Systematic Review Article

Epigenetic Effects of Prenatal and Early Life Tobacco Smoke Exposure on AHRR Methylation

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ABSTRACT

Prenatal tobacco smoke exposure is an important public health concern, particularly in settings where tobacco use and secondhand smoke (SHS) exposure remain widespread. This systematic review examined the relationship between prenatal tobacco exposure and DNA methylation changes, with emphasis on the aryl hydrocarbon receptor repressor (AHRR) gene, while also considering developmental outcomes and implications for high-exposure settings such as Indonesia. PubMed and Google Scholar were searched between January and June 2026, with the final search conducted on 14 June 2026. Studies published between 2005 and 2026 were eligible if they were English-language, peer-reviewed original research articles investigating prenatal tobacco exposure and offspring DNA methylation or relevant developmental outcomes. Studies from any country-income setting were eligible. Study selection followed predefined eligibility criteria and PRISMA 2020 guidelines. Three observational studies, including cohort and cross-sectional designs, were included. Direct evidence linking prenatal SHS exposure with AHRR methylation was limited. Most studies examined maternal active smoking during pregnancy and identified associations with altered offspring DNA methylation, including changes at tobacco-associated AHRR CpG sites. Prenatal SHS exposure was also associated with adverse neonatal outcomes, including lower birth weight. Findings were limited by the small number of eligible studies, observational designs, and limited representation of low- and middle-income countries. Current evidence suggests that prenatal tobacco exposure may contribute to epigenetic and developmental effects; however, further longitudinal research is needed, particularly in populations with high tobacco exposure burdens and in low- and middle-income countries where evidence remains limited.

Keywords: Secondhand Smoke (SHS); Prenatal Tobacco Exposure; DNA Methylation; Aryl Hydrocarbon Receptor Repressor (AHRR); Epigenetics; Birthweight; low-and middle-income countries

INTRODUCTION

Secondhand smoke (SHS) exposure during pregnancy is a significant public health concern in low- and middle-income countries, where tobacco use and household exposure remain prevalent. One such example is Indonesia where roughly 30%–34% of the population use tobacco, with estimates showing that 65% of adult males smoke (1). Even when pregnant women do not smoke themselves, exposure to SHS can affect the developing fetus and cause biological changes. Recent research has

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Accepted August 20, 2026
https://doi.org/10.70251/HYJR2348.4412831293

shown that epigenetic changes run alongside prenatal exposure to tobacco smoke (2). Epigenetics refers to the heritable changes in gene expression that happen without altering underlying DNA sequences (Figure 1). Epigenetic regulation is necessary for human development because it controls when and where genes are expressed throughout the body. Although every cell contains the same sequence of DNA, the different epigenetic mechanisms in the human body allow the various cell types to perform their specialized functions by regulating patterns of gene activity. These mechanisms are especially important during fetal development, when cells rapidly divide and differentiate into tissues and organs.

Many major epigenetic mechanisms have been identified including but not limited to, DNA methylation, histone modification, and noncoding RNA regulation. Among these, DNA methylation has been the most widely studied in relation to tobacco smoke exposure. DNA methylation occurs when methyl groups, which act as small chemical tags, are added to cytosine bases located next to guanine nucleotides in DNA at CpG sites. CpG sites are locations in a DNA sequence where cytosine (C) nucleotide is immediately followed by a guanine (G) nucleotide connected by a phosphate backbone. These methylation patterns, specifically the arrangement of where methyl groups are attached and not attached, help determine whether genes are transcribed or silenced. Increased methylation, meaning when more methyl groups are added into the gene regulatory regions, blocks the cell from reading the gene and is often associated with reduced gene expression, whereas decreased methylation can lead to increased gene activity. Abnormal methylation patterns have been linked to several diseases: cancer, cardiovascular disease, asthma, diabetes, and neurological disorders such as Alzheimer's disease. One such example is the hypermethylation of tumor suppressor genes potentially contributing to cancer development, while hypomethylation of inflammatory or stress-response genes have been associated with chronic inflammation and cardiovascular disease (3). The role of epigenetic mechanisms in regulating cellular processes and influencing health outcomes is illustrated in Figure 1.

Epigenetics is especially relevant to studies of prenatal SHS exposure because the fetal epigenome is highly sensitive to alteration during development.

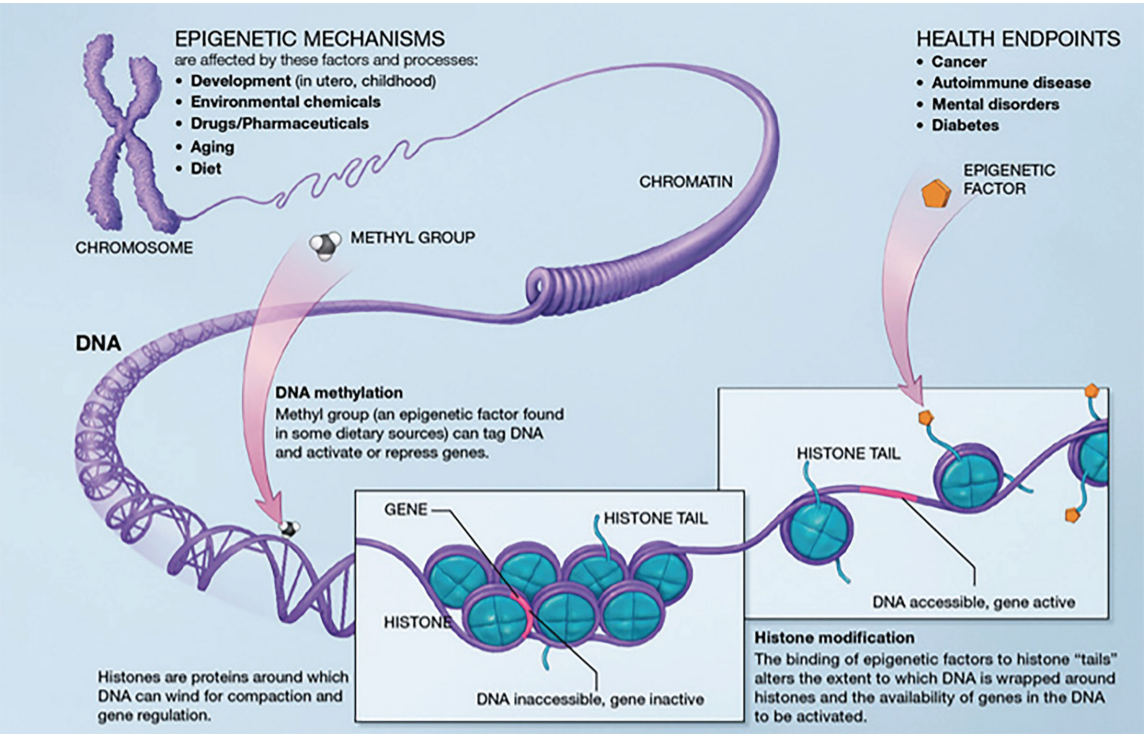

Figure 1. ***Illustration of How Epigenetic Mechanisms Can Affect Health.*** *Note: This figure shows how epigenetic mechanisms affect histone configuration in cells. Reproduced from Nature Education, "An illustration of How Epigenetic Mechanisms can affect health" Used with permission from The World Library of Science.*

Environmental exposures during pregnancy can alter normal methylation patterns and can create long-term biological effects that persist into adulthood. Prenatal exposure to tobacco smoke has been associated with adverse developmental outcomes and persistent epigenetic changes in offspring, including alterations in DNA methylation patterns (5, 6). These findings are evidence that environmental exposures during pregnancy can influence health outcomes before and after birth. AHRR plays an important role in how the body responds to harmful chemicals found in tobacco smoke (2). AHRR is part of the aryl hydrocarbon receptor (AHR) signaling pathway, which helps the body detect and process environmental toxins such as polycyclic aromatic hydrocarbons found in cigarette smoke. When these toxic compounds are inhaled, they activate the AHR pathway, which then increases the production of enzymes that help break down and remove these harmful substances. The biological role of the AHR/AHRR pathway and its negative feedback regulation in response to tobacco smoke constituents is illustrated in Figure 2.

This mechanism is especially important in low- and middle-income countries, where prenatal tobacco smoke exposure remains a significant public health concern due to high rates of tobacco use and secondhand smoke exposure. Although research has demonstrated associations between tobacco exposure and epigenetic alterations, evidence specifically examining prenatal secondhand smoke exposure and AHRR DNA methylation in low- and middle-income country populations remains limited. Therefore, this review focuses on the relationship between prenatal tobacco smoke exposure and alterations in AHRR DNA methylation, while recognizing that evidence from maternal active smoking studies may provide relevant biological context but cannot be assumed to represent identical effects of secondhand smoke exposure (8).

The objective of this systematic review is to examine whether prenatal tobacco smoke exposure is associated with changes in AHRR DNA methylation and related developmental outcomes. The review question is: Among pregnant individuals and their offspring in low- and middle-income country settings, is prenatal tobacco smoke exposure, including secondhand smoke exposure and maternal smoking exposure, compared with no prenatal tobacco smoke exposure, associated

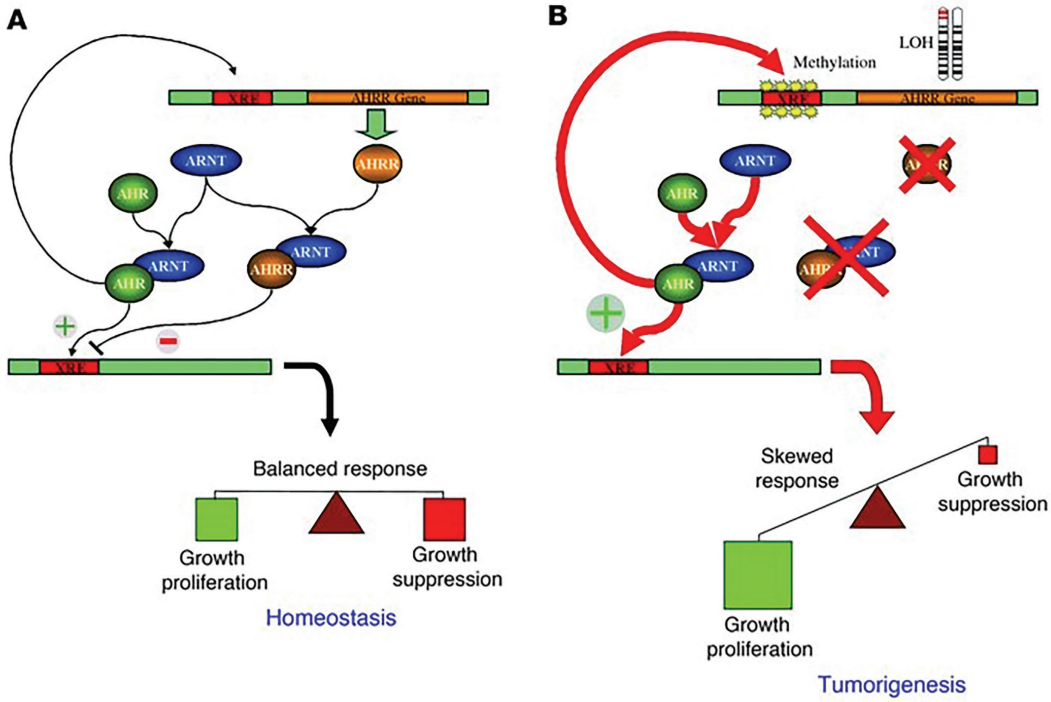

Figure 2. AHR/AHRR feedback regulation pathway. *Note: Activation of AHR by tobacco smoke constituents induces detoxification enzymes and stimulates AHRR expression. AHRR subsequently inhibits AHR activity through negative feedback. Reproduced from the article "The Aryl Hydrocarbon Receptor Repressor is a putative tumor suppressor gene in human cancers" Used with permission from The Journal of Clinical Investigation.*

with alterations in AHRR DNA methylation and developmental outcomes in offspring? Eligible study designs include observational cohort, cross-sectional, and case-control studies that evaluate prenatal tobacco exposure and biological or developmental outcomes.

Tobacco Smoke in Low Income Countries

General smoking info on Indonesia

In Indonesia, smoking culture is so prevalent that there is a rate of SHS exposure of about 30% (1). Exposure remains widespread across public settings, with the 2021 Global Adult Tobacco Survey finding that 74.2% of adults were exposed to SHS in restaurants, 44.8% in workplaces, 41.4% in government buildings, and 40.5% on public transportation (9). The impact of SHS exposure is very significant in low-and middle-income countries such as Indonesia, where indoor smoking is more common and public health regulations may be limited. As a result, non-smokers, including pregnant women and children, are the most susceptible to tobacco smoke within household settings. A global analysis of data from the Global Adult Tobacco Survey (GATS) found that 79% of Indonesian children under 15 years are exposed to SHS in their homes, and more than 70% of young children live with at least one smoker (10). This continuous exposure increases the risk of harmful health outcomes and contributes to a higher overall burden of tobacco related harm compared with countries that have stricter smoke-free policies like in high income countries. Recent tobacco use prevalence data from Indonesia are presented in Table 1, highlighting differences in tobacco use patterns among adult and adolescent populations.

In many high-income countries, smoking prevalence has declined with association to tobacco control policies, including advertising bans, increased tobacco taxation, and smoke-free legislation (11). For example, adult smoking prevalence is now approximately 11–12% in the United States, 12–14% in Canada, 12–13% in the United Kingdom, and 11–13% in Australia, reflecting long-term reductions in settings with strong regulatory frameworks (1).

METHODS

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A systematic literature search was performed using PubMed and Google Scholar between January and 14 June 2026, with the final search conducted on 14 June 2026. Studies published between 2005 and 2026 and written in English were considered for inclusion.

Search terms were developed around three main concepts: tobacco smoke exposure, prenatal/fetal populations, and epigenetic outcomes. Terms included combinations of “AHRR,” “aryl hydrocarbon receptor repressor,” “DNA methylation,” “epigenetics,” “methylome,” “prenatal tobacco exposure,” “maternal smoking,” “secondhand smoke,” “environmental tobacco smoke,” “pregnancy,” “fetal development,” and “offspring.” Boolean operators (AND, OR) were used to combine search terms.

Reference lists of all included studies and relevant

Table 1. *Tobacco use prevalence from the latest survey completed by 31 December 2024.*

	Tobacco Use		**Tobacco Smoking**		**Cigarette Smoking**		**Smokeless Tobacco Use**		**E-cigarette Use**	
	Current	*Daily*	*Current*	*Daily*	*Current*	*Daily*	*Current*	*Daily*	*Current*	*Daily*
Adults Survey: Survei Kesehatan Indonesia (SKI), 2023; National, ages 15+										
Male	*57.9*	*48.4*	*57.3*	*48.1*	*57.3*	*48.0*	*...*	*...*	*2.0*	*1.5*
Female	*3.3*	*1.8*	*1.2*	*0.8*	*1.2*	*0.9*	*...*	*...*	*0.1*	*0.0*
Both	*30.8*	*25.2*	*29.5*	*24.6*	*29.4*	*24.6*	*...*	*...*	*1.0*	*0.8*
Adolescents Survey: Global School-Based Student Health Survey, 2023; National, ages 13-17										
Male	*38.8*	*...*	*...*	*...*	*35.3*	*...*	*...*	*...*	*19.7*	*...*
Female	*8.2*	*...*	*...*	*...*	*4.7*	*...*	*...*	*...*	*5.0*	*...*
Both	*23.4*	*...*	*...*	*...*	*19.9*	*...*	*...*	*...*	*12.4*	*...*

Note: Comparison of tobacco use across Indonesian adults and adolescents surveyed in 2024. Used with permission from the World Health Organization, 2024.

review articles were manually screened to identify additional eligible publications. Google Scholar was used as a supplementary source to identify potentially relevant literature not retrieved through PubMed. Literature, including WHO reports and policy documents, were searched only to provide background information and were not included in the primary evidence synthesis. Duplicate records were identified and removed automatically before title and abstract screening. Remaining records were screened independently against the predefined eligibility criteria, followed by full-text assessment of potentially eligible studies. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 3). This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (12). No review protocol was registered in PROSPERO or the Open Science Framework.

Eligibility

Studies were considered eligible if they included pregnant individuals and their offspring who were exposed to tobacco smoke during fetal development. Eligible exposures included prenatal tobacco smoke exposure resulting from maternal active smoking during pregnancy as well as prenatal secondhand smoke exposure. he primary outcomes of interest were alterations in DNA methylation, particularly within the AHRR gene, and developmental outcomes associated with prenatal tobacco smoke exposure were considered as secondary outcomes. Only original, peer-reviewed observational studies, including cohort, case-control, and cross-sectional designs, were included. Studies were excluded if they were reviews, editorials, conference abstracts, animal or in vitro studies, did not assess prenatal tobacco smoke exposure, or did not report DNA methylation or relevant developmental outcomes.

Studies conducted in any country-income setting were eligible for inclusion. Studies from high-income countries were included because evidence examining prenatal tobacco smoke exposure and epigenetic outcomes, particularly AHRR methylation, remains limited in low- and middle-income countries. These studies were considered relevant for characterizing biological mechanisms and epigenetic patterns associated with prenatal tobacco exposure, while recognizing that differences in exposure prevalence, socioeconomic conditions, and environmental factors may influence the generalizability of findings to low- and middle-income settings. Studies were excluded if they focused exclusively on active smoking in nonpregnant adults, did not evaluate prenatal tobacco exposure, did not report relevant epigenetic or developmental outcomes, or were conference abstracts, editorials, commentaries, or non-primary research articles. Background sources, including WHO reports, policy documents, and review articles, were used to provide contextual information regarding tobacco exposure prevalence, tobacco control, and epigenetic mechanisms but were not included in the primary evidence synthesis.

Risk of bias among included observational studies was assessed using the Newcastle–Ottawa Scale (NOS). Risk-of-bias assessments are presented in Table 2. Higher NOS scores indicated lower risk of bias. Risk-of-bias assessments and overall ratings for each included study are presented in Table 2.

Data Extraction

The study selection process is illustrated in the PRISMA 2020 flow diagram (Figure 3).

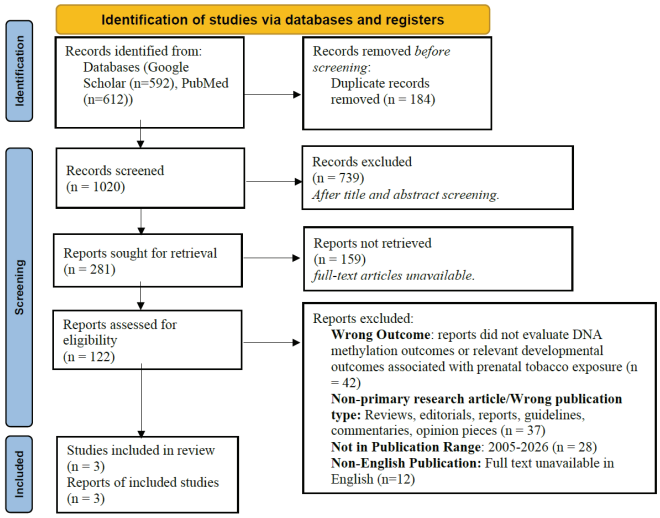

Figure 3. *Flowchart illustrates the multi-stage search and screening strategy used in this review, detailing the databases queried, total records identified, and sequential exclusion criteria applied at the title-and-abstract and full-text review stages, culminating in the 3 original articles included in the final synthesis. Created by Author in Word for the web. The layout and standardized wording were adapted from the PRISMA 2020 flow diagram published by Page et al.(13). licensed under CC BY 4.0. Study counts and review-specific information were updated for the present review.*

Table 2. *Characteristics of Included Studies.*

Study	Country	Study	Sample/ population	Exposure assessment	Biological sample & methylation method	AHRR CpG site(s) (If applicable)	Outcomes	Main findings/ Reported Effect estimates	Follow up	Risk of bias
Joubert *et al*. (2012)	Norway	Cohort	1,062 newborns from the Norwegian Mother and Child Cohort Study (MoBa); Replication cohort included 36 newborns (18 exposed to maternal smoking and 18 unexposed).	Maternal smoking during pregnancy (self-reported)	Cord blood DNA	AHRR-associated CpG sites (including smoking-associated regions)	Differential DNA methylation at birth	Maternal smoking during pregnancy was associated with differential DNA methylation in newborns, including reduced methylation at the AHRR cg05575921 CpG site. Effect estimates were reported for differentially methylated CpG sites; confidence intervals were not consistently reported.	Birth	Low risk of bias (NOS: 9/9)
Tehranifar *et al*. (2018)	USA	Cohort	Adult offspring from the New York Women's Birth Cohort (n=89)	Maternal smoking during pregnancy	Blood DNA; methylation analysis of smoking-associated CpG sites	cg05575921	constant methylation changes in adulthood	Maternal smoking during pregnancy was associated with altered offspring AHRR methylation in midlife. AHRR cg05575921 showed reduced methylation ($\beta = -0.05$; 95% CI: −0.10 to 0.00). Cg23916896 showed reduced methylation ($\beta = -0.04$; 95% CI: −0.06 to −0.02).	~40 years	Low risk of bias (NOS: 8/9)
Ramadani *et al*. (2019)	Indonesia	Cross-sectional	128 nonsmoking pregnant women and newborns	Prenatal SHS exposure measured through nicotine in umbilical cord blood	Umbilical cord blood nicotine measurement	Not assessed (study evaluated prenatal SHS exposure and neonatal outcomes only)	Birth weight	Prenatal SHS exposure was associated with lower neonatal birth weight (mean difference: −205.6 g; 95% CI: −348.6 to −62.6; $p = 0.005$). DNA methylation and AHRR methylation were not assessed.	Birth	Low risk of bias (NOS: 9/10)

AHRR = aryl hydrocarbon receptor repressor; SHS = secondhand smoke; CpG = cytosine-phosphate-guanine.

RESULTS

The characteristics of the three included studies are summarized in Table 2.

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS), with the version selected according to study design. Cohort studies were assessed using the original NOS (14), whereas cross-sectional studies were assessed using a modified NOS adapted from Herzog *et al*. (2013) (15). The risk-of-bias assessments for cohort and cross-sectional studies are presented in Tables 3 and 4, respectively.

Prenatal Maternal Smoking Exposure and AHRR DNA Methylation

A study by Joubert *et al*. examined the association between maternal smoking during pregnancy and DNA methylation changes in newborns using an epigenome-wide approach. Researchers analyzed DNA methylation patterns in newborn cord blood to determine whether prenatal tobacco exposure was associated with differential methylation at specific CpG sites. The study identified multiple differentially methylated regions associated with maternal smoking exposure, including alterations within the AHRR gene. Reduced methylation was observed at smoking-associated CpG sites within AHRR among newborns exposed to maternal smoking during pregnancy compared with unexposed newborns. These findings demonstrate that prenatal tobacco exposure is associated with measurable DNA methylation changes at birth and provide evidence that AHRR methylation may be altered during early development following tobacco smoke exposure (5).

The New York Women's Birth Cohort included 89 women born between 1959 and 1964 whose mothers provided information on maternal smoking during pregnancy. DNA methylation was measured using blood samples collected from participants between 2001 and 2007, when the women were approximately 43 years old. Researchers investigated whether prenatal exposure to maternal smoking was associated with persistent alterations in DNA methylation at CpG sites previously linked to maternal smoking exposure. The study identified differential methylation at multiple CpG sites, including cg05575921 within the AHRR gene. Maternal smoking during pregnancy was associated with lower methylation

Table 3. *Newcastle–Ottawa Scale (NOS) domains and scoring criteria for included cohort studies.*

Study	Selection			
	Cohort representativeness	**Selection of the non-exposed cohort**	**ascertainment of exposure**	**Demonstration that the outcome of interest was not present at the start**
Joubert *et al*. (2012)	★	★	★	★
Tehranifar *et al*. (2018)	★	★	★	★

Study	Comparability	
	The study controlled for the most important confounding factor. (ex. Maternal age, Maternal smoking intensity, cotinine level)	**The study controlled for additional important confounding factors. (ex. Maternal BMI, Parity, Child sex, Maternal folate, nutritional status, Offspring's own smoking)**
Joubert *et al*. (2012)	★	★
Tehranifar *et al*. (2018)	★	★

Study	Outcome			Total
	assessment of outcome	**was follow-up long enough for results to occur?**	**fitness of follow-up of cohorts**	
Joubert *et al*. (2012)	★	★	★	9/9
Tehranifar *et al*. (2018)	★	★	—	8/9

Note: Cohort studies were assessed using the original Newcastle–Ottawa Scale (14).

Table 4. *Modified Newcastle–Ottawa Scale (NOS) criteria used to assess the risk of bias of cross-sectional studies.*

Study	Selection				
	Cohort representativeness	**Justified sample size**	**ascertainment of exposure**	**Non-respondents**	**inclusion criteria**
Ramada-ni *et al*. (2019)	★	★	★	__	★

Study	Comparability	
	The study controlled for the most important confounding factor. (ex. Maternal age, Maternal smoking intensity, cotinine level)	**The study controlled for additional important confounding factors. (ex. Maternal BMI, Parity, Child sex, Maternal folate, nutritional status, Offspring's own smoking)**
Ramada-ni *et al*. (2019)	★	★

Study	Outcome			Total
	assessed outcome	**STAT**	**report of result data**	
Ramada-ni *et al*. (2019)	★	★	★	9/10

Note: Cross-sectional studies were assessed using a modified Newcastle–Ottawa Scale adapted from Herzog et al. (15). STAT = appropriateness of the statistical analysis for the study design, exposure, outcome, and data.

at cg05575921 (β = −0.08; 95% CI: −0.13 to −0.02; p = 0.004), indicating that prenatal smoke exposure was associated with an estimated 8% decrease in methylation at this CpG site. The negative β coefficient represents reduced methylation among individuals exposed to maternal smoking during pregnancy. However, after further adjustment for years of active smoking, the association was attenuated and was no longer statistically significant (β = −0.03; 95% CI: −0.08 to 0.02; p = 0.29). These findings suggest that prenatal tobacco smoke exposure may be associated with long-term alterations in AHRR methylation that persist into adulthood, although the influence of an individual's own smoking behavior should also be considered. Statistical significance indicates the strength of evidence against the null hypothesis but does not establish causality or confirm biological importance of the observed methylation changes (6).

Prenatal Secondhand Smoke Exposure and Birth Outcomes

Unfortunately, in low-and middle-income countries we do not see the same strong decline (10). Additional research has shown that SHS exposure in low-and middle-income settings increases the risk of adverse outcomes such as low birth weight, stillbirth, and congenital complications. A study conducted among pregnant women in Indonesia examined the association between prenatal secondhand smoke (SHS) exposure and neonatal outcomes by measuring nicotine concentrations in umbilical cord blood. The study included 128 nonsmoking pregnant women and found that newborns with evidence of SHS exposure had significantly lower birth weights compared with those without detectable exposure (2,916.5 ± 327.3 g vs. 3,094.1 ± 371.9 g, p = 0.005) (16). These findings demonstrate that prenatal SHS exposure is associated with measurable differences in neonatal outcomes. However, the authors noted limitations, including that exposure assessment relied on umbilical cord blood nicotine concentrations as a biomarker and did not account for exposure to other potentially harmful components of tobacco smoke or variations in exposure intensity.

DISCUSSION

These findings have important public health implications. In low-and middle-income countries where exposure to SHS is more prevalent the association between SHS exposure and reduced birth weight highlights the potential for both immediate and long-term health consequences. Additionally, the persistence of AHRR methylation changes into adulthood suggests that prenatal exposure may lead to long-term epigenetic programming.

Biological Effects of SHS Exposure

AHRR functions as a negative feedback regulator, often described as a "brake," on the AHR signaling pathway. This pathway is activated when toxic compounds in tobacco smoke, such as PAH's, bind to the AHR, leading to increased expression of detoxification enzymes. AHRR helps turn off this response once activation has occurred, preventing prolonged or excessive detoxification signaling (5*)* Studies have also shown that even indirect exposure to tobacco smoke can influence biological outcomes. Repeated exposure to toxic substances, such as nicotine, carbon monoxide and polycyclic aromatic hydrocarbons (PAHs), can lead to changes in gene regulation and cellular function over time. These biological effects are particularly concerning during pregnancy, as the developing fetus is highly sensitive to environmental exposures.

Repeated exposure to tobacco smoke can alter DNA methylation patterns in the AHRR gene, particularly in regulatory regions. These epigenetic changes may reduce AHRR gene expression, weakening its ability to suppress AHR pathway activity. As a result, the AHR pathway may remain activated for longer periods than normal. Downstream effects of this disruption may include prolonged cellular stress responses which can contribute to broader biological impairment over time. A systematic review published in Clinical Epigenetics identified AHRR as the most consistently affected gene in relation to smoking, highlighting its importance as a key biomarker of exposure (2). This review identified 1,460 smoking-related DNA methylation sites in a mixture of individuals who smoke and don't smoke and found that CpG sites within AHRR showed the strongest and most consistent associations with smoking exposure.

Even in the absence of active smoking, second hand tobacco smoke (SHS) exposure has been associated with alterations in AHRR DNA methylation. Although the studies included in this review focused specifically on prenatal tobacco exposure, evidence from adult populations provides additional context regarding the broader relationship between SHS exposure and epigenetic modification. For example, a study using data from the Multi-Ethnic Study of Atherosclerosis (MESA) reported that higher levels of recent indoor SHS exposure (≥10 hours per week) were inversely associated with methylation at the AHRR CpG site cg05575921 ($\beta = -0.28 \pm 0.09$, $p = .003$) (8), indicating that greater SHS exposure was associated with lower methylation at this site. The negative β coefficient reflects reduced methylation levels among individuals with higher SHS exposure, while the statistically significant p-value indicates that this association was unlikely to have occurred by chance. As this study examined adult participants rather than prenatal exposure populations and was outside the scope of the formal systematic review, these findings work to provide additional context regarding AHRR methylation patterns and the broader epigenetic effects associated with tobacco smoke exposure. Similarly, a systematic review of smoking-related DNA methylation identified AHRR as one of the genes most consistently associated with tobacco exposure (2), providing additional biological context that supports the plausibility of the epigenetic mechanisms discussed in the present review.

Limitations and Future Research Directions

There is a lack of recent research examining AHRR methylation in relation to secondhand smoke exposure during pregnancy specifically in Indonesia. As a result, most current evidence is drawn from studies in high-income populations, limiting understanding of how these epigenetic effects may manifest in low-and middle-income settings with higher exposure levels. Epigenetic research is expensive and infrastructure heavy. Measuring DNA methylation like AHRR at cg05575921 requires expensive lab equipment, biobanking, and advanced molecular analysis that are more commonly concentrated in high-income research institutions. Existing evidence from high-income countries suggests that prenatal SHS exposure alters AHRR methylation. There is also a lack of large-scale epigenetic studies in low-and middle-income countries, which limits the generalizability of current findings. Given Indonesia's high smoking prevalence and SHS exposure rates, similar effects may occur, but direct evidence remains limited.

Future research should focus on large-scale, longitudinal cohort studies in low-and middle-income countries that track secondhand smoke exposure during pregnancy using objective biomarkers, such as cotinine, alongside consistent measurements of epigenetic markers like AHRR methylation because it's the only research method that can demonstrate how exposure early on can lead to changes over time. In addition, research could account for additional biological exposures such as indoor air pollution, socioeconomic status, and nutrition to isolate the specific effects of tobacco smoke on the body. By doing this researchers could clarify if that not only SHS causes long-term epigenetic changes, but also how these changes translate into disease risk across different populations.

CONCLUSION

This review found that available evidence suggests prenatal tobacco smoke exposure is associated with changes in DNA methylation patterns, including alterations in the AHRR gene, as well as adverse developmental outcomes in newborns (8,16). However, the current evidence is primarily observational, and direct evidence examining prenatal secondhand smoke exposure and AHRR methylation remains limited, particularly in low- and middle-income countries where tobacco exposure remains a significant public health concern (9, 10). While studies of maternal active smoking during pregnancy provide important insight into tobacco-related epigenetic mechanisms, these findings cannot be assumed to represent the effects of secondhand smoke exposure alone (5, 6). Overall, reducing prenatal secondhand smoke exposure remains an important public health concern, and additional research is needed to specify the long-term biological significance and developmental implications of tobacco on epigenetic changes, particularly in low- and middle-income country settings (9, 10).

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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