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Review Article

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Epigenetic alteration in response to particulate matter exposures: A review on DNA methylation

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ABSTRACT

Globally, air pollution contributes to more than seven million premature deaths each year and is responsible for over 3% of all disability-adjusted life years lost. The adverse health impacts of air pollution, especially Particulate Matter (PM) are extensive, playing a major role in the onset and progression of coronary artery disease, various respiratory conditions, and multiple pulmonary disorders. Despite extensive evidence documenting the health impacts of PM, the underlying biological mechanisms remain only partially elucidated. Recent advances in epigenetics, particularly studies focusing on DNA methylation, offer a promising avenue for understanding how PM exposure translates into adverse health effects. An expanding body of research demonstrates strong associations between PM exposure and genome-wide alterations in DNA methylation, suggesting that these modifications play a pivotal role in mediating the biological and health effects of PM exposure. This comprehensive review explores the intricate relationship between DNA methylation and PM exposure. Representative epidemiological and experimental studies emphasize the connections between PM-induced methylation alterations and the indirect impact of DNA methylation on health. By providing valuable insights into gene-specific alterations, the review contributes to a deeper understanding of the potential implications of PM exposure on DNA methylation and its broader health consequences.

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Review

Global atmospheric pollution represents a significant public health challenge, with the World Health Organization (WHO) indicating that 92% of the global population lives in areas where air quality exceeds acceptable standards. This issue is particularly pronounced in low- and middle-income countries, which face the highest levels of exposure to harmful pollutants [1, 2]. The consequences are profound, as annual global mortality due to ambient air pollution surpasses 3 million, exceeding the combined toll of Acquired Immunodeficiency Syndrome (AIDS), tuberculosis, and malaria [3]. While the immediate health impacts of air pollution are well-documented, the intricate molecular mechanisms underlying these effects, particularly in relation to DNA methylation in the lungs and other organs, remain incompletely understood [4].

Emerging evidence suggests that air pollution, especially exposure to Particulate Matter (PM) with a diameter of 2.5 μm or less ($PM_{2.5}$), is intricately linked to alterations in DNA methylation, a key epigenetic modification that regulates gene expression. Exposure to $PM_{2.5}$ has been linked to global DNA hypomethylation, marked by a decrease in overall methylation levels, which may compromise chromosomal stability and trigger oncogene activation, ultimately facilitating carcinogenesis [1, 2]. Studies have demonstrated that both acute and chronic exposure to $PM_{2.5}$ can induce hypomethylation in tissues such as the lungs and heart, emphasizing its systemic effects.

Conversely, $PM_{2.5}$ exposure can also cause hypermethylation in specific gene promoters, resulting in gene silencing. This phenomenon is particularly critical for tumor suppressor genes, where hypermethylation inhibits their protective functions and promotes tumorigenesis. Furthermore, hypermethylation in promoter regions of genes associated with synaptic function may impair neuronal responses, potentially contributing to cognitive impairments and neurodevelopmental disorders [3]. These dual effects of $PM_{2.5}$ on DNA methylation, both global hypomethylation and gene-specific hypermethylation, highlight its multifaceted role in disease pathogenesis.

This review synthesizes existing evidence on PM-induced alterations in DNA methylation, highlighting both gene-specific and broader systemic epigenetic modifications and their relevance to human health. Gaining insight into these pathways is essential for formulating targeted interventions aimed at reducing the adverse health effects associated with air pollution.

Overview of the epigenetic mechanism

Epigenetics plays a vital role in regulating gene expression by inducing heritable changes that occur without altering the underlying nucleotide sequence. Key epigenetic mechanisms include DNA methylation, histone modifications, and microRNA-mediated regulation, as illustrated in Fig. 1.

Histones are essential globular proteins that play a critical role in the organization and regulation of DNA within eukaryotic cells. They form the core of nucleosomes, which are the fundamental structural units of chromatin, consisting of approximately 146 base pairs of DNAs wrapped around an octamer of histone proteins, specifically two copies each of H2A, H2B, H3, and H4 [5]. The N-terminal tails of these histones protrude from the nucleosome core and are subject to various post-translational modifications that significantly influence chromatin structure and gene expression. Among these, histone acetylation represents one of the most extensively characterized modifications. This process involves the enzymatic transfer of an acetyl group from acetyl-CoA to the

ε-amino group of lysine residues located on histone tails. This reaction is catalyzed by Histone Acetyltransferases (HATs), which use acetyl-CoA as a cofactor to donate the acetyl group to target lysine [6, 7]. Conversely, Histone Deacetylases (HDACs) reverse this process by removing the acetyl groups. Acetylation neutralizes the positive charge of lysine residues, weakening the interaction between histones and the negatively charged DNA backbone. This reduction in electrostatic attraction promotes the formation of a more open chromatin configuration, termed euchromatin, which facilitates the binding of transcriptional machinery, which is generally associated with active gene expression.

In contrast, deacetylation by HDACs strengthens the interaction between histones and DNA, leading to a condensed chromatin state called heterochromatin, which is typically transcriptionally inactive [6, 7].

MicroRNAs (miRNAs) are essential components of epigenetic regulation, functioning as post-transcriptional modulators of gene expression and influencing a wide range of cellular processes, including differentiation and development. A reciprocal interaction exists between miRNAs and epigenetic mechanisms, forming a key regulatory layer that fine-tunes gene expression programs. Epigenetic processes such as DNA methylation and histone modifications can directly modulate the transcription of miRNA genes. For example, methylation of CpG islands within miRNA promoter regions can suppress their transcription, while specific histone modifications can alter chromatin structure and accessibility, thereby influencing miRNA expression. Conversely, miRNAs can regulate components of epigenetic machinery by targeting transcripts encoding critical enzymes, including DNA methyltransferases (DNMTs) and Histone Deacetylases (HDACs). Through this miRNA-mediated regulation of epigenetic modifiers, broader shifts in DNA methylation patterns and histone modification profiles can occur, ultimately reshaping the epigenetic landscape [8]. The interplay between miRNAs and epigenetics forms a reciprocal regulatory network, where epigenetic alterations can dysregulate miRNA expression, which in turn can modulate the epigenetic machinery, creating feedback loops. These miRNA-epigenetic feedback loops are crucial for maintaining normal cellular function, and their disruption has been implicated in the development and progression of various diseases, including cancer [9]. The reciprocal relationship between miRNAs and epigenetics is an important mechanism for the fine-tuning of gene expression programs during cellular processes like differentiation and development, as well as in the context of disease pathogenesis.

DNA methylation is one of the most widely studied epigenetic mechanisms and is stably inherited during somatic cell division. It involves the addition of a methyl group (CH_3) to the C-5 position of cytosine, generating 5-methylcytosine (5mC), as illustrated in Fig. 2. This modification occurs primarily at CpG dinucleotides and plays a central role in regulating gene activity [10]. In plants, cytosine methylation can take place in both symmetrical contexts (CG and CHG) and asymmetrical contexts (CHH, where H represents A, T, or C). In mammals, methylation can occur at cytosines across different genomic regions; however, the majority of 5mC is concentrated within CpG sites, representing approximately 2–5% of all cytosines in the genome [11, 12]. Notably, more than 98% of DNA methylation in somatic cells is confined to CpG dinucleotides, where it is essential for maintaining genomic integrity and controlling gene expression. In contrast, embryonic stem cells (ESCs) exhibit a distinctive pattern of DNA methylation. Up to 25% of all methylation in these cells occurs in a non-CpG context, primarily at CpA sites [11,

12]. This non-CpG methylation is facilitated by the same DNMT enzymes but serves different regulatory roles, potentially influencing pluripotency and differentiation processes.

Hypermethylation of DNA is typically linked with transcriptional repression, whereas hypomethylation may result in aberrant gene activation or increased genomic instability. DNA methyltransferases are the key enzymes that catalyze the addition of methyl groups to DNA, while members of the Ten–Eleven Translocation (TET) enzyme family drive the demethylation process by oxidizing 5-methylcytosine (5mC). This oxidation produces 5-hydroxymethylcytosine (5hmC), an intermediate commonly associated with transcriptionally active regions. Continued TET-mediated oxidation can convert 5hmC into 5-formylcytosine (5fC), further advancing the demethylation pathway. Cytosine, in its unmodified state, is the foundational base from which these epigenetic modifications arise. Such chemical alterations influence gene regulatory patterns without altering the nucleotide sequence, thereby contributing to essential biological processes including embryonic development, cellular differentiation, and the pathogenesis of various diseases [13]. Normally, during early development, global DNA methylation levels decline in the zygote and are subsequently restored during implantation in the embryo. This reprogramming is vital for processes such as genomic imprinting, X-chromosome inactivation, and the silencing of repetitive genetic elements to prevent their expression and mobilization [14, 15].

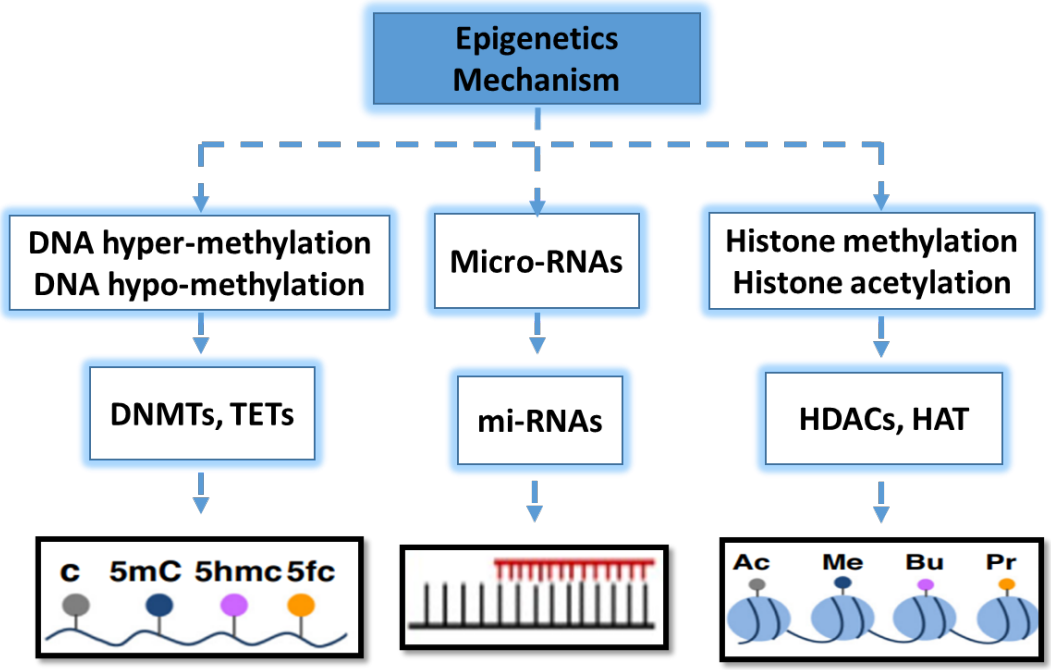

Fig. 1. Epigenetic mechanism and role of DNA Methylation, Histone Modifications, and MicroRNA control [6, 7].

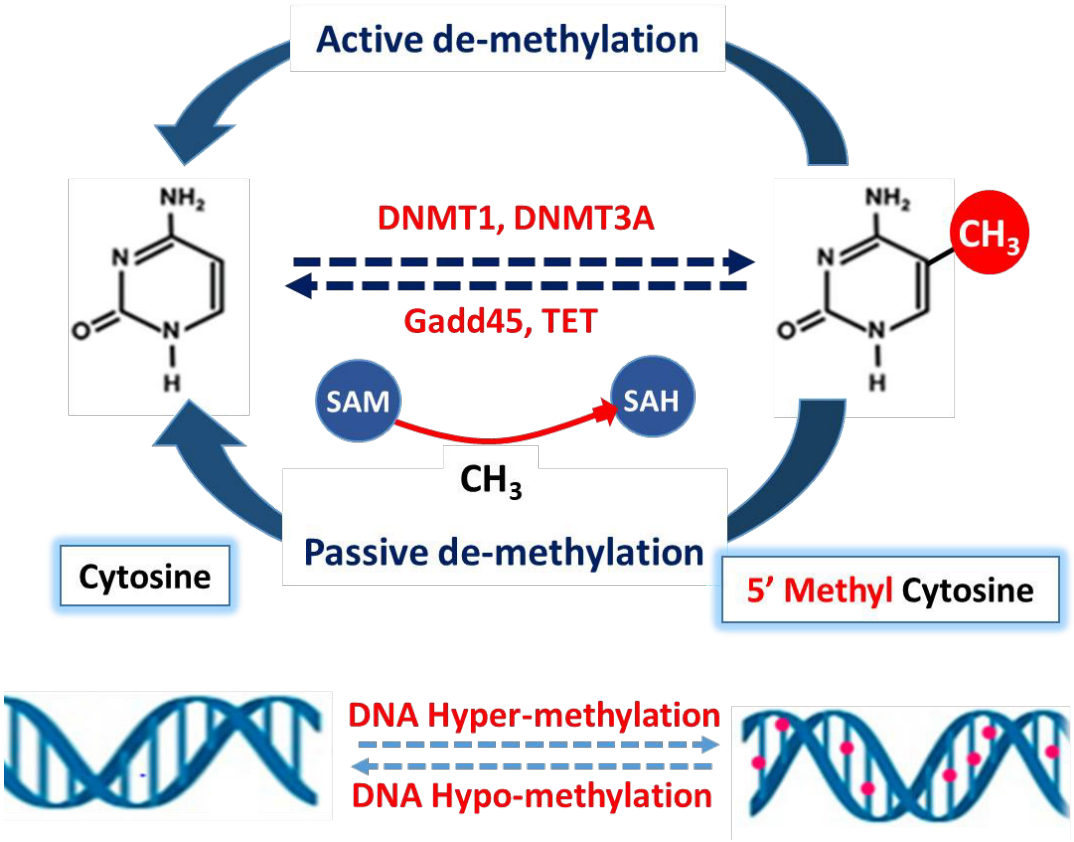

Fig. 2. DNA methylation and de-methylation process: Transfer of a methyl group to the C-5 position of cytosine by DNA methyl transferases (DNMTs) [14, 15]

Particulate matter affects DNA methylation

Particulate Matter (PM) is widely recognized as a critical environmental pollutant that poses substantial risks to human health, impacting multiple physiological systems. Emerging evidence suggests that one of the key biological mechanisms underlying PM-related toxicity involves alterations in DNA methylation. Fine and ultrafine particles ($PM_{2.5}$ and less) major components of ambient air pollution have been shown to induce measurable changes in DNA methylation profiles [16]. PM encompasses a broad spectrum of particle sizes, ranging from the nanometer to micrometer scale, and is commonly classified into three categories. Coarse particles (PM_{10}), the largest fraction, are largely generated through mechanical processes such as the fragmentation of soil, dust from agricultural lands and unpaved surfaces, and emissions from mining activities. Biological materials including pollen, fungal spores, and plant–insect fragments also contribute to this size range. Due to their size, PM_{10} primarily affects the upper respiratory tract, causing irritation in the nasal passages, throat, and eyes [17]. Fine particles are smaller and capable of infiltrating deep into the lung alveoli, where they may induce tissue injury. These particles are predominantly formed through combustion processes, including vehicle exhaust, biomass burning, and emissions from power plants.

Ultrafine particles (<0.1 μm), the smallest subset, typically arise from nucleation events. Their extremely small size allows them to cross into the bloodstream and exert systemic effects, including disruptions in oxygen transport. However, these ultrafine particles remain airborne only briefly due to rapid deposition or aggregation into larger fine particles [18].

Exposure to PM is known to elicit a range of harmful biological responses in the respiratory tract and other tissues, largely through the induction of inflammatory and oxidative pathways. PM stimulates the generation of Reactive Oxygen Species (ROS), disrupting cellular redox balance and promoting oxidative stress. This oxidative burden activates multiple inflammatory cell types, leading to the release of pro-inflammatory cytokines [19, 20] thereby establishing a cycle of persistent inflammation and tissue damage. Additionally, PM enhances airway inflammatory responses by modulating several key intracellular signaling pathways. These include the Nrf2–Keap1–ARE pathway, which governs antioxidant and cytoprotective gene expression; the MAPK pathway, which coordinates cellular responses to environmental and oxidative stress; and the PI3K/Akt pathway, a central regulator of cell survival and inflammatory signaling [21]. These molecular mechanisms collectively play a crucial role in PM-induced various diseases, including cancer, hypertension, heart failure and atherosclerosis as shown in Fig. 3.

In addition to these pathological outcomes, emerging evidence suggests that alterations in DNA methylation induced by air pollution may have transgenerational effects, potentially impacting the health of future generations. The precise mechanisms through which particulate matter affects DNA methylation are not fully understood; however, oxidative stress, chronic inflammation, and direct interactions of PM components with DNA are believed to play significant roles. These epigenetic modifications may lead to long-term health consequences, highlighting the importance of understanding how environmental pollutants like PM influence the epigenome [22]. Fig. 3 shows the particulate matter involved in epigenetic mechanisms possess detrimental health impacts [23].

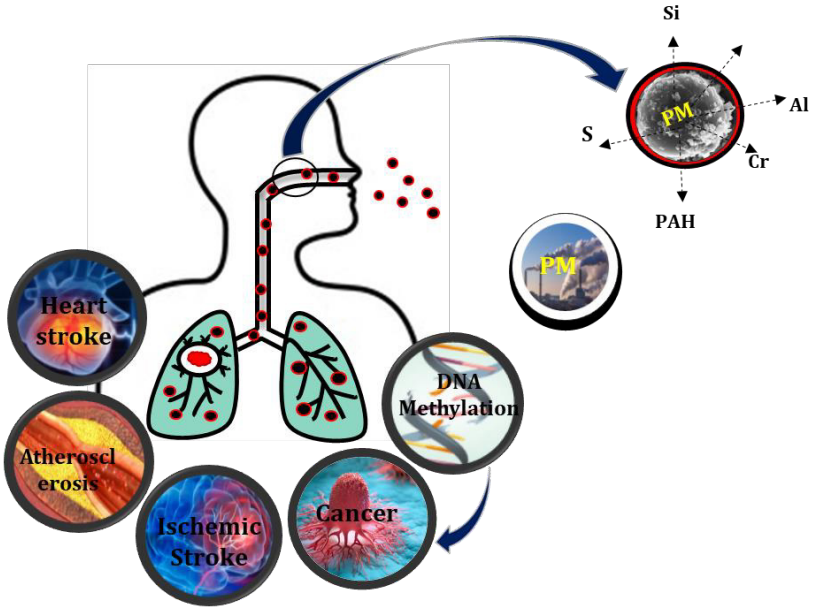

Fig. 3. Particulate matter involved in epigenetic mechanisms possess detrimental health impacts [23]

Table 1 illustrates the effects of PM on genes associated with hyper- and hypomethylation. For instance, exposure to fine Concentrated Ambient Particles (CAP) has been linked to reduced Alu methylation, while exposure to coarse concentrated particles is associated with decreased TLR4 methylation, which plays a key role in asthma etiology [24]. Variations in the methylation of these genes are connected to various diseases, highlighting the critical need to address air pollution for the well-being of both general and vulnerable populations, including children and the elderly.

Table 1. Describing associations between pollutants and DNA methylation

Study design	Exposure level/Duration	Epigenetic mark and effect	References
Cross-sectional	$PM_{2.5}$ (26-40 μg/m^3) (2006–2011)	Significant correlation observed among $PM_{2.5}$ exposure and increased methylation of AHRR genes	[25]
Cross-sectional	$PM_{2.5}$ (22-100 μg/m^3) (2006–2011)	Elevated SOX2 promoter methylation levels were significantly linked to exposure to $PM_{2.5}$	[26]
Panel study	$PM_{2.5}$ (78.38±30.4 μg/m^3) (1 month)	$PM_{2.5}$ constituents were significantly associated with DNAm changes in eight ICRs and CYP1B1, with imprinted genes being more sensitive than non-imprinted ones.	[27]
Panel study	PAHs (1 to 19.66 pg/g) (4 months)	Methylation was significantly lowered but negatively correlated with urinary 1-hydroxy pyrene	[28]
Cohort study	$PM_{2.5}$ and PM_{10} (40.2 ± 17.2 and 57.6 ± 21 μg/m^3) (1 month)	Detection of 58 CpG sites in various genes with methylation level disparities exceeding 10%	[29]
Cohort study	$PM_{2.5}$ and PM_{10} (13.8 and 30.2 μg/m^3) (7-days mean)	Short-term PM exposure was linked to reduced iNOS methylation; specifically, each 5 μg/m³ increase in $PM_{2.5}$ concentration corresponded to a 0.30% decrease in iNOS methylation	[30]
Cross-sectional study	$PM_{2.5}$ (26.7 μg/m^3) (Annual mean)	Changes in methylation observed in clock genes (CRY1, CRY2, NPAS2) associated with the occurrence of ischemic stroke	[31]
Sub-cohort study	$PM_{2.5}$ (9.3 μg/m^3) (Annual mean)	A 5 μg/m³ rise in ambient $PM_{2.5}$ levels was associated with a 7.33% reduction in TNF-α methylation at the cg21370522 site	[32]
Cohort study	$PM_{2.5}$ Weekly Mean (12.97 μg/m^3) (1 year)	The disease risk is associated with modified DNA methylation in the IGF2/H19 gene in cord blood.	[33]
Cohort study	$PM_{2.5}$ (1 year)	CpG methylation and DMRs) observed in circulating monocytes, associated with the pathogenesis of atherosclerosis	[34]

Table 1. Continued

Study design	Exposure level/Duration	Epigenetic mark and effect	References
Cohort study	$PM_{2.5}$ (1 year)	Exposure is responsible for DNA methylation at DMRs and CpG sites associated with immune response and inflammation	[35]
Panel study	$PM_{2.5}$ 24 hr. mean (42 μg/m^3) (6 months)	Prolonged exposure to $PM_{2.5}$ is positively linked with DNA hypo-methylation and reduced TNF-alpha methylation	[36]
Crossover study	$PM_{2.5}$ and PM_{10} (33 and 49 μg/m^3) (3 months)	Short-term PM exposure raises the methylation of the pro-inflammatory gene IFN-gamma and alters the parasympathetic regulation of heart function	[37]
Cohort study	Short-term $PM_{2.5}$ exposure (10 μg/m^3)	Short-term exposure of PM was associated with asthma and iNOS promoter methylation	[38]
Case-control study	PM_{10} (58 -7 6μg/m^3) (2 year)	First-trimester exposure significantly correlated with methylation in Line-1 genes	[39]
Longitudinal Cohort Study	Environmental exposure	Study identified genome-wide DNA methylation changes in stroke and identified altered MTRNR2L8 methylation.	[40]
Cross-sectional Study	PM_{10} and $PM_{2.5}$ (50-110 and 20-43 μg/m^3) (1 year)	Significant association with placental global DNA methylation	[41]
Study (29 sibling pairs)	Environmental exposure	Altered the 5-methylcytosine and 5-hydroxymethyl cytosine associated with the transcriptional factors, contributing to the development of respiratory diseases and asthma	[42]
Observational Study (22 severe and non-severe asthmatic children)	Environmental exposure	The study observed modifications in the patterns of CpG sites associated with Asthma including 816 differentially methylated CpG positions and 10 differentially methylated regions	[43]
Crossover-controlled study	$PM_{2.5}$ (300 μg/m^3) 4 - weeks	Methylation at CpG sites is responsible for the development of allergic diseases	[44]
Cohort study (143 current and 311 never smokers)	Cigarette smoke	Coronary heart disease is 25% more likely to develop in female smokers than in male smokers who are exposed to the same amount of tobacco smoke.	[45]

Methylation of disease-specific genes

Methylation of disease-specific genes is a key epigenetic mechanism that significantly shapes the development and progression of numerous health conditions. Aberrant DNA methylation patterns, including both hypermethylation and hypomethylation, can lead to major regulatory shifts in gene expression [46]. Such alterations are implicated in a wide spectrum of diseases—for example, in cancer, hypermethylation of DNA repair and cell-cycle genes facilitates tumor growth, whereas in cardiovascular disorders, disrupted methylation profiles impair vascular function and contribute to the pathogenesis of atherosclerosis and heart failure [47]. Changes in methylation also influence inflammatory pathways, thereby affecting the expression of genes linked to respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Exposure to particulate matter further modifies these methylation patterns, improving our understanding of the molecular pathways that drive the onset and progression of various health outcomes [48]. Additionally, identifying disease-specific methylation signatures provides valuable direction for the development of early diagnostic biomarkers and potential therapeutic targets aimed at reducing the adverse effects associated with PM exposure. Table 2 shows the differentially Methylated Genes in response to particulate matter exposure [49, 50].

Table 2. Differentially Methylated Genes in Response to Particulate Matter Exposure [49, 50].

Disease	Hyper-methylation	Hypo-methylation
Cancer-related genes	• APC gene • MGMT gene • RASSF1 gene • BRCA1, BRCA2 promoter • GSTP1, CDH1, TIMP3, SOCS1, gene	• MYC gene • LINE-1, Alu • IL6 and TNF-α, gene • CCND1, PD-L1 gene • VEGF, MMP9 gene
Heart failure-related genes	• HEY2 gene • MSR1 gene • CTGF gene • COX17 gene • MMP2 gene	• PON1 gene • MMP2 gene • miR-155 gene • COX17 gene

Table 2. Continued

Disease	Hyper-methylation	Hypo-methylation
Ischemic-related genes	• AHRR gene • IL6 gene • MDM2 gene • CDKN1A gene • TNF alpha promoter	• IGFBP3 gene • PRDM6 gene • AMH, HDAC8 gene • C17ORF82 gene • TBX2 gene
Atherosclerosis-related genes	• MAP4K4 gene • KLF2 promoter • KLF4 promoter • ZEB1, FYN gene • SMAD7 promoter • ADRB2 gene	• EBF1 promoter • HECA promoter • NOD2 promoter
Hypertension related genes	• DSCR3 gene • ACE2 promoter • SULF1 promoter • ER-alpha promoter • HSD11B2 promoter • MTHFD1 promoter	• AGT promoter • sACE promoter • ADD1 promoter • NKCC1 promoter • SERPIN3 CpG island • miRNA-34alpha promoter

Cancer-related genes

Particulate matter exposure is a significant environmental factor in cancer development, influencing gene regulation through both hypermethylation and hypomethylation. Hypermethylation of several cancer-related genes leads to their silencing and contributes to carcinogenesis [51]. For instance, CDKN2A (Cyclin Dependent Kinase Inhibitor 2A) encodes the p16^INK4A protein, which is crucial for regulating the cell cycle by inhibiting cyclin-dependent kinases (CDK4/6) and cyclin D complexes. Hypermethylation of the CDKN2A promoter leads to its silencing, which removes the inhibitory control on the cell cycle, allowing unchecked cell proliferation. and responsible for lung and colorectal cancers [52]. Similarly, RASSF1A (Ras Association Domain Family Member 1) is a tumor suppressor gene involved in apoptotic signaling, microtubule stabilization,

and mitotic progression which acts as a negative Ras effector, inhibiting cell growth and inducing cell deaths. During PM exposure RASSF1A gene often silenced, promoting tumor progression in lung and breast cancers [53]. The MGMT (Methylguanine-DNA Methyltransferase) gene encodes an enzyme responsible for DNA repair by excising alkyl groups from guanine, hence preventing mutations. Hypermethylation of the MGMT promoter silences this gene, reducing its repair function and increasing sensitivity to alkylating agents used in chemotherapy [54], while hypermethylation of BRCA1 (BReast CAncer gene 1) promoter, leads to its silencing, impairing DNA repair and increasing susceptibility to breast and ovarian cancers [55]. Similarly other tumor suppressors, such as GSTP1 (Glutathione S-Transferase Pi 1), CDH1 (E-Cadherin), TIMP3 (Tissue Inhibitor of Metalloproteinases 3), and SOCS1 (Suppressor of Cytokine Signaling 1) shown in table 2, are also, facilitating oxidative DNA damage, metastasis, and immune evasion, contributing to gastric and lung cancers [56].

In contrast, PM exposure also induces hypomethylation of specific genes, activating oncogenes and destabilizing the genome, further driving tumor progression. Oncogenes such as MYC (Myelocytomatosis Oncogene), which drive cell growth by regulating the genes responsible for ribosome biogenesis, and the metabolism. They bind to DNA with their partner MAX to amplify gene expression, leading to increased cellular proliferation and metabolic reprogramming. Hypomethylation, leads to their overexpression and promoting uncontrolled cell division, migration, and invasion in cancers like lung and colorectal [57]. Repetitive elements like LINE-1 (Long Interspersed Nuclear Element-1) and Alu (Alu Repetitive Elements) sequences also experience hypomethylation, resulting in genomic instability and increased mutation rates, particularly in lung and bladder cancers [58]. Similarly, hypomethylated pro-inflammatory genes, including IL6 (Interleukin 6) and TNF-α (Tumor Necrosis Factor Alpha), can regulate DNA methyltransferases, leading to altered gene expression and contributing to cancer progression. This regulation includes decreased promoter methylation and increased expression of genes like EGFR, which are involved in growth-regulatory pathways [59]. However, hypomethylation of genes involved in cell cycle regulation, immune checkpoints (PD-L1), angiogenesis (VEGF), and metastasis (MMP9) also plays a significant role in disrupting cell cycle control and promoting tumor growth, invasion, and metastasis [60]. Together, these dual mechanisms of hypermethylation and hypomethylation caused by PM exposure disrupt normal gene function, driving cancer development and progression.

Heart failure-related genes

Heart Failure (HF) is a multifaceted cardiovascular condition, and recent research has underscored the role of epigenetic alterations in shaping its molecular foundation. These modifications influence the expression of genes that govern cardiac structure and function, creating an important link between environmental exposures and HF progression. Among various epigenetic processes, DNA methylation has emerged as a central regulator of gene activity in HF. Exposure to fine and ultrafine particulate matter can substantially modify the methylation profiles of genes essential for cardiac performance, promoting apoptosis, myocardial hypertrophy, and overall cardiac dysfunction. Both increased and decreased methylation of HF-related genes have been reported, as outlined in Table 2 [61].

For instance, PM exposure induces hypermethylation in genes such as HEY2

and MSR1, which are essential for cardiac development and structural integrity. Disruption in the normal expression and function of these genes contributes significantly to the development of heart failure. HEY2 regulates the proliferation and differentiation of cardiac progenitor cells, ensuring proper heart formation, which can lead to congenital heart defects [62]. MSR1 is involved in inflammation and immune responses within the heart. PM induced hypermethylation of both genes, reducing their expression and being responsible for heart failure [63]. Similarly, hypermethylation of CTGF (Connective Tissue Growth Factor) exacerbates fibrosis and inflammation, driving pathological remodeling of the heart. The mitochondrial function gene COX17 (Cytochrome C Oxidase Assembly Protein) also suffers hypermethylation, disrupting energy metabolism and weakening myocardial performance [64]. Additionally, MMP2 (Matrix Metallopeptidase 2), critical for extracellular matrix turnover, experiences hypermethylation, impairing tissue repair and contributing to cardiac dysfunction [65].

However, hypomethylation of specific genes also significantly contributes to PM-induced heart failure. For instance, hypomethylation of miR-155 (MicroRNA-155), is known to promote inflammation by targeting suppressor of cytokine signaling 1 (SOCS1), which leads to enhanced STAT3 and NF-κB signaling pathways. This results in increased production of inflammatory cytokines and chemokines, exacerbating inflammatory response. This excessive inflammation disrupts normal cardiac function and is a major contributor to the progression of heart failure [66]. Similarly, hypomethylation of MMP2 (matrix metallopeptidase 2) enhances its expression, driving extracellular matrix remodeling and degradation, which weakens cardiac structure and function [67]. Genes like COX17, involved in mitochondrial energy metabolism, may also exhibit hypomethylation, disrupting energy production and increasing myocardial stress. Additionally, PON1 (Paraoxonase1), critical for vascular integrity and oxidative stress regulation, becomes hypomethylated, resulting in vascular dysfunction that further exacerbates heart failure [68]. These alterations are largely attributed to PM-induced oxidative damage and inflammatory responses, which disrupt the normal function of DNA methyltransferases (DNMTs) and Ten-Eleven Translocation (TET) enzymes, thereby shifting the cellular methylation equilibrium. Collectively, PM exposure-induced hyper and hypomethylation disrupts the expression of key genes, amplifying the molecular mechanisms underlying heart failure

Ischemic stroke related genes

Stroke is a significant global health issue, characterized by the sudden loss of brain function due to disrupted blood supply. Ischemic stroke accounts for nearly 87% of all reported cases. Contemporary epigenetic investigations have increasingly demonstrated the relevance of DNA methylation in modulating stroke pathology, offering deeper insight into the molecular effects of environmental determinants. Among these environmental factors, $PM_{2.5}$ has emerged as a key contributor to stroke risk through its ability to induce epigenetic modifications. Notably, $PM_{2.5}$ exposure can lead to hypermethylation in genes pivotal to inflammation and cellular repair.

For instance, hypermethylation of AHRR (Aryl Hydrocarbon Receptor Repressor) disrupts its ability to regulate the AHR (aryl hydrocarbon receptor) pathway effectively. This disruption can lead to enhanced AHR activity, resulting in altered inflammatory responses and potentially contributing to the development of inflammatory diseases [69]. Similarly, hypermethylation of

IL-6 (Interleukin 6), can potentially exacerbate systemic inflammation linked to ischemic stroke by increasing IL-6 levels and promoting inflammatory pathways. This heightened inflammatory response can lead to more severe brain damage and poorer functional outcomes in stroke patients [70]. The upregulation of MDM2 (Mouse Double Minute 2), a principal regulator of the tumor suppressor protein p53, can compromise essential cellular stress-response mechanisms, thereby increasing susceptibility to ischemic injury. Likewise, the hypermethylation of CDKN1A (Cyclin Dependent Kinase Inhibitor 1A), commonly known as p21, interferes with its role in controlling the cell cycle and mediating apoptosis, ultimately hindering effective cellular recovery during ischemic conditions [71]. Furthermore, the exposure of PM also found to increase the expression of pro-inflammatory cytokines, including TNF-α (Tumor Necrosis Factor), which can contribute to stroke pathogenesis by promoting vascular endothelial dysfunction and systemic inflammation [72]. These hypermethylation-induced disruptions in gene expression highlight how $PM_{2.5}$ exposure undermines critical pathways, elevating stroke risk.

On the contrary, PM exposure also induces hypomethylation in several genes, further compounding the risk of ischemic stroke. For example, hypomethylation of AMH (Anti-Müllerian Hormone) impacts vascular health and inflammatory responses, while alterations in HDAC9 (Histone Deacetylase 9) disrupt gene expression regulation and cellular stress responses, promoting vascular remodelling and inflammation [73]. IGFBP3 (Insulin-like Growth Factor Binding Protein 3) plays a significant role in regulating cell growth, apoptosis, and proliferation. Hypomethylation of the IGFBP3 promoter leads to its increased expression, which has been shown to Induce Apoptosis, Inhibit Cell Growth and Enhance Chemosensitivity [74]. Similarly, PDE3A (Phosphodiesterase 3A) hypomethylation affects vascular signaling pathways, heightening vulnerability to ischemic events. The role of PRDM6 (PR Domain Containing 6) in vascular development is also disrupted by hypomethylation, compromising vascular homeostasis and elevating stroke risk [75]. Additional genes, such as C17orf82 (chromosome 17 open reading frame 82) and TBX2 (T-Box 2), also exhibit hypomethylation linked to stroke, with TBX2 hypomethylation specifically associated with increased stroke mortality [76]. By disrupting critical pathways related to inflammation, vascular function, and cellular repair, $PM_{2.5}$ exposure exacerbates stroke risk and impacts patient outcomes.

Atherosclerosis-related genes

Atherosclerosis, a chronic inflammatory disorder, is defined by the accumulation of cholesterol, extracellular matrix, and lipids in the inner layers of large and medium-sized arteries. This process involves smooth muscle proliferation, immune cell infiltration (particularly macrophages), and endothelial dysfunction, leading to the formation of arterial plaques. As the disease progresses, it poses a risk of acute cardiovascular events such as myocardial infarction, peripheral vascular disease, aneurysms, and stroke [77].

Researchers have delved into the molecular aspects of atherosclerosis, particularly focusing on DNA methylation. Exposure to $PM_{2.5}$ has been linked to hypermethylation of specific genes, which in turn affects their expression. For instance, $PM_{2.5}$ induced hypermethylation of the ADRB2 (Adrenoceptor Beta 2) gene results in the downregulation of β 2-Adrenergic receptor (β 2AR), which inhibits the PI3 K/Akt pathway and activates the Bcl-2/BAX and p53 pathways, leading to cardiomyocyte apoptosis and cardiac dysfunction [78]. Furthermore, exposure of

$PM_{2.5}$ exposure has been shown to disrupt flow-dependent methylation patterns and suppress the expression of the KLF4 (Krüppel-like factor 4) promoter, a key regulator of endothelial homeostasis and an important protective factor against atherosclerosis [79].

In the early stages of atherosclerosis, investigators examined DNA methylation patterns in promoter regions of genes implicated in disease development to identify potential biomarkers. Notable methylation changes have been detected in the peripheral blood of individuals with atherosclerosis, particularly within the promoters of ATP binding cassette subfamily A member 1 (ABCA1), TIMP metallopeptidase inhibitor 1(TIMP1), and Acetyl-CoA acetyltransferase 1 (ACAT1) [80]. Additionally, the promoter region of SMAD7 (SMAD Family Member 7) has been reported to undergo hypermethylation following exposure to $PM_{2.5}$, leading to reduced SMAD7 expression—an important regulator of inflammatory and fibrotic processes within atherosclerotic plaques. Elevated methylation of the SMAD7 promoter has likewise been observed in the peripheral blood of atherosclerosis patients and shows a significant association with circulating homocysteine levels [81].

Conversely, Certain genes such as EBF1 (Early B-Cell Factor 1), HECA (Homeobox and EST-Containing CpG Island), and NOD2 (Nucleotide-Binding Oligomerization Domain Containing 2) have been linked to reduced methylation (hypo-methylation) following $PM_{2.5}$ exposure, potentially enhancing the gene expression and thereby influencing inflammatory pathways, cellular differentiation and immune responses that contribute to atherosclerosis [82]. Moreover, hypo-methylation due to NOD2 promoter, involved in pathogen recognition and immune response, which in turn increased NOD2 expression, responsible for disrupting normal immune function and contribute to chronic inflammation associated with atherosclerosis [83]).

These findings exhibited a positive correlation with the severity of coronary atherosclerosis, shedding light on the epigenetic modifications associated with the disease. Table 2 illustrates the genes related to atherosclerosis, highlighting both hyper-methylation and hypo-methylation patterns.

Hypertension related genes

Arterial hypertension is a complex, multifactorial condition influenced by various mechanisms and metabolic systems. The emergence of hypertension results from a complex interplay between genetic factors and environmental influences [84]. Environmental factors during intrauterine development, such as malnutrition, obesity, and exposure harmful environmental toxins, are directly correlated with hypertension development in progeny [85].

Emerging research highlights the role of DNA methylation, specifically hypermethylation and hypomethylation, in modulating hypertension-related genes, thereby impacting cardiovascular health. Exposure to particulate matter is a key environmental factor influencing these epigenetic modifications.

PM exposure has been linked to hypermethylation of several genes that regulate cardiovascular functions. For instance, hypermethylation of the DSCR3 (Down Syndrome Critical Region Gene 3) gene disrupts calcium signaling pathways and impairs vascular smooth muscle function, contributing to vascular dysfunction and hypertension. Similarly, hypermethylation of the ACE2 (Angiotensin-Converting Enzyme 2) promoters reduce ACE2 expression, a critical regulator of the renin-angiotensin system, leading to elevated angiotensin II levels and increased hypertension risk [86]. Another

example is the hypermethylation of the SULF1 (Sulfatase 1) promoter, which impairs growth factor signaling, potentially contributing to vascular remodeling and elevating blood pressure [87]. Additionally, hypermethylation of the ER-alpha (Estrogen Receptor Alpha) decreases estrogen receptor alpha expression, diminishing estrogen's protective cardiovascular effects and heightening the risk of hypertension. Furthermore, hypermethylation of the HSD11B2 (Hydroxysteroid 11-Beta Dehydrogenase 2) promoter, which regulates cortisol activity at mineralocorticoid receptors, increases cortisol activity and sodium retention, exacerbating hypertension [88].

On the other hand, exposure to particulate matter has been associated with the hypomethylation of many hypertension-related genes, which significantly contributes to the disruption of vascular and blood pressure control (Table 2). For instance, hypomethylation of the AGT (Angiotensinogen) and sACE (Soluble Angiotensin-Converting Enzyme) promoters, key regulators angiotensinogen in the renin-angiotensin system, leads to increased angiotensinogen expression and elevated blood pressure [89]. Similarly, hypomethylation of the ADD1 (Adducin 1) and NKCC1 (Sodium Potassium Chloride Cotransporter 1) promoters, which are crucial for sodium transport regulation and vascular tone, contributes to enhanced sodium retention, further driving hypertension. Additionally, the SERPIN3 (Serine Protease Inhibitor 3) CpG island, involved in inflammation and maintaining vascular integrity, undergoes hypomethylation, resulting in increased SERPIN3 expression and heightened vascular inflammation [90]. Lastly, hypomethylation of the miRNA-34alpha promoter alters microRNA expression profiles, contributing to vascular remodelling and the progression of hypertension [91]. These epigenetic changes underscore the profound impact of PM exposure on cardiovascular health.

Conclusion

The review underscores the complex relationship between particulate matter exposure and DNA methylation, emphasizing its importance in the development and progression of many disorders. Epidemiological and experimental evidence indicates that PM-induced epigenetic modifications, such as hypermethylation and hypomethylation of specific genes, influenced critical biological processes like inflammatory responses, oxidative stress, and immune regulation. These mechanisms contribute to the development and progression of conditions such as cancer, cardiovascular diseases, and respiratory disorders. Notably, the effects of PM exposure are not uniform; they can vary significantly based on factors such as the size and composition of PM particles, exposure duration, and individual susceptibility due to genetic and environmental factors.

However, a comprehensive understanding of the mechanisms driving these DNA methylation changes remains elusive. Discrepancies in findings arise from variations in PM composition, exposure durations, and population-specific characteristics. While genome-wide methylation profiling has identified PM-associated CpG sites, these findings remain underutilized. This highlights the need for integrating advanced bioinformatics approaches to extract their full potential and better understand the implications of these epigenetic alterations.

Future research should prioritize tissue- and cell-specific investigations that combine genetic and epigenetic insights to unravel the molecular mechanisms underlying PM toxicity. Developing improved methodologies for quantifying PM exposure such as real-

time monitoring technologies and exploring its effects on epigenetic pathways is essential for advancing targeted interventions. Such efforts hold promise for identifying robust biomarkers that can assess individual susceptibility to air pollution and monitor long-term health effects. Moreover, a more nuanced exploration of the interactions between PM exposure, DNA methylation, and human health is required. Continued research in this field will provide valuable insights into epigenetic mechanisms, ultimately enabling the development of effective strategies to address the health burdens posed by air pollution. The identification of particular DNA methylation changes linked with air pollution exposure could serve as useful indicators for evaluating individual vulnerability and tracking long-term health effects in communities affected by air pollution. Additionally, public health activities targeted at lowering PM exposure may benefit from our research by shaping regulations that protect vulnerable groups, ultimately contributing to better health outcomes throughout communities.

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Competing interests

The authors declare that they have no conflicts of interest.

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Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

References

1. Roser M. Our World in Data [Internet]. 2021. Available from: https://ourworldindata.org/data-review-air-pollution-deaths

2. Reed ZE, Suderman MJ, Relton CL, Davis OSP, Hemani G. The association of DNA methylation with body mass index: distinguishing between predictors and biomarkers. Clin Epigenetics. 2020;12(1):1–13.

3. Wang M, Zhao J, Wang Y, Mao Y, Zhao X, Huang P, et al. Genome-wide DNA methylation analysis reveals significant impact of long-term ambient air pollution exposure on biological functions related to mitochondria and immune response. Environmental Pollution. 2020;264:114707.

4. Rider CF, Carlsten C. Air pollution and DNA methylation: effects of exposure in humans. Clin Epigenetics. 2019;11(1):1–15.

5. Luger K, Mä Der AW, Richmond RK, Sargent DF, Richmond TJ. Crystal structure of the nucleosome core particle at 2.8 A ˚ resolution. Vol. 389, Nature © Macmillan Publishers Ltd. 1997.

6. Chaturvedi P, Tyagi SC. Epigenetic mechanisms underlying cardiac degeneration and regeneration. Int J Cardiol. 2014;173(1):1–11.

7. Yao Q, Chen Y, Zhou X. The roles of microRNAs in epigenetic regulation. Curr Opin

Chem Biol. 2019;51:11–7.

8. Arif KMT, Elliott EK, Haupt LM, Griffiths LR. Regulatory mechanisms of epigenetic miRNA relationships in human cancer and potential as therapeutic targets. Cancers (Basel). 2020;12(10):2922.

9. Saito Y, Saito H, Liang G, Friedman JM. Epigenetic alterations and microRNA misexpression in cancer and autoimmune diseases: a critical review. Clin Rev Allergy Immunol. 2014;47:128–35.

10. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet. 2012;13(7):484–92.

11. Patil V, Ward RL, Hesson LB. The evidence for functional non-CpG methylation in mammalian cells. Epigenetics. 2014;9(6):823–8.

12. Jang HS, Shin WJ, Lee JE, Do JT. CpG and non-CpG methylation in epigenetic gene regulation and brain function. Genes (Basel). 2017;8(6):148.

13. Li J, Wang T, Wang Y, Xu M, Zhang L, Li X, et al. Particulate matter air pollution and the expression of microRNAs and pro-inflammatory genes: Association and mediation among children in Jinan, China. J Hazard Mater. 2020;389:121843.

14. Ambrosi C, Manzo M, Baubec T. Dynamics and context-dependent roles of DNA methylation. J Mol Biol. 2017;429(10):1459–75.

15. Ghazi T, Arumugam T, Foolchand A, Chuturgoon AA. The impact of natural dietary compounds and food-borne mycotoxins on DNA methylation and cancer. Cells. 2020;9(9):2004.

16. Mukherjee S, Dasgupta S, Mishra PK, Chaudhury K. Air pollution-induced epigenetic changes: Disease development and a possible link with hypersensitivity pneumonitis. Environmental Science and Pollution Research. 2021;28(40):55981–6002.

17. Sharma R, Kurmi OP, Hariprasad P, Tyagi SK. Health implications due to exposure to fine and ultra-fine particulate matters: a short review. International Journal of Ambient Energy. 2024;45(1):2314256.

18. Morawska L, Agranovski V, Moore M. State of Epidemiological Evidence for the Health Impacts of Ultrafine Particles. In: Proceedings of the 14th International Union of Air Pollution Prevention and Environmental Protection Associations (IUAPPA) World Congress 2007. Clean Air Society of Australia and New Zealand; 2007. p. 1–7.

19. Risom L, Møller P, Loft S. Oxidative stress-induced DNA damage by particulate air pollution. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2005;592(1–2):119–37.

20. Valacchi G, Magnani N, Woodby B, Ferreira SM, Evelson P. Particulate matter induces tissue oxinflammation: from mechanism to damage. Antioxid Redox Signal. 2020;33(4):308–26.

21. Zhuang C, Wu Z, Xing C, Miao Z. Small molecules inhibiting Keap1–Nrf2 protein–protein interactions: a novel approach to activate Nrf2 function. Medchemcomm. 2017;8(2):286–94.

22. Prunicki M, Cauwenberghs N, Lee J, Zhou X, Movassagh H, Noth E, et al. Air pollution exposure is linked with methylation of immunoregulatory genes, altered immune cell profiles, and increased blood pressure in children. Sci Rep. 2021;11(1):4067.

23. Jin J, Zhong X bo. Epigenetic Mechanisms Contribute to Intraindividual Variations of Drug Metabolism Mediated by Cytochrome P450 Enzymes. Drug Metabolism and Disposition. 2023;51(6):672–84.

24. Yang Y, Yang T, Zhou J, Cao Z, Liao Z,

Zhao Y, et al. Prenatal exposure to concentrated ambient PM2. 5 results in spatial memory defects regulated by DNA methylation in male mice offspring. Environmental Science and Pollution Research. 2023;30(12):35142–52.

25. Tantoh DM, Wu MC, Chuang CC, Chen PH, Tyan YS, Nfor ON, et al. AHRR cg05575921 methylation in relation to smoking and $PM_{2.5}$ exposure among Taiwanese men and women. Clin Epigenetics. 2020;12:1–9.

26. Su CL, Tantoh DM, Chou YH, Wang L, Ho CC, Chen PH, et al. Blood-based SOX2-promoter methylation in relation to exercise and PM2. 5 exposure among Taiwanese adults. Cancers (Basel). 2020;12(2):504.

27. Liang Y, Hu L, Li J, Liu F, Jones KC, Li D, et al. Short-term personal PM2. 5 exposure and change in DNA methylation of imprinted genes: panel study of healthy young adults in Guangzhou city, China. Environmental Pollution. 2021;275:116601.

28. Shi W, Gao X, Cao Y, Chen Y, Cui Q, Deng F, et al. Personal airborne chemical exposure and epigenetic ageing biomarkers in healthy Chinese elderly individuals: evidence from mixture approaches. Environ Int. 2022;170:107614.

29. Rossnerova A, Tulupova E, Tabashidze N, Schmuczerova J, Dostal M, Rossner Jr P, et al. Factors affecting the 27K DNA methylation pattern in asthmatic and healthy children from locations with various environments. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2013;741:18–26.

30. Salam MT, Byun HM, Lurmann F, Breton C V, Wang X, Eckel SP, et al. Genetic and epigenetic variations in inducible nitric oxide synthase promoter, particulate pollution, and exhaled nitric oxide levels in children. Journal of Allergy and Clinical Immunology. 2012;129(1):232–9.

31. Cantone L, Tobaldini E, Favero C, Albetti B, Sacco RM, Torgano G, et al. Particulate air pollution, clock gene methylation, and stroke: effects on stroke severity and disability. Int J Mol Sci. 2020;21(9):3090.

32. Wang C, O'Brien KM, Xu Z, Sandler DP, Taylor JA, Weinberg CR. Long-term ambient fine particulate matter and DNA methylation in inflammation pathways: results from the Sister Study. Epigenetics. 2020;15(5):524–35.

33. Wang C, Plusquin M, Ghantous A, Herceg Z, Alfano R, Cox B, et al. DNA methylation of insulin-like growth factor 2 and H19 cluster in cord blood and prenatal air pollution exposure to fine particulate matter. Environmental Health. 2020;19(1):1–12.

34. C. Chi G, Liu Y, MacDonald JW, M. Reynolds L, Enquobahrie DA, L. Fitzpatrick A, et al. Epigenome-wide analysis of long-term air pollution exposure and DNA methylation in monocytes: results from the Multi-Ethnic Study of Atherosclerosis. Epigenetics. 2022;17(3):297–313.

35. Eze IC, Jeong A, Schaffner E, Rezwan FI, Ghantous A, Foraster M, et al. Genome-wide DNA methylation in peripheral blood and long-term exposure to source-specific transportation noise and air pollution: the SAPALDIA study. Environ Health Perspect. 2020;128(6):67003.

36. Wang C, Chen R, Shi M, Cai J, Shi J, Yang C, et al. Possible mediation by methylation in acute inflammation following personal exposure to fine particulate air pollution. Am J Epidemiol. 2018;187(3):484–93.

37. Tobaldini E, Bollati V, Prado M, Fiorelli EM, Pecis M, Bissolotti G, et al. Acute particulate matter affects cardiovascular autonomic modulation and IFN-γ methylation in healthy volunteers. Environ Res. 2018;161:97–103.

38. Zhang Y, Salam MT, Berhane K, Eckel SP, Rappaport EB, Linn WS, et al. Genetic and epigenetic susceptibility of airway inflammation to PM2. 5 in school children: new insights from quantile regression. Environmental Health. 2017;16(1):1–10.

39. Cai J, Zhao Y, Liu P, Xia B, Zhu Q, Wang X, et al. Exposure to particulate air pollution during early pregnancy is associated with placental DNA methylation. Science of The Total Environment. 2017;607:1103–8.

40. Shen Y, Peng C, Bai Q, Ding Y, Yi X, Du H, et al. Epigenome-wide association study indicates hypomethylation of MTRNR2L8 in large-artery atherosclerosis stroke. Stroke. 2019;50(6):1330–8.

41. Maghbooli Z, Hossein-Nezhad A, Adabi E, Asadollah-Pour E, Sadeghi M, Mohammad-Nabi S, et al. Air pollution during pregnancy and placental adaptation in the levels of global DNA methylation. PLoS One. 2018;13(7):e0199772.

42. Zhang X, Biagini Myers JM, Burleson JD, Ulm A, Bryan KS, Chen X, et al. Nasal DNA methylation is associated with childhood asthma. Epigenomics. 2018;10(5):629–41.

43. Zhu T, Zhang X, Chen X, Brown AP, Weirauch MT, Guilbert TW, et al. Nasal DNA methylation differentiates severe from non-severe asthma in African-American children. Allergy. 2021;76(6):1836–45.

44. Clifford RL, Jones MJ, MacIsaac JL, McEwen LM, Goodman SJ, Mostafavi S, et al. Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. Journal of Allergy and Clinical Immunology. 2017;139(1):112–21.

45. Chatziioannou A, Georgiadis P, Hebels DG, Liampa I, Valavanis I, Bergdahl IA, et al. Blood-based omic profiling supports female susceptibility to tobacco smoke-induced cardiovascular diseases. Sci Rep. 2017;7(1):1–13.

46. Kumaran M, Devarajan B. eyeVarP: a computational framework for the identification of pathogenic variants specific to eye disease. Genetics in Medicine. 2023;100862.

47. Cao Y. Environmental pollution and DNA methylation: carcinogenesis, clinical significance, and practical applications. Front Med. 2015;9(3):261–74.

48. Ferrari L, Carugno M, Bollati V. Particulate matter exposure shapes DNA methylation through the lifespan. Clin Epigenetics. 2019;11:1–14.

49. Zeng M, Zhen J, Zheng X, Qiu H, Xu X, Wu J, et al. The Role of DNA Methylation in Ischemic Stroke: A Systematic. Therapeutic Agents and Targets to Minimize Ischemic Brain Injury. 2021;

50. Soler-Botija C, Gálvez-Montón C, Bayés-Genís A. Epigenetic biomarkers in cardiovascular diseases. Front Genet. 2019;10:950.

51. Yuasa Y. DNA methylation in cancer and ageing. Mech Ageing Dev. 2002;123(12):1649–54.

52. Zhao R, Choi BY, Lee MH, Bode AM, Dong Z. Implications of genetic and epigenetic alterations of CDKN2A (p16INK4a) in cancer. EBioMedicine. 2016;8:30–9.

53. Dammann R, Schagdarsurengin U, Seidel C, Strunnikova M, Rastetter M, Baier K, et al. The tumor suppressor RASSF1A in human carcinogenesis: an update. Histol Histopathol. 2005;

54. Soejima H, Zhao W, Mukai T. Epigenetic silencing of the MGMT gene in cancer. Biochemistry and cell biology. 2005;83(4):429–37.

55. Bai X, Fu Y, Xue H, Guo K, Song Z, Yu Z, et al. BRCA1 promoter hypermethylation in sporadic epithelial ovarian carcinoma: Association with low expression of BRCA1, improved survival and co expression of DNA methyltransferases. Oncol Lett. 2014;7(4):1088–96.

56. Zhang Y, Qu X, Jing W, Hu X, Yang X, Hou K, et al. GSTP1 determines cis-platinum cytotoxicity in gastric adenocarcinoma MGC803 cells: regulation by promoter methylation and extracellular regulated kinase signaling. Anticancer Drugs. 2009;20(3):208–14.

57. Hsieh AL, Dang C V. MYC, metabolic synthetic lethality, and cancer. Springer; 2016.

58. Ikeda K, Shiraishi K, Eguchi A, Shibata H, Yoshimoto K, Mori T, et al. Long interspersed nucleotide element 1 hypomethylation is associated with poor prognosis of lung adenocarcinoma. Ann Thorac Surg. 2013;96(5):1790–4.

59. Wehbe H, Henson R, Meng F, Mize-Berge J, Patel T. Interleukin-6 contributes to growth in cholangiocarcinoma cells by aberrant promoter methylation and gene expression. Cancer Res. 2006;66(21):10517–24.

60. Hoffmann MJ, Schulz WA. Causes and consequences of DNA hypomethylation in human cancer. Biochemistry and cell biology. 2005;83(3):296–321.

61. Kucher AN, Nazarenko MS. Epigenetics of Cardiomyopathy: Histone Modifications and DNA Methylation. Russ J Genet. 2023;59(3):226–41.

62. Jordan VK, Rosenfeld JA, Lalani SR, Scott DA. Duplication of HEY2 in cardiac and neurologic development. Am J Med Genet A. 2015;167(9):2145–9.

63. Liu CF, Tang WHW. Epigenetics in cardiac hypertrophy and heart failure. JACC Basic Transl Sci. 2019;4(8):976–93.

64. Glezeva N, Moran B, Collier P, Moravec CS, Phelan D, Donnellan E, et al. Targeted DNA methylation profiling of human cardiac tissue reveals novel epigenetic traits and gene deregulation across different heart failure patient subtypes. Circ Heart Fail. 2019;12(3):e005765.

65. Koshman YE, Patel N, Chu M, Iyengar R, Kim T, Ersahin C, et al. Regulation of connective tissue growth factor gene expression and fibrosis in human heart failure. J Card Fail. 2013;19(4):283–94.

66. Heymans S, Corsten MF, Verhesen W, Carai P, Van Leeuwen REW, Custers K, et al. Macrophage microRNA-155 promotes cardiac hypertrophy and failure. Circulation. 2013;128(13):1420–32.

67. Nagalingam RS, Safi HA, Al-Hattab DS, Bagchi RA, Landry NM, Dixon IMC, et al. Regulation of cardiac fibroblast MMP2 gene expression by scleraxis. J Mol Cell Cardiol. 2018;120:64–73.

68. Bhattacharyya T, Nicholls SJ, Topol EJ, Zhang R, Yang X, Schmitt D, et al. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. JAMA. 2008;299(11):1265–76.

69. Vogel CFA, Haarmann-Stemmann T. The aryl hydrocarbon receptor repressor–more than a simple feedback inhibitor of AhR signaling: clues for its role in inflammation and cancer. Curr Opin Toxicol. 2017;2:109–19.

70. Dziedzic T. Systemic inflammation as a therapeutic target in acute ischemic stroke. Expert Rev Neurother. 2015;15(5):523–31.

71. Watanabe M, Nakahata S, Hamasaki M, Saito Y, Kawano Y, Hidaka T, et al. Downregulation of CDKN1A in adult T-cell leukemia/lymphoma

despite overexpression of CDKN1A in human T-lymphotropic virus 1-infected cell lines. J Virol. 2010;84(14):6966–77.

72. Cui G, Wang H, Li R, Zhang L, Li Z, Wang Y, et al. Polymorphism of tumor necrosis factor alpha (TNF-alpha) gene promoter, circulating TNF-alpha level, and cardiovascular risk factor for ischemic stroke. J Neuroinflammation. 2012;9:1–11.

73. Yang C, Croteau S, Hardy P. Histone deacetylase (HDAC) 9: versatile biological functions and emerging roles in human cancer. Cellular Oncology. 2021;44:997–1017.

74. Dar AA, Majid S, Nosrati M, De Semir D, Federman S, Kashani-Sabet M. Functional modulation of IGF-binding protein-3 expression in melanoma. Journal of investigative dermatology. 2010;130(8):2071–9.

75. Kato N, Loh M, Takeuchi F, Verweij N, Wang X, Zhang W, et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. Nat Genet. 2015;47(11):1282–93.

76. Zhu T, Qiao L, Wang Q, Mi R, Chen J, Lu Y, et al. T-box family of transcription factor-TBX5, insights in development and disease. Am J Transl Res. 2017;9(2):442.

77. Della Corte V, Todaro F, Cataldi M, Tuttolomondo A. Atherosclerosis and Its Related Laboratory Biomarkers. Int J Mol Sci. 2023;24(21):15546.

78. Yang X, Zhao T, Feng L, Shi Y, Jiang J, Liang S, et al. PM2. 5-induced ADRB2 hypermethylation contributed to cardiac dysfunction through cardiomyocytes apoptosis via PI3K/Akt pathway. Environ Int. 2019;127:601–14.

79. Jiang W. Vascular Injury Induces Epigenetic Mechanisms to Promote Restenosis After Angioplasty. Creighton University; 2019.

80. Duan L, Hu J, Xiong X, Liu Y, Wang J. The role of DNA methylation in coronary artery disease. Gene. 2018;646:91–7.

81. Hou H, Zhao H. Epigenetic factors in atherosclerosis: DNA methylation, folic acid metabolism, and intestinal microbiota. Clinica Chimica Acta. 2021;512:7–11.

82. Ji HW, Kang J, Kim HC, Jung J, Lee SJ, Jung JY, et al. The association between cumulative exposure to PM2. 5 and DNA methylation measured using methyl-capture sequencing among COPD patients. Respir Res. 2024;25(1):335.

83. Prunicki M, Cauwenberghs N, Lee J, Zhou X, Movassagh H, Noth E, et al. Air pollution exposure is linked with methylation of immunoregulatory genes, altered immune cell profiles, and increased blood pressure in children. Sci Rep. 2021;11(1):4067.

84. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. Circ Res. 2015;116(6):937–59.

85. Gómez-Roig MD, Pascal R, Cahuana MJ, García-Algar O, Sebastiani G, Andreu-Fernández V, et al. Environmental exposure during pregnancy: influence on prenatal development and early life: a comprehensive review. Fetal Diagn Ther. 2021;48(4):245–57.

86. Daniel G, Paola AR, Nancy G, Fernando SO, Beatriz A, Zulema R, et al. Epigenetic mechanisms and host factors impact ACE2 gene expression: Implications in COVID-19 susceptibility. Infection, Genetics and Evolution. 2022;104:105357.

87. Takashima Y, Keino-Masu K, Yashiro H, Hara S, Suzuki T, van Kuppevelt TH, et al. Heparan sulfate 6-O-endosulfatases, Sulf1 and Sulf2, regulate glomerular integrity by

modulating growth factor signaling. American Journal of Physiology-Renal Physiology. 2016;310(5):F395–408.

88. Alikhani-Koopaei R, Fouladkou F, Frey FJ, Frey BM. Epigenetic regulation of 11β-hydroxysteroid dehydrogenase type 2 expression. J Clin Invest. 2004;114(8):1146–57.

89. Liang M. Epigenetic mechanisms and hypertension. Hypertension. 2018;72(6):1244–54.

90. Sánchez-Navarro A, González-Soria I, Caldiño-Bohn R, Bobadilla NA. An integrative view of serpins in health and disease: the contribution of SerpinA3. American Journal of Physiology-Cell Physiology. 2021;320(1):C106–18.

91. Lin CY, Lee HL, Hwang YT, Huang PC, Wang C, Sung FC, et al. Urinary heavy metals, DNA methylation, and subclinical atherosclerosis. Ecotoxicol Environ Saf. 2020;204:111039.