoylation, ubiquitination, deamination, and ADP ribosylation 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 related to gene silencing. This intricacy may be due to interactions between ubiquitination, histone acetylation, and histone methylation. Because tiny ubiquitin-like modifier proteins may affect both transcription co-repressors and co-activators, ubiquitination is associated with both gene silence and gene transcription. [8].

Non-coding RNA (ncRNA), once viewed as unimportant, has become an essential gene expression regulator and, as a result, a epigenetic mediator. 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 histone modification and DNA methylation. NcRNAs can, however, also activate gene expression. Some miRNAs are capable of binding to DNA methyltransferase, preventing DNA methylation and increasing gene expression. Furthermore, by acting at gene promoters to regulate gene transcription, lncRNAs can change post-translational processes like as splicing, mRNA translation, and protein localisation. 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. One putative mechanism through which exposure to nicotine during development leads in long-term health impacts is nicotine-induced epigenetic alterations in children. 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. MiR-146a targets TRAF6 mRNA, which has been implicated in inflammatory responses. This suggests that downregulation of miR-146a may result in TRAF6-mediated inflammatory responses, that may increase postnatal health difficulties because inflammation throughout the postnatal period may disrupt with development, as demonstrated 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 production of cholesterol. Thus, the acetoacetyl-CoA synthetase gene's altered DNA methylation functions as an epigenetic mechanism that might mediate the deleterious consequences of neonatal and prenatal nicotine consumption on development [12].

* 1. *Exposure throughout development and behavioural and cognitive 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 methylation of histones. Both postnatal and prenatal 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. Nicotine usage at this critical period can have long-term consequences for 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-term effects in mental health and behaviour caused by teenage nicotine consumption might be altered by epigenetic modifications. According to the findings, teenage nicotine exposure influenced the DNA methylation of mature 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 research, neonatal and adult mice subjected to nicotine prenatally by cigarette smoke have enhanced nicotine metabolic in the liver [15]. It seems to reason that prenatal consumption of nicotine would enhance a person's likelihood to develop a nicotine addiction later in life. According to research, prenatal exposure to nicotine is linked to a 5.5-fold rise in the chance of juvenile tobacco smoking, 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 nicotine was administered to the rats 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 are critical in regulating blood flow and tone in the coronary arteries. It's interesting to note that adult rats administered prenatal nicotine exhibited increased expression levels of the miRNA miR-181a, which binds to the BKCa 1 mRNA. This suggests that nicotine exposure during pregnancy may have negative consequences 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 implies that males might have been more susceptible to the epigenetic impacts of prenatal nicotine on cardiovascular function.

* 1. *Endocrine system changes and developmental exposure*

Exposure to nicotine or tobacco smoke is linked to alterations in hormone signalling throughout a person's life. Because these alterations are long-lasting, it is possible that epigenetic pathways have a role in modifying endocrine function. Adult rats exposed to nicotine from postnatal day 2 to postnatal day 16 had alterations in thyroid-related mRNA and miRNA expression in the liver, lending support to this theory [18]. According to variables like sex and differences in pre-existing health, tobacco use changes the functioning of the thyroid, and the path of these changes is unknown and 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, Nicotine therapy was observed to reduce the level of expression in the steroidogenic acute regulating protein gene in primary human foetal adrenal cortical cells and cell culture [19]. The steroidogenic acute regulatory protein is essential in the rate-limiting phase of steroid hormone production. The steroidogenic acute regulatory protein gene was discovered 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 changed thyroid-related signalling and was associated with alterations in the expression of certain miRNAs. Furthermore, nicotine exposure during pregnancy caused epigenetic changes that hampered testicular development, elevated the foetus' vulnerability to maternal glucocorticoids, and lowered testosterone levels. These alterations, when combined, explain the lower body weight and impaired development associated with prenatal nicotine exposure. 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 reduced 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. As a result, the study demonstrates that prenatal exposure to nicotine negatively impacts immune function via epigenetic alterations that govern cell death within the thymus.

1. **Epigenetics and developmental exposure**

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), neural development (CNTNAP2), diabetes (GALNT2) and Alzheimer's Disease (FRMD4A). Many of these changes persisted into adolescence. Additionally, miRNA changes related to cardiovascular function (miR-181a), thyroid function (miR-224 and miR-383), and inflammation (miR-146a) were observed. Furthermore, Nicotine exposure throughout development resulted in DNA methylation changes related to lung development (PPARγ), nicotine metabolism (Cyp2a5), and cardiovascular function (Gata4 and Tbx5). p66shc, a gene involved in apoptosis, and Mef2c, a gene associated with cortical development, both showed altered histone methylation patterns. It's astounding how many different biological processes and systems are impacted by the epigenetic modifications caused by cigarette smoke and nicotine exposure throughout development. These changes have the potential to be harmful to one's health. This highlights how critical it is to protect children from tobacco and nicotine products while they are developing in order to improve their general 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 epigenetic alterations may have an impact. According to research, Nicotine has the potential to act as a gateway drug, facilitating the start of substance misuse and addiction for various substances. 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 mental health and cognition. Cigarette smoking has been connected to lung illness 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 arthritis and cancer. Smoking history was linked to changes in AHRR methylation. Epigenetic studies on smokers and electronic cigarette users demonstrated LINE-1 hypomethylation, a cancer marker. The expression of AHRR is also influenced by developmental nicotine exposure, which is related to poor cancer outcomes. In a cell line from a kidney cancer, nicotine was also discovered to change the methylation of histones. These findings suggest that nicotine's epigenetic targets may impact disease susceptibility and development. 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 changes have been associated to prenatal tobacco and smoke exposure. The methylation of genes in kids has been connected to changes in mother smoking, with consequences for diseases such as cancer, diabetes, addiction, alzheimer's disease, and neurological development. These changes in DNA methylation raise the prospect that prenatal exposure to nicotine may affect development and increase the chance of developing numerous disorders. 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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